DEPARTMENT OF HEALTH & HUMAN SERVICES Office of the Secretary

Secretary's Advisory Committee on
Human Research Protections
Washington, DC 20201

OCT 13 2011

The Honorable Kathleen Sebelius
Secretary of Health and Human Services
200 Independence Avenue, S.W.
Washington, D.C. 20201

Dear Ms. Sebelius:

In accordance with the provisions of the charter for the Secretary's Advisory Committee on Human Research Protections (SACHRP), I respectfully submit for your consideration a set of recommendations relative to the Department's recent Advance Notice of Proposed Rulemaking (ANPRM) entitled "Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators" and that appeared in the Federal Register 76, 143:44512, 2011.

On July 22nd, U.S. Department of Health and Human Services (HHS) announced proposals to revise and modernize Title 45 Code of Federal Regulations, Part 46, often referred to as the "Common Rule," which Common Rule focuses on regulations governing informed consent and the operations of the institutional review board (IRB) in federally funded research. Proposals to revise and harmonize Title 45 CFR Part 160 and 164 (OCR) and Title 21 CFR Parts 50 and 56 (FDA) were also announced. The ANPRM represents the first such effort to modernize and update the Common Rule in more than 20 years. The proposals are aimed at decreasing burden, improving effectiveness of research oversight, and enhancing protections for research participants. There are many changes proposed. SACHRP applauds the significant efforts and vision on the part of each of the offices and agencies involved in this substantial undertaking, and specifically of the Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA), the Office for Civil Rights (OCR), and many others in drafting this ANPRM. SACHRP appreciates the fact that HHS, in concert with the other Common Rule agencies, acknowledges the burden placed on investigators, sponsors, and institutions by the current system; the potential to enhance protections for research participants; and the fact that our current regulations have not kept pace with the evolution of the research enterprise.

Certain elements of the ANPRM reflect changes previously considered and recommended by SACHRP and its subcommittees. SACHRP further appreciates the creativity and inspiration evident in many of the proposed changes to the Common Rule,leading one to acknowledge and recognize that significant changes will be required to achieve the goals of the Common Rule and the ANPRM.

These changes have the potential to significantly impact human subjects and the research community. The process by which SACHRP arrived at a consensus opinion to respond to the ANPRM involved work both by subcommittees and the parent committee. The Subpart A Subcommittee (SAS) and the Subcommittee on Harmonization (SOH) each met separately to consider the ANPRM. The two subcommittees then met in a two-day joint meeting to discuss and prepare a draft response for further consideration by SACHRP at its October meeting. The comments, criticisms, and recommendations proposed below represent a consensus opinion by SACHRP; strongly held and important minority opinions are included and annotated as such.

SACHRP acknowledges that the ANPRM has interlocking recommendations that must be considered in conjunction rather than individually. In particular, these are the proposals to reduce IRB oversight of minimal risk research, to increase the requirement for consent for future use of biospecimens and data, and to increase data protection requirements. We have addressed each of these elements individually and provided both critiques and suggestions. We have not addressed in depth the relationship of the three interlocking recommendations because it is difficult to envision the resulting system that would result from implementing all three recommendations simultaneously. This is because there is a substantial amount of variability in how these broad recommendations could be implemented, and therefore it is difficult to provide meaningful commentary. We would like to note that it would seem that there would be a shift of administrative burden away from IRBs and towards other entities, and that there seems to be significant potential that the net administrative burden on the conduct of research would be increased. At the same time, there is an effort to enhance data security in minimal risk research, including the future use of biospecimens and data. Because of the potential variability in implementing the three recommendations, it is difficult to comment with specificity.

1. IRB Review Changes

Minimal Risk

The ANPRM proposed numerous substantial changes in the way human subjects research is categorized, reviewed, and approved. Many of these changes are predicated on the assumption that the time IRBs spend reviewing research is not commensurate with the level of risk presented by the proposed research, leading to over-review of minimal risk research, thus detracting from the time IRBs spend with research that is greater than minimal risk. SACHRP agrees that calibrating the level of IRB review to ensure that it is commensurate with the level of risk is appropriate. However, many of the proposed changes in the ANPRM are tied directly to a determination that research either is or is not minimal risk. The definition of minimal risk has been the topic of continuous debate, with an inconsistent understanding of the definition by the

regulated community. 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 is an oversimplification. Such a definition may well lessen human research protections.

SACHRP has previously recommended an analytical framework for understanding, interpreting and applying the existing definition of minimal risk, and provided case examples to guide IRBs and investigators.

In its previous recommendation transmitted on January 31, 2008, SACHRP noted that the regulatory intent of minimal risk is to define a threshold of anticipated harm or discomfort associated with the research that is "acceptably-low" or "low enough" to justify expedited review or waiver of consent. The IRB's evaluation of the harms and discomforts of the research should take into account the nature of the study procedures, other study characteristics, and 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, anticipated harms and discomforts of research involvement.

To satisfy the current regulatory definition of minimal risk, the estimate of the anticipated harms and discomforts of the research for the proposed study population may not be greater than an estimate of "the harms and discomforts ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." While the harms and discomforts ordinarily encountered differ widely among individuals and individual populations, an ethically meaningful notion of "harms and discomforts ordinarily encountered" should reflect "background risks" that are familiar and part of the routine experience of life for "the average person" in the "general population." It should not be based on those ordinarily encountered in the daily lives of the proposed subjects of the research or any specific population, because that could result in an unjust distribution of risks.

The following proposed definition recognizes that risks are procedure-specific and population-dependent, but that the notion of "acceptably-low" risk is fixed. When the harms and discomforts of the proposed research, as they are anticipated to impact the study participants, are judged to fall below this acceptably low risk threshold, the research is "minimal risk."

> *Minimal Risk means that the probability and magnitude of harm or discomfort 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 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.

"Excused" Research

The current regulations describe six categories of activities that are considered exempt from the Common Rule regulations, though it is noted that they are expected to conform to the ethical principles described in the Belmont Report. This exempt research is not required to undergo a review to meet the criteria for IRB approval at Title 45 Code of Federal Regulations, Part 46.111, or the continuing review requirements at §46.109, or the informed consent requirements of §46.116 and §46.117. In addition, the regulations do not restrict who is able to make a determination that a proposed activity meets the criteria for exemption. Historically, guidances issued by the federal government have dictated that determinations of exemption be made by a representative of the institution's human research protections program. The current rationale for placing this responsibility within the purview of IRB functions is as follows:

- Institutions, rather than researchers, are held responsible when research is improperly designated as exempt;
- IRBs are better suited to understand the nuances of the regulations and to apply them consistently;
- Researchers have an inherent conflict of interest, and may not be able to objectively apply exempt categories; and
- Researchers often underestimate the risk of their proposed research.

The ANPRM envisions major changes to the current exempt framework. Significant changes include renaming exempt research "excused" and expanding the current exempt categories. In addition, all of the current exempt categories would be revised to make them more understandable to the research community. In the proposal, investigators would have the authority to make determinations of exemptions for their own research. A registration system would be used to notify the IRB of proposed research, which would then be allowed to commence either immediately or after a prescribed waiting period of a few days. The authors of the ANPRM state that with clearly defined "excused" categories and mandatory data security standards, this minimal risk research does not merit the IRB's attention. Finally, the ANPRM suggests that institutions should exercise quality control oversight of the excused/registered process through mandated audits of selected excused research.

SACHRP appreciates the amount of time IRBs spend on minimal risk review, and, in principle agrees with an effort to simplify the process. However, SACHRP notes several significant concerns related to the implementation of the excused/registered framework. First, if investigators will be given the authority to make excused determinations, then the new rule must craft a new regulatory framework in which the investigator, and not the institution, is held directly responsible for determining whether research requires IRB review. With only one exception in the opening paragraph of 45 CFR Part 46.116, the current regulations are silent on investigator responsibilities; the proposed rulemaking offers the opportunity to more clearly outline the responsibilities an investigator assumes when conducting research. We have included a separate section describing Investigator Responsibilities elsewhere in this document. Second, the excused categories must be rewritten in a way that allows for correct, consistent decision-making on the part of investigators. SACHRP recommends that the list be revised by a

convened multidisciplinary panel of experts. Third, the categories should be expanded carefully, and not merely based on proposed methods. The categories should take into account the sensitivity of the topic, the nature of the research, the target audience, and context in which the research will be done. If this is not done, then the categories should not be expanded. Fourth, if investigators are to be held accountable for their decisions, they must have required ongoing training in general research ethics issues and investigator responsibilities, as well as specific training on making the new excused determinations.

While the ANPRM may presume that the kinds of harm likely to arise in the context of the newly described "excused" category do not warrant prior review, this is true only when harm is equated with physical harm and the purpose of IRB review is restricted to a safety review. Ethics review considers a broader range of risk, and serves to support the ethical principles that guide investigator/subject interaction.

With regard to question 25, SACHRP does not believe there are disciplines or fields of study that should not be covered by the Common Rule. The determination that an activity constitutes research involving living human subjects or identifiable information about living subjects is not dependent on the scholarly discipline or occupation of the researcher(s). That said, it would be of great value if OHRP would consider providing guidance about how to assess whether a proposed data collection/generation activity meets the generalizability standard.

Mandatory Auditing

SACHRP believes that mandated auditing creates unnecessary regulatory burden on researchers, IRBs, and federal regulators. It is certainly not clear against what standards such audits will be conducted. Absent such direction, audit requirements may drive unnecessary documentation in research that is now exempt and may undermine the intent of the new rule. Mandatory requirements also place an unnecessary economic burden on institutions. In addition, it is unclear as to what the expectations would be if/when IRBs discover activities that were inappropriately registered as "excused." Institutions should be encouraged to engage in appropriate, ongoing quality improvement activities, but the specifics should not be dictated in the regulations. Institutions should have the flexibility to establish quality assurance/quality control mechanisms in a manner that is appropriate for each institution. Guidance should address performance standards and corrective actions for institutions as they establish quality assurance/quality control mechanisms and to educate investigators.

Post hoc monitoring should be implemented as an educational, operational activity by institutions to assess experience with investigator classifications and make adjustments where necessary. Furthermore, this should not be approached as a compliance activity that results in sanctions or penalties for investigators who acted reasonably and in good faith and proceeded with registered studies, or reporting by their institutions.

The ANPRM indicates that survey research of "competent adults" should be classified as "excused." SACHRP notes that under existing categories of "exempt" research, some survey research not of "competent adults" (e.g., observation of children's public behavior without

involvement of researchers) is exempt. Any changes to the "exempt" category should be carefully tailored so that they do not inadvertently make "non-excused" all research that is currently "exempt."

Expedited Review

The expedited review list has only been revised once since it was implemented in 1981. That revision occurred in 1998. SACHRP agrees with the recommendation that this list should be subject to careful review by a convened, multidisciplinary task force on a more frequent basis and updated as necessary. The frequency of such reviews should be, at a minimum, once every five years. The first review should occur immediately, and careful consideration should be given to revising the existing categories and adding additional categories. Occupational health activities such as walking, deep breathing, mild exercise, balance exercises with support equipment, lifting light weights, and stretching may be appropriate additions. Expanding category 5 to allow materials collected for other research purposes would be a useful modification. The inclusion of radiologic exposure on the list should be determined by the expert panel. However, caution is urged. The more comprehensive the list of activities that qualify for expedited review, the greater the risk that IRBs will perceive the list as constituting all the activities that can be reviewed in an expedited fashion[1]; conversely, a shorter list is more likely to be seen as merely illustrative of the factors that allow for expedited review rather than as exhaustive. An alternative to a list would be a list of study prototypes. SACHRP encourages the consideration of inclusion of a list merely as examples, allowing the IRB to determine the level of risk and thus whether a specific proposal would be eligible for expedited review. SACHRP encourages a model in which the responsibility for setting the terms for expedited review at each institution results from each IRB determining the level of review for minimal risk research that is appropriate under local circumstances.

SACHRP believes that most research involving no greater than minimal risk should qualify for review under expedited procedures. This would involve a change from the current presumption, as well as that proposed in the ANPRM, which envisions that minimal risk research requires full-board review unless it involves only those procedures included in the published list. The Committee recommends that regulations be changed to allow expedited review of research that is judged by the IRB Chair or designee to be minimal risk. To facilitate consistency in decision making, HHS should publish a list, to be updated periodically, of examples of protocols and procedures that presumptively entail no greater than minimal risk. The preamble to this list should make clear that the list is intended only to provide examples, and not to constitute a comprehensive set.

If the regulatory framework is changed such that minimal risk research is presumptively eligible for expedited review, HHS may nevertheless believe that specific categories of protocol or research procedures should undergo full-board review. If so, HHS should publish a list, to be

[1] Equating research that involves a set of defined procedures on the list with research that may be expedited without considering population, context, etc, may in fact lessen protections [vide supra, 'minimal risk'].

updated periodically, of categories of protocols or procedures that would *not* qualify for expedited review.

SACHRP does not favor mandatory reporting by IRBs when they choose to override provisions for expedited review. There is little to be gained by adding such a reporting requirement and it is not clear what the government would do with this information. In addition, such a requirement increases the burden for institutions and IRBs and could foster an adversarial relationship between IRBs and investigators. 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 must continue to have this ability to objectively review research and determine the appropriate level of review.

Criteria for IRB Approval

The ANPRM questions whether or not the criteria for IRB approval of research at §46.111 are appropriate for research that qualifies for expedited review. SACHRP recommends that research that is reviewed using expedited procedures should meet the criteria at §46.111. SACHRP cautions against the establishment of a double-standard for research that requires prospective IRB review and approval, and notes that this would be further complicated for those research studies that start as expedited then move to full IRB review, and vice versa. 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 should be given to adding "when appropriate" to the introduction at §46.111(a) or by providing revised guidance indicating how IRBs should apply §46.111, generally, when reviewing research under expedited review procedures.

Continuing Review

The current regulatory requirement that all non-exempt human subjects research undergo continuing review at least once per year has not proved useful or necessary. SACHRP has previously endorsed the extension of the continuing review period *[March 14, 2007]*. However, with a revised definition of minimal risk and a new emphasis on protection from informational risks, institutions should be given flexibility to determine if and when continuing review of approved research is appropriate. This would also have the effect of reducing unnecessary paperwork. SACHRP recommends that this flexibility be extended to review of both minimal risk research and research that poses greater than minimal risk.

Reducing Administrative Burden

Additional unnecessary administrative burden could be reduced by eliminating the federal guidance that requires IRBs to review complete funding applications (i.e., grant applications) for support for all research submitted to the IRB. The notion that a review of a complete grant application will enhance human subjects protections is flawed. The grant applications themselves only offer a static view of proposed research at a point in time that is often long before actual implementation. Moreover, grant applications do not evolve as research is refined and revised. Often, the research as it is ultimately implemented is different from what was

proposed in the original grant application. Institutions should continue to be required to ensure that researchers correctly implement funded research.

Appeals Mechanism

As noted in the ANRPM, beyond providing an investigator whose study has been disapproved with an opportunity to address the IRB in person, the current regulations do not mandate an IRB appeals process. In practice, many institutions have established mechanisms for investigators to seek reconsideration of IRB decisions. SACHRP does not support the addition of a mandated appeals process in the regulations. A strength of the current system is that IRBs are able to work independently and without fear that institutional leadership will override IRB decisions. Procedures for managing disputes of IRB decisions should be left to institutions. If there is a need to encourage institutions to establish reasonable conflict resolution processes, this can be handled through regulatory guidance.

Additional Reporting

The ANPRM contemplates required reporting of instances in which IRBs exceed the regulations. SACHRP has two basic concerns about this proposal. First, such a requirement undermines the independence of the IRB. As noted previously, the ability of an IRB to make independent, objective determinations regarding the review of human subjects research is paramount. A requirement to report IRB activities that exceed the regulatory minimum would discourage critical thinking and runs directly counter to the laudable principle of encouraging flexibility in interpreting the regulations. Second, this requirement unnecessarily burdens 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 costs as well as straining already limited human resources.

2. Mandatory Review of Multi-Site Studies by Single IRBs

The current proposal would mandate the use of a central, or single, IRB (hereinafter referred to as "single IRB") in any multi-site study whose sites are located within a U.S. jurisdiction. The proposal promotes the mandatory use of central IRBs in order to increase efficiency of IRB review and prevent disparities among protocols and informed consent forms in multi-site studies that often attend review by multiple local IRBs. The movement toward central IRBs has been championed, and even in some instances required, by NIH, the Department of Veterans Affairs (VA), and multiple industry sponsors of clinical trials.

In general, SACHRP supports the increased use of a single IRB, as such use would tend to decrease arbitrary disparities among site implementation of protocols. This, in turn, could bring about a more rapid and efficient IRB review and continuing review processes; could increase predictability for researchers, all of whom would be operating under the same approved protocol and consent documents; and could make IRB review of unanticipated problems in the course of a study more meaningful and accurate, thus potentially better protecting the welfare of subjects.

At the same time, however, as set forth below, SACHRP is mindful that the adoption and use of the single IRB model has not been without incident or obstacles; mandatory adoption will likely be more complex and unless carefully planned and implemented, could degrade the research review process by eliminating meaningful site-specific, local considerations and concerns.

The proposal to require a single IRB in a study with only domestic sites assumes that all domestic sites are sufficiently similar such that a single IRB could assess the research appropriately for Common Rule purposes, and conversely assumes that all non-U.S. sites are sufficiently different that a single IRB should not similarly be required for studies that involve only those sites. These assumptions are over- and under- inclusive in scope: some domestic sites may have subject populations and risks attendant to the research that are radically different, while some studies with international sites may include subject populations, attendant risks, and legal and regulatory environments that are sufficiently similar that a single IRB could and should be used (for example, studies of diabetes in hospital centers treating a largely affluent subject base in New York and Amsterdam).[2]

Further, in some categories of studies, the consideration of local and regional variations will be critical to assuring welfare of subjects, and the issue therefore will become how the single IRB will be able to take account of these variations among sites. In addition to widely different subject populations factors with significant variations among sites would include:

- State laws governing special categories of subjects and/ research data (e.g., genetic testing, genetic privacy, health information laws that go beyond HIPAA, mental health information, mental retardation and developmental disabilities information, surrogate consent, inclusion of children in research, age of majority, age of consent to certain medical treatment such as for substance abuse, investigator licensing requirements, etc.);
- Investigator conflicts of interest, requiring disclosure by investigators and analysis by local institutions relating to disclosures to subjects and other conflicts management strategies, which will vary from site to site, as potential conflicts vary from site to site;
- "Emergency research" undertaken without subject consent, for which the FDA requires local community consultation;
- Disparate cultural norms among populations targeted for recruitment, as in preference in some cultures for "family consent," as opposed to individual consent; and
- Varying investigator and research team experience, which may require more or less oversight during the conduct of the research.

The challenge, therefore, is to define a system in which issues that are decidedly and unalterably local are adequately considered and addressed during the process of single IRB review. If a single IRB is used for a multi-site study, whether the sites are domestic or foreign, one procedural measure by which partially to assure that local variations have been considered might

[2] Given the widely disparate legal and regulatory regimes in effect in different national jurisdictions, it may be difficult – but not impossible – for an international single IRB to understand and comply with the regulatory structure applicable to each international site. One can imagine, for example, a single IRB that is so often used for multi-site international studies that it gains sufficient expertise in a group of national regulatory regimes sufficient to assure compliance with all of them applicable to a study.

be to require the designated single IRB to assess whether, to the best of its knowledge, there may be significant local variations in essential aspects of the study and protection of subjects, and if so, to establish written standard operating procedures relating to how that consideration of local conditions will be undertaken. Minutes of single IRB meetings, and the documents supporting those meetings, would be expected to include evidence of the single IRB plan for local input, the actual local input, and the ways in which the local variations were considered in the single IRB's review and approval of the study. Such a process at least accommodates the "known unknowns" of significant local variations – that is, contemplates that some single IRBs may be aware of the possibility or probability of such significant local variations that would require local review. It does not, however, accommodate the possibility of "unknown unknowns" – that is, that a single IRB may be so unaware of the possible local variations that it cannot accurately judge whether local review, or other intensive consideration of local conditions, must be undertaken.

Alternately, to remedy more fully these gaps in knowledge that may attend a single IRB, a practice could be established (as it has been in the VA Central IRB) by which the single IRB could invite all participating sites to consider the proposed study in regard to any unique risks to their specific study populations, or in regard to any unique ethical or regulatory issues that might arise in their conduct of the study.[3] The site IRBs (or other local reviewers designated by the institutions engaged in the research) would then, within a specified time period (e.g., 30 days, as in the VA model) forward their comments to the single IRB, which could consider those site-specific comments in its overall review of the protocol, and reflect the consideration of local reports in the IRB minutes. Each site could then consider the terms of the single IRB's approval, and could opt into, or out of, participation in the study.

There remains the matter of how, in such a system, the single IRB would interact on an ongoing basis with local IRBs or designated ethics reviewers in regard to, for example, the emergence of risks that might be unique to a site and its study population, and the implementation of uniform or site-specific measures to mitigate those risks. Single IRBs in multi-site studies should be expected, as part of their initial review and approval, to establish formal written standard operating procedures for accomplishing this in an ongoing way during the course of the approved studies. Yet this may be so complicated that without careful planning and implementation, such a system coupling local review with a single IRB would, in the end, be less efficient than the current practice of each IRB performing its own separate review.

The method of selection of a single IRB in a specific study is critical; the IRB selected should have the appropriate expertise for the research being reviewed, and the capacity to act as coordinator, receiver and dispenser of critical study-related data to the sites, their research teams, their IRBs and their institutions. However, allowing an investigator or the research team to select the single IRB would risk exacerbating a process of "forum shopping" by which investigators might seek to secure the most lenient or permissive IRB.[4] Previous experience has

[3] A process by which all site IRBs or designated reviewers would conduct their own study review and forward their non-binding comments to a single IRB could also be used for studies with international sites, because the process would allow a single IRB to know and consider specific foreign site issues and unique research risks.

[4] We note that this process of selecting central IRBs by industry sponsors or funders likely would lead to a situation in which IRBs of the largest, most influential institutions or well-known commercial, independent IRBs

been that industry sponsors and the NIH have selected single IRBs that are eminently capable of undertaking this role; but at the same time, less sophisticated industry sponsors, investigators who must also fulfill the duties of study sponsor, as well as others, may be tempted to designate a single IRB that is permissive, quick in turnaround, and relatively lax in regard to monitoring. This problem could be addressed by implementing heightened standards for single IRBs, as discussed below, so that inappropriate incentives for forum shopping are reduced due to high standards necessary to become a single IRB.

For these reasons, if single IRBs are increasingly used, as a result of this proposal or of an organic process within the research community, OHRP and FDA should increase their oversight of how these IRBs operate in the multi-site study context, and be willing to impose sanctions, as appropriate, to assure that single IRB review is at least as effective in protecting subjects as local review. Consideration also should be given to a process for qualifying a single IRB through accreditation or other means, to assure that its practices contemplate the "known unknowns" and "unknown unknowns" significant local variations and issues, as described above. SACHRP recommends that guidance be issued that includes/describes points to consider for IRBs serving in a centralized capacity. Points to consider could include:

- Adequate record keeping systems and written standard operating procedures for tracking each site independently, including the ability to manage site-specific emergency care, conflicts of interest, sub-studies, unique consent forms, subject complaints, compliance issues, and unanticipated problems.
- Adequate state law data base for all states (or countries) where the single IRB reviews research sites,
- Written SOPs describing how local cultural and resource context information will be gathered, both at initial and continuing review,
- Capacity to provide for-cause site visits, as necessary,
- Written SOPs describing how the central IRB and institutions will coordinate issues such as review by other committees (IBC, Radiation, etc.,) and unique institutional policies,
- Accreditation by AAHRPP or an equivalent body,

Even if – as suggested below – OHRP foregoes this proposal to require a single IRB for all domestic multi-site studies, the implementation of these standards for single IRBs should be addressed explicitly by OHRP and FDA, as a means of improving the quality of, and thus encouraging the voluntary use of, single IRBs.

Costs of review and legal responsibilities for monitoring research and assuring its appropriate conduct would need to be appropriately allocated among a central IRB, local sites and their local IRBs, or other designated study reviewers. The cost of a required central IRB would need to be apportioned among the participating sites, or somehow accommodated in the overall research budget. It would be unreasonable to require one single IRB to review and monitor a study but

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would assume, over time, an increasing "market share" of central IRB review, eclipsing the IRBs of smaller institutions.

not adopt a corresponding mechanism by which costs for that central review and monitoring would be shared among the sites, or paid for by sponsors and funders; a plan for cost allocation and recovery would have to be developed,. Any required local review, however, would need to continue, with attendant residual local costs. A cost allocation, therefore, cannot be a categorical decision to fund a single IRB but not any local review. There could be significant cost savings in a central IRB model for multi-site studies, but such a model would not eliminate the need for, and costs of, some measure of local review.

If a single IRB were used, presumably all IRB-related regulatory and legal liabilities would shift to the single IRB and its parent institution, if any, while each research site and researcher would remain responsible (and potentially liable as a regulatory and legal matter) for its own implementation and conduct of the approved protocol. Even if – as suggested below – OHRP foregoes mandating a central IRB for all domestic multi-site studies, the allocation of regulatory liability when a central IRB is used should be addressed explicitly by OHRP[5], as a means of clarifying roles and responsibilities for, and thus encouraging the voluntary use of, central IRBs.

Central IRBs are operating now in many NIH-funded and industry-sponsored studies, but details of legal responsibility and liability remain murky. More detailed enforcement guidance and enforcement protocols therefore would need to be considered and issued, allocating legal responsibilities in a central IRB model. Additional guidance is needed regarding allocation of legal and ethical responsibilities for reviewing, approving, monitoring, and conducting studies, among and between a central IRB, local institutions and sites, local IRBs or other designated reviewers, and researchers themselves. In turn, institutions that defer to one another in a central IRB process need inter-institutional agreements, by which central IRBs and institutions engaged in research can more specifically describe what each party would do in a functioning central IRB model. Without more specific OHRP guidance on these points, it would likely not be possible for the entire research community to establish template inter-institutional agreements, while issuance of such specific guidance likely would ease and speed the emergence of templates.

Given the various complexities discussed above, it is not surprising that adopting a central IRB model, when tried, has presented some tough challenges. Even the VA, with its unitary organization, has experienced numerous challenges in instituting a central IRB model for multi-site studies based in VA facilities. For example, it has been difficult to develop information technology systems across sites to track studies and study reporting, and to coordinate communication among investigators, local facilities, and the VA Central IRB members and staff. Other challenges include considering and accommodating unique local conditions and affiliation arrangements, establishing methods for collecting, analyzing and then reporting back to local sites regarding unanticipated problems, and coordinating study monitoring that is necessarily done by the VA facility sites. If these issues have occurred within the VA system, then one would expect the problems to be more serious, complex, and acute if a mandate for single IRBs for all domestic site studies were simply imposed by regulation.

[5] We note that FDA regulations currently hold IRBs directly accountable.

Currently, a significant barrier to institutional adoption of a single IRB of multi-site research is the information technology required to ensure adequate review, communication, and oversight. Systems currently serving IRBs and institutional human research protection programs differ from one another, are complex and expensive, and are not interoperable. Institutions incur significant expense to build technical solutions to ensure appropriate communication or secondary systems that represent incremental work and cost. SACHRP recommends that HHS develop a common information technology (IT) infrastructure, built to ensure interoperability and communication. We propose that each institution would then adopt the common platform; reporting would be simplified; forms, language, guidance would be written and directed by the responsible federal agencies and utilized by the regulated community. The IT application would be built as a "smart" form, embedding information and further questions that appear dependent on given answers; compliance would increase. Importantly, such an IT application would empower (and force) the federal agencies to harmonize their regulations. The consequences of the introduction of such a resource would include significant cost savings, increased compliance, harmonization, and increased utilization of single IRB review for multi-site research.

There are other resources that could be developed by the federal agencies that would decrease the barriers to adoption of a single IRB. SACHRP recommends that the federal agencies develop a database of state and country laws relevant to reviewing human research protocols that would be publicly accessible. Further, SACHRP recommends that HHS issue a regulation holding external IRBs directly accountable. Guidance should also clarify the responsibilities and obligations that will remain with local sites that rely on an external IRB. In addition, SACHRP recommends that HHS provide a revised standard template of an IRB reliance agreement that would delineate expectations for both the reviewing and the relying institutions.

Funders such as NIH, CDC, HRSA, non-HHS Common Rule agencies, and industry sponsors all have it within their power now, and without a change in the Common Rule, to mandate investigators' use of single IRBs in multi-site studies that they fund. Their preference for single IRB review when evaluating potential sites – to encourage consistency of protocol, informed consent and other aspects of a study among sites – is, in many instances, entirely appropriate, and they should carefully drive the system toward the greater uniformity and efficiency that is inherent in single IRB review, as competently practiced. Although many private industry sponsors of clinical research already use site selection policies favoring single IRB review, the FDA also potentially has the authority, if indeed it is convinced that single IRB review is more effective at assuring protocol compliance and protecting subjects, to support industry use of single IRB review of multi-site studies submitted to support FDA applications. However, the ability of government funders, industry sponsors and FDA to encourage the use of a single IRB as the IRB of record is dependent upon the willingness of individual institutions and their sites to accept the decision of a single IRB. For this reason, it would be helpful to find ways to encourage individual institutions and their sites to be more open to and prepared for the use of a single IRB as the IRB of record. For example, helpful actions might include using guidance and education to outline expected standards for and capabilities of single IRBs of record in multi-site research, to encourage institutions and sites to develop processes for communicating with single IRBs and for addressing allocation and recovery of research-related costs, and to prompt institutions to separate the administration of IRB related research activities from non-IRB related

research activities. These steps can be taken now, would be meaningful ways to move toward increased single IRB use, and would firmly establish an experiential basis for any future increase in single IRB use.

SACHRP believes, strongly, that at this time, a uniform mandate of single IRB review for all domestic multi-site studies is premature. SACHRP believes, instead, that a more measured and careful process of *encouraging* single IRB use, accompanied in a step-wise way by issuance of guidance on critical issues implicated in the use of single IRB review, would result in less disruption of the research enterprise, and eventually, improvements in a single IRB process that is anchored in deep collective experience.

3. Informed Consent

This section of the SACHRP commentary on the ANPRM speaks to the general questions regarding informed consent in Section IV, specifically questions 35 to 44. SACHRP is addressing the issue of consent for future use of data and biospecimens in a separate section of this response.

The ANPRM proposed changes with respect to certain aspects of the informed consent process. In general, we believe that this section of the ANPRM focuses too much on the consent *form* as opposed to the consent *process*, but we do recognize that some improvements to the overall process can be achieved through improvements to the consent form and related consent documentation.

One change to the regulations that could provide more flexibility for the consent process would be to modify 45 CFR 46.117. As currently drafted, §46.116 addresses the process of consent very briefly in the opening paragraph, and also provides the elements of consent. §46.117 addresses the consent form and obtaining signatures. One change that would help to provide flexibility would be to change 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 revision would provide flexibility for IRBs to make the written consent form a shorter, more useful document.

Consent in other cultural settings should be addressed for international research, where community consent and other cultural requirements may be necessary. 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 applicable to research even above minimal risk if ethically and culturally appropriate.

Currently, consent forms may be long and legalistic for a number of reasons. The first reason is because institutions, IRBs, and sponsors are concerned about minimizing the potential risk of adverse legal actions. This creates an incentive to list all possible risks in the consent form. This underlying concern has especially affected sections of the consent forms dealing with risk, compensation for injury, and cost. It is difficult to address the issue of legal risk, because

plaintiffs will continue to file lawsuits when they feel that they have been wronged, and the plaintiffs' attorneys will continue to use breach of informed consent and failure to warn as legal arguments. The second reason that such forms tend to be long and legalistic is due to regulatory oversight. OHRP, FDA, and other agencies have at times made very detailed criticisms of consent forms for not meeting regulatory requirements regarding the elements of consent. This creates an incentive to make sure that each of the elements of informed consent is addressed ad infinitum, regardless of whether it is applicable, and encourages IRBs to include study-specific regulatory citations in cases where they are not necessarily applicable. For example, many IRBs include an "alternatives" section in their informed consent form regardless of whether the research involves any type of intervention or clinical care. The regulatory incentives could be lessened if the agencies were careful to limit their citation letters to instances where the intent of the regulations was clearly not met. An example of regulatory oversight that created a great deal of excessive consent language in subsequent consent forms were the OHRP citation letters regarding tidal volume and pressure in the ICU setting.

SACHRP believes that there is very little additional information that should be included in consent forms as a regulatory requirement. The only suggestions SACHRP would make for consideration are: (1) provisions to protect confidentiality, and (2) payment(s) to subjects. Each of these could also be addressed in guidance rather than by changing the regulations. Much of this information, as well as other information as discussed below, could be disclosed in an addendum(s) to the informed consent document.

SACHRP believes that there are several items that could be moved to the section of the regulations addressing the additional elements of consent (45 CFR 46.116(b)). These include discussion of alternative treatments, compensation for injury, and information about GINA and clinicaltrials.gov. This information, i.e., 45 CFR 46.116(b), would also be appropriate to place in an addendum(s) rather than in the main consent form.

The ANPRM asks whether there should be limitations on the acceptable length of various sections of a consent form. SACHRP does not believe this would be useful or warranted. Research projects and procedures vary greatly, and investigators, IRBs and sponsors should be allowed to appropriately address specific issues and elements of consent in a manner necessary to inform subjects.

The ANPRM asks whether certain types of information should be included in appendices and not in the main body of the consent form. SACHRP strongly supports this idea. Only core, critical elements specific to the research itself should be contained in the main body of the consent form. The rest of the information, including many required elements of consent, could be included in an addendum(s). The core elements that need to be in the main body of the consent include the: (1) statement that the project involves research; (2) purpose; (3) "voluntary statement" (including withdrawal); (4) duration of participation; (5) risks related to the research itself; (6) potential benefits of the research to subjects and society. In general, a short description of the study design is often helpful to prospective participants. All other information could be codified in an addendum to the extent appropriate to disclose. This should be permissible as opposed to required so that IRBs have flexibility to change their approach as empirical research on this

proposed change is conducted. Information included in the addendum could include, for example, the HIPAA authorization and the details for each study visit.

Clearly there is a great deal of institutional boilerplate that is included in consent forms for risk management reasons and simply because it is a convenient single document in which to disclose information. The examples vary widely depending on the institution, but a classic example is the requirement to include notice that if a subject earns more than $600 in a year, the institution will send a 1099 form for tax purposes. Another common example is lengthy "compensation for injury" statements that address multiple conditional factors affecting the receipt of compensation.

The ANPRM offers to make available standardized template consent forms. This could be helpful with caveats. Many organizations, including institutions, sponsors, IRBs, and non-profit organizations, make such templates available; such templates prove to be of limited use because of the variability of research. In addition, one area that may be helpful for a template would be to illustrate how researchers could utilize a short form consent format together with an addendum that contains more detailed information.

Further, guidance should encourage that, for certain types of studies, investigators assess how well potential research subjects comprehend the information provided to them before they are allowed to sign the consent form. Previous SACHRP recommendations have addressed this in detail for populations with impaired decision-making capacity. [Secretarial letter dated July 15, 2009] In addition, assessment of understanding may sometimes be appropriate for individuals even where the concern of impaired decision-making capacity does not arise.

Additionally, the current four criteria for waiver of informed consent are difficult to interpret and are not consistently applied. One way to address this issue would be to provide definitions of the criteria. For example: Does "minimal risk" in §46.116(d)(i) apply to the whole study or just the waiver of consent? What are the "rights and welfare" addressed in section (2)? What does "not practicably" mean in section (3)? This clarification could be accomplished through either guidance or simplified regulations. SACHRP has previously commented on the waiver criteria [January 31, 2008], including that guidance clarify what rights the IRB should consider when making a determination that a waiver of informed consent is appropriate.

§46.116(d) also currently addresses waiver of one or more elements of consent. However, it is unclear whether the study as a whole must be of minimal risk, or whether it is appropriate to interpret only the waiver of the element of consent to be of minimal risk. In addition, it requires time to document the four §46.116(d) criteria. For this reason alone, IRB members often find it easier to leave in an inapplicable or unnecessary element of consent, as it is easier to simply include the element of consent that is required by the regulations than to document the alteration and the reasons for waiver. Clarity could be provided to ease this confusion through either regulation or guidance. It might be preferable to have a new regulatory section addressing only waivers of single or multiple elements of consent. The regulatory criteria could be simply that an IRB must document that any waiver of an element of consent does not increase risk to the subject and the reason that the element is inapplicable or unnecessary, as opposed to documenting all of the §46.116(d) requirements. These issues apply equally to both written

consent (i.e., with written documentation) and oral consent (i.e., without documentation). SACHRP does not believe there is any difference between the elements for oral versus written consent.

The ANPRM asks whether there are there additional circumstances under which it should be permissible to waive the usual requirements for obtaining or documenting informed consent. The SACHRP Subcommittee on Harmonization has been working for a year on this topic, and other questions, as it pertains to interpretation of the FDA regulatory definitions of "clinical investigation" and "human subject." The FDA regulations do not include the §46.116(d) waiver of consent provisions, and thus research that does qualify for a waiver of consent under the Common Rule will not qualify for a waiver of consent under the FDA regulations, if it is interpreted to be a clinical investigation with FDA-regulated test articles involving human subjects. IRBs spend considerable time and differ greatly in practice as to whether studies, such as medical record reviews, are FDA regulated, and thus whether or not it is acceptable to waive consent under §46.116(d). It is not uncommon for a single study to be found exempt with no consent required by some IRBs, to qualify for a waiver of consent by other IRBs, and to undergo full board review and written consent at other IRBs. SACHRP believes that the ANPRM provides a significant opportunity for FDA to address this issue in a careful manner with the ability to modify regulations as appropriate.

Finally, the current regulations offer considerable flexibility that is often underappreciated. At a minimum, SACHRP supports the development and dissemination of guidance to illustrate the currently available flexibility, a guidance that may be of particular utility to those involved in social and behavioral research.

4. **Strengthening Data Protections to Minimize Information Risk**

This section of the ANPRM is intended to address perceived gaps in the protection of confidential information and to simultaneously relieve the burden on IRBs and investigators for those studies that are limited to informational risks. To that end, the ANPRM proposes several changes grouped under two major thematic headings, as follows:

Consistently Characterizing Information with Respect to Potential for Identification

What is considered to be "identifiable" is an important factor in determining what research requires IRB oversight, and how that research is conducted. The ANPRM notes that there is inconsistency between the definitions of identifiability under the Common Rule and the HIPAA Privacy Rule, and proposes to address this by adopting the HIPAA standards for determining what is considered individually identifiable, a limited data set, and de-identified information.

The Common Rule approach has more flexibility in its definitions because it considers information not to be identifiable if the subject's identity is not "readily ascertainable" by the investigators conducting the research. The HIPAA Privacy Rule, on the other hand, 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), and the covered entity cannot have 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. For example, consider a study that enrolls individuals who have had a flu shot within the last year (i.e., pre-existing clinical information), and that includes no identifiers except for date of flu shot, zip code, and a 10-digit code that includes the person's initials. Many IRBs would consider these data not to be identifiable under the Common Rule, but the data would be identifiable under HIPAA's stricter definitions. Researchers also often use codes that are tied in small part to another lengthier number (e.g., medical record number), and even if the researchers did not have access to the key to the code, the data would be considered identifiable under HIPAA.

SACHRP's interpretation of the proposed change to use HIPAA standards is that, without concomitant revisions to several other requirements, this could increase the circumstances under which informed consent and IRB approval are required. As the examples above indicate, even the use of pre-existing clinical data with very minimal identifiable information would require consent (under Table 1) because the data would be identifiable under HIPAA. This would appear to work against the stated aims of removing unnecessary burden on the research community for little gain in the protection of subjects. If this interpretation is not correct, it should be addressed and clarified in subsequent iterations of the rulemaking process.

Moreover, this change could be particularly burdensome to investigators in the social and behavioral sciences, and those conducting educational research. There is debate in some quarters as to whether HIPAA has had a beneficial effect in the research to which it already applies (i.e., clinically-oriented research that relies on access to Protected Health Information (PHI), as defined by HIPAA). To the contrary, there is widespread concern that HIPAA has constrained research efforts; this is partly because HIPAA's rules fit somewhat awkwardly with certain well-established research practices (e.g., recruitment for clinical trials from external community practices), and partly because some HIPAA-regulated entities, concerned with strict compliance, adopt overly conservative practices for data access and data sharing. HIPAA is a highly structured regulation with little nuance allowed, to the extent it imposes a predetermined, all-or-nothing paradigm on (a) identifiability and (b) risk assessment. That is, there is little flexibility for IRBs to calibrate review based on likelihood or magnitude of 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. Indeed, SACHRP has previously recommended that research be exempted from HIPAA, as was originally considered when the Privacy Rule went into effect. The current proposal would take the field and the public in the opposite direction. Extending strict definitions and protections that were designed primarily for the clinical care setting to the clinical research arena has been problematic in several respects, and extending it further to non-clinical areas of research will be even more so. Extending HIPAA 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.

Despite the value of flexibility, SACHRP recognizes the need for clear definition of what constitutes identifiable data. SACHRP believes that the current HIPAA definition of a limited dataset (allowing for certain dates, geographic subdivisions, etc.) might be used as a starting point for developing a new definition of identifiability if the proposed excused framework is implemented.

Standards for Data Security and Information Protection

The ANPRM proposes to adopt new data security standards patterned after the HIPAA Security Rule for research involving identifiable data or limited data sets. Such requirements could include data encryption, new breach notification standards, and prohibitions on re-identifying subjects (for both limited data sets and de-identified data). Mandating new requirements such as encryption could create significant new administrative and cost burdens for investigators and sponsors; burdens must be justified and balanced with the risk that the requirement is intended to address. There is also no indication of who would be responsible for implementation and oversight at the agency level. This mandatory security-standards proposal needs to be carefully assessed from an administrative burden standpoint.

There is concern that that extension of breach notification requirements to all research (where data sets of greater than 500 records are commonplace) will result in increased number of *pro forma* notifications, with little meaningful gain. This will be especially problematic if notification is extended to breaches involving research Limited Data Sets, where risk is typically very small. The HITECH breach reporting rules currently extend to PHI Limited Data Sets, and require entities to undertake an assessment of whether a breach of even such a minimal data set is reportable, and document the justification if it is not reportable. This is time- and resource-intensive, particularly because entities have *no* identifiers of the individuals (because identifiers are by definition excluded from the data set). If these breach rules were extended to Limited Data Sets in research, these same challenges would apply. Moreover, IRBs often will not have reviewed projects involving Limited Data Sets because the data are not viewed as identifiable. So, it is unclear to whom the researchers adhering to these rules would report, as these studies largely have been deemed to be outside of IRB jurisdiction. Here again, the breach notification rule has been questionable in the clinical research realm (in that current HITECH rules may lead to over-notification out of institutional concerns for strict compliance), and would be even more questionable if extended to all research. Application of rules intended for Protected Health Information in the clinical care setting to research where data may or may not have the same sensitivity is not a solution we can support.

The Office for Civil Rights has clarified that the HIPAA security standards are meant to be "flexible and scalable" in terms of how they are applied by local institutions or circumstances, without specific requirements that would be imposed on all institutions, regardless of size, function, technical infrastructure, and costs. OCR also noted that the security standards are intended to be technology neutral. This flexibility is something that may be lost in the current

reading of the ANPRM and perhaps in current application of HIPAA by covered entities. For example, the ANPRM discusses data security standards in the context of requiring adherence to a strict set of standards, such as requiring encryption or other mandatory standards, whereas the Security Rule does not mandate encryption or certain other controls across-the-board. If, indeed, the ANPRM intends to allow greater flexibility in security standards, which would ameliorate some of SACHRP's concerns, this should be clarified in subsequent proposals.

An alternative way to enhance security of research data is for OHRP to address data security in its guidance on reporting of unanticipated problems. OHRP could clarify that if a data breach occurs but the data have been encrypted, then the incident is not reportable as an unanticipated problem because the data were sufficiently secured. This approach parallels the approach that the Department and OCR have taken to breach reporting under HITECH, through the "Guidance to Render Unsecured Protected Health Information Unusable, Unreadable, or Indecipherable to Unauthorized Individuals." This type of approach would enhance harmonization and facilitate compliance by covered entities that must satisfy both HITECH and Common Rule reporting requirements. And, for the research community that is not covered by HIPAA/HITECH, this type of OHRP guidance would encourage entities and researchers that have not already addressed data security to adopt stronger controls.

SACHRP is also concerned with the implication that informational risks should be approached as primarily or solely a security issue. The ANPRM does not in fact appropriately calibrate risk to subject protections because risk is defined solely in terms of the likelihood of identifiability and security. Even studies without physical interventions and attendant risks have risks beyond data security. Surveys on sensitive or intrusive topics (e.g., illicit drug use, psychiatric illness, illegal activity, sexual activities, genetic risk) may carry interactional risks related to identification and recruitment of subjects, timing in relation to precipitating events, emotional duress due to the nature of questions, and so on. For example, a study that intends to interview grieving family members within days of a loved one's death may raise all of these issues; this kind of research may well be appropriate and approvable, but needs safeguards that will be lost if (1) IRB review is eliminated and (2) risks are seen as "merely informational."

Therefore, there are concerns that a blanket approach that handles all studies that are (in theory) limited to informational risk will exclude from independent review those studies where such oversight may be warranted. Institutions need a mechanism to consider oversight and/or review for those studies that may need it, while excluding the majority that arguably may not.

In general, SACHRP supports the prohibition against unauthorized re-identification of data that has been de-identified. However, it is important for the public's well-being that any new rules provide the flexibility to re-identify in limited, compelling cases (e.g., identification of treatable diseases), with proper IRB oversight of those cases.

Of note, there are new modalities (e.g., cloud computing) that many IRBs and institutions have not dealt with or anticipated in their policies and procedures. Crafting *regulations* to deal with rapidly evolving technologies risks both over- and under-protecting subjects. Technological

advances are rapid and dynamic: providing the research community with proactive, current guidance on emerging technologies would be helpful.

We note questions that may arise with overlapping jurisdictions for enforcement, should HIPAA be extended in the manner proposed. SACHRP has been informed that OCR would continue to enforce HIPAA, while OHRP (and other agencies) will continue to enforce the Common Rule. However, the extension of HIPAA requirements to all research under the Common Rule would appear to blur those lines of jurisdiction. Investigators, IRBs and covered entities are already struggling to accommodate the overlap and internal contradictions that currently exist; extending HIPAA further would only exacerbate this situation.

Finally we wish to make the general statement that one reading of the ANPRM opens up the possibility of extending the HIPAA standards as they currently apply to covered entities to all research under the Common Rule. We believe that this approach would be exceedingly difficult to implement, burdensome to the research community and generally excessive in relation to the benefits realized. We believe it is essential to ensure proportionality between the information risks and the data protection requirements of any revised regulations.

5. AE Reporting

The ANPRM proposes certain changes with respect to the collecting and reporting of adverse event information. The scope of events that must be reported under current policies, including the reporting of ‘‘unanticipated problems’’ as required under the Common Rule, is generally adequate for the assessment of the protection of subjects on a single study basis. The revised unanticipated guidance documents from OHRP and FDA are each very useful, but there remains a need for harmonization of the two documents as they provide somewhat different definitions. These guidance documents do serve to drive IRBs to assess issues for subject safety and to report such incidents to the agencies. However, the current policies do not serve to provide data on subject safety across studies or to provide complete information to assess the effectiveness of the human subjects protection regulations.

Requiring reporting of the number of subjects enrolled in research might be useful in creating metrics, but it is unclear what the value of such metrics would be. Reporting to a central authority the number of subjects enrolled in federally funded research (paired with safety and efficacy data, adverse events and unanticipated problems) could have some limited utility for systematic data analysis and safety monitoring of all federally funded research. It is our understanding that this information is being reported in progress and final reports, which routinely provide the number of subjects enrolled in federally funded or FDA regulated research. However, given that the required collection of the number of subjects enrolled in research would have costs – and significantly increase administrative burden – the value of the information should be carefully evaluated as compared to the expected costs associated with gathering and maintaining it. Further, if such metrics were to be used for setting policy across the U.S., the number of subjects enrolled in privately funded research under FDA and EPA jurisdiction must also be included. Understanding the aim of such data collection would be important in order to

determine whether all human subjects should be counted or only those involved in biomedical (or interventional) research. If the goal of increased data collection and monitoring by a central authority is heightened safety, then the proposed effort should focus on greater than minimal risk research and interventional studies. Strategies may be identified from assessment of similar data repositories.

Given the cost of implementing and maintaining a centralized authority, we do not see the value of setting up a system for reporting and maintaining numbers of subjects. Also, the potential benefits of adding another layer of data access and safety monitoring should be considered in tandem with the costs of creating another level of bureaucracy.

Several questions must be answered to determine the utility of additional data collection: What types of data are currently collected? What is the purpose of an "overall empirically based assessment of the risks of particular areas of research"? Couldn't this information be extrapolated from what is currently provided?

However, one type of additional data, not currently being collected, about participants in human subjects research that would be helpful to collect systematically — in order to provide an empirically-based assessment of the risks of human subjects research — is the number of injuries caused by participation in clinical research, and the amount of resources expended to treat those injuries. This would help to provide data on the actual risk of research participation, and the cost of treating such injuries. This would be very resource intensive data to collect in a meaningful way, as it is often difficult to determine whether the harm was caused by the research interventions or by underlying disease or standard treatment. In addition, it would be difficult to collect data on the costs expended, as there are many separate payers in the U.S. health care system. Given those resource requirements, this is not a realistic proposal. As with the collection of the number of subjects, this data would be more useful if it included privately funded research under FDA and EPA jurisdiction. If a central authority housed and monitored accrual data, safety and efficacy data, clinical outcomes data, and adverse and unanticipated events it might be possible to engage in a more systematic empirical assessment of both the safety and outcomes of specific areas of human subjects research. If such a collection of data were to be implemented, it would be interesting to include all types of research, but for cost reasons this is not feasible.

The ANPRM also asks if the data thereby collected would be useful to assess the effectiveness of the human subjects protection system. While the data collection as described above would provide basic information about the number of subjects and the relative risk, it is not clear that it would provide any meaningful information about the effectiveness of the system. To date, no one has put forth an accurate and meaningful method to measure the effectiveness of IRBs. It may be more cost effective to use other methods such as random samples of research projects, or surveys or questionnaires of the stakeholders in research, to assess the effectiveness of the human research protection system.

The ANPRM asks whether it would be desirable to have all data on adverse events and unanticipated problems collected in a central database accessible by all pertinent federal agencies.

In the long run, a single database of serious adverse drug reactions (SADRs), and unanticipated problems could be useful for the analysis of the protection of human subjects and thus the effectiveness of the human subjects protection system. The current lack of uniform reporting requirements (e.g., definitions, forms, timelines, etc.) does create administrative burdens. It would be useful to harmonize these differences. However, before moving to the development of an extremely large, difficult to manage database that is not likely to be useful to most parties due to its size and complexity, there are a number of things to consider. One way to address the issue of different agencies having differing systems is to evaluate a conversion to systems that have interoperability. Particularly as new systems are designed, they should be made accessible to identified users from across the government in a read-only format.

The adoption of electronic medical records (EMRs) may obviate the need for the creation of an additional database, as data may be accessible to those who need to evaluate it through planned information systems. Spending significant time and resources on the creation of a new, separate database seems wasteful given the evolution of the EMR.

Developing common terminology and definitions is a major undertaking. Device, drug and therapies not utilizing regulated products use different standards and definitions of unanticipated risks. Moreover, each subject population is evaluated differently from a risk-benefit perspective, (e.g., pediatric subjects, the elderly, etc.)

The cost of maintaining this single large repository would be significant. The costs of development of ClinicalTrials.gov and the work involved with maintaining and operating this site should be reviewed prior to making any decision on a database, especially because it may be somewhat redundant in function to ClinicalTrials.gov. Secondly, individual subject information is anecdotal unless it is evaluated within an appropriate context. Assuming that what happens to one individual is important to the next subject is something that takes significant evaluation in each individual trial. Patterns need to be established before this information becomes data that are useful for consideration. Given that each trial is different, trying to establish these patterns in a large data set from diverse studies will be difficult if even possible. This will therefore take a lot of time and resources to be useful.

If the focus is subject protection, then the simplest issues are related to the designated subject population, the focus of the research and what risks that were seen are unanticipated. That is the information that would be useful in protecting the next set of subjects. Such analysis is best done at the close of the trial and on the complete data set, and not on each individual subject. To demand that reporting be done in a short period and placed in a database without complete evaluation is likely to lead to significant noise and little signal – but much chasing of events and expended effort for little gain.

As stated under the heading below, "Web-Based Repository to House All Safety Data in Order to Conduct Integrated Analysis and Comparative Studies," SACHRP has concerns regarding the cost of development of such a system without consideration of existing systems that may already be achieving the stated goals. FDA already has layers of safety reporting with Data and Safety

Monitoring Boards (who have the benefit of unblinded data), AE reporting, MedWatch, and the Adverse Event Reporting System (AERS) analysis database.

If gaps do remain, a cost-benefit analysis should be conducted with significant investigation regarding strengths and limitations of similar data repositories and the scope to which this would apply (e.g., high risk, interventional research only?). One key element to assess is the validity of the data and ability to draw generalizable conclusions based on data amalgamated from varied sources and contexts.

The International Committee of Medical Journal Editors (ICMJE) Uniform Requirements for publication and the Food and Drug Administration Amendments Act of 2007 (FDAAA) have driven compliance with the requirement to register and provide summary results for clinical trials that meet the specific criteria as a designated "applicable" clinical trial. The scope was not intended to capture overall safety of ALL human subjects research. Expanding the scope to include non-clinical human research would likely offer little benefit relative to safety data. Beyond providing access to clinical research opportunities, much of the impetus for ClinicalTrials.gov was to enhance transparency in disclosing results, particularly in response to multiple discoveries of unpublished data from antidepressant drug studies. Disclosure was a means to enhance public trust in clinical research. To that end, the database is adequate.

A goal of the Clinical Trials Transformation Initiative (CTTI) is to facilitate the use of a publicly accessible data set for aggregate analysis available to assess the clinical trial system. While data sets such as ClinicalTrials.gov are publicly available, they are designed for analysts to conduct empirical research on the strengths and weaknesses of clinical research. The ClinicalTrials.gov data set is being analyzed to determine how to make it more useful and accessible. SACHRP believes that adverse event data in ClincalTrials.gov merit consideration as a source of systematic data on research risk, including potential expansion of the scope to include Phase 1 trials. However, any approach considered by a proposed regulation clearly should wait until the CTTI has concluded its analysis of ClinicalTrials.gov before making any decisions on what is left out, if anything, and how to capture those data.

SACHRP is concerned about use of single-study summary data by the general public for medical purposes;this is research data, not clinical consensus. For the lay public to try to interpret findings from a summary result table and make any sort of broad generalizations beyond the context of the study could be misleading, if not actually dangerous. It can be risky for a lay individual to apply research study results to his/her own situation without the guidance of and interpretation by a medical professional.

An unintended consequence may be to cause sponsors and investigators to become overly cautious in an attempt to anticipate more issues so that they are "expected" if they occur (and thus not reportable, rather than unanticipated). Evaluation of complete data sets from trials reduces the noise and illuminates only important signals, thus generating information that is useful for the next trial. Trials that are of similar populations and interventions can be evaluated to determine what would add to subject protection for the next similar trial.

A side benefit of result disclosure is that it has provided a systematic way for individual research subjects to learn about the outcomes of trials in which they participated (a rare occurrence in the world of large, international, multi-site trials). If nothing else, this might provide research subjects with a sorely needed sense of having contributed to the greater good. While we agree with FDA's efforts to ensure subjects are informed about how to access results of trials in which they participated, we would prefer the information not be a required informed consent element. This stance is consistent with the efforts to limit informed consent information to only that information that would directly affect a subject's consideration regarding participation. Such standard information could be communicated via another mechanism such as a consent addendum or participant bill of rights.

To fully evaluate changes to improve the current system proposed in the ANPRM, many other questions would also need to be answered, including the following:

- What is status of blinding?
- When does unblinding occur, who gets access to unblinded data?
- How do you protect the integrity of the research?
- How would subject confidentiality be protected in this system?
- What is the effect of this proposed data collection on proprietary rights of commercial sponsors?
- Would current FDA regulations regarding the protection of proprietary data affect the proposed data collection?

Finally, any such data collection system should be harmonized as closely as possible with other existing reporting requirements and initiatives both domestically and internationally, such as ICH.

6. Extension of Federal Regulations

There are currently several areas or types of research that are not subject to federal regulations. For example, surgical studies without federal funding; research in private practices, dedicated research sites, or community hospital settings that does not involve FDA-regulated products; 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 that does not involve FDA-regulated products (e.g., Gates Foundation, March of Dimes, American Heart Association); and research funded by federal agencies that are not signatory to Common Rule (e.g., National Endowment for the Humanities). While voluntary application of the Common Rule regulations does occur in some cases, it is not required. These studies may also be subject to state laws governing research. SACHRP agrees that the current gaps in coverage are not desirable, from the standpoint of protecting human subjects at a system-wide level. Accordingly, SACHRP believes that a solution is needed to extend appropriate protections to all research subjects, without arbitrary limitations or gaps in coverage.

Unfortunately, the ANPRM proposal in this regard does not close those gaps where most needed. Most institutions with a Federal Wide Assurance (FWA) apply the Common Rule to all research

regardless of funding; even those institutions that have "unchecked the box" – meaning that they do not extend the Common Rule to all research conducted at the institution – generally apply the regulations in principle and in practice, even when not required. It is also not clear that a large percentage of the unregulated research occurs at institutions regulated under the Common Rule. The proposed solution, therefore, would do little to affect these institutions or areas of research, but also do little to affect those that fall outside current coverage (i.e., aforementioned examples that slip into the gaps). The proposal also has the effect of increasing regulatory burden for institutions by expanding the scope of prompt reporting required for research that is not subject to the Common Rule for unanticipated problems involving risks to subjects or others, serious or continuing noncompliance, and suspensions or terminations of IRB approvals.

Pushing forward a partial solution (i.e., limited to institutions that receive federal funding, as currently proposed) could lead to unintended consequences and potential abuses. While gaps currently exist, ambiguity does not exist in what is covered (namely, research with federal funding is regulated by the Common Rule and research with investigational drugs and devices is governed by the FDA regulations). A partial solution would create ambiguity where it does not currently exist. Of even greater concern, it would foster an environment where investigators and sponsors would have motivation to seek out institutions that receive no federal funding (and were thus exempt from the Common Rule) and avoid those that do receive federal funding. Observers have even questioned whether institutions would now have motivation to avoid receipt of federal funds, in order to make themselves more attractive to investigators and sponsors, or as a risk-management strategy. The net result would be to punish those institutions that receive federal funding, while doing nothing to reach those currently operating outside the regulations.

There will also be myriad practical questions related to implementation. For example, 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 revoke with the end of funding? What about funding from federal agencies that have not themselves adopted the Common Rule? Finally, there may be questions about the authority of the Executive branch to extend coverage through rule-making , raising the potential for legal challenges to the extension.
Despite these concerns, we reiterate our support for the underlying premise, and the laudable goal of closing the current gaps in coverage. Toward that goal, a more comprehensive solution would be congressional legislation to bring all human subjects research under a single set of regulations, presumably through the Interstate Commerce Clause. A separable consideration is whether this common set of regulations could/should be enforced by a single regulatory agency.

7. Clarifying and Harmonizing Regulatory Requirements and Agency Guidance

It is critical that any changes undertaken as a result of any final rule issued in accordance per the ANPRM be harmonized across OHRP, FDA, OCR, NIH and all federal agencies that are involved with the support or oversight of research. At present, it is not clear that this harmonization will indeed occur, even if necessary. For harmonization to occur in some departments or agencies, congressional legislation may be required.

Of vital importance to the clinical research community is how the proposed changes to 45 CFR Part 46 contemplated in the ANPRM will mesh with FDA regulations at 21 CFR Parts 50 and 56. It is not over-stating the situation to observe that many of the proposed changes will have little meaningful impact unless the FDA endorses and/or adopts identical changes, given that much clinical research falls under the FDA's regulations and not under the Common Rule.

Beyond the regulations, there is an urgent need to address and harmonize, to the extent possible, inconsistencies in interpretation and implementation across Common Rule agencies. Some agencies are active in issuing guidance, while others are seldom heard from, and inconsistencies abound as a consequence. Examples of contradictory guidance include, but are not limited to, the definition and handling of protocol deviations, and whether recruitment activities are considered research. Simply put, the Common Rule will not be "common" until this interagency discord is resolved. There is also a related need to address the enforcement of guidance, which vary by agency.

It would be helpful to issue common guidance wherever possible. 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 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. While there has been positive movement to reverse years of counterproductive practices in this area, the research community, sponsors, and IRBs have struggled with the separate guidance that was ultimately issued. Wherever possible, guidance should be harmonized and issued jointly.

SACHRP recommends that such an undertaking should be subject to careful review by a convened, multidisciplinary and multi-agency task force on a regular, periodic basis and updated as necessary. The frequency of such reviews should be no less than once every five years.

8. Authorizing Future Research Uses of Data and Biospecimens

The ANPRM proposals contemplate some significant changes to the ways in which data and biospecimens would be collected and used for research purposes.

Under current rules, in general, study subjects must provide written informed consent by which they allow their personal data and biospecimens to be collected for research, and the informed consent document must describe the study protocol with some specificity. In banking studies, in which the primary intervention with subjects is data and biospecimen collection, a consent process and form therefore describes the collection and storage, as well as the range of future research uses of those data and biospecimens. In a clinical or other study in which the primary intervention is not solicitation of data from subjects or collection of their biospecimens, but these collections occur in the course of the study as part of the protocol, these collection processes are also typically described in the informed consent process and form. Finally, there are non-research collections of data and tissues, such as (but not limited to) collections in the course of standard clinical care, to which patients are not routinely asked specifically to consent; these

compilations of data and biospecimens occur in the normal course of such activities as the delivery of, for example, health care, social services, and educational services.

When researchers therefore seek to use collected, identifiable personal data or biospecimens for specific research to which the human sources of those data and biospecimens have never specifically consented, researchers can sometimes return to those individuals to obtain a new consent for the new study. This process is often cumbersome, costly and, in the words of the Common Rule, "not practicable." Researchers therefore currently have few options for using these data and biospecimens for research, without returning for consent. Those options include:

- De-identifying data and biospecimens, so that they can no longer readily be traced to specific persons, and then using them for specific studies; or
- Recording existing identified data, or using biospecimens with identified data, in a manner in which, as part of the research, identifying characteristics are not recorded in the research record, and no "link" is retained between the de-identified research record and the identifying information that was viewed by the researcher; or
- Applying to an IRB for a waiver of informed consent to allow for the new research use; assuming the proposed new use meets certain requirements set forth in the Common Rule (i.e., research is of minimal risk to subjects, impracticability of obtaining new informed consent, no adverse effects on subjects' rights or welfare, and consideration of debriefing subjects), the IRB can waive the necessity of obtaining a new written consent.

Proposed significant changes to these complex existing alternatives for future uses of existing data and biospecimens without additional consent are set forth in several different parts of the ANPRM. As a baseline, the ANPRM endorses the concept that there must be general consent for future research uses agreed to by a subject, in order for future research uses of that subject's data and biospecimens to be allowed. The ANPRM further suggests that subjects must be allowed to "opt out" of future research uses of their data and biospecimens, and that a subject's enrollment into a study cannot be conditioned upon the subject's consent to such future research uses. Such a "general consent for future research," would not need to be study-specific, but could be very general and allow for open-ended, non-specified future research.

In regard to the requirement that such general consents be obtained from subjects, the ANPRM distinguishes between biospecimens and data. For future use of a subject's biospecimens, whether collected for research or non-research purposes, whether identified or non-identified, the proposal would require that there be a general consent for future research uses. Without such a general consent for future research uses, no future use of those biospecimens would be allowed, even if associated data were de-identified; and waivers of informed consent would not be allowed for their future use.[6] The proposal further would classify biospecimens as never able to

[6] 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.

be considered de-identified or anonymized, due to the remote possibility of re-identification by a third party's obtaining and analyzing other biospecimens from the subject, or correlation of the subject's biospecimen data with other, existing, databases.

The proposal further distinguishes between requirements for future research uses of data collected for research purposes, and data collected for non-research purposes, as in the course of clinical or social service delivery, receipt of education or public benefits, or in the course of business or commercial activities. For those data collected for non-research purposes, a general consent for future use would only be required if researchers are, in the subsequent research use, obtaining and recording data that identify subjects. Data originally collected for non-research purposes would be able to be de-identified and then used by researchers without a subject's consent, and presumably without any IRB approval because the activity would qualify as not "human subject" research. Standards that apply to data collected for research purposes would be stricter, with general consent for future use being required for any subsequent research use, regardless of whether those data are identified or de-identified.

The aspect of this proposal approach that varies most significantly from current practice of research review and approval is that it would essentially eliminate the option – described above – by which a researcher could 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 the ANPRM suggests would be gathered at the point of initial contact with the research subject), it would not be possible for a researcher later, for new research, to use or re-use any previously collected biospecimens or any previously collected identified data, 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, biospecimens previously collected for any purpose could not be considered de-identified for new research.

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.

The conceptual basis of this commitment in the ANPRM to allowing the subject to say "no" to future uses, or to opt out of future uses, would seem to lie in the value of personal autonomy. This approach – which would not even allow a study to condition enrollment on consent to future research – seems disharmonious with the allowance of a waiver of consent that would specifically override the subject's prior refusal to consent. It is difficult, given the value presumptions implicit in the ANPRM's proposals on this issue, to conceive of circumstances in which an IRB should allow research in direct opposition to a subject's prior refusals.

Nevertheless, to the extent that waiver can be preserved for cases in which there may not have been consent for future uses, but the specific future use offers significant research promise or is a matter of public health urgency, and the risk to subjects would be minimal, then this would be salutary, in SACHRP's estimation.

SACHRP is mindful that there has been some public concern over future uses of personal data and biospecimens without informed consent, as in the case of cell lines derived from those obtained from Henrietta Lacks and of biospecimens obtained from the small Havasupai tribe. The questions raised in these cases, however, require careful identification and analysis, and may not, in fact, be identical to the concerns expressed in the ANPRM, and may not have been prevented by the regulatory solutions suggested.[7] In any case, SACHRP 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 present 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 therapies for breast cancer; isolation of the 1918 flu virus; and the identification of *helicobacter pylori* as a cause of gastric ulcers, which also has been linked to the development of stomach cancer. It should be noted that many of these discoveries were obtained from the use of previously existing pathology collections for which it would have been impossible to obtain consent.

SACHRP believes that a more attainable approach would rely on public education about the process and value of these future research uses of data and biospecimens, provide more rigorous IRB analysis of potential individual and group harms from the waiver of informed consent for research, and include specific measures that would penalize, even criminally, researchers and others who would attempt to re-identify subjects through use of their personal data and biospecimens.[8] SACHRP prefers this targeted approach to these issues over the approach suggested in the ANPRM, which, by comparison, seems less targeted, less workable, and less protective of subjects.

First, SACHRP questions an approach that would rely upon the "general consent for future research uses" as the primary means of protecting subjects from future harms, and, moreover, as the necessary predicate for any future research use of data and biospecimens that have been collected in research or in the delivery of standard of care services. SACHRP is not opposed to

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[7] 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 to apply properly 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 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.

[8] At the same time, SACHRP 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.

informing patients and subjects, on an individual basis through the consent process, and when feasible, of the possibility of future uses, or even asking for consent to future uses. Yet SACHRP believes that a general consent for future use should not be a necessary predicate for any and all future research uses, and that such a general consent cannot act as a substitute for careful consideration by an IRB, through the existing waiver of consent process, of specific future research uses and their risks for subjects.

SACHRP notes, for example, that in many industry-sponsored clinical trials, the industrial sponsor asks the site investigator to include in the consent form a clause, or an "opt-in" provision, that informs subjects of the range of future research uses and by which they are asked to consent to those uses. Similarly, in many non-clinical trial studies, or in clinical trials not sponsored by industry, researchers inform subjects of likely future uses of their data and biospecimens, and ask their consent for it. Informing subjects in these ways of the possible future uses by the sponsor of their data and biospecimens is a salutary practice, but is different in essential ways from the ANPRM proposal. These are studies in which there is present knowledge of the researchers and/or sponsors that there likely will be future uses, and in the case of non-industry-sponsored studies, failure to get this general consent for future research uses does not preclude future uses, because, presently, researchers have the option of seeking from an IRB a waiver of informed consent for the future use. Finally, even when there has been a general consent for future research uses obtained in the primary study (or primary clinical or other service setting), no researcher, under current Common Rule interpretations, would believe that such a consent would obviate the need, in the case of future specific research uses, for that researcher to seek and obtain from an IRB a waiver of consent; the theory in such cases is that although the subject may have been informed of and may have consented to future research uses, that consent could not have included specific future studies, for which the IRB, in considering waiver of consent, would seek to protect the welfare of the subjects.

Similarly, in industry-sponsored studies (which may be conducted in an academic or clinical setting under the Common Rule and OHRP jurisdiction), data and biospecimens may be transferred to the sponsor's research operations for future research use. It is important to note that models for industry conduct of research are evolving and increasingly involve collaborative and contractual relationships with institutions that are subject to the Common Rule and OHRP jurisdiction. In some circumstances, sponsors, in their internal company research activities, may not be subject to the Common Rule or to OHRP enforcement. In such circumstances, sponsors still abide by any applicable FDA requirements, state-specific laws that apply in their research locations, laws of other nations intended to protect human research subjects and the privacy of individuals, and internationally recognized ethical guidelines. Sponsors may apply to an IRB for a waiver of consent, to allow future research use in the event that they believe that the original consent does not adequately contemplate the specific secondary research, but this may not be required by sponsors whose internal research involves reuse of data and biospecimens. Obtaining, as part of the primary study, a general consent for a sponsor's future uses is an obvious, feasible method of more consistently assuring some element of consent. Further, from a practical standpoint, when a sponsor asks for such a general consent for its own future uses, there is only one entity involved that must retain and track that consent – the sponsor itself. That is an altogether different situation than in the course of research, clinical care and social services

in entities acting under the Common Rule, in which data and biospecimens are appropriately and lawfully transferred among and between many different legal entities and collaborating research partners; under this ANPRM proposal, the scale and demands of compliance for most entities under Common Rule jurisdiction are at least daunting, if not, as a practical matter, insurmountable.

At this time, no researcher would have a reliable way of predicting, for purposes of informed consent adequate under the Common Rule, the full range of specific future research uses of data and biospecimens that would be widely acceptable to American society in 25, 50 or 100 years; such a general future consent therefore could not be sufficient under the Common Rule to obviate the necessity, prior to a researcher's undertaking a later specific study, of applying to an IRB for waiver of informed consent. In this context, it is – at the least – uncertain and more likely, impossible, for subjects signing such a general consent to know enough of the specific information to satisfy our current practices under the Common Rule. They cannot accurately and fully be apprised of future benefits, or of risks, or even of the research methods that might be employed, to an extent that would allow a researcher to "skip the step" in future specific studies of seeking either IRB waiver of consent, or subject re-consent, under the Common Rule. In addition, if prospective research consent were required to use 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 are principally responsible for assisting patients or clients before their clinical tests, procedures or interviews. If the main point of contact were an administrative office, such as registration, 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 staff charged with obtaining consent likely would have little understanding of the research enterprise and could in fact be completely disconnected from it (especially in systems where research is conducted by a university or medical school, and clinical care is provided at independent but affiliated hospitals). 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.

Further, 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. Again, it would be difficult if not impossible to predict all potential research uses, and any list of "opt-outs" would be insufficient. There still may be questions that are raised downstream as to the appropriate use of a biospecimen. An individual, for example, may sign a general consent, but opt out of having his or her tissue used in a couple of known research modalities. Later, that same individual may be unavailable, her location unknown. How would one then determine whether that individual's biospecimens may be used for a research use from which she had not specifically opted out because it was not contemplated at the time of consent? The matter 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.

Under the current regulatory structure, situations where researchers are unable to provide accurate information about future and presently unknown studies, or are unable adequately to track "opt-ins" and "opt-outs" during complex data and biospecimen sharing across institutions, are accommodated by application of the waiver of informed consent process. Under that process, a group of people empanelled as an IRB are trusted to consider specific future uses, and to determine whether each research use meets 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 obtain new consent from them. Instead, appropriately, IRBs under the current regulatory regime require re-consent only when practicable and when the study risk exceeds a minimal level. We trust IRBs to make "go" and "no-go" 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 for which we routinely rely on IRBs to decide. SACHRP believes that this mechanism of IRBs 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, combined with enhanced public education, is, SACHRP 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 not likely to provide meaningful consent that would be sufficiently specific as to obviate the need for future IRB waivers of consent (because the present consent cannot contemplate the full extent of future research uses and inform subjects accurately about all those uses), and is burdensome, the existing waiver of consent process should be retained, and as necessary, improved.

The new proposal would also eliminate the possibility that researchers could simply de-identify 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 in order ostensibly to protect subjects from the risks of re-identification of data and biospecimens and consequent compromises of their privacy. In the view of some members of SACHRP, 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, sharing with others, in unlimited and unsupervised ways. 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 de-identify patient data and use it for any purpose whatsoever, were applied in this way, 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 whatsoever, 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 as impossible because, it is conjectured, 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 could be done through re-identification via data matches than through matches of biospecimens. Yet, as set forth above, within the specific legislative and regulatory construct of HIPAA, we have made a social decision, nearly a decade ago, to allow HIPAA covered entities to freely de-identify data and then use it for any purpose at all, with no express prohibition on sale to others or public posting. For these reasons, the rationale for the proposal's stricter standards for future research uses of biospecimens seems weak.

Further, HHS notes the benefits of research on biospecimens and, throughout the ANPRM, attempts to strike a balance between enabling such research to take place and protecting human subjects through streamlined consent requirements. A requirement that automatically defaults to

a 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 proposal. Before adopting such an approach, HHS should carefully consider whether, as SACHRP believes, such an inflexible position would severely limit the 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 obtain the consent of prior 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 – with a greater risk to privacy, and 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 that can actually lead to patient harm from incorrect findings based on incomplete data.

If HHS does choose to implement a standardized general consent requirement for the future research use of biospecimens, it should consider how such a change might affect other applicable consent requirements. For example, in July 2009, the NIH promulgated new federal funding Guidelines on Human Stem Cell Research (the "NIH Guidelines"). See http://stemcells.nih.gov/policy/2009guidelines.htm. The NIH Guidelines include specific and detailed informed consent requirements related to embryo donations for stem cell research, in the context where the materials originally were collected for clinical purposes. HHS should consider and clarify how the proposed standardized general consent rule might be applied in conjunction with the detailed informed consent requirements of these Guidelines. The NIH stem cell guidelines on this topic are only one example; if this proposal is adopted, OHRP and its parent agency, HHS, would need carefully to examine each and every existing research consent guideline or requirement, so that they may be harmonized with the measures proposed.

If current proposals relating to general consent for future research uses are adopted, HHS presumably would, as suggested in the ANPRM, consider "grandfathering" existing biospecimens to exempt them from the new consent requirements proposed by the ANPRM, because applying the new consent rules retroactively would negatively impact the conduct of critical research. SACHRP endorses this aspect of the proposal. HHS also should 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, SACHRP 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,

SACHRP 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.

Finally, and perhaps most tellingly, SACHRP would point out 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 given consent to every use, even if in general terms, or has opted out of a use and had that opt out respected, the ANPRM proposal may seem to suggest in a theoretical sense that respect for persons invariably trumps beneficence and justice. Absent from the proposal are the other two critical values in research ethics.

Beneficence in this case lies in the obligation that all of us have, one to the other, to participate in activities that benefit society at large, and that yield benefit and promise for those who come after us. SACHRP believes that individuals should not undergo, without consent, research on their data and tissues that may cause harm to them. Instead, SACHRP 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 SACHRP 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 the 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 may refuse use of their own data and biospecimens, even when risk to them is negligible, but who nevertheless themselves benefit from such research by depending upon the beneficence of others. Further, one cannot then ensure that the results of any such research will be representative and not biased or skewed.

There is also the need for greater transparency. The public is relatively unaware that such research is occurring ubiquitously. Education should focus on why they 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 or negative) may leave the public feeling that their rights were disregarded and their trust was violated. The public should have the right to know about the uses to which their data (information or biospecimens) were used. The importance of trust in the research enterprise cannot be overstated.

In summary, SACHRP believes that a more attainable, more practical approach, and one more protective for research subjects, 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 and insular communities whose individual members may be directly affected by use of apparently de-identified or anonymized data and/or biospecimens;
- Legislative efforts to penalize, even criminally, researchers and others who would attempt to re-identify subjects through use of their personal data and biospecimens[9] ; 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.
- SACHRP believes that there are circumstances in which prospective informed consent for future use of biospecimens and data may not be required or a waiver may be appropriate.
- SACHRP does not endorse the presumption that all biospecimens are inherently identifiable.
- SACHRP believes that all secondary research use of existing biospecimens with identifiers should be registered with the institution.
- SACHRP does not believe that all secondary research use of existing biospecimens without identifiers should be registered with the institution.

9. Areas to Address that were not Included in the ANPRM as Proposed

A. Requirement to Address Investigator Regulatory Responsibilities in the Common Rule

The Common Rule, unlike FDA regulations, does not directly address the roles and responsibilities of investigators involved in human subjects research. This deficiency is all the more problematic as aspects of the ANPRM suggest removing IRBs from their historical approval and monitoring role. Notwithstanding SACHRP's comments above, consideration of such a shift in responsibility should only be considered if certain responsibilities are concordantly transferred from the IRB to the investigators as clear and direct duties under federal regulation. Appropriate responsibility should be placed on those who initiate and conduct research and are in the best position to protect human subjects. IRBs are removed from the day-to-day research activities and thus their ability to monitor research activities is limited. SACHRP notes that NIH and FDA have partially addressed the need for training in grant

[9] At the same time, SACHRP 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.

requirements, guidance and product approval regulations; however, these regulations address only clinical and biomedical investigators. The Common Rule should be harmonized with the FDA in containing regulations that apply to the responsibilities and expectations of all investigators.

Investigator responsibilities are appropriate to consider independent of any other change in the Common Rule. The ANPRM affords an opportunity to amend the Common Rule regulations to include three new sections that clearly elucidate investigator responsibilities. The three sections should cover, at a minimum: (1) responsibilities of biomedical and non-biomedical investigators; (2) qualification standards for investigators (e.g., training); and (3) investigator documentation/records.

New regulations to ensure investigator accountability would codify the current ethical expectations for investigators who conduct human subjects research. Regulations addressing investigator responsibility should emphasize the critical role of the investigator and hold the investigator directly accountable for his/her actions. As part of the FWA requirements, institutions are responsible for ensuring that the regulations are effectively applied. The oversight authority (45 CFR Part 46.103(a)) is already in place: "each institution engaged in research … shall provide written assurance … that it will comply with the requirements set forth in this policy."

Should investigator responsibility be added to a revised rule, federal guidance would be useful to facilitate the development of appropriate institutional procedures to meet the new regulations (in this case, complying with investigator responsibilities). It may, however, be useful to amend 45 CFR Part 46.103 to add a specific requirement that research institutions provide investigators with initial and ongoing training and education in conflicts of interest, research integrity, and scientific conduct as part of an institutional human subjects protection program. To decrease the administrative burden and cost, guidance should allow reasonable flexibility for institutions to develop responsive training programs.

Adding investigator responsibilities to the Common Rule would harmonize HHS regulations with those of the FDA and international standards, uniting and simplifying the regulatory expectations and decreasing burden. Models for delineating investigator responsibilities can be found in the drug and device regulations of the FDA (i.e., Subpart D, 21 CFR Part 312 and Subpart E, 21 CFR Part 812) and in internationally accepted guidelines such as the ICH standards (Good Clinical Practice E-6, Section 4) and the CIOMS International Ethical Guidelines For Biomedical Research.

While HHS will consider the regulations carefully, we suggest the following as an example of this section:

§46.104 Responsibilities of Investigators.
(a) Investigators are responsible for ensuring that research is conducted according to:

(1) sound research design and generally accepted scientific methods;

(2) the terms of the grant, contract and/or signed funding agreements, if any;
(3) the study plan (protocol) and when applicable as submitted to, and approved by, the IRB; and
(4) applicable laws and regulations including those for protecting the rights, safety, and welfare of human subjects.

(b) Unless exempt from review, investigators are responsible for obtaining initial approval and, as required, continuing review of the research by an IRB formed and operating under this part.
(c) Investigators are responsible for providing the IRB with sufficient information and materials to make the required determinations in §46.111.
(d) When consent is required, investigators are responsible for ensuring that informed consent is provided and obtained in accordance with §46.116. Unless waived, investigators are responsible for obtaining signed consent to the extent required by §46.117. When vulnerable populations are involved in research, investigators are responsible for complying with any additional safeguards as required.
(e) Investigators and their institutions are required to permit and facilitate monitoring and auditing, at reasonable times, by the IRB of record, funding agencies, the Secretary, and other federal and state regulatory agencies, as appropriate.
(f) For research that collects data through intervention or interaction with human subjects, the investigator is responsible for ensuring that the research project and each subject is appropriately monitored for subject safety.
(g) In compliance with §46.103(b)(4) of this subpart, investigators shall ensure prompt reporting to the IRB and appropriate institutional officials of any unanticipated problems involving risks to subjects or others.
(h) Qualified investigators must personally conduct or supervise the research.

§46.105 Qualification Standards for Investigators.
(a) Investigators must be sufficiently qualified by education, training, and experience to assume responsibility for the proper conduct of human subjects research. Qualified investigators who retain the final responsibility for the research must supervise student investigators.
(b) As part of the qualification to conduct research, investigators should have sufficient time to properly conduct or supervise the research and they are responsible for ensuring that adequate resources (e.g., qualified staff and adequate facilities) are available.
(c) Investigators should be responsible for reporting to the all financial interests relevant to their institutional commitments; such reports would in turn be addressed by the institution in accordance with requirements to eliminate or manage any conflict of interest.[10]

§46.106 Investigator Records, Reports and Documentation.
(a) Investigators are responsible for the accuracy, completeness, legibility, and timeliness of the data recorded and reported in research and in publications about the research.

[10] This obligation should be harmonized with FDA regulations and the recent NIH policy on financial conflicts of interest.

(b) Investigators should maintain a study-file of pertinent documents appropriate to the research (e.g., the study plan, consent forms, and correspondence from the IRB) and permit inspection of the research records in accordance with §46.104(e).
(c) Investigators must maintain records for at least three years after the research ends or for the length of time specified in applicable regulations, whichever is longer, and should take measures to prevent accidental or premature destruction of these documents.
(d) Investigators must submit written reports to the IRB as requested/required by the IRB.
(e) Upon completion of the research, the investigator shall provide:
(1) the IRB with a notice of completion and summary of the outcome; and,
(2) any funding and regulatory agencies with required reports, as applicable.

B. Pediatrics

While the actual ANPRM proposed changes in regulations do not apply specifically to Subpart D, there are several concerns that would result if Subpart A were changed as proposed. The following are the concerns of SACHRP:

1. The proposal to mandate a central IRB for all domestic studies has the potential to eliminate or diminish the special expertise required to review pediatric research. It is essential that pediatric research be reviewed by individuals who have experience in the medical, psychological, social, and emotional needs of children. Many studies cover an age range of childhood through adulthood. When this happens, the pediatric portion is often sent to a pediatric IRB and the adult portion to another IRB experienced with adults. If there is mandate for only one IRB, and the research involves children, then there must be a mechanism by which to ensure that an IRB with appropriate experience in pediatrics is utilized.

2. The ANPRM proposes new "excused" criteria; of these, category two is limited to competent adults. There are some protocols that involve procedures listed in category two that also present no risk for child-subjects. Research involving children should not categorically be excluded from category two. Conversely, there are some studies in children where the "excused criteria" should not apply to children and expedited or full review should occur. Individual IRBs are best suited to determine when and if a procedure that falls within category two may be excused for children and this flexibility should be allowed in both regulations and guidance.

3. There are some significant concerns regarding the proposed changes to specimen use as it will impact pediatric research. At the current time, HHS has issued the following guidance on their website:

> *What happens if a child reaches the legal age of consent while enrolled in a study?*
> *The Office for Human Research Protections (OHRP) notes that informed consent should be viewed as an ongoing process throughout the duration of a research project. When a child who was enrolled in research with parental or guardian*

> *permission subsequently reaches the legal age of consent to the procedures involved in ongoing research, the subject's participation in the research is no longer regulated by the requirements of 45 CFR part 46.408 regarding parental or guardian permission and subject assent.*
> *Unless the Institutional Review Board (IRB) determines that the requirements for obtaining informed consent can be waived, the investigators should seek and obtain the legally effective informed consent, as described in 45 CFR 46.116, for the now-adult subject for any ongoing interactions or interventions with the subjects. This is because the prior parental permission and child assent are not equivalent to legally effective informed consent for the now-adult subject. However, the IRB could approve a waiver of informed consent under 45 CFR 46.116(d), if the IRB finds and documents that the required conditions are met. Similarly, if the research does not involve any ongoing interactions or interventions with the subjects, but continues to meet the regulatory definition of "human subjects research" (for example, it involves the continued analysis of specimens or data for which the subject's identity is readily identifiable to the investigator(s)), then it would be necessary for the investigator(s) to seek and obtain the legally effective informed consent of the now-adult subjects. The IRB may consider, if appropriate, a waiver under 45 CFR 46.116(d) of the requirements for obtaining informed consent in order for the subjects to continue their participation in the research.*

If all research on human biospecimens requires written consent and waivers are no longer permitted per the ANPRM, the above guidance would lead regulatory agencies to conclude that consent from the newly-adult (e.g., 18 year-old) subject is required in order to continue using the samples. This would apply to samples in repositories as well as to left-over clinical samples that have been stored. If consent at the age of majority is not obtained, then samples could not continue to be used. Although this is not specifically stated anywhere in the proposed revisions, the rationale and reasoning used to modify the current regulations leads to this conclusion. This would invariably result in the inability to use some pediatric samples for research and would have obviously important consequences for the pediatric research community.

A potential solution would be to allow waivers of consent, which is included in the current regulatory guidance when children legally become adults and the regulatory criteria for waiver of consent can be met. This would apply to biospecimens for newly-adult subjects, even if not permitted elsewhere.

4. The last concern is that OHRP has received three advisory committee reports regarding guidance for interpretation of Subpart D. The recommendations from all of the groups are very similar. While the ANPRM has concentrated on Subpart A, there are many inefficiencies and inconsistencies in IRB review of pediatric research that result from lack of clear guidance concerning the terms used in the pediatric regulations. OHRP should issue definitive guidance. It is essential that all IRBs work with a common understanding of some of the issues that Subpart D presents. Clear guidance based on the consensus of the three advisory committee reports would help eliminate these differences.

SACHRP recommends removing all references to "competent adults" throughout the ANPRM as inclusion of this qualifying language is more restrictive than the current regulations and would introduce numerous unintended consequences. Sufficient provisions already are in place for protecting the rights and welfare of other subject populations.

C. Vulnerable Subjects

Vulnerability, as commonly held, involves two discrete but often interrelated phenomena that are relevant to human subjects protections and should be more directly considered in any revision to the Common Rule. Vulnerability to "coercion or undue influence" (45 CFR 46) reflects an understanding that some individuals, by virtue of illness (e.g., dementia), circumstance (e.g., socio-economically disadvantaged) or context (e.g., imprisonment) may be unable to adequately protect themselves through the protections afforded by the informed consent process. Vulnerability is also understood in common parlance as *susceptibility* to harm. Protections embodied in the regulatory structure must achieve a proper balance between protecting the vulnerable individuals and unnecessary paternalism that may interfere with subject rights, access to novel therapies, and more broadly, the benefits of research. Our comments here relate to the vulnerability of the individual and not community-level vulnerability.

The ANPRM raises questions and concerns in relation to vulnerability that can be addressed with reference as follows:

- With regard to Questions 1, 5, and 6: The ANPRM relies on a procedure-based "calibration" of risk that perhaps too closely links level of review (and in the proposal, excusal from review) to specific research procedures. As explained in SACHRP's January 2008 letter to HHS:

  > "The IRB's evaluation of the harms and discomforts of the research should consider the nature of the study procedures, other study characteristics, subject characteristics, and steps taken to minimize risk.
  > In its estimate of research-related risk, the IRB should 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 anticipated harms and discomforts of research involvement."

  An MRI of the brain in a healthy adult may introduce very little risk of physical or psychological harm. The same procedure in an adult with autistic spectrum disorder, without necessary protections, may be a terrifying experience and may also require special procedures to avoid harm (for example, use of a metal detector if there is less confidence in patient history). Therefore, the definition of minimal risk and related guidance should incorporate SACHRP's previous recommendation in this regard.

- The ANPRM states, "We are considering whether to include on the list of excused studies certain types of social and behavioral research, conducted with competent adults,

that would involve specified types of benign interventions…that are known to involve virtually no risk to subjects, and for which prior review does little to increase protections to subjects." (Questions 14 and 22)

The ANPRM provides few examples, or anchors, that might help define which "types of social and behavioral research" or which "benign interventions" are being considered for excusal, or where an appropriate upper limit of harm should be set. In our July 2009 letter, SACHRP wrote:

i. In determining level of review, IRBs should be especially mindful of any unique circumstances and susceptibilities of the proposed research participants. The serious medical, neurological, and psychiatric illnesses that give rise to impaired consent capacity may place participants at increased risk of harm and discomfort from research participation. Further, for participants who are unable to express discomfort, describe untoward effects or otherwise communicate their wishes once enrolled, research participation may involve added risk.
ii. An IRB may determine that research that includes individuals who lack consent capacity may fulfill criteria for minimal risk and/or expedited review; the fact that a study includes individuals who lack consent capacity should not, in and of itself, mean that review by the convened IRB is required.
iii. However, the expedited review of research involving such participants should be conducted by reviewers with appropriate expertise and in accordance with well defined, written policies and procedures for expedited review. These policies should describe requirements for consent by the LAR, and provide examples of additional safeguards required in the recruitment, identification, and approval of research with such individuals.
iv. Minimal risk research that fulfills the requirement for waiver of informed consent but will include individuals with impaired consent capacity may be reviewed by expedited review procedures without the additional requirements outlined in item a(iii), above.

- Question 11 in the ANPRM asks, "What are the advantages of requiring that expedited review be conducted by an IRB member?" With regard to subjects who lack consent capacity, item (iii) in the above bulleted section addresses this directly; i.e., with regard to minimal risk determination in other research populations, familiarity with subject populations and research interventions requires expert review by an individual (whether an experienced IRB member or staff) accountable to the parent committee.

- Question 34 asks about the selection of a single IRB for multi-site domestic studies. With regard to vulnerable populations, a mandate for single IRB review may serve to exclude review by the specialty or single-population IRB, especially those at smaller institutions. Such IRBs may offer unique expertise and experience in the review and risk minimization techniques for research with vulnerable populations. A rigid mandate will interfere with the development of more flexible, collaborative, and creative approaches to shared oversight responsibilities.

- Question 38 asks if, for certain types of studies, investigators should be required to assess how well potential research subjects comprehend the information provided to them. In its July 2009 letter to Secretary Sebelius, SACHRP wrote:

> "For all studies, investigators and research staff who obtain consent should consider each participant's capacity to consent to the research. In studies where the recruitment of individuals with impaired consent capacity is not anticipated, the judgment that prospective participants have the capacity to consent to the research can ordinarily be made informally during routine interactions with the participant during the consent process…
> "The method used to assess capacity, and when appropriate, the documentation of this assessment, should be tailored to the study population, the level of study risk, and the likelihood of the involvement of participants with impaired consent capacity…
> "In making the determination as to methods to be used to ascertain consent capacity, it is important to note that more intensive approaches involve burdens for participants and researchers alike. Therefore, these should be reserved for those situations in which impairment is more likely to be present, anticipated benefits are fewer, and foreseeable risks are greater."

  Informed consent is an appropriate protection only when the voluntary choice to participate by the subject derives from the understanding and consideration of relevant information disclosures. Absent some assessment of this understanding, it is meaningless to assert that informed consent has occurred.

- The ANPRM makes reference to physical, psychological, and informational risks, and acknowledges that other categories of risk may fall within these broad categories. In support of expanded exemptions to include "procedures commonly used in social and behavioral research that are known to involve virtually no risk to subjects, and for which prior review does little to increase protections to subjects" the ANPRM may inadvertently define an overly narrow definition of harm. For example, unwarranted access by researchers to prospective subjects in healthcare settings and intrusive screening, recruitment, and follow-up procedures may represent intrusions to privacy and fail to create a context that supports free and informed consent, especially for those vulnerable to coercion or undue influence. These essential components of research may well fall outside the purview of IRB review under the proposed rule.

- The ANPRM, seeking to define a threshold to exclude certain "surveys and related methodologies" (Question 16) refers to topics that are "emotionally charged such as sexual or physical abuse" and asks what entity should be responsible for determining whether a topic is "emotionally charged."

  "Emotionally charged" is an unusual term, and unless understood in terms of context (e.g., newly diagnosed patient), the physical setting (e.g., private room, waiting room), population (e.g., job candidates), and research goals would not provide a meaningful

threshold for either excusal or expedited review. A history of physical or sexual abuse and other trauma, for example, is routinely elicited during routine psychiatric evaluations. Questions about mood, thoughts of death, and suicidal intent, similarly, should not in and of themselves serve as "the calibration" point to determine level of review. A survey, interview or focus group dealing with parenting, religion, or sexual practices may be benign or may introduce risk depending on the duration, setting, population, the researcher collecting the data, and procedures introduced to minimize risk. While such work may fall well-within a minimal risk determination, the value of prior expert review, consultation, and approval seems clear. It is unlikely that simply listing categories relating to study content will enable researchers to self-categorize their work for the purpose of exclusion.

D. International Research

Revisions to the Common Rule should consider studies conducted in countries outside the U.S. The current regulations contain two requirements with respect to research conducted in foreign countries. The first is "This policy does not affect any foreign laws or regulations which may otherwise be applicable and which provide additional protections to human subjects of research." (§46.101(g)) and the second is "…if a Department or Agency head determines that the procedures prescribed by the institution afford protections that are at least equivalent to those provided in this policy, the Department or Agency head may approve the substitution of the foreign procedures in lieu of the procedural requirements provided in this policy…" To date, OHRP has not deemed any foreign institution's or country's procedure to be at least equivalent to those regulations set forth in 45 CFR Part 46.

When 45 CFR Part 46 was published in 1981 and adopted as the Common Rule in 1991, few countries, if any, had laws or regulations or even guidance in this area. Today, with the vast expansion of industry-sponsored clinical trials outside the U.S., many countries have laws or guidelines based on ICH-GCP (E6). These laws or guidelines primarily apply to drug trials and sometimes studies involving medical devices and other types of clinical research. Some countries have adopted laws or guidelines that are based on 45 CFR Part 46. Some countries have laws that are more expansive than the U.S. regulations. With few exceptions, foreign laws do not apply to behavioral and social science research.

Revisions to the Common Rule should take into account that more and more research studies are being conducted outside the U.S., that many clinical trials are multi-national in nature, and that many countries have laws that are equivalent to or surpass the U.S. regulations. For biomedical research, specifically, SACHRP suggests that:

1. OHRP develop a process for determining when foreign laws and regulations as equivalent to the U.S. regulations and use the process to determine when foreign laws and regulations are equivalent to the U.S. regulations. This would reduce a tremendous burden on IRBs and researchers without compromising subject protections. In fact, human subject protections could be enhanced, even bolstered, by allowing foreign countries to apply their own regulations and laws.

2. OHRP should develop guidance for U.S. IRBs that review research conducted in foreign countries, including when it is acceptable to rely upon the foreign IRB's review.
3. The use of a single IRB to review multi-national research should include foreign sites for clinical trials and epidemiological studies where the research protocols are set and not easily altered.

E. Incurred Cost and Resource Commitment

We understand that changes to the Common Rule, whether from the ANPRM, SACHRP recommendations or other sources would carry substantial institutional costs of implementation. There will also be significant agency costs but those are not the subject of this review. The unfunded expenses that are concomitant with the adoption of this rulemaking are not addressed nor provided for. Among the significant costs (to be borne by small and large institutions alike) include rendering obsolete or replacing current electronic information systems and creating interoperability of such systems (or recreating where they currently exist), existing IRB forms, institutional policies, and AAHRPP accreditation standards. Proposed requirements for post hoc auditing, additional informed consent requirements would also add substantial costs. Further cost implications include educating the public at large, reeducating the research community, implementing a new data security system (not yet defined), establishing new legal agreements among collaborating institutions, and revising other institutional policies that include or compliment the current regulations.

SACHRP appreciates the opportunity to comment on the ANPRM and commends OHRP, FDA, OCR and the other HHS agencies on the vision embodied in this effort. SACHRP committee members and subcommittee members worked diligently to complete this letter in the time allotted, and we realize that this letter is incomplete. We look forward to working closely with our federal colleagues as this effort advances and continuing the work to enhance human research protections for the benefit of all human participants.

Sincerely,

/s/

Barbara E. Bierer, M.D.
Chair, Secretary's Advisory Committee
on Human Research Protections
(SACHRP)

cc: Jerry Menikoff, M.D., J.D., Executive Secretary, SACHRP
Julia Gorey, J.D., Executive Director, SACHRP