DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary

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

// Dated AUG 5 2011//

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

Dear Ms. Sebelius:

The Secretary's Advisory Committee on Human Research Protections (SACHRP) is charged with providing the Secretary, HHS, with advice and recommendations on issues relating to human research protections, with the dual aims of improving the protection of human subjects and the quality of protection programs, and of decreasing regulatory burdens that do not meaningfully contribute to the protection of such subjects. The protection and promotion of scientifically rigorous and ethically sensitive research in the public interest is our collective concern.

In consideration of our charge, SACHRP has considered the *Request for Comments on Human Subjects Protections in Scientific Studies* emanating from the Presidential Commission for the Study of Bioethical Issues ("the Commission"). We summarize herein the major topics that have been discussed in our deliberations, and recommend that these comments be forwarded to the Commission through the Secretary, HHS.

SACHRP Comments Regarding *Request for Comments on Human Subjects Protections in Scientific Studies*

SACHRP has previously considered a number of the areas mentioned below, and substantive and detailed recommendations have been forwarded to the Secretary in the past. That said, much of SACHRP's work to date has focused on subpart A of 45 CFR Part 46, the "Common Rule" and its additional subparts (B, C and D), and more recently on the overlap and dissonance between the regulations espoused by OHRP and other agencies (e.g., FDA, OCR). We find that the basic framework of the regulations in 45 CFR Part 46, coupled with the bedrock principles of the Belmont Report, have served the regulated community – and the human subjects that it serves– well over the past decades. We note, however, that only a portion of studies is governed by these regulations, and the Request for Comments by the Commission provided us with the opportunity to comment on the patchwork system of regulatory oversight, and on certain specific issues within. There are compelling issues that

have emerged since the regulations for human subjects protections were introduced. These issues include differences in interpretations of identifiability, future research uses of data and tissues that are identified to specific human subjects, and significant inconsistencies between FDA and HHS regulations and guidance, as in the availability of waivers of the consent process for minimal risk research. Further, the fact that human subjects research is increasingly international, prompting considerations of the globalization of research, and increasingly involving vulnerable subjects—because vulnerability is often dynamic—has not been adequately addressed in the current regulatory framework.

We would strongly encourage the Commission to recognize, and consider a solution for, a basic structural deficiency in the organization of regulatory oversight of human subject research at the federal level, in that there is presently no public forum for all the federal agencies that fund and regulate human research to share issues and perspectives, and – to the greatest extent possible – to harmonize or reconcile their regulations and guidance in this area. Although SACHRP performs this function for HHS, and the Common Rule agencies have ex-officio members on SACHRP, there is no standing analog to SACHRP for the many other federal offices and agencies that routinely promulgate and enforce human research regulations. Until just this year, the Committee of Science in the Office of Science and Technology convened the Human Subjects Research Subcommittee, which met regularly for decades and was co-chaired by OHRP and NSF. Unfortunately this subcommittee had no authority to make changes to the regulations and issue guidance.

The lack of federal-wide coordination has resulted in a confusing, complex, and, not infrequently, inconsistent welter of regulations and guidance documents. Researchers and research institutions incur significant transaction costs in seeking to comply with these disparate requirements without, in our judgment, yielding any research processes that are superior in terms of protection of human subjects. An alternative worth exploring would, in our judgment, be the establishing of a new public advisory committee working under, for example, the Office of Science and Technology Policy, which would have authority to make recommendations for all the Common Rule agencies, similar to the way in which SACHRP is structured within HHS.

The purpose of this committee would not be to recommend steps that each federal agency or office might take in regard to its own regulation of human subjects research, but rather to make, on a continuing basis, recommendations for how agencies and offices can adopt common, consistent, and effective standards for this research. What seems needed at this point is not an advisory committee that would sustain each agency in any unique aspects of its regulations and interpretations, but an advisory committee that would seek to steer all the agencies into a common, harmonious approach to this heavily regulated area of academic and industrial activity. To make such an advisory committee effective, its charter could require federal offices and agencies to respond meaningfully to the committee's formal recommendations within a set period of time, and in case of failures to adopt its recommendations, for elevation of these recommendations directly to the Secretarial or agency director level.

We offer these comments, and more specific comments below, for SACHRP's consideration, and respectfully request that these be forwarded to the Presidential Commission for the Study of Bioethical Issues.

1. Harmonization

The current legal framework for protection of human subjects is composed of an overlapping and non-uniform set of regulations and other requirements. The basic reason for this patchwork of regulatory provisions is that each federal agency has own authority to write regulations and to promulgate additional regulations or guidance to the "Common Rule" (subpart A of 45 CFR 46). Further, the triggers for applicability of the existing regulatory structure are either federal funding from a federal agency that is a signatory to the "Common Rule," or involvement of a product regulated by FDA or EPA. Other research falls within sometimes inconsistent state law jurisdictions. The result of this patchwork structure is that there are gaps in oversight for certain research and overlaps in regulations for other research. These gaps and overlaps have led to differences in application, interpretation and implementation of the regulations. The President's Commission should consider recommending a legislative solution that would close the gap in oversight and harmonize the overlapping regulations governing human subjects protections.

The HHS regulations apply to all human subject research that is funded by HHS, whereas the FDA regulations apply to all human subject research that involves an FDA regulated test article (e.g., a food, cosmetic, dietary supplement, drug or medical device). Research funded by one of the other federal agencies is subject to that agency's codification of the "Common Rule," for example 38 CFR 16 and 17 for VA. Thus, research that does not involve federal funding from a signatory to the "Common Rule" or an FDA regulated article often will not be subject to any federal oversight, and some research that involves federal funding and an FDA regulated article will be subject to both sets of regulatory requirements. To make this scheme more complicated, multiple federal agencies (e.g., VA, DOD, ED) have their own regulations that superimpose additional requirements. For example, the VA requires its medical facilities to provide necessary medical treatment to a research subject injured as a result of participation in a VA research study, while most other agencies do not. The Department of Navy requires a separate FWA addendum with training requirements (type and scope) that differ from and expand upon the OHRP requirements. Similarly, HHS, FDA, ED and other agencies require additional protections for children in research (subpart D), but some agencies do not. Another agency, EPA, has additional protections and prohibitions for children and pregnant women that diverge significantly from those of any other department or agency.

True systemic reform would demand a critical look at integrating, harmonizing and simplifying this regulatory system. One possible solution, which has been introduced as a Congressional bill and was proposed by the National Bioethics Advisory Commission, is to create a single federal regulatory agency or office for oversight of research involving human subjects; another solution would be to expand the legislative authority of an existing regulatory entity (e.g., OHRP) with

oversight authority for all human subject research (presumably through the interstate commerce power or other applicable basis for federal jurisdiction), even if it does not involve federal funding or an FDA regulated article.

Such legislation should also harmonize existing federal requirements governing human subject protections, while maintaining the appropriate distinctions in the regulatory framework for FDA and HHS that are essential to fulfilling their respective legislative mandates. The federal requirements should preempt all state laws in this field. When state laws offer additional protections for human subjects, and those protections are reasonable, effective, and efficient, those should be considered for adoption in the national research regulations.

2. Alternatives to local IRB review for multi-site research

The current system of protections was largely established 40 years ago, when research was conducted much differently than it is today, and is predicated on local review by IRBs at individual institutions. Redundant review by multiple IRBs has been identified as a hindrance to the efficient and effective conduct of research in today's environment, and may be of questionable benefit in multi-site scenarios, because the protocol must be conducted consistently across all sites for scientific validity and rigor. Further, subject protections might be lessened when multiple IRBs review a protocol and do not have complete study-wide data, such as for data and safety monitoring.

There is nothing in the current regulations to prohibit IRBs from sharing IRB reviews. However, the complexity of current agreements and concerns over institutional liability, accountability, and jurisdiction discourage their widespread use. Alternative models exist and their use should be explored and expanded.
Effective review models that have mechanisms to account for local issues, address institutional liability concerns, and address other barriers to their use should be encouraged. Prior SACHRP recommendations have supported these efforts, and led to national conferences in 2005 and 2006 that explored related issues (summary reports available at: www.aamc.org/initiatives/clinicalresearch/irbreview/).

3. HIPAA

The Health Insurance Portability and Accountability Act of 1996 (HIPAA) has had various negative impacts on human subjects research, often without demonstrable benefit in further protecting the subjects of that research. SACHRP has previously developed several recommendations for changes in HIPAA (see Secretarial Letters dated Sept 27, 2004 and July 15, 2009) that focus on decreasing regulatory burden without decreasing human subject protection.

HHS has recently proposed some regulatory changes to HIPAA that would ease some HIPAA

burdens on research, and while SACHRP has been supportive of these recent proposals, SACHRP would encourage full implementation of its own past recommendations in this area, in addition to adoption of the recommendations of the 2009 Institute of Medicine committee on HIPAA and research.

In addition, the Presidential Commission should examine whether a comprehensive national data privacy scheme would provide better privacy protections to U.S. citizens and promote global harmonization of standards. Most countries have comprehensive data protection schemes that are patterned after the EU Data Protection Directive. These comprehensive schemes govern all aspects of data protection including, but not limited to, health related information, and are administered by data protection authorities that have broad enforcement powers. The U.S., on the other hand, is one of the few countries with sector-specific rules governing data privacy (e.g., HIPAA, FERPA, drug and alcohol abuse treatment regulations, state regulations on information relating to genetic testing, HIV and mental health treatment). The use of personal information outside of one of these sector-specific legislative schemes is not regulated. The Commission should examine whether the adoption of a comprehensive scheme would provide better protections and promote harmonization with international standards for data protection.

4. Minimal Risk Research

IRBs today are required to apply the same criteria for approval of (a) research involving high or moderate risk, and (b) research involving little to no risk. For example, data analysis when identifiers are present is an example of research that engenders confusion and discord over the level of oversight needed. As a result, there is an imbalance in the time that IRBs spend reviewing minimal risk research, resulting in less time and resources available for higher and moderate risk studies, where closer review and more exacting attention are merited. The existing categories for exemption should be examined to determine if additional types of research could be accommodated within current categories or within new or revised categories. Simplified criteria for approval and continuing review could be developed for minimal risk studies, including greater flexibility for initial review and relaxation of continuing review requirements, thus relying more heavily on investigators to signal any problems in research through their reporting of unanticipated problems. Overall, the processes for review and approval of this type of research could be reconsidered and revised, with a view toward allocating an increased share of IRB time and attention to higher risk studies, thus reducing time and attention focused on research with lower risk to subjects. These issues occur with particular frequency in social science, behavioral and educational research as detailed in the section that follows.

5. Social Science, Behavioral and Educational Research (SBER)

A distinction is often drawn between biomedical human research and SBER. The types of research subsumed under this shorthand abbreviation are broad, and include a range of

methods/techniques as well as a range of scientific fields. Nevertheless some regulatory and subject protection issues regularly emerge in discussion of SBER.

Regarding research methods and techniques, SBER often makes use of surveys, interviews, review of existing records/data, observations of public behaviors, etc. These are the same methods and techniques that non-regulated professions such as journalism, market research and public polling use – generally without abuse of subjects, public outrage or mistrust. These methods are also used in quality assurance activities that the biomedical field employs routinely without the "protection" of regulatory oversight.

Regarding scientific approaches, fields such as anthropology, ethnography, and community participatory research often have striking differences from clinical research. IRBs are accustomed to structured protocols for clinical studies, but SBER protocols may include only a general overview with a brief outline of procedures, and the focus of the research develops over the course of time in cooperation with communities and participants. Consent forms and study plans (protocols) thus may be more difficult to review because specifics are unknown in advance.

It has been long and loudly argued that the burden imposed on researchers and IRBs by human subjects research oversight in SBER seems out of proportion to the potential harms to research subjects, which are rarely physical or irreversible. Delineation of high and low risk research is, however, an exacting task, and these categories are not invariably correlated with clinical and non-clinical research. Indeed, the Milgram Study, Wichita Jury Study, and Zimbardo Prison Study, to name a few examples, all resulted in great concern about subject harms, and yet none was a clinical study.

As stated above in the minimal risk section, a solution may be for the IRB to focus on making the determination whether a SBER project presents no more than minimal risk to subjects; if so, the IRB should be allowed to determine that the study does not require further review. This step would require a regulatory change.

6. Banking and Secondary Uses of Identifiable Data and Biospecimens

In large, population-based studies, as well as in clinical trials of drugs, devices and biotechnology agents, massive amounts of health data, including data relating to past and present family and medical history, are routinely collected; these data are often preserved after a study ends and placed either into a unique database or aggregated into larger databases with data from other studies. Further, with increasing frequency, biospecimens collected for immediate study purposes are preserved after the study ends, and are placed into biobanks or biospecimen repositories, and thus preserved for future research uses, the nature and contours of which are presently unknown, and to a large extent, unknowable. Similarly, in academic medical centers both in the U.S. and abroad, treatment data and biospecimens collected in the course of standard of care treatment are now often preserved long after any period of required retention has ended,

in order to allow future researchers to use these data and biospecimens for future, presently unspecified studies. These practices of data and biospecimens preservation coincide, not unexpectedly, with increasingly frequent federally-mandated requirements in many types of biomedical and behavioral research, which require that data and biospecimens collected in federally funded studies be placed into large databases or repositories maintained by federal agencies or entities they fund to perform these functions.

With these data banking and tissue banking practices increasing in frequency and scope (a phenomenon seemingly attributable to the increasing scientific value of the uses of these data and tissue banks and the promise of precision or personalized medicine), IRBs, research institutions, and sponsors are struggling with what data and tissues are appropriate to share or to request, how to share or request them, what level of review is required to support this sharing, and what future research uses, if any, may not be appropriate. For example, current regulations are inadequate to address whether and when subsequent uses of biospecimens (particularly when individual identifiers are removed) must be compatible with the original terms of consent under which they were obtained and how this would be determined. While some case law has addressed the issues of ownership and control of specimens once they have been obtained, and of data, once they have been collected, there is a need for greater regulatory clarity and predictability. Further, complex and often ill-drafted state laws relating to genetic testing (and also, in some cases, privacy of medical information) further cloud the issues, and confuse the legalities of trans-state research.

In sum, it is critical for progress in science and medicine that these data and tissues be banked, shared and used in responsible and accountable ways, by responsible and accountable parties, with appropriate protections for the privacy, rights and welfare of subjects. Concerns have also been raised about the effect of research use of databases and biorepositories on close families and discrete and insular communities; these concerns should be considered in formulating regulations and guidance in this area. The legality and ethics of practices in this area need swift clarification, with consistency of regulation and guidance among FDA, OHRP, other federal offices and agencies, and, if possible, the state jurisdictions as well.

7. Informed Consent

Consent documents have been transformed from tools of individual (subject) protection and information sharing into tools of regulatory compliance documentation and investigator, sponsor and institutional protection. These forms have become increasingly lengthy and complex, describing every conceivable risk and tending to a level of detail that often obscures the information needed for subjects to make an informed choice. We encourage the PCSBI to examine how to best facilitate a shift in focus on the part of all parties involved in the human research enterprise from the *form* to the *process* of consent. This could include the use of pre-consent education tools, with ongoing education throughout the duration of the study, and exit interviews. Forms must be simplified and alternative formats (both written documents and use

of other technologies such as computer-assisted and video formats) should be encouraged. The consent process, including the forms employed in that process, must be restored to its intended role as a tool for protecting research subjects.

8. Education

Education regarding research and research participation is critically important for all stakeholders including institutional leadership, IRBs, investigators and research staff, policymakers, sponsors, research subjects and the general public. This will be especially vital as changes to human subjects protection requirements are considered. Currently, unless funding support for a researcher's salary or project falls under certain categories of NIH or NSF programs, educational requirements -- whether for responsible conduct of research, in general, or for human subjects protections in particular – do not apply. Educational efforts should include public campaigns, public service announcements, community outreach and creation of a model curriculum. An improved understanding of the processes of research will promote transparency. An informed public is more likely to consider research participation in advance of being approached for possible study enrollment and to be more knowledgeable about their options, rights, and the requirements of participation, resulting in greater protections and higher quality research results.

9. International Research

The increased globalization of clinical research has highlighted the inadequate resources and oversight authority by federal agencies for international research. OHRP and FDA have too few resources and potentially inadequate legislative authority to provide adequate monitoring and oversight of international research. For instance, foreign institutions that have obtained Federal Wide Assurances receive little in the way of guidance, and foreign IRBs that review FDA-regulated research are not required to register with the FDA. The Presidential Commission should review the legislative authority and resources allocated to FDA and OHRP to ensure they are adequate for those agencies to operate effectively in a global environment.

In addition, the "Common Rule" allows for the recognition of international standards that provide protections to human subjects that are at least equivalent to those of subpart A of 45 CFR 46. However, there have been no determinations of equivalent protections, even as research has globalized and several countries have developed robust human subjects protection and regulatory mechanisms, consistent with their own national laws and cultural values, and requested that OHRP deem their systems of protection to be equivalent. At the same time, FDA accepts foreign data developed in studies that are performed in compliance with foreign laws and standards if they are completed before the FDA application filing; the FDA thus tacitly accepts an equivalent standard (e.g., ICH and CIOMS) in its own approval process, in significant contrast to OHRP's current stance on these "equivalence" issues. The lack of determinations of

"equivalence" – and of acceptable methods to determine "equivalence" – has led to circumstances in which U.S.-based researchers and research institutions must insist on foreign entities' and foreign researchers' strict adherence to what can seem, to them, confusing and even impenetrable U.S. regulations and guidance documents. The solution is for the equivalent standard regulation to be implemented, as recommended by the Equivalent Protections Working Group, the National Bioethics Advisory Commission, and others.

When addressing federal and international standards for protecting the rights and welfare of participants in scientific studies, the PCSBI is encouraged to specifically examine the standards to protect populations that may be uniquely burdened or harmed by participation in research such as children, the mentally ill, severely socially and economically disadvantaged, displaced persons and others.

Finally, guidance for U.S.-based IRBs that review multinational research is lacking. Current standards do not clearly enable non-local IRBs to judge whether they have sufficient knowledge of local context, or when local practices in areas such as legally effective consent may be considered acceptable under U.S. regulations.

10. Financial Conflicts of Interest

Financial conflict of interest regulations in human subject research originate from several set of regulations including those of FDA, PHS and NSF, and the Common Rule prohibition on conflicts of interest among IRB members. In these different sets of regulations and corresponding guidance documents, there is significant inconsistency in approach, procedure, and definition of cognizable financial interests. This inconsistency would be exacerbated by adoption of the proposed PHS revisions to that set of regulations. Indeed, during the comment period on those proposed regulations, SACHRP elaborated on the ways in which the proposed regulations would widen the gulf between the FDA and PHS approaches to financial conflicts of interest. These inconsistencies were also noted by SACHRP's predecessor committee, the National Human Research Protections Advisory Committee (NHRPAC), in a 2001 report to HHS. Recent heightened attention to the issues of investigators' financial interests in human subjects research has also led to a number of states enacting their own laws governing these issues, thus leading to further complexity of the legal regimes applicable to this area of activity. Viewed globally, there is even less uniformity, as PHS regulations are rarely enforced in foreign institutions that receive NIH funds directly or as subrecipients.

Interests of research subjects and the research enterprise as a whole would be better served if there were a coherent and consistent national approach to conflict of interest in human subjects research, with uniform standards for disclosure of financial interests that may affect such research, and with common procedural approaches and norms for the management of identified conflicts of interest.

11. Sharing individual research test results with participants

Imaging, genomic, proteomic and other technologies increasingly permit the performance of sophisticated tests and assays on specimens obtained from human research participants, or on the participants themselves. These technologies, such as whole-genome sequencing, are increasingly high-throughput, i.e., they permit simultaneous collection of thousands or even millions of data points. Although the vast majority of these data points will lack validated clinical implications, the result of a test may occasionally have clinical or perhaps personal meaning for the participant

The ability to perform high-throughput testing in the research context presents investigators and IRBs with a conundrum. Responsible investigators and IRBs conducting or overseeing such studies seek to minimize risk to participants, maximize benefit, enhance partnership, and demonstrate respect for participant autonomy. It is difficult, however, for investigators employing high-throughput research tools to simultaneously achieve all these goals. On the one hand, a broad policy of sharing research results risks physical, psychological or financial harms as a result of actions taken in response to results of uncertain clinical meaning. There is also concern that the requirement of returning research results, with appropriate education and counseling, will be impracticable for some research studies. On the other hand, such a policy respects the autonomy of participants who desire their results and demonstrates a commitment to partnership with participants. In addition, results of tests performed in the research context may occasionally have significant and actionable implications for participants, as in the incidental detection of a cancer predisposition mutation for which actions to mitigate risk are available. Many observers have argued that policies regarding the handling of research results should make it possible--or indeed should require--that investigators make such results available to participants. The requirements of the Clinical Laboratories Improvements Act (CLIA) create an additional barrier as well as a protection to sharing such results with participants, whether motivated by a desire to benefit participants or to respect their autonomy and foster partnership. As currently interpreted by CMS, only results that have been obtained in a CLIA-certified laboratory may be returned to individuals. Much research testing, however, occurs in non-CLIA-certified laboratories, in part because the specialized testing performed in many research studies is not yet available in CLIA-certified laboratories. Given the increasing use of genomic and other high-throughput technologies, federal guidance is urgently required regarding whether, when, and how research results should be returned to individual participants, as well as how this is reflected in the informed consent process. In addition, if results may be returned in some instances, the development of a mechanism for recommending which results should be considered for return, such as an advisory panel housed within the National Institutes of Health or other appropriate agency, would greatly assist the research community in addressing this challenging issue.

12. Third Parties in Research

Human subjects research increasingly involves persons who, although perhaps not originally intended as research subjects, nevertheless participate in the conduct of research and have

identifiable data about them collected as part of the research. These "third parties" to research can often become research subjects themselves (e.g., educational research on students but involving teachers, health research on patients but involving medical providers, research on individuals that involves data collection on family members). There is a current lack of clarity on whether and when and under what circumstances these "third parties" may become research subjects themselves, and guidance on this issue is needed.

13. Evidence-based Protections

There is an inadequate evidence base to inform regulation and best practices in many areas of human subjects protections. Increased federal support for research to enhance this evidence base is essential to facilitate improvements in human subjects research regulations and practices.

The Presidential Commission is urged to use its broad charge and trans-agency scope to contemplate appropriate revisions and harmonization of human research protection statutes and regulatory standards that are necessary to keep pace with the evolving advances in the conduct of human subjects research.

On behalf of SACHRP, I would like to thank you for your consideration of this report, and ask again that it be provided to the Commission. The committee, the Subpart A Subcommittee and the Subcommittee on Harmonization share the Commission's dedication to human subjects protections, and hope that these remarks provide assistance in their current endeavor.

Sincerely,

// signed//

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