This document, completed in October 2011, consists of a letter in response to the US Department of Health and Human Services (HHS) "Advance notice of proposed rulemaking" (ANPRM) dated July 26, 2011 in regard to revising and updating HHS human subject research protections.

This letter provides opinions and recommendations from several epidemiology organizations and senior epidemiologists.

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Our online comment field (searchable):

The Joint Policy Committee of the Societies of Epidemiology (JPC-SE), formed in 2006, represents an international consortium of thirteen organizations, focused on epidemiology, that are working jointly together on policy issues. Since the release by the Office of the Secretary, HHS and the Food and Drug Administration, HHS of its advance notice of proposed rulemaking (ANPRM), the JPC-SE has been sharing information & viewpoints among our societies. We commend the request for comments. We agree that it is time to revise current regulations for protecting human subjects who participate in research. We believe that it is possible to better protect human subjects who are involved in research while facilitating research and reducing burden, delay, and ambiguity for investigators. This submission represents the official response to the ANPRM for SIX specific organizations:

- Epidemiology Section of the American Public Health Association (APHA-Epi)
- International Epidemiological Association (IEA)
- Society for Pediatric and Perinatal Epidemiologic Research (SPER)
- Society for the Analysis of African-American Public Health Issues (SAAPHI)
- International Society for Environmental Epidemiology (ISEE)
- American College of Epidemiology (ACE).

This letter also represents the personal opinions of nineteen individual signatories, each of whom is a senior epidemiologist who has participated in the JPC-SE deliberative processes.

We particularly draw your attention to our response to Ques. 24 (see especially pp. 13 & 14). The JPC-SE considers the differentiation of "practice" from "research" to be of exceptional importance. We further urge the OHPR to adopt our definitions and approach in this regard, and to integrate this throughout any new regulations that are issued.

Note that the present document fully replaces the document uploaded previously, HHS-OPHS-2011-0005-0961, with just the cover letter changed.

The Joint Policy Committee of the Societies of Epidemiology provides a forum for surveillance of and communication about the funding, regulatory and legislative environment as it relates to epidemiology. Through coordinated joint action, the Committee strives to impact policies and influence opinion leaders relevant to epidemiologic research and practice.

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October 26, 2011

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REF: Comments on 45 CFR 46, 160, and 164 Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators.
Docket ID Number: **HHS-OPHS-2011-0005**

Dear Dr. Menikoff:

The Joint Policy Committee of the Societies of Epidemiology (JPC-SE), formed in 2006, represents an international consortium of thirteen organizations, focused on epidemiology, that are working jointly together on policy issues. It should be noted by OHRP that U.S. regulations also greatly affect research abroad for at least three reasons: 1) funds may come from US sources; 2) US institutions may participate in the project; and 3) other countries often look to US policies when formulating policies for their own countries.

Since the release by the Office of the Secretary, HHS and the Food and Drug Administration, HHS of its advance notice of proposed rulemaking (ANPRM), the JPC-SE has been sharing information and viewpoints among our societies. We commend the request for comments. We agree that it is time to revise current regulations for protecting human subjects who participate in research. We believe that it is possible to better protect human subjects who are involved in research while facilitating research and reducing burden, delay, and ambiguity for investigators.

This letter REPLACES our submission from earlier today, HHS-OPHS-2011-0005-**0961;** the board of another major organization has now officially endorsed its submission and asked to be added to this communication. **Our comments on the following pages reflect a consensus set of opinions of all signatories below.** (Additional comments are being submitted separately by some parties.)

This letter represents **the official response** to the ANPRM for **SIX** specific organizations [along with their respectively designated primary organizational contact(s)]:

- **Epidemiology Section of the American Public Health Association** (APHA-Epi), represented by Drs. Alleyne and Gaudino.
- **International Epidemiological Association** (IEA), represented by Dr. Franco.
- **Society for Pediatric and Perinatal Epidemiologic Research** (SPER), represented by Drs. Kirby and Platt.
- **Society for the Analysis of African-American Public Health Issues** (SAAPHI), represented by Dr. Hasson.
- **International Society for Environmental Epidemiology** (ISEE), represented by Drs. Al-Delaimy and Wartenberg.
- **American College of Epidemiology** (ACE), represented by Drs. Hiatt and McKeown.

Joint Policy Committee Societies of Epidemiology

This letter **<u>also</u> represents the personal opinions of the nineteen individual signatories below**, who are senior epidemiologists who have participated in the JPC-SE deliberative processes. These individuals' organizational affiliations and positions are included here for identification purposes. These affiliations do not necessarily indicate organizational or institutional agreement with the views stated herein. (It should be noted that given the timing of board meetings, it was not possible to vet our JPC-SE response below through every board in time for the OHRP response deadline.)

[*Names appear in alphabetic order]*

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- Stanley H. Weiss, MD (please see immediately below for his titles)

Respectfully yours, and
Submitted on behalf of the above parties as noted, and to whom any correspondence should be directed,
by

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Our comments follow on the next page

Joint Policy Committee
Societies of Epidemiology

JPC-SE Comments on 45 CFR 46, 160, and 164 -
Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators

Docket ID Number: HHS-OPHS-2011-0005

October 26, 2011

The Joint Policy Committee of the Societies of Epidemiology (JPC-SE) applauds the Office of the Secretary, HHS and the Food and Drug Administration, HHS for issuing this advance notice of proposed rulemaking (ANPRM). We agree that it is time to revise current regulations for protecting human subjects who participate in research. We believe that it is possible to better protect human subjects who are involved in research while facilitating research and reducing burden, delay, and ambiguity for investigators.

We first provide some general comments, followed by comments on some of the specific questions posed in the ANPRM, an Appendix dealing with some related issues, and finally a list of some key sources.

We wish to particularly draw your attention to our response to Question 24 (see especially pp. 13 and 14 below). The JPC-SE considers the differentiation of "practice" from "research" to be of exceptional importance. We further urge the OHPR to adopt our definitions and approach in this regard, and to integrate this throughout any new regulations that are issued.

General Comments

The Common Rule has served the public and research communities well for decades. New technologies and accessibility of information require revising the Common Rule so that the review process is calibrated to the risk of research. Given the enormous challenges to protect human subjects who participate in research, the Common Rule should focus on research that carries the greatest risks. Therefore, we propose excluding from the Common Rule all routine use of existing clinical and administrative records used for comparative effectiveness, quality improvement, quality assessment, program evaluation, and public health practice. We support strengthening the mandatory data security and information protection standards for all identifiable or potentially identifiable data.

Proposals that address research that uses only existing data collected for non-research purposes when the data are identified are problematic and of great importance and concern. As proposed, there will be a new requirement for written consent for secondary use of data collected for non-research purposes if the data are identified.

If the proposed changes put in place a requirement for written consent for secondary use of data collected for non-research purposes, much epidemiologic research and a high proportion of all outcomes, comparative effectiveness and health services research would not be able to be conducted.

Some specific examples of research that could not be done if written consent is required for secondary use of non-research data are as follows:

- **Research on adverse drug events using computer-stored prescription data linked with hospital data.**
- **Research linking birth certificate and death certificate data.**
- **Research linking cancer registry data with mortality data.**
- **Research linking cancer registry data with Medicare data.**

In all of these types of research, it is necessary to have information on identifiers in order to link the data that permits the research to be done.

Currently researchers who wish to use such data, with identifiers, can request that the IRB waive the requirement for consent, which the IRB can approve (based either on expedited or full committee review) based on CFR 46-116:

> **d) An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:**
> **(1) The research involves no more than minimal risk to the subjects;**
> **(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;**
> **(3) The research could not practicably be carried out without the waiver or alteration; and**
> **(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.**

In the case of research involving all large administrative and clinical databases (where data are collected for non-research purposes) it is impracticable to obtain consent. When procedures are put in place by the researchers to assure that the identifiable data are protected from risk of disclosure by, at a minimum, limiting access to named individuals involved in the research all of whom have undergone training in human subjects protection and assuring that the data are secure from unauthorized access and making plans for destroying identifiers when the research is complete, the research involves no more than minimal risk. Thus, the IRB may approve it without consent. Further, under the current HIPAA privacy rule, the IRB, acting as a Privacy Board, may also approve a waiver of HIPAA authorization as well as the requirement for consent.

The proposed changes appear to be trying to bring the rules into alignment with HIPAA by defining a category of research that uses a limited dataset that does not then require consent. The proposal may give the impression that a limited dataset does not require written consent, thus making the kind of research described above possible under the new rules.

There may be a misunderstanding of how a dataset becomes a limited dataset. As you know, a HIPAA-defined limited dataset is one that contains none of the 18 HIPAA-defined identifiers except dates (such as date of birth and death and date of service) and geographic information that would not be identifying (such as zip code if the number of people in the zip is large enough that, combined with date, it would not permit identification of an individual). A limited dataset used for research is almost always created from data that were at some point identifiable.

There are apparent contradictions regarding easing burdens for research vs. new requirements for consent for use of secondary use of data: See "3. Moving Away from Concept of Exempt" (page 44518)

Discussion of research involving the use of existing information or biospecimens (page 44519, Column 1, 3.)

"the limitation that the research cannot record and retain information that identifies the subjects would be eliminated."

This proposal is excellent, but its value is eliminated by the newly proposed requirements for "Consent rules for excused research" (page 44519, Column 3) being proposed for use of pre-existing data or biospecimens in Section 3(a)(3).

The only relief from this newly proposed requirement might be found on page 44520, Column 1,

"there would be rules (to be determined) that would allow for waiver of consent under specified purposes…"

We have further addressed this issue in our response below to Question # 23.

Family and Educational Rights and Privacy Act – Implications for Research and Public Health Practice

The Joint Policy Committee of the Societies of Epidemiology (JPC-SE) requests that OHRP engage in effecting a remedy for a policy problem that is increasingly impeding the ability of state and local health departments to gather health data from schools to protect and promote public health. While not directly germane to the proposed changes in the Common Rule, efforts to harmonize use of personal health information for research and for public health practice can improve the protection of research participants. We are responding under OHRP's call for comments on broad matters that will harmonize and improve the regulatory environment *en toto* and enhance safety.

The policy problem concerns the Family and Educational Rights and Privacy Act (FERPA; 20 U.S.C. § 1232g; 34 CFR Part 99) enacted in 1974 to protect the privacy of school education records. Student health records maintained by publicly funded educational institutions are an important source of information for public health authorities for the prevention and control of disease, injury or disability as authorized under state law. However, in recent years, regulatory measures under FERPA have restricted disclosure of identified student health information to public health authorities without parental consent unless a declared emergency situation exists. This has significantly impeded accurate surveillance, investigation, and control of communicable diseases such as meningitis, chickenpox and pertussis, monitoring immunization levels, and public health investigation of adverse health conditions.

The restrictive nature of FERPA and its regulations also significantly impeded timely, accurate surveillance and intervention activities in conjunction with the H1N1 pandemic. Public health authorities in states and counties across the nation have had to seek emergency exceptions on a case-

by-case basis in order to gather information they are authorized to collect under state law in order to effectively implement disease control measures to protect the entire community.

The Council of State and Territorial Epidemiologists (CSTE) met with the Family Policy Compliance Office within the Department of Education in February, 2008 to discuss the adverse impact of recent changes to FERPA on public health, and ask for assistance in finding a remedy, but without success. The most recent changes to FERPA regulation were adopted later in 2008 following a period of public comment. CSTE submitted the attached comments at that time. However, the final rule adopted on December 9, 2008 did not improve the restrictive nature of FERPA regulation with regard to the release of information to public health authorities. In fact, DOE officials concluded that a change in legislation would be required for DOE to change regulation in a fashion that would address public health need.

Numerous medical and public health organizations advocate for a remedy to the FERPA problem by amending FERPA so that school health records are protected under HIPAA (Health Insurance Portability and Accountability Act) rather than FERPA. Recognizing the importance of health information for public health, HIPAA contains provisions to allow sharing of protected health information with public health authorities for the purpose of protecting public health. These provisions have been thoroughly tested since the enactment of HIPAA regulations and reflect the widely accepted standards for balancing the need to protect individual health information privacy with that of protecting public health.

The JPC-SE requests that OHRP investigate the adverse impact of FERPA on research and public health and actively work towards harmonizing protections and access to student health records.

Streamlining Documentation Requirements for Expedited Studies:

We are strongly supportive of the proposals for streamlining documentation requirements for research that poses no more than minimal risk and qualifies for expedited review. There is substantial variability in the documentation requirements between IRBs. Some, perhaps many, IRBs have very burdensome documentation requirements. There is no evidence that IRBs that require more documentation better protect human subjects. Excessive requirements contribute to the perception of researchers that IRBs act as bureaucracies for the sake of bureaucracy. The excessive requirements and inconsistencies among IRB undermine the research enterprise and do not contribute to the protection of research participants. Please see the Appendix (p. 19 below) for further details.

Comments responding to specific questions asked in the notice: (Our responses are indented and in bold)

Question 1: Is the current definition of "minimal risk" in the regulations (45 CFR 46.102(i) -- research activities where "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests") -- appropriate? If not, how should it be changed?

We believe that the current definition of "minimal risk" is appropriate and widely understood by researchers and IRBs. We see no need to change it.

Question 2: Would the proposals regarding continuing review for research that poses no more than minimal risk and qualifies for expedited review assure that subjects are adequately protected? What specific criteria should be used by IRBs in determining that a study that qualifies for expedited initial review should undergo continuing review?

We are strongly in support of the proposal to change the default for studies that qualify for expedited initial review to require no continuing review.

Question 3*:* For research that poses greater than minimal risk, should annual continuing review be required if the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category described in section 3, below (e.g., a study in which a physical intervention occurred in the first year, all subjects have completed that intervention, and only annual written surveys are completed for the next five years)?

We believe that annual continuing review should NOT be required for research that poses greater than minimal risk when the remaining study activities only include those that could have been approved under expedited review or would fall under the revised exempt (Excused) category.

The requirements for continuing review should be based on level of risk at the time that human subjects incur that risk, not at the time the research was initially proposed.

Question 7: What research activities, if any, should be added to the published list of activities that can be used in a study that qualifies for expedited review? Should any of the existing activities on that list be removed or revised? For instance, should the following be included as minimal risk research activities:

- Allergy skin testing
- Skin punch biopsy (limited to two per protocol)
- Additional biopsy during a clinical test (e.g., performing an extra colonic biopsy in the course of performing a routine colonoscopy)
- Glucose tolerance testing among adults

Examinations that involve only the exposure to ultrasound except in pregnant women and children probably should be added. These do not involve exposure to ionizing radiation and pose minimal risk.

We also recommend adding as "minimal risk activities" phlebotomy in healthy adults of up to 60 ml (2 ounces, but perhaps somewhat larger quantities might be permitted if there were careful evaluation by a clinician to help ensure that the subject is indeed "healthy"), plus provision of non-invasively acquired specimens, such as urine and saliva.

We have not systematically reviewed nor have we tried to reach consensus on all of the existing activities on the current list. We are in agreement that "skin punch biopsy (limited to two per protocol)," and "glucose tolerance testing among adults" seem reasonable to be included on the "minimal risk activities" list. We assume that these are being done in appropriate clinical settings with appropriate monitoring by specialists when appropriate.

If OHRP meant to inquire about performance of an "anergy skin test panel," that is an issue the JPC-SE has not discussed. With respect to "allergy skin testing," which suggests testing in persons who may have a propensity to allergies, if this is done by an experienced allergist in a setting where appropriate clinical support is readily available, the American College of Allergy, Asthma & Immunology has judged this acceptable as an office-based procedure with a low risk of serious reactions. Thus, as long as these ancillary caveats are added as part of the specification, it also seems reasonable for it to be included on the "minimal risk activities" list. Note that the study protocol must be required to fully and carefully document these ancillary safety requirements and that they will be in place at the time of such procedures.

Some of us were somewhat concerned that "additional biopsies" as described, that are being done solely due to research as opposed to clinical needs, should NOT be "minimal risk" as there is an acknowledged risk of serious sequelae that occur with low but measurable frequency in the best hands, including complications such as serious infections and perforations that may require surgical correction, and thus where full board review may be more appropriate.

Question 9: How frequently should a mandatory review and update of the list of research activities that can qualify for expedited review take place? Should the list be revised once a year, every two years, or less frequently?

A review at three years seems reasonable.

Question 10: Which, if any, of the current criteria for IRB approval under 45 CFR 46.111 should not apply to a study that qualifies for expedited review?

The requirement for consent (4 and 5) should not apply to a study that qualifies for expedited review if all of the other criteria for a waiver of consent are met. The requirement for data monitoring for safety (6) should not apply if there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

To qualify for expedited review, a study must pose no more than minimal risk. The minimal risk posed by the research is inherent in the type of activity being performed and is not something that the researcher controls. Many, indeed most, of the current criteria for IRB approval under 45 CFR 46.111 are meant to assure the risks of the research are minimized. But if risks are already minimal, requiring that they be met does not follow.

"1. Risks to subjects are minimized:
(i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
(ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by § 46.116.
[See our comments above]
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by § 46.117.
[See our comments above]

6. When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.
[See our comments above]
7. When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.
8. When some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, additional safeguards have been included in the study to protect the rights and welfare of these subjects."

Question 12: Are there other specific changes that could be made to reduce the burden imposed on researchers and their staffs in terms of meeting the requirements to submit documents to an IRB, without decreasing protections to subjects? Are there specific elements that can be appropriately eliminated from protocols or consent forms? Which other documents that are currently required to be submitted to IRBs can be shortened or perhaps appropriately eliminated? Conversely, are there specific additions to protocols or consent forms beyond those identified in this notice that would meaningfully add to the protection of subjects? What entity or organization should develop and disseminate such standardized document formats?

This is an excellent question to ask. However, it is contradictory to attempt to eliminate unnecessary forms and paperwork by establishing new requirements for researchers to file paperwork on exempt research as proposed under 4. i and 4.ii (Column 2, page 44515). Why should researchers have to register research that is exempt from the Common Rule, especially when "review is not required or recommended"? This newly proposed revision should be dropped entirely.

However, see Appendix A for examples of misinformation about what federal regulations permit with regard to IRB review of exempt research and the large variability in the burden that different IRBs place on researchers seeking to use de-identified data. If a requirement to have documentation that research is exempt is kept, then we would support 4. i. "Require that researchers file with the IRB a brief form (approximately one page) to register their exempt studies, but generally allow the research to commence after the filing." We would suggest changing from "approximately one page" to "not more than one page."

We also strongly support the proposal on page 44515, bottom of first column to eliminate continuing review for all minimal risk studies that undergo expedited review and studies initially reviewed by a convened IRB after the study reaches the later stages identified.

Society itself should always be considered in these contexts as one of the *de facto* subjects, so that society is also "protected' when appropriate.

Question 13: Given the problems with the current system regarding wide variations in the substance of IRB reviews, would it be appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the defaults described in Sections B(1), B(2)(a)(ii), and B(2)(b) above? Should IRBs have to report instances in which they require continuing review or convened IRB review of a study which involves only activities identified as being on the list of those eligible for expedited review? If an IRB that chose to override these defaults was required to submit a report to OHRP, would this provide useful information about any lack of appropriate consistency among IRBs so that clarifying guidance could be provided as needed, or provide useful information to OHRP about the possible need to revise the expedited review list or the continuing review requirements?

We believe it is appropriate to require IRBs to submit periodic reports to OHRP in the instances in which they choose to override the default by requiring continuing review or convened IRB review of a study which involves only activities identified as being on the list of those eligible for expedited review. This information would help the OHRP to know when clarifying guidance is needed.

We believe that OHRP should conduct audits of IRBs that continue to override the defaults since lack of attention to guidance on this issue may be evidence of overall lack of attention to OHRP guidance.

We believe the regulations should make it clear that consistency among IRBs in the requirements for review of research that involves minimal risk is important and that consistency contributes positively to the overall program of human subjects protection.

Periodic evaluation of IRB performance should be required. This periodic review should explicitly, by regulation, encompass an assessment of whether the IRB is inappropriately requiring full committee or expedited review of research that is exempt or excused. Review should monitor whether IRBs are rejecting research on false grounds. Review should use metrics that track the time from submission to final decision for research that uses both the full committee and expedited mechanisms. Performance standards for timeliness of review should be established. Other straightforward criteria for assessing performance might include a decision by a local IRB to reject approval for participation in a multi-site study that has been approved by a multiplicity of other IRBs. Collection and documentation of examples of inappropriate reviews, inconsistency, or mis-application of the Common Rule should be required and made widely available so that education of IRB members can occur over time.

Question 23: Under what circumstances should it be permissible to waive consent for research involving the collection and study of existing data and biospecimens as described in Section 3(a)(3) above? Should the rules for waiving consent be different if the information or biospecimens were originally collected for research purposes or non-research purposes? Should a request to waive informed consent trigger a requirement for IRB review?

The secondary use of data, whether the data are collected for research or non-research purposes, should assure that informational risks are minimized through establishment of mandatory data security and information protection standards. There should be no requirements for written consent for the secondary use of data that poses only informational risks. The JPC-SE feels very strongly about this issue.

Question 24: The Common Rule has been criticized for inappropriately being applied to—and inhibiting research in-- certain activities, including quality improvement, public health activities, and program evaluation studies.[50, 51, 52] Regarding quality improvement, for example, these activities are in many instances conducted by health care and other organizations under clear legal authority to change internal operating procedures to increase safety or otherwise improve performance, often without the consent of staff or clients, followed by monitoring or evaluation of the effects. It is far from clear that the Common Rule was intended to apply to such activities, nor that having it apply produces any meaningful benefits to the public. Indeed, its application to such activities, and requiring IRB review and compliance with informed consent requirements, might have a chilling effect on the ability to learn from, and conduct, important types of innovation. We seek comment on whether and, if so, how, the Common Rule should be changed to clarify whether or not oversight of quality improvement, program evaluation studies, or public health activities are covered. Are there specific types of these studies for which the existing rules (even after the changes proposed in this Notice) are inappropriate? If so, should this problem be addressed through modifications to the exemption (Excused) categories, or by changing the definition of "research" used in the Common Rule to exclude some of these studies, or a combination of both? And if the definition of research were to be changed, how should the activities to be excluded be defined (e.g., "quality improvement" or "program evaluation")? Are there some such activities that should not be excluded from being subject to the Common Rule because the protections provided by that rule are appropriate and no similar protections are

provided by other regulations? With regard to quality improvement activities, might it be useful to adopt the distinction made by the HIPAA Privacy Rule (45 CFR 164.501(1)), which distinguishes between "health care operations" and "research" activities, defining "health care operations" to include "conducting quality assessment and improvement activities, including outcomes evaluation and development of clinical guidelines, provided that the obtaining of generalizable knowledge is not the primary purpose of any studies resulting from such activities"?

Public health activities authorized by law, and certain routine health care operations such as quality assessment, quality improvement, and development of clinical guidelines using clinical and administrative data should not fall under the Common Rule, because these activities are not research involving human subjects. Research that uses only existing data collected for non-research reasons and that involves only informational risks also should not fall under the Common Rule and should not require written consent or a waiver of consent by an IRB even when the data are identifiable. This research involves only informational risks. Protection from informational risks can best be assured through strengthening requirements for data security and information protection. The current proposal is confusing with regard to the requirements under the new rules for research that uses only existing data collected for non-research reasons when the data are identified.

Even if all of the changes proposed in the ANPRM were adopted, we recommend changing the current definition of research and adding a new definition of practice. It is remarkable that the Belmont Report highlighted the importance of distinguishing between research and practice, yet the Common Rule contains only a definition of research and not also a definition of practice.

We propose the following <u>definition of practice</u>: "Practice refers to activities that experience and scientific evidence show have a reasonable expectation of success. Practice includes, but is not limited to, public health activities authorized by state and local laws, rules, and regulations to assess or improve health of individuals and populations that are conducted by or subject to the approval of federal, state, and local of public health authorities as defined by HIPAA, and health care operations as defined in 45 CFR 46.501 such as quality assessment, quality improvement, and development of clinical guidelines. <u>Practice is not research for the purposes of 45 CFR Part 46.</u>" (Please carefully note this exclusionary principle; once judged as practice, then the project is *de facto* now NOT "research.)

We propose the following <u>definition of research</u>: "Research means a systematic investigation, including testing and evaluation of new or unproven interventions designed to test a hypothesis, and permit conclusions to be drawn."

<u>Both practice and research can contribute to generalizable knowledge</u>.
<u>The JPC-SE feels very strongly about all of these issues.</u>

Question 28: For research that requires IRB approval, the Common Rule does not currently require that the researcher always be allowed some form of appeal of a decision (e.g., disapproval of a project). Some institutions have voluntarily chosen to provide appeal mechanisms in some instances, by, for example, allowing the researcher to present the project to a different IRB, or by having it reviewed by a special "appeal" IRB that is composed of members chosen from among the membership of the institution's other IRBs. Should the Common Rule include a requirement that every institution must provide an appropriate appeal mechanism? If so, what should be considered acceptable appeal mechanisms? Should such appeal mechanisms, or different ones, be available for appeals asserting that the investigation is not research, or that the research does not require IRB approval?

Under the existing system for human subjects protection, there is no oversight of IRBs and no process of appeal from an IRB decision. The Common Rule should be amended to establish a researcher's right of appeal. There is substantial experience with local IRB review of multi-site research where research that has been approved by numerous other IRBs was denied. Yet, in such instances, there is no mechanism for appeal or redress. The individuals who were denied the opportunity to participate in the study have no protection from the harm that their exclusion potentially caused. Inclusion of an appeal process would provide redress for researchers, including situations where multi-site research is being conducted and IRBs respond inconsistently.

Similarly, if some local IRB denies approval of a multi-site research project, the rationale for their denial when it is not institution specific (e.g., lack of questionnaires and forms in Spanish when a significant proportion of the local populations only knows Spanish well) must be circulated to the local IRBs governing all other study sites. This dissemination should be carried out expeditiously by the central study-wide IRB upon its receipt from the IRB issuing the denial. See also our response to Question 30.

Question 29: As noted above, IRBs sometimes engage in activities beyond those that are required by the regulations. For example, an IRB might review some studies for the purpose of determining whether or not they qualify for exemption (the new Excused category), or might review studies involving the analysis of data that is publicly available. Would it be helpful, in furtherance of increased transparency, to require that

each time an IRB takes such an action, it must specifically identify that activity as one that is not required by the regulations?

We believe that the regulations, and the OHRP acting to oversee the proper implementation of the regulations, should instruct IRBs NOT to engage in activities beyond those that are required by the regulations. Imposing burdens on researchers in the name of regulatory compliance without a contribution to the protection of human subjects undermines research and directly damages the public. These activities waste the resources that should be used to conduct research and damage society as a result.

Requiring that an IRB specifically identify that an activity is not required by the regulations each time an IRB takes such action might be helpful. At the least, it would educate the research community at the institution engaging in these activities to what the regulations require and what they don't require. Positive action to change local practice might occur when an IRB was found to be engaging in a broad range of activities beyond those that are required by the regulations.

An alternative would be to require that activities required at a local institution that are beyond those required by the regulations could not be labeled as IRB activities and would require a separate designation such as "local review requirement."

Question 30: What are the advantages and disadvantages of mandating, as opposed to simply encouraging, one IRB of record for domestic multi-site research studies?

There are only advantages of mandating one IRB (and one consent form) of record for domestic multi-site research studies. There are no disadvantages. The use of one IRB (and one consent form) should be mandated for domestic multi-site research studies. It should not be discretionary. Review of multi-site studies by multiple IRBs is inefficient and it creates the risk that some subjects receive information that is inaccurate and misleading and that some populations are not afforded the opportunity to participate in research that might benefit them directly. We respect that local IRBs may have important issues that affect small populations in ways not apparent to academic, multi-site IRBs. The requirement that one IRB should function as the IRB of record for multi-site domestic studies should require a mechanism for solicitation of local IRB input to the study approval and consent form.

Question 31: How does local IRB review of research add to the protection of human subjects in multi-site research studies? How would mandating one IRB of record impair consideration of valuable local knowledge that enhances protection of human subjects? Should the public be concerned that a centralized IRB may not have adequate knowledge of an institution's

specific perspective or the needs of their population, or that a centralized IRB may not share an institution's views or interpretations on certain ethical issues?

Local IRB review of research in multi-site research studies provides little to no contribution to human subjects protection, and there is substantial experience that the current system requiring local IRB review impedes research.

Also see our response to Question 28 above.

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

The second criterion for waiver of informed consent requires that the IRB determine that "the research could not practicably [emphasis added] be conducted without the waiver or alteration."

The word "practicable" is widely confused with "practical." More importantly, the word is variously defined. One dictionary defines practicable as something that is "capable of being done" and another as "capable of being done with means at hand and circumstances as they are." Using the first definition, given sufficient money, obtaining consent, or trying to obtain consent, would almost always be strictly practicable. Using the latter definition, an IRB might waive consent based on the unavailability of resources to obtain consent. In practice, different IRB come down differently in terms of the degree to which availability of resources is permitted to affect the waiver.

It is not clear that meeting this criterion should be required for a waiver of consent when the other three criteria are met.

We recommend that the regulations clarify the meaning of "practicable" or, preferably, drop impracticability as a criterion for a waiver of consent.

Questions 48 & 49: What, if any, are the circumstances in which it would be appropriate to waive the requirement to obtain consent for additional analysis of biospecimens? Is it desirable to implement the use of a standardized, general consent form to permit future research on biospecimens and data? Are there other options that should be considered, such as a public education campaign combined with a notification and opt-out process?

Regulations for using biological specimens should not be combined with regulations for using existing health data. The use of biological specimens from which human DNA can be extracted should require specific IRB approval for primary and secondary

use whether the biological specimens have been collected for research or have been collected for non-research reasons (e.g. "left over tissue"). Special precautions will need to be detailed and taken in handling and protecting these data from information risks given the inherent possibilities of identification. OHRP should periodically (perhaps every 5 years) revisit guidelines on this issue given the rapid progress in the field.

Appendix:

Examples of misinformation about what federal regulations permit with regard to IRB review of exempt research and the large variability in the burden that different IRBs place on researchers seeking to use de-identified data whether data from administrative records or biospecimens.

CURRENT GUIDANCE FROM OHRP: (DATE OF ISSUANCE OF GUIDANCE NOT KNOWN):
http://answers.hhs.gov/ohrp/categories/1564

Must there be review by someone other than the investigator before a research study is determined to be exempt?

No, the regulations do not require that someone other than the investigator be involved in making a determination that a research study is exempt. What they do require is that there be accurate determinations so that non-exempt research ends up being reviewed by an IRB. Because of the potential for conflict of interest in this situation, OHRP's long-standing recommendation is that investigators not be given the authority to make an independent determination that human subjects research is exempt.

> "OHRP recognizes that some institutions will wish to take advantage of the regulatory flexibility so that exemption determinations can be made in a manner that minimally delays research, while at the same time not diminishing human subject protections. While an institutional policy that allowed investigators to make their own exemption determinations, without additional protections, would likely risk inaccurate determinations, institutions may be able to craft policies that build in protections which lead to accurate determinations by appropriately dealing with investigator conflicts of interest and lack of detailed knowledge of the regulations.
>
> For example, an institution might craft a checklist for certain exemption categories, with questions that are easily answered "yes" or "no" by an investigator, with certain answers leading to a clear conclusion that the study is exempt. The institution might allow a researcher to immediately begin a study after having completed such a checklist and filed it, together with accompanying documents, with an appropriate institutional office, without waiting for or requiring any prior review of that filing. Similarly, a web-based form might be created that served the same purpose, allowing the researcher to begin the research immediately after submitting the required information using the web form. In both instances, the key issue would be whether these procedures lead to correct determinations that studies are exempt."

There are some routine matters where some local IRBs currently require their IRB to approve any and all changes, but where this should instead be relegated to the principal investigator. For example, if study personnel are added (who have completed all

institutional requirements including (but not limited to) certified, current completion of human subjects research protection and HIPAA training, or removed, this should be accomplished by "notification" (containing all appropriate documentation) from the Principal Investigator to the governing IRB, not IRB approval. Some institutions currently require approval for this administrative task, with documented delays of weeks and even months.[1] This will unburden IRBS from routine administrative tasks, expedite the research, and enhance subject protection by helping to ensure the fullest complement of study personnel working on the project. Note that the IRB would remain a repository of all relevant information pertaining to the project, and that the IRB would still need to perform due diligence in checking that the investigator(s) had correctly complied with administrative regulations.

[1] For example: the local IRB at one of our institutions takes an average of 3-4 weeks to approve this type of minimal administrative change, and furthermore forbids the new personnel from working on the project until formal IRB approval is received back from the IRB by the PI. Delay has routinely occurred despite IRB officials stating they would expedite handing, and even when the personnel involved have merely been students at the institution hoping to work for a limited period on the project. Neither promises by IRB administrators to improve overall processing nor bringing such matters directly to the IRB administrators for prompt attention have remedied the situation there. This type of delay should be rectified in the new regulations, as per our comment above.

REFERENCES AND REQUIRED FORMS FROM SEVERAL ENTITIES AND STATEMENTS COPIED FROM LINKS TO THESE IRB WEBSITES

(DATES OF ACCESS IN GENERAL WERE ON 8/30/2011)

University of Arizona: http://orcr.vpr.arizona.edu/irb/forms (see form F309)

Kaiser Permanente Southern California: http://xnet.kp.org/irb/appformrept.html

University of California Los Angeles: http://ohrpp.research.ucla.edu/pages/exempt-certifications

COPIED FROM UCLA:

> "***Certification of Exemption:*** Exempt categories of research are defined by the Department of Health and Human Services (DHHS) regulations for protection of human subjects in 45 CFR 46.101 (see Exemption Categories below). If an investigator believes his or her study qualifies for certification of exemption from Institutional Review Board (IRB) review, then the investigator must complete and submit an application via webIRB to the HRPP office for review and certification. **Federal guidance and University policy do not allow investigators to make this determination on their own." {EMPHASIS ADDED}**

University of Southern California: http://www.usc.edu/admin/oprs/hsirb/howto/#exemption

University of California San Francisco:
http://www.research.ucsf.edu/chr/Guide/chrExemptApp.asp

California Department of Health Services:
http://www.oshpd.ca.gov/Boards/CPHS/forms.html#15 (form 15)

COPIED FROM CALIFORNIA DEPARTMENT OF HEALTH SERVICES:

> "Researchers are not permitted to independently determine that their activities satisfy these criteria for exemption. OHRP has a useful set of decision charts (http://www.hhs.gov/ohrp/humansubjects/guidance/decisioncharts.htm) to assist researchers and staff from entities sponsoring the research or providing the data to evaluate whether a research project may be exempt from IRB review. Researchers must apply to the CPHS for exemption following instructions in Section V below."