Date: January 4th, 2016

Attn: Jerry Menikoff, MD JD, Office for Human Research Protections (OHRP),
Department of Health and Human Services, 1101 Wootton Parkway, Suite 200,
Rockville, MD 20852

From: American College of Epidemiology Board of Directors Ad Hoc Sub-Committee

Re: **Comments on HHS-OPHS-2015-0008 federal rulemaking from the American College of Epidemiology Board of Directors**

Dear Dr. Menikoff,

On behalf of the **American College of Epidemiology (ACE)** Board of Directors, we are writing to express broad support and some specific concerns about the proposed changes to current federal policy for the protection of human subjects. ACE is an organization of epidemiologists that serves the interests of the profession and its members through advocating for issues pertinent to epidemiology. We also sponsor scientific meetings, publications and educational activities, and recognize outstanding contributions to the field. Our members conduct research and train young scientists at universities, federal, state and local governments, hospitals, clinics, health departments, and independent research organizations in the United States, and we maintain strong links to related international organizations.

We strongly applaud the effort to revise the Common Rule to "*better protect human subjects involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators*" and support many aspects of proposed changes to the ruling. In particular, we support the general approach taken to the proposed changes pertaining to: (1) reduction of oversight commensurate with risk, and (2) clarity and parsimonious content of informed consent documents. We have minor comments and concerns regarding each of these that we describe below. We have more substantial concerns regarding the proposed changes to the use of informed consent for secondary research involving prospectively collected biospecimens, and we agree that routine re-assessment of any changes made will be needed to ensure that the stringency being applied to biological specimen use are appropriate and necessary. Please note that the views expressed here represent those of the Board of Directors only and not those of our membership at large.

Thank you in advance for your careful attention to our comments.

RESEARCH CONTEXT

Prior to providing our detailed responses, we have summarized our interpretation of the current research context which shapes our recommendations:

The impetus for the policy update is the recognition that some research deemed to be low risk is being delayed while under review, and, with the rapid development of big data, IRB review time can delay important research. One of the main changes is the policy proposes a 'broad consent' strategy for the use of de-identified biospecimens. The proposed revision suggests this will foster greater transparency and enable potential participants to make a more informed decision about whether to participate in the research. Three additional elements of consent are proposed, including informing prospective participants about details surrounding commercial profit; the requirement that individual research results may be disclosed to them and under what circumstances; and their options, including to refuse to consent.

ACE supports the concept and use of broad consent. Especially in epidemiology and public health, there is increasing need to be able to conduct research on de-identified specimens and health data. Broad consent at the outset will facilitate this at low risk to those who consent. Although there is no doubt that research participants must be protected against both harms and wrongs, it is our view that most people support the health research enterprise and value its results. They understand that contributing to those results – especially when risks are small – is both a signal of trust in the nation's research mission and a commitment to enlightened self-interest. We should not make it difficult for citizens and research institutions to contribute to population health. However, we acknowledge decreasing participation rates in epidemiologic studies and that some citizens may be inclined to not support a broad consent strategy without knowing specific use of their personal data. Additionally, grant and manuscript reviewers are quick to critique low participation rates. Given challenges in identifying and recruiting potential research participants, it is harder to conduct population-based epidemiologic research in the present era.

Generally, we endorse policies that foster ethically-optimized return of study results, management of incidental findings, ongoing reassessment of risks, and community participation in the research mission. Institutions conducting research should foster governance systems to oversee details and challenges arising in particular studies. In the same way IRBs are tasked with making judgments about acceptable risk, there should be mechanisms and entities to provide guidance and oversight about particular uses of de-identified data and biological material. Research on de-identified samples is necessary and a well-established paradigm that needs to continue, as it often would be impossible to consent these individuals. However, does the burden of consent lie with registry staff or with end-user investigators? Perhaps registries feel it their duty to protect patients and consent them to share names with researchers. However, in some circumstances registries are less informed about the research and investigators are more informed/willing to explain the research project significance to potential participants. Our bias is that the scientist is the better person to invite patients to participate.

Regarding surveillance, the ability of governments and academic institutions to use existing data sets and biorepositories should be maintained and access broadened when data and results are put to appropriate use. Likewise, surveillance efforts such as SEER cancer registries provide legally mandated public health functions exempt from consent and are utilized for a variety of etiologic or survivorship studies. In the end, many if not all of these special studies appropriately consent subjects, especially when there is additional data collected through interviews or biologic samples.

DETAILED RESPONSE

Our detailed comments on section "II. Major Proposal to Modernize the Common Rule" are as follows:

A. Proposed Changes to the Scope and Applicability of the Regulations

(1) **Expanding the Definition of Human Subject to Cover Research with Non-identified Biospecimens -** ACE generally supports the primary proposal over alternate rulings A and B given that biotechnologies change rapidly and limitation of the ruling to certain biotechnologies (either whole genome sequencing specifically or the category of 'technology applied to a biospecimen that generates information unique to an individual') may cause confusion in implementation when interpreting intent and cannot anticipate changing technologies or uses in the future. ACE agrees about the importance that consent is required for biospecimen collection regardless of identifiability in order to reduce public erosion of trust about research and in recognition of how rapidly the ability to identify individuals can occur given the dynamic state of technology at the genomic and other -omic arenas combined with the growing computer capacity to link identifiable information.

(2) Explicit Exclusion of Activities From the Common Rule

a. Exclusion of Activities that are Deemed Not Research (NPRM at § __.101(b)(1))

i. Program Improvement Activities - We support this proposed explicit exclusion due to the broader public benefits that can be obtained from such activities, but we find the text of the proposal ambiguous with respect to the subsequent (unanticipated) use or sharing of findings obtained from such activities for generalizable knowledge. Specifically, is the subsequent use of such information excluded from the Common Rule under the later proposed change numbered *NPRM at § __.101(b)(1)(ii)*? Also, please clarify the meaning of the below underlined text from the proposal: "The first exclusion, proposed in the *NPRM at § __.101(b)(1)(i)*, is for data collection and analysis, including the use of biospecimens, for an institution's own internal operational monitoring and program improvement purposes, *if the data collection and analysis is limited to the use of data or biospecimens originally collected for any purpose other than the currently proposed activity, or is obtained through oral or written communications with individuals (e.g., surveys or interviews)."* We do not feel additional restrictions are required for biospecimen collection under this exclusion, as adequate protections are obtained from the proposed change regarding the use of secondary research with biospecimens.

ii. Oral History, Journalism, Biography, and Historical Scholarship Activities – We support this proposed exclusion.

iii. Criminal Justice Activities - We support this proposed exclusion.

iv. Quality Assurance and Quality Improvement Activities – We support this proposed exclusion.

v. Public Health Surveillance - We support this proposed exclusion. In response to the question posed for public comment, it would help to cross-reference the

fact that routine behavioral surveys to collect surveillance information on prevalence of behavioral risk factors (e.g. cigarette smoking, cancer screening, flu vaccination) or self-reported diagnoses of health conditions (e.g. diabetes, hypertension) is also excluded under the proposed change regarding excluding low-risk activities such as survey procedures (*NPRM at § __.104(e)(1)*).

vi. Intelligence Surveillance Activities - We support this proposed exclusion.

b. Exclusion of Activities That Are Low-Risk and Already Subject to Independent Controls (NPRM at § __.101(b)(2))

i. Educational Tests, Survey Procedures, Interview Procedures, or Observation of Public Behaviors – We support this proposed exclusion and believe that any alternate approach of sustaining expedited review would only provide minimal additional participant protection. We support this exclusion with the provision that investigators should follow regulatory requirements and standard of practice to give notice to prospective subjects or their legally authorized representatives in the form of an informed consent process that outlines the research purpose, privacy safeguards, contact information, and ability to opt-out. We advocate that investigators make and document self-determinations for the types of research activities covered in this particular exclusion category. Institutions may opt to use web-enabled tools to determine excluded studies, similar to the method proposed under the "Proposed Exemptions" section, which would require the investigator to complete a screening tool, sign and submit to their institution. For exclusion categories, however, this would not require institutional review or audit, but mainly serve as formal notification of the activity and its determination, as well as official documentation of research attestation of activity components. Surveys that explicitly inquire about topics that may impart psychological risk (e.g. suicide ideation or attempts, domestic violence experience, child abuse) should be considered for human subjects review (undergo exempt and possibly full review) to ensure that appropriate safeguard protocols are in place to aid participants if needed.

ii. Research Involving the Collection or Study of Information that has been or will be Collected - We support this proposed exclusion and believe that an alternate approach of sustaining expedited review would only provide minimal additional participant protection. As with other proposed exclusion categories, we advocate that investigators make self-determinations for the types of research activities covered in this particular exclusion category.

iii. Research Conducted by a Government Agency using Government-Generated or Government-Collected Data - We support this proposed exclusion and believe it applies equally to federal, state and local government entities where there are comparable privacy safeguards established by state laws and regulations. We believe that an alternate approach of sustaining expedited review would only provide minimal additional participant protection. As with other proposed exclusion categories, we advocate that investigators make self-determinations for the types of research activities covered in this particular exclusion category.

iv. Certain Activities Covered by HIPAA - We support this proposed exclusion and believe that HIPAA Rules for identifiable health information used for health care operations, public health activities, and research activities are sufficient to protect human subjects involved in such activities. We do not believe that the current process of seeking IRB approval meaningfully adds to the protection of human subjects involved in such research studies.

c. Applicability of Exclusions to the Subparts - We believe that research involving prisoners should be allowed to use any or all of the exclusions found at *§ __.101(b)(2) and (3),* as currently proposed, as prisoners have the same abilities to make informed decisions as other research participants.

(3) **Proposed Exemptions** (NPRM at § __.104)

a. Making Exempt Research Determinations - NPRM at § __.104(c). We support this proposed change to expedite the process for making exemption determinations by developing a determination tool to either be directly used by institutions and investigators or to serve as a template. We agree that this proposal (alongside clarification of exempt categories and recommendations that IRB office not make additional change recommendations for exempt status projects) should reduce unnecessary delays in initiating research. We do not believe that an auditing requirement is necessary but it can be recommended as one option for institutions adopting the web-based tool determination approach or could be employed on a random basis for periodic assessment that the determination tool is being used ethically and appropriately. Given the current large IRB review burden placed on institutions and widespread criticisms of the IRB review process at the moment, we do believe it would be likely that some institutions would allow an investigator to independently make an exempt determination for his or her own research, but institutions that do so may take on additional human subjects training responsibilities. Institutions may vary with respect to level of additional review by an individual who is not involved in the research and immersed in human research protection, Maintaining some level of institutional review (through auditing or routine review) would potentially increase public trust in the research enterprise and thus could be recommended. While it is possible that an investigator would be able to contrive his or her responses to the automated exemption decision tool in order to receive a desired result, training and audit/reduce this likelihood, especially if institutional penalties for knowingly falsifying information were heavy. Additional material to be provided by the investigator could include any informed consent forms and promotional material.

b. Exemptions Subject to the Documentation Requirements of § __.104(c) and No Other Section of the Proposed Rule –

i. *Research Conducted in Established or Commonly Accepted Educational Settings (NPRM at § __.104(d)(1); Current Rule at § __.101(b)(1))* We support this proposed exemption revision but ask that a general process for determining burden to students be explicitly described. When individual-level student information is obtained and used, notification of the research should be provided to families that includes information on the research purpose, privacy safeguards, data collection timeframe and contact information. Privacy

safeguards should be applied when information on individual-level student grades or health status is collected.

ii. *Research and Demonstration Projects Conducted or Supported by a Federal Department or Agency (NPRM at § __.104(d)(2); Current Rule at § __.101(b)(5*)) We support this proposed exemption and its interpreted scope. We also support the publication of such projects by departments performing the research. We do not agree that it should apply only to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement, as we doubt the feasibility and effectiveness of notification processes in all circumstances. The re-interpretation of scope and broader proposed changes to the exemption category reduce the duplicative aspect of this ruling with other federal requirements. We do not believe privacy safeguards of § __.105 should be applied, as other safeguards suffice.

iii. *Research involving benign interventions in conjunction with the collection of data from an adult subject (NPRM at § __.104(d)(3*) – We support the proposed new exemption category, with the caveat that it apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement, including the research purpose (if authorized deception is not utilized), privacy safeguards, and contact information.

iv. *Taste and Food Quality Evaluation and Consumer Acceptance Studies (NPRM at § __.104(d)(4); current Rule at § __.101(b)(6)*) – We support sustaining this exemption and do not believe it needs to be limited to research in which notice is given to prospective subjects or their legally authorized representatives.

c. <u>Exemptions Subject to the Documentation Requirements of § __.104(c) and the Privacy Safeguards Described in § __.105.</u> We support the proposed privacy and security standards being promulgated for these proposed exemption categories and find them to align with widespread standards already in operation. Institutions would benefit from having institutional-level privacy standards that IRBs support, as opposed to expecting IRBs to have the expertise in house to monitor compliance with these. Having institution-wide standards would reduce the likelihood that these security requirements unrealistically expand IRB responsibilities beyond current competencies.

i. Research Involving Educational Tests, Surveys, Interviews, or Observation of Public Behavior if the Information is Recorded with Identifiers and even if the Information is Sensitive (NPRM at § __.104(e)(1)) – We support this proposed exemption for adults and children. However, due to the sensitive nature of private information being collected, we agree that this exemption should only apply to research activities in which notice is given to prospective subjects or their legally authorized representatives as a regulatory requirement, including research purpose, privacy safeguards, and contact information and that prospective subjects be given the explicit opportunity to opt out of such research.

ii. Secondary Research Use of Identifiable Private Information (NPRM at § __.104(e)(2)) – We support this proposed new exemption category in its primary proposal format, not the alternate narrower or broader versions. For example, given new proposed processes for managing exempted research, it is not overly burdensome for researchers to reapply for new uses of secondary data as they emerge (as opposed to allowing researchers to proceed with unintended use that may exacerbate security or privacy risks without additional documentation and oversight). We agree that this additional exemption category is necessary because it clarifies uses of non-research data for secondary research purposes, despite some overlap with other proposed revisions, but we would advocate that few limitations on the scope of research covered under this section be placed to allow protections and processes under other sections to take precedence and reduce confusion. For example, we do not think this exemption should be limited to research in which individuals had been informed of the potential future research use of their information, given the fact that this pertains to secondary use of a wide range of possible data sources. We think the protection standards outlined in § __.105 are adequate for research using clinical registries.

1. Exemptions Subject to the Documentation Requirements of § __.104(c), the Privacy Safeguards Described in § __.105, Limited IRB Review as Described in § __.111(a)(9), and Broad Consent in Accordance With § __.116(c)

   We agree with the exemption for limited IRB review of such documentation. However depending on the scope of the original IRB review the need for another review might be subject to interpretations of the IRB about this scope of research and add to the burden of the IRB. Therefore consideration at the initial IRB review of the scope of the research and any secondary research that could be included in this IRB review should strongly be considered.

2. Exemption for Secondary Research Use of Biospecimens or Identifiable Private Information where Broad Consent has been Sought and Obtained (NPRM at § __.104(f)(2))

   We agree with this exemption by broad consent for use in secondary analysis as many biospecimens are discarded after their initial/primary use in clinical settings and patients may not be aware they are discarded and be interested in improving knowledge with their use. We also recognize that ideally patients might be made aware of their future contribution to science as a means of improving trust in research and the beneficence of their act. Should any information arise that might benefit the patient then there should be a caveat to provide the information to the individual(s) in either patient dissemination or publication form.

d. Applicability of Exemptions to the Subparts (NPRM at § __.104(b); Current Rule at Footnote 1) – We support the proposed clarification regarding the applicability of

exemption criteria to include research involving prisoners when the research consists mostly of non-prisoners and only incidentally includes some number of prisoners. We believe exemptions should not apply for research intending to explicitly involve prisoners as research subjects to ensure appropriate external review of appropriateness of study procedures.

(4) Proposed Changes To Obtaining, Waiving, and Documenting Informed Consent (§§ __.116 and __.117)

a. Required Elements of Informed Consent (NPRM at § __.116(a), (b)). We applaud the proposed elements in this section for informed consent, including the 3 new elements.

b. Broad Consent to the Storage, Maintenance and Secondary Research Use of Biospecimens and Identifiable Private Information (NPRM at § __.116(c), (d)). We agree with this proposal. We recognize that such broad consent does not identify the optimal conditions for storage and maintenance and therefore a statement that biospecimen and identifiable private information will be stored and maintained in state of the art facilities with back-up should be emphasized when consent is obtained. This additional statement would reinforce the notion that the material and information are of utmost importance to the patient.

c. Waiver of Informed Consent or Documentation of Informed Consent (NPRM at §§ __.116(e), (f) and __.117)

d. **Newborn Screening Saves Lives (New) Law: Newborn blood spots now require consent whereas IRBs could waive this before.** We understand the new law and support its intent, however given this law, issues that may arise include: whether additional blood spots beyond those required for routine assessment are collected, how many additional blood spots are needed; and when the additional blood spots are collected i.e. during the 'usual' collection of blood spots or after. A parent might consent for an additional blood spot during routine collection but not do so for collection later and the number of additional blood spots requires consideration of multiple factors including the use of the blood spot e.g. genetic or other analysis; the health of the newborn; maternal health; and timing of the consent relative to labor and delivery. Thus consenting for additional blood spots would optimally co-occur when maternal and paternal consent for routine ones with clear description of the number of additional blood spots, the reasons for them, and the limitations on the number of attempts to obtain additional blood spots including newborn stress. If consent occurs following routine collection, this may hinder approvals. Assurance that the information will be non-identifiable to the index child may be paramount here as parents may wish to provide biospecimen to benefit research knowledge but not wish to identify the child. Further consideration whether the results of the analysis provide information about risk of the newborn for disease across the life course must also be weighed in the resolution of this issue. Thus if this law remains, the proposed changes may not achieve the goals of decreasing administrative burden, delay for investigators, and institutions. An alternative option would be to require an additional blood spot for all newborns for safe keeping until X age at which time the blood spot could be used for research. On the other hand if the parents wished to have access to the blood spot before such age, then

the parents might benefit from preclinical information to help in any diagnosis or treatment should the index child become ill.

e. Posting of Consent Forms – We support this new proposed requirement to post consent forms for clinical trials

(5) Proposed Changes To Protect Information and Biospecimens (NPRM at § __.105)
ACE agrees with the proposal to limit exemption to the IRB approval for the initial analysis and the alternative that individuals will be given the opportunity to opt out of any secondary research with their identifiable private information and thereby permit subjects to exercise their autonomy to choose and to allow their information to be used or not. ACE also agrees that the balance would be struck even more in favor of respect for persons by limiting the exemption to research where more than prior notice was required.

(6) Harmonization of Agency Guidance (NPRM at § __.101(j)). No comment –we support the general intention of this proposed required agency consultation

(7) Cooperative Research (NPRM and Current Rule at § __.114) and Proposal To Cover Unaffiliated IRBs Not Operated by an Institution Holding a Federalwide Assurance (NPRM at § __.101(a)) We support the proposed rulings under this proposed change. We advocate that IRB-approved protocols and related documentation be submitted to local IRBs of institutions conducting research that was approved by another institution. If a local IRB had cause for concern regarding the ethics of a study protocol or its privacy/security standards, there should be established procedures for a local IRB office to appeal or investigate the decision. There should also be mechanisms clarified to address locally submitted complaints from participants or community members. We do believe that 3 years is adequate timing in which to implement this proposed change.

(8) Changes To Promote Effectiveness and Efficiency in IRB Operations

a. Continuing Review of Research (NPRM at § __.109(f); Current Rule at § __.109(e)) - No comment –we support the general intention of this proposed elimination of continuing review of research that involves minimal risk

b. Expedited Review Procedures and the Definition of "Minimal Risk" (NPRM at §§ __.110 and __.102(j)) We support the proposal to allow projects engaging in activities on the Secretary's list to be presumed to be minimal risk unless an IRB reviewer determines and documents otherwise, with routine updating of the Secretary's list. We anticipate that updating the list every 8 years would be sufficient. Use of this list does not represent a loss of IRB flexibility in risk determination, as IRB reviewers can still make an alternate ruling upon review.

(9) Proposed Changes to IRB Operational Requirements

a. Proposed Criteria for IRB Approval of Research (NPRM at § __.111) – We support the proposed criteria listed in this section, including adding physically disabled persons to the list of individuals vulnerable to coercion.

b. Proposed Revisions to IRB Operations, Functions, and Membership Requirements – No comment – we support these proposed operational requirements

(10) Other Proposed Changes

a. Proposal To Extend the Common Rule to All Clinical Trials (With Exceptions) (NPRM at § __.101(a)(1)). We support the proposal to extend Common Rule to all clinical trials

irrespective of funding source, and we do not have major concerns about unanticipated consequences. Increased oversight of commercially-led clinical trials, together with published consent forms, adds an important level of transparency that has been lacking to date. Clarifying the extent to which this covers trials to affect physical and mental health-related outcomes and social practices in non-clinical (e.g. community) settings will be important.

b. Changes to the Assurance Process (NPRM at §§ __.103 and __.108; Current Rule at § __.103). We support these proposed changes. Periodic auditing of local IRB membership and written procedures for compliance responsibilities would potentially increase public trust in the research enterprise.
c. Department or Agency Discretion about Applicability of the Policy (NPRM at § __.101(c), (d), (i)) and Discretion Regarding Additional Requirements Imposed by the Conducting or Supporting Department or Agency (NPRM and current Rule at § __.124) - No comment. We support this provision.
d. Research Covered by This Policy Conducted in Foreign Countries (NPRM at § __.101(h)) – No comment. We support this provision.

(11) **Effective and Compliance Dates of New Rule (NPRM at § __.101(k))** – No comment.