December 22, 2015

Jerry Menikoff, M.D., J.D.
Office for Human Research Protections (OHRP)
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Docket No. HHS-OPHS-2015-0008 – "Federal Policy for the Protection of Human Subjects"

Dear Dr. Menikoff:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics, and medical devices – from discovery, pre-clinical, proof of concept, and first-in-man studies through post-approval and pharmacovigilance research. With more than 110,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, efficiency, and safety of biomedical research.

Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 research sponsors annually and we have a broad and unique understanding of the roles, responsibilities, and behavior of all the stakeholders – research sponsors, investigators, Institutional Review Boards, clinical trial participants, and ancillary providers of all types – that are part of the enterprise process.

I. Introduction

In general, CROs are not Common Rule organizations; rather, most clinical trials that CROs are involved in are sponsored by pharmaceutical, biotechnology, and medical device companies and are subject to regulation and oversight by the FDA, not OHRP. However, CROs work closely with investigators and IRBs in Common Rule institutions, and in some cases, are involved in the conduct of federally-supported or –conducted research under a federal-wide assurance (FWA). In addition to clinical trials, ACRO member companies perform a great deal of late-phase work, including safety surveillance and epidemiology studies, patient registry and health outcomes analyses, comparative effectiveness research (CER), and other information-based research, frequently using limited data sets and de-identified data as defined by HIPAA.

The proposed regulatory changes in the Notice of Proposed Rulemaking (NPRM) reflect an interest in ameliorating inefficiencies in the current system of human subject protections, as well as an attempt to peer into an uncertain future where new risks to human subject privacy and data security will emerge. While predictions regarding technological developments are difficult at best, ACRO commends OHRP's attempt to proactively address emerging issues, including the secondary use of biospecimens.

The three Belmont Report ethical principles (respect for persons, beneficence, and justice) that undergird the changes proposed in the NPRM should not produce differing approaches to human subject protections based on the funding source of the research, and ACRO has long advocated for harmonization of human subject policies between OHRP and the FDA as a way of ensuring consistent research participant experiences and, we believe, greater trust in the research enterprise.

The NPRM aims to increase transparency of the research process, permitting patients to better understand the full range of available care options, including clinical trials. ACRO believes that the attempts of OHRP in the NPRM to increase an informed engagement in the research process, particularly as such engagement is fostered by genuinely informed consent, are potentially useful to an increasingly medically-aware public.

Among the eight large proposed changes to the Common Rule, there are a number of steps taken toward improving the landscape of clinical trials. ACRO thanks the many agencies for their involvement and pointed questions. Below is an attempt to contextualize the proposed changes for CROs and research generically, as well as an expression of our support for and concerns about specific modifications. This response is targeted to changes we view as high-impact, and organized by significance.

II. Expanding the Definition of Human Subjects to cover Research with Non-identified Biospecimens

This section, proposing an expanded definition of Human Subjects with biospecimens such that an informed consent would need to be gathered for secondary research, reflects a commendable desire to preemptively provide security provisions for research participants. However, we are concerned that the proposed change to the definition of "human subject" has been made without proper threat analysis and without considering the larger implications of such a substantive shift. The NPRM suggests that a failure to adopt this new definition could "diminish public support… and ultimately jeopardize our ability to be able to conduct the appropriate amount of future research with biospecimens." The NPRM asserts that the proposed definition is consistent with the majority of the public's wishes, and that investigators will be able to "readily ascertain" an individual's identity from a biospecimen in the, potentially near, future. ACRO is concerned about this proposal for a variety of reasons, ranging from the destabilization of the concept of de-identified data, to business operations issues, and ethical concerns that could stem from a broader view of "human subject."

The current definition of a human subject in the Common Rule is straightforward: A human subject is a living individual about whom an investigator conducting research obtains data (through intervention or interaction with the individual) or identifiable private information (data that allows the investigator to readily ascertain the identity of the subject). The contention in the NPRM is that, at some unknown but near-term time, individuals will be able to be readily identified based solely on data from a biospecimen, and thus there is no such thing as "de-identified data" as it relates to genetic information. However, even in some fantasied CSI world of the near future, re-identification of individuals will rely on external mechanisms ranging from sophisticated technologies to comprehensive biospecimen registries – which OHRP seems to believe will be accessed without any regulation or law that would prohibit or protect against such access. While such an unregulated Wild West access to biospecimens may be conceivable, it is a dangerous precedent to dramatically alter regulatory definitions to protect against a future threat, especially one that can be addressed without altering the very definition of "human subject."

A more reasonable position, we believe, is that research with biospecimens – which today are not readily identifiable – should be appropriately regulated. For an example of an appropriate regulatory approach, ACRO would commend to OHRP the treatment of a "limited data set" under HIPAA; even if not readily identifiable by a user, such a data set is considered "protected health information" (PHI) that can only be used or disclosed accompanied by a "data use agreement," which specifically prohibits re-identification and imposes a variety of other restrictions. With these contractual and administrative controls in place, even though it is considered a form of PHI, research use of a limited data set does not require individual consent nor review by an IRB.

There are also business operations issues and costs associated with the proposal to define biospecimens as human subjects. A major operations issue, and the one most necessary to ensure compliance with such a change, is the appropriate cataloging of samples. Inherent in this new process are costs that will vary greatly based on the size of the stock of biospecimens held. Using the proposed "broad consent" will make this process more complex, not more flexible. Each biospecimen would have to be "tagged" with either a signed consent or refusal to consent and, thus, a longitudinal system that could adapt to continuous revisions to previous consents or refusals for each biospecimen would be required. For all organizations that store biospecimens, this new tagging and cataloging system will become as important as informed consent processes (not to mention as important as developing experimental designs that utilize non-identified biospecimens). This seems, to us, to be a new regulatory burden that uses scarce resources without providing any actual benefit to either researchers or citizens.

Finally, it is important to consider the ethical shift signaled by the new definition of a human subject to include biospecimens. If a biospecimen is by definition a source of identifiable private information, regardless of whether it has been re-identified, then the specimen itself is a human subject – which is an extraordinarily broad view of what constitutes a human being. This view could easily be co-opted by groups looking for regulatory definitions of human life. In essence, an effort intending to guarantee additional dignity and autonomy to subjects could be used by groups for political and other purposes entirely unrelated to the research enterprise which seeks to improve our society.

Notwithstanding our objections noted above, if a fundamental change to the definition of "human subject" were undertaken, ACRO would support Alternative Proposal A offered in the NPRM. This proposal suggests that the risk of re-identification of Whole Genome Sequencing (WSG) is clear, and thus would require informed consent when WSG, the type of test needed for re-identification, takes place. In research where re-identification is not readily ascertained, such as partial genomic sequencing, the definition of "human subject" would not be reached, and practices informed by the Common Rule would not be necessary. Alternative Proposal A embodies the logic of the NPRM – low-risk research should be encouraged and the regulations simplified – without posing significant alteration to the very definition of "human subject."

III. Exemption for Secondary Research Use of Biospecimens or Identifiable Private Information where Broad Consent has been Sought and Obtained AND Broad Consent to the Storage, Maintenance and Secondary Research Use of Biospecimens and Identifiable Private Information

This section of the NPRM is intricately linked to the comments above, as broad consents would render secondary research with biospecimens, or other identifiable private information, exempt from Common

Rule requirements. A broad consent template will be developed by the Secretary of HHS, and it is anticipated to comply with the goals of the new informed consent processes: to not be excessive in length, and to be clear in regards to what a subject is consenting to. One of the proposed benefits of these broad consents is "an increase in trust and partnership" that is "likely to increase participation rates in research." This exemption at §__.104(f)(2) intends to respect patient privacy safeguards and the limited IRB review proposed at §__111(a)(9).

Responding to Question for Public Comment number 54, this is not the best method for this exemption. The need for this exemption is discussed above, and relies on a presumption that biospecimens constitute human subjects. While, in theory, the proposal makes individuals more informed as to the use of his or her biospecimen sample, a broad consent only makes clear to the individual that some unspecified research may occur. ACRO fears that this opt-in process, particularly an opt-in process that does not provide specific details regarding future research, will lead to significantly lower rates of participation. Moreover, those providing a broad consent do not gain any insight or protection from agreeing to the consent. In an effort to advocate a goal of increased patient autonomy, this change muddles the picture of research on de-identified biospecimens.

To return to Question for Public Comment number 54, there is a better method to balance respecting individuals and facilitating research: at the point of specimen collection, educate individuals on de-identification of biospecimens, including the current risks to re-identification, and permit individuals to opt out of having their biospecimen stored for future research. This proposal increases patient autonomy by increasing patient awareness of known concerns rather than distracting the patient with a "consent" that does not address any of the privacy concerns.

A broad consent can provide information to patients to help them feel an increased sense of autonomy, and the proposed general elements of a broad consent seem to provide crucial elements that will foster improved patient understanding of the research process. Question number 62 addresses the utility of the elements at §__.116(c). These elements promote the NPRM goal of increasing subject autonomy by clarifying rules for engagement as well as communication expectations. ACRO particularly supports the elements of broad consent that clarify patient's rights at §__116(c)(iv). By stating that "participation is voluntary, refusal to participate will involve no penalty or loss of benefits, … [and that] the subject may withdraw consent … at any time" participants can better trust their role as partners in the research process. Also, the addition that subjects may not be informed of specific research studies that could be conducted or the purpose of the research, at §__116(c)(v), is beneficial to patients as it ensures that they understand the nature of secondary research. There is concern that subjects will be less likely to provide such a broad consent, but it will foster the goals of this proposed rule.

In reference to our previous point, §__116(c)(vi) again raises the concern of re-identification of biospecimens. This broad consent form, if utilized, would be an appropriate place to inform patients of the current feasibility of that risk, serving as an educational opportunity at the point of collection. Despite our concerns about inconsistencies in consent requirements and the potential for decreased participation in regard to the use of biospecimens, ACRO strongly supports the availability of a broad consent process for identifiable private information. Simply, we believe that many individuals will consent to the use of private information, and that they will "donate" their data for research, even if they would be less likely to donate their biospecimen for unspecified future research.

IV. Proposed Changes to Obtaining, Waiving, and Documenting Informed Consent

ACRO values the effort to increase patient autonomy and understanding during the consent process by addressing the organization of information relevant to patients and for trying to present a clear, understandable text to research participants. The goal of reorienting the required information such that clear descriptions of the study and an analysis of the risks are placed at the beginning of the document will aid individuals as they consider participating in any research. Theoretically, the desire to eliminate lists of facts in favor of information organized with the intention of allowing an individual to make an informed decision could decrease the length of the body of the consent. It is likely, though, that much of the information currently in consents will simply be moved to the appendix. While this migration of information may not truly facilitate short, "user friendly" consent forms, ACRO believes that the organization of information and separation of required and non-required elements may be useful to research participants.

With regard to new elements to be included in the informed consent forms, ACRO appreciates the updates made to increase transparency for patients. The change at §__.116(a)(9) ensures that participants are aware that non-identified data could be shared or used for future research; while not a fundamental shift, this change clarifies for patients how their data can be used. Similarly, the proposed new elements at §__.116 (b)(8) and §__. 116.(b)(9) further patient understanding of the trial by clarifying the disclosure of results and the possibility for investigators to re-contact participants. We believe that these elements may help to increase patient autonomy in relation to the consent process, reduce the potential for harm by clarifying information around consent, and increase beneficence by reducing ambiguity over these areas. In contrast to these clarifying elements, the proposed inclusion of information relating to the potential commercial profit stemming from biospecimens will at best cause confusion and consternation for individuals, and ACRO believes that this proposal should be dropped.

V. Explicit Exclusion of Activities from the Common Rule

The creation of excluded activities is of particular value to the research process and the institutions engaged in research and review, and ACRO appreciates the attempts of OHRP to reduce confusion regarding the need to follow Common Rule requirements in certain instances. Of note in the first six exclusions which are deemed not to be research are the first and fourth exclusions for program improvement activities and quality improvement. These exclusions for data collection and analysis, including biospecimens, for "an institution's own internal operational monitoring and program improvement processes" is in line with HIPAA, thus harmonizing regulation, and is an integral part of business development. This is also the case for exclusion number seven whereby certain activities covered by HIPAA are excluded. In reference to Question for Public Comment number 7, ACRO believes that it is crucial to include biospecimens as part of this exclusion. Failing to include biospecimens would add hurdles to organizations looking to make business improvements and expand technologies while offering no safety advantages to patients.

ACRO strongly supports the transition of low-risk research from being exempt from the Common Rule to being excluded. Removing the need for administrative or IRB review for low-risk studies – those that "do not entail physical risk, and where both the probability and magnitude of other risks … are hypothesized to be low" – will encourage research that provides valuable insights. The view that "consent is inherent to participation" in these types of studies is straightforward and reasonable. Question for Public Comment number 9 asks if covering any of these activities under the Common Rule would substantially

add to the protections provided to human research subjects, and the view of ACRO is that participants would not be safer if this research was covered. Relieving IRBs from reviewing these low-risk studies allows for additional time to be spent on complicated studies. This is a better use of IRB time and truly does have the possibility of improving patient care. Simply, reducing the burdens on overstretched review boards allows members to focus on the most relevant and important cases. As such, these activities should remain as intended by the NPRM, as exclusions rather than simply as exemptions. Question for Public Comment number 12 suggests that being exempt from the Common Rule only has benefits to the researchers. But, the larger impact of having exclusions is that the entire process of research and review can be relieved of responsibilities that produce limited benefit.

VI. Cooperative Research and Proposal to Cover Unaffiliated IRBs Not Operated by an Institution Holding a Federal-wide Assurance

Connected to the point above, ACRO strongly supports the goal of the NPRM to use IRBs more efficiently and effectively. The mandate that "all institutions located in the United States engaged in cooperative research [will] rely on a single IRB as their reviewing IRB" for a given study is a very positive step towards simplifying processes and reducing redundancies. Additionally, as noted, it would allow for external IRBs to truly act as responsible parties, actively engaged in the safety of subjects as it relates to the procedures and interventions involved in the research. Question for Public Comment number 74 asks about the feasibility of a single IRB, as well as any costs/benefits at this time, and the potential for savings in the future. We do believe that a single IRB process is possible at this time. This could dramatically reduce the amount of reviews needed for a given site, which benefits researchers and patients alike. Researchers will receive feedback on their studies in an increasingly prompt fashion, and patient safety is improved as issues may be addressed in a timelier fashion. For these reasons, ACRO supports the proposal.

VII. Changes to Promote Effectiveness and Efficiency in IRB Operations

In addition to mandating single IRBs for cooperative research, the proposals to eliminate continuing review for minimal risk studies is a crucial step towards decreasing the burden on IRBs in low-risk studies. Similarly, removing the continuing review requirement for studies that are doing data analysis or accessing follow-up data gathered from routine care will further aid the IRBs. ACRO supports these proposals in the NPRM. With appropriate checks, such as first having studies qualify for expedited review and having annual follow-ups by researchers with IRBs, OHRP is ensuring that patient safety is a priority while simultaneously making the review process commensurate with the risks involved.

VIII. Conclusion

ACRO thanks OHRP for the opportunity to comment on proposed changes to the Common Rule. We appreciate the attempt to address new technologies and evolving security concerns, but we are concerned that one proposed change – altering the very definition of "human subject" – would significantly impede biomedical research. We urge the office not to adopt this new definition, and to engage in much more extensive consultation with all stakeholders, including patients, before issuing any further proposals regarding the Common Rule.

1990 K Street, NW, Suite 401, Washington, DC 20006
T 202 464 9340 E info@acrohealth.org www.acrohealth.org

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS

Please do not hesitate to contact ACRO if we can provide further information.

Respectfully submitted,

Douglas Peddicord, Ph.D.
Executive Director

1990 K Street, NW, Suite 401, Washington, DC 20006
T 202 464 9340 E info@acrohealth.org www.acrohealth.org

ACRO
ASSOCIATION OF CLINICAL RESEARCH ORGANIZATIONS