January 5, 2016

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

RE: NPRM "Federal Policy for the Protection of Human Subjects"

Dear Dr. Menikoff,

The International Neonatal Consortium (INC) is a global collaboration formed to forge a predictable regulatory path for evaluating the safety and effectiveness of therapies for neonates (http://c-path.org/programs/inc/). The consortium engages the global neonatal community – families, neonatal nurses, academic scientists, regulators, pharmaceutical investigators, advocacy organizations, and funders – to focus on the needs of the neonate. Launched by the Critical Path Institute, an independent non-profit organization established in 2005, INC aims to advance regulatory science for this underserved population through teams that share data, knowledge, and expertise.

On behalf of Critical Path Institute (CPath), we appreciate the opportunity to offer comments on the notice of proposed rulemaking (NPRM), "Federal Policy for the Protection of Human Subjects", Docket No. HHS-OPHS-2015-0008, "Advanced Notice of Proposed Rulemaking (ANPRM) on Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators." The Office for Human Research Protections (OHRP) is to be commended for its efforts to strengthen protections for research subjects, promote important research and reduce burden, delay and ambiguity for stakeholders.

In this letter, we will provide comments related to the most critical implications for both basic science and clinical research in the pediatric population. While we support the overall intent of the proposal, there are a number of areas that will need greater clarity and special considerations in order to achieve the proposal's goals. We urge the OHRP to examine these areas closely to ensure that well-intended changes to the Common Rule do not create new (or intensify existing) hurdles in pediatric research. To assist in reducing this risk, we've developed both general, cross-cutting

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comments as well as more specific responses to the proposed changes. Our responses are focused on the following topics [refer to the Appendix for a mapping of INC comments to specific sections of the ANPRM]:

- **General, Cross-Cutting Comments & Considerations:**
  - *Pediatric Research – Expert Assessment*
  - *Overlap in Statutes, Regulations & Guidelines*
  - *Legally Authorized Representative*
  - *Age of Majority*
- **Specific Comments & Considerations:**
  - *Informed Consent*
  - *Identifiable Biospecimens used in Secondary Research*
  - *Non-identifiable Biospecimens used in Secondary Research*
  - *Single IRB for Cooperative Studies*

General, Cross-Cutting Comments & Considerations:

Pediatric Research – Expert Assessment

The complexity and breadth of the proposed changes have led to our first general recommendation which is to have the proposal, in its entirety, evaluated and assessed by experts in pediatric, obstetric and perinatal research during the next rounds of edits. These experts should be knowledgeable about the unique clinical, scientific, ethical, psychological and social needs of children. Parents and patient advocates should be invited to be integral to this process. Such a step would increase the likelihood that the proposal will, indeed, improve protections for children, enable valuable research and provide a clearer framework for sponsors, researchers, pediatric patients and their families involved in pediatric research (regardless of funding source). In the meantime, we trust that our commentary will provide early insight into the key areas of focus we selected. We welcome further discussion to clarify our points.

Overlap in Statutes, Regulations & Guidelines

Several statutes, regulations and guidance that pertain to the protection of human subjects in pediatric research currently intersect and overlap with the Common Rule. We respectfully request that a thorough review of the proposed changes be conducted to (1) minimize unintentional negative impacts that the proposed Common Rule changes may have on pediatric research across these statutes, regulations and guidance; (2) clarify applicability ; (3) ensure that terminology changes consider the nuances, unique circumstances and inherent challenges in pediatric research

and (4) clearly distinguish terms used in the Common Rule from the same or similar terms used in related statutes, regulations and guidance. As an international consortium focused on developing standardized methods that can be universally applied in clinical trials to evaluate the safety and efficacy of therapies for neonates, we recommend aligning the U.S. Common Rule with the global pediatric research environment.

There is an increased risk of confusion due to the broadening of the current scope of the Common Rule (primarily by extending applicability beyond HHS funded research and expanding the definition of human subject). This risk is further compounded by the complexities inherent in planning and completing studies involving children. Stakeholders will need assistance in understanding applicability across a number of U.S. and international statutes, regulations and guidance (not comprehensive):

- HHS: 45 CFR part 46, subpart B: Additional Protections for Pregnant Women, Human Fetuses, and Neonates
- HHS: 45 CFR part 46, subpart D: Additional Protections for Children
- FDA regulations especially, 21 CFR part 50, Subpart D: Additional Safeguards for Children in Clinical Investigations
- FDA Guidance: Using a Centralized IRB Review Process in Multicenter Clinical Trials (2006)
- ICH E11 Guideline - Pediatric Clinical Investigations, International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use

Legally Authorized Representative

We support a re-examination of how legally authorized representative (LAR) is defined. In certain states where no applicable law exists, an LAR (according to the Common Rule's current definition) may be the person who can legally consent on behalf of a child for a particular clinical procedure but it is not clear if the LAR also has the authority to consent for ***research participation***. We agree that this ambiguity presents an unintended barrier to pediatric research in some States and we support a change in the definition to remove this barrier.

However, we urge the OHRP to examine closely the implications of a change in the definition since children constitute a significant portion of research subjects who depend on LARs. We also recommend that the OHRP provide commentary to support the change, as this will ensure that the intent is clear. We believe that this will support the appropriate application at the State and local level and will assist in other situations where interpretation of the Common Rule may be a challenge.

FDA identified a similar need when the definition of "guardian" was revised in the Final Rule, "Additional Safeguards for Children in Clinical Investigations of Food and Drug Administration-Regulated Products" (21 CFR part 50, subpart D). Their commentary was helpful and is provided for your reference, *"This revised definition makes it clear that under FDA regulations a legally authorized guardian for general medical care may consent on behalf of a child to participate in research in the absence of specific laws granting (or restricting) that authority. It remains the responsibility of an IRB to determine if there are any applicable State or local laws that either grant or restrict that authority."*

Age of Majority

Changes to LAR and to the informed consent process may also have unintended negative implications for adolescents. Adolescents currently have the right to provide consent (without parental notification) under certain circumstances prescribed by State or local laws (and this is permitted under FDA regulations for reasons noted below). As an example, State and local authority to permit confidential medical treatment and/or participation in research has been instrumental in saving lives for adolescents with HIV/AIDs. Therefore, it is critical to ensure that this authority is not inadvertently removed or impaired in any way as a result of a change in the (1) definition or rights of LARs or (2) the role of LARs in the informed consent process.

Of particular concern is that such changes could impact decision rights and procedural requirements pertaining to consent (since LAR and consent are usually interdependent). As demonstrated in the HIV/AIDs example above, age of majority may not be the defining threshold for consent since States or local jurisdictions may determine that certain adolescents (e.g. mature minors and emancipated minors) can consent for themselves. In both scenarios, these individuals may also have the right to consent for their infants. This is only one example of a complexity that is specific to pediatrics that may be overlooked and negatively impacted during Common Rule changes to LAR or the informed consent process.

This specific issue was raised during proposed changes to FDA regulations (21 CFR part 50, subpart D) and was appropriately addressed. An excerpt from the preamble is provided for reference, "…in some situations a State may grant certain classes of mature adolescents of a specific age the right to consent to treatments or procedures involved in a clinical investigation. These mature minors would not meet the definition of children under § 50.3(o) and thus would not be subject to the requirements of this subpart. Similarly, minors deemed ''emancipated'' by state law also would not meet the definition of children under § 50.3(o) and would not be subject to the requirements of this subpart. Mature or emancipated minors would be allowed to consent to participation in FDA-regulated research without the need for parental or guardian permission. Thus, we consider reliance on established state and/or

local laws that establish an adolescent as mature and/or emancipated to be appropriate in this context."

Specific Comments: Informed Consent

We support the principles that underlie the changes to the informed consent process. We believe the related changes will result in shorter forms that place a greater emphasis on useful information to support decisions to participate in research. We applaud the OHRP's efforts to create transparency and drive accountability for higher quality informed consent forms "ICFs". However, a few of the proposed changes will create more of an impediment to pediatric research than a benefit. We request that the OHRP consider making the following changes to enhance applicability in pediatric research, achieve a more favorable balance in beneficence and autonomy and address practical implementation challenges that we foresee. *Note: our commentary in this section excludes Broad Consent since that is addressed in the Biospecimens section that follows.*

Consent for Future Contact

There is likely to be a negative impact on scientific discovery and/or advancement of knowledge regarding children's diseases and conditions if the need to obtain consent to re-contact the patient or LAR is required. We recommend an exemption for pediatrics for the following reasons:

- Not likely to be "informed" consent: We believe there is a high probability that consent to re-contact will be denied since LARs and patients will be asked to agree to the unknown. It will be very difficult to effectively explain the range of possible types of future research that may be needed and why it may be necessary to re-contact them. The clinical and scientific benefits will not be known either. In order for patients or LARs to provide "informed consent" some of these matters should be addressed but it will likely be impossible to present these unknowns in a meaningful way. In absence of useful information upon which to make a decision, we believe this process will generate unnecessary concern/fear and, therefore, will lead to more denials than approvals.
- Inability to Track: If consent for re-contact is required, it will be very difficult to know if a pediatric patient who is about to enroll in a trial had a "no contact" request for future studies. Conversely, it will take a lot of effort to keep track of those who agreed to be re-contacted. The cost to track these patients is significantly higher than the benefit of having autonomy to consent.
- Beneficence over autonomy: In pediatric research, there is a much higher reliance on re-contact of LARs and/or patients due to the small number of pediatric patients and the need for follow-up in most studies. Therefore, the flexibility in re-contacting a pediatric patient is

critically important. We believe beneficence should outweigh autonomy in order avoid introducing an unintended reduction in access to potential subjects.

Public Posting of ICFs

While we support the introduction of new mechanisms to ensure an improvement in the quality of ICFs, we are not supportive of the public posting of ICFs. Instead, we see tremendous value in building quality in up front by publishing a "model" ICF that could be widely used as a template for clinical trials. Input from parents/patients and advocacy organizations should be sought for both the "model" template and the study-specific ICF prior to submission to the central IRB. Review of the "model" and study-specific ICFs by parents/patients will serve to assure transparency and quality of ICFs.

Specific Comments: Identifiable Biospecimens used in Secondary Research

Timing for Re-Consent

We support the proposed requirement to obtain Broad Consent for future, unspecified secondary research if the biospecimen is identifiable. Furthermore, we support the proposal to obtain re-consent when a child reaches the legal age to consent for a research study, but as mentioned in the Age of Majority section above, we request that consideration be given to modifying the language to account for State and local jurisdictional authority regarding mature minors, emancipated minors and other situations that are not defined strictly by legal age. This approach is consistent with other statutes and regulations governing research in the pediatric population.

We do not see a need, nor do we believe it is reasonable, to seek re-consent after 10 years following biospecimen collection. Instead, we believe that the age of majority or a State's determination of mature minor attainment or emancipation should mark the time for re-consent. From the standpoint of moving from one family to another, potential name changes, and changes in LAR, children are more mobile than adults, and tracking them is already difficult. The 10-year limit is especially problematic for biospecimens collected from neonates as they will be 10-years old when the consent expires.

Waivers for Re-Consent

Upon reaching the age of majority (or a State's determination of mature minor attainment or emancipation), every effort should be made to obtain re-consent from the now-adult participant. If this is not possible, the IRB should be asked to consider a waiver of informed re-consent. Guidance will be needed to ensure when this step applies since ICF waivers are not permitted in FDA regulated studies (except in rare instances) but may be permitted, under certain circumstances, in studies governed only by the Common Rule.

Specific Comments: Non-identifiable Biospecimens used in Secondary Research

Pediatric Exclusion from Broad Consent Except for Whole Genome Sequencing (WGS)

We recommend that pediatric research involving non-identifiable biospecimens used in secondary research be excluded from the Broad Consent requirements EXCEPT in those instances where the aim is to generate whole genome sequencing (WGS) data. We believe that excluding research that does not generate WGS would satisfy the intent of *Exclusion of Activities That Are Low-Risk and Already Subject to Independent Controls (NPRMat §ll.101(b)(2))* which covers situations that do "not entail physical risk and are nonintrusive, either in themselves or because they are subject to policies that provide oversight independent of the Common Rule". The current proposal treats non-identifiable and identifiable biospecimens the same, thereby eliminating ambiguity. In doing so, the proposal takes an extreme position to address all re-identification concerns. As an alternative, we'd advocate for zeroing in on the research that poses the highest risk for re-identification. This is the basis for our focus on whole genome sequencing. The ethical, scientific and clinical assessment of each study would continue to be subject to IRB review and approval, providing the subject protection oversight required.

By requiring Broad Consent only for pediatric research involving whole genome sequencing, we believe our recommendation would (1) minimize risk and reduce the number of invasive procedures required to collect biospecimens; (2) enable investigator access to biospecimens that would otherwise be discarded – left over blood, tissue, stool samples, etc.; (3) provide autonomy to patients and LARs in the area of highest risk of re-identification. These leftover biospecimens are especially critical in pediatrics since the patient population is already relatively small and blood volumes are relatively low. In addition, rapid developmental changes mean that bio-components present while infants, for example, may no longer be present as a toddler. Given the rapid growth and development of children, the biology changes such that samples from different ages yield different information so more samples are needed – barriers will reduce access and volume. This challenge is not found in adult studies. Finally, there is a disproportionate prevalence of rare conditions in children, making the availability of biospecimens scarce and, therefore, the utility of leftover biospecimens is very high.

In reviewing our recommendation, we encourage that there be greater consideration given to pediatric-specific needs to minimize physical risk, support non-intrusive methods, promote advancement of scientific knowledge and focus on the most critical re-identification risks.

Specific Comments: Single IRB for Cooperative Studies

We support the proposal to require the use of a single IRB of record for multi-center studies. Pediatric studies rely on multiple sites to a greater extent than any other area of medicine due to the small number of patients and occurrence of rare diseases. For example, a 100 patient study may require 50 sites across 20 countries. The multiple IRB reviews add unnecessary bureaucratic complexity to the review process and delay initiation of studies significantly. We believe that a single IRB would enhance and streamline the review process, reduce inefficiencies, support regulatory compliance and promote consistency.

However, it will be important to ensure that the single IRB has well-regarded scientific, clinical and ethics expertise in perinatal care and pediatrics. In fact, we feel strongly that the IRB be credible and capable of reviewing and assessing a range of perinatal studies (since studies may impact the fetus and newborn) and pediatric studies. Although both FDA and ICH-E11 cover key considerations related to IRBs that regularly review research involving children (and OHRP is encouraged to refer to those), we would explicitly put forth the following recommendations. The members of the IRB should:

- Be knowledgeable about and experienced in working with pregnant women and children (including sub-population specialists such as neonatologists)
- Be expert in pediatric and perinatal clinical, scientific, ethical, psychological and social issues in order to assess study designs, the quality of protocols, etc.
- Include parent and patient advocates
- Have sub-specialists to assess a broad spectrum of diseases and conditions and other specialties (e.g. pharmacology, formulation, etc.)
- Be knowledgeable about the availability and suitability of alternative treatments for the disease or condition to be studied
- Receive continuing education (ethics, scientific, medical, regulatory science, etc.)

The goal is to build confidence in the single IRB such that local institutions will be comfortable relying on their review. We recommend that clear expectations / guidelines be issued related to the role and scope of local IRBs (as some will choose to also conduct a review) to avoid the potential for an added layer of complexity. This recommended enhancement is required to achieve the quality of review and streamlined process that the proposal intends.

Again, we thank the OHRP for the opportunity to provide comments on the proposed changes to the Common Rule. We trust that our commentary has provided insight into ways that the proposal can improve protections for children while at the same time promote valuable research in this vulnerable population. We welcome the opportunity afforded by revisions to the Common Rule to

align best practices around the globe and look forward to further discussion to assist in the next steps of the review process.

Sincerely,

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Attachment: Appendix A: Mapping of INC Comments to ANPRM

APPENDIX A: *High-Level Mapping of INC Comments to the "Federal Policy for the Protection of Human Subjects", Docket No. HHS-OPHS-2015-0008, "Advanced Notice of Proposed Rulemaking (ANPRM) on Human Subject Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay, and Ambiguity for Investigators." Page numbers and columns refer to Federal Register / Vol. 80, No. 173 / Tuesday, September 8, 2015 / Proposed Rules. Mapping does not identify all references in the Federal Register.*

Major Topic	Federal Register Page #, Column #	Proposed Language	Highlights
General, Cross-Cutting Comments & Considerations			
Potential Change in Definition of "Legally Authorized Representative" (LAR)	Page 53969 Column 2, bottom ½	"In addition to the specific changes proposed to § ll.116, comment is sought on whether Common Rule agencies should modify the definition of ''legally authorized representative'' (LAR). The current Rule defines LAR at § ll.102(c) as an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. While the NPRM proposes to retain this language, OHRP is aware that this definition has been problematic for states in which there is no applicable law permitting an LAR to consent in either a clinical or a research context."	• Supportive of the re-examination of LAR definition • Caution OHRP to examine any change in the definition closely since implications for pediatric research is high
Specific Comments: Informed Consent			
Consent for Future Contact	Page 53971 Column 3, top ½	"The proposed new element at § ll.116(b)(9) would provide subjects or their legally authorized representatives with an option to consent, or refuse to consent, to investigators re-contacting the subject to seek additional information or biospecimens or to discuss participation in another research study."	• Not supportive of requirement to obtain consent for future contact; exemption for pediatrics is requested

Public Posting of ICFs	Page 53969 Middle column, bottom ½ Additional information is on page 53978	"As an additional means of increasing transparency and facilitating the development of more informative informed consent forms, it is proposed that a copy of the final version of the consent form for clinical trials conducted or supported by a Common Rule department or agency would need to be posted on a publicly available Federal Web site. Within 60 days after the trial was closed to recruitment, the awardee or the federal department or agency conducting the clinical trial would be required to post the consent document, the name of the clinical trial and information about whom to contact for additional details about the trial."	• Agree that transparency is a good way to drive behavioral change but we do not believe the current proposal will be effective • Modifications recommended: o Develop a "model" ICF o Engage patients in reviewing the model and study-specific ICFs o Remove a requirement for public posting
Specific Comments: Identifiable Biospecimens used in Secondary Research			
Timing for Re-Consent	Page 53973 Column 3, bottom ½ Page 53973 & 53974 Column 3, bottom ½ and Column 1, top ½ , respectively	"…the NPRM proposes that broad consent for the research use of biospecimens or identifiable private information obtained for non-research purposes would [apply to] …biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained for adult subjects, and, for research involving children as subjects, biospecimens or identifiable private information that will be collected up to 10 years after broad consent is obtained or until the child reaches the legal age of consent to the treatments or procedures involved in the research, whichever comes first." "The NPRM proposes to include the standard for who is a child based upon the definition of ''children'' as defined at 45 CFR 46.402(a). At the time the child became an adult, the broad consent or permission would no longer be valid and either broad consent would need to be sought from the child-turned adult, or the need would need to seek a waiver of informed consent in order to use the individual's biospecimens or identifiable private information for research, unless one of the exclusions or exemptions were applicable."	• Supportive of broad consent for identifiable biospecimens used in secondary research but not supportive of 10-year expiry for broad consent • Recommend broad consent expiry at age of majority or State's determination of mature minor attainment or emancipation (instead of 10-year mark); then re-consent
Waivers of Informed Consent	Page 53945 Column 3, bottom ½	" …the proposal permits IRBs to waive the requirement for informed consent, but the requirements for approval of such waivers would be very strict, and such waivers will only occur in rare circumstances."	• Highlighted practical implications for pediatrics: need to seek IRB waiver for re-consent from now-adult subject • Guidance needed (Common Rule vs. FDA differences re: waivers)
Specific Comments: Non-identifiable Biospecimens used in Secondary Research			

Pediatric Exclusion from Broad Consent Except for Whole Genome Sequencing	Page 53950 Column 2, bottom ½	"Proposed Rules Exclusion of Activities That Are Low-Risk and Already Subject to Independent Controls (NPRM at § ll.101(b)(2))…The NPRM proposes to exclude four categories of research activities that do not entail physical risk and are non-intrusive, either in themselves or because they are subject to policies that provide oversight independent of the Common Rule."	• Recommend that pediatric studies be excluded from broad consent requirements except for whole genome sequencing
Specific Comments: Single IRB for Cooperative Studies			
Single IRB	Page 53984 Column 1, bottom ½ and All of Column 2	"That provision states that for non-exempt research involving human subjects covered by this policy that takes place at an institution in which IRB oversight is conducted by an IRB that is not affiliated with the institution, the institution and the IRB should establish and follow written procedures identifying the compliance responsibilities of each entity. These procedures should be set forth in an agreement between the institution and the IRB specifying the responsibilities of each entity in ensuring compliance with the requirements of this policy…This proposal only affects the decision regarding how an IRB would be designated as the reviewing IRB… An agency may solicit input regarding which IRB would be most appropriate to designate as the IRB of record. Public comment is sought on how this will work in practice. This policy would not relieve any site of its other obligations under the regulations to protect human subjects. Nor would it prohibit institutions from choosing, for their own purposes, to conduct additional internal IRB reviews, though such reviews would no longer have any regulatory status in terms of compliance with the Common Rule. Although a local IRB may conduct its own additional internal review, such a review would not be binding on the local site if not adopted by the single IRB… Relevant local contextual issues (e.g., investigator competence, site suitability) pertinent to most studies can be addressed through mechanisms other than local IRB review.	• Supportive of single IRB • Emphasized importance of ensuring well-regarded scientific, clinical and ethics expertise in pediatrics and perinatal care