January 6, 2016

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

Dear Dr. Menikoff,

The undersigned organizations committed to the health and wellbeing of pregnant women, infants, children and families appreciate this opportunity to comment on proposed changes to the Federal Policy for the Protection of Human Subjects (the Common Rule), as contained in the Notice of Proposed Rulemaking (NPRM) published in the *Federal Register* on September 8, 2015.

Our organizations would like to commend the Department of Health and Human Services' Office of Human Research Protections (HHS OHRP) for taking on the considerable task of updating the Common Rule. Both the scientific enterprise and the societal environment in which it takes place have changed

over recent decades, while the Common Rule has remained largely static. In drafting the NPRM, OHRP has attempted to balance a range of challenging and often competing interests and imperatives, allowing innovative and lifesaving medical research to proceed while providing appropriate protections to those who participate in it.

Our organizations would like to focus attention on the NPRM's implications for newborn screening (NBS), a critical and unique public health function. Newborn screening has existed for over fifty years in our nation as a vital public health program. Today, every newborn born in the United States is tested after birth for over 30 conditions that, if left untreated, can cause disabilities, developmental delays, illnesses or even death. An estimated 1 in every 300 infants has a condition that can be detected through newborn screening.

After newborn screening takes place, the residual dried blood spot may be stored for some period of time and, in some states, may be made available for use in research. A great deal of variability exists among states in the term for which bloodspots are retained, and in whether and how they are used or made available to researchers for studies. As a result, the changes proposed in the NPRM will impact state programs differently depending upon their practices.

For the purposes of the proposed changes to the Common Rule, the research that takes place with residual NBS dried blood spots is special in three important respects. First, these samples are collected in the context of a public health program, rather than strictly associated with traditional clinical care or research. If consent for secondary research must be sought, this process must not inadvertently erode the public's trust and participation in the public health aspect of newborn screening for clinical purposes. We must be careful to make sure families understand the consent is only for research portion of the dried blood spot usage, not for the initial newborn screen itself.

Second, samples are collected from every newborn in the nation, although only a modest percentage are stored for long periods of time or used in secondary research. The universality of newborn screening makes these samples unique in that they comprise a fully representative sample of each state's population. These samples therefore enable certain types of public health and other research that might otherwise be impossible to perform.

Third, the NPRM seems to presuppose that one would know at the time of collection whether the deidentified biospecimen will be used for secondary research if consent is given. In the case of newborn screening, there is no way for those collecting the sample at a hospital, birthing center, or provider's office to know whether a particular sample will be selected for use in secondary research. Many eligible dried blood spots are never used for secondary research at all, in which case a consent process would have been superfluous.

Our organizations would therefore urge that all aspects of the Common Rule be examined closely to determine their potential impact on the NBS enterprise. We would like to draw your attention to the following issues of special interest.

Exclusions Important to NBS Programs

We commend OHRP for proposing to exclude from Common Rule coverage both quality assurance/quality improvement activities (QA/QI) and public health surveillance. For NBS programs, it is not only essential but mandatory under the Clinical Laboratories Improvement Act (CLIA) that they perform certain QA/QI activities to ensure the accuracy of their equipment and tests. It would be helpful if the final rule explicitly excluded any CLIA-mandated QA/QI requirements. In addition, we appreciate the exclusion for public health surveillance that takes place in NBS programs. Public health reporting associated with NBS provides critical insights into the rates of various conditions and their temporal, geographic and other variation.

Broad Consent for Secondary Research Using Newborn Bloodspots

Our organizations have significant concerns with the NPRM's proposal to require that broad consent be obtained for the secondary research use of dried bloodspots. While we support the notion of promoting autonomy over these biospecimens, the practical challenges and burden of obtaining consent may be so high as to represent a cost disproportionate to the benefit conferred. Our major concerns include the following issues

Long-term unfunded mandate for states: Requiring all states to obtain broad consent before the secondary research use of samples will require the establishment of permanent consent programs, representing a significant new ongoing cost. It is unclear whether states are prepared to accept this burden and, if so, if these programs will be part of NBS programs, which are usually modestly staffed and funded. States will be required to create and maintain systems to manage the consent process, pair consents with biospecimens, and deal with the biospecimens accordingly. In some states, this new mandate will require the investment of millions of dollars each year.

Lack of clarity about responsibility for consent: The NPRM is silent on the question of who is ultimately responsible for obtaining broad consent for secondary use of NBS bloodspots. Hospitals and providers have direct access to parents, but little motivation to ensure consent forms are completed for the downstream users in public health and research. Public health officials and researchers will be keenly interested in having consent in order to perform their work, but have limited access to parents. The situation represents an unfortunate misalignment between those performing the consent process and future users of the biospecimens.

Long-term unfunded mandate for providers: Assuming hospitals or clinical care settings are expected to obtain broad consent from parents, the NPRM will impose a major unfunded mandate on these entities, as well. Health care providers may incur significant costs in counseling parents, answering questions, and collecting and processing paperwork. Some stakeholders have questioned whether it is possible to train large numbers of health care personnel to answer questions about the nuances of secondary use appropriately and consistently.

Templates for broad consent: It is difficult to offer comprehensive comments without having seen the proposed templates OHRP would issue for broad consent. However, stakeholders have raised several

concerns about the practicality of using a broad consent template for NBS. First and foremost, it is critically important that a broad consent form for secondary research not inadvertently dissuade parents from participating in the initial collection for the purpose of screening for conditions. Second, given that NBS is a universal public health program, one or more templates would have to be developed specifically for this purpose. Templates would have to be available in many languages and might need to address certain cultural issues. Such templates must also be customizable in order for states to address the specifics of their NBS storage and use practices. Finally, there is a high degree of concern that a broad consent template would have to strike an appropriate balance in describing the possible but very rare risks from allowing secondary use against the much more likely benefits to human health. Ultimately, a template is not a substitute for the informed consent process.

Enforcement for violations: The NPRM does not state who would monitor, enforce or levy penalties for a failure to obtain consent or maintain such consent properly, or the intentional or inadvertent use of biospecimens where an individual had refused consent or not responded. Given that it is unclear who would be legally responsible for obtaining broad consent for NBS biospecimens, the further lack of clarity around enforcement adds to our concern.

Halting research: In conversations with state-level stakeholders, the possibility has been raised that some states may simply decline to perform any secondary research with NBS biospecimens in order to avoid having to establish systems to obtain and manage consent. If this came to pass, it would represent a serious blow to efforts to improve and protect the health of our nation's children.

As HHS considers development of the final rule, we urge you to consider carefully whether broad consent for secondary research use of biospecimens collected as part of NBS programs represents the best balance between autonomy and beneficence. Our organizations can point to numerous benefits from such research, including the development of lifesaving new NBS tests. Given the enormous burden this requirement would impose upon multiple players in the health and public health systems, an alternative approach may be warranted for deidentified biospecimens collected in a public health context.

Development of New Newborn Screening Tests

One of the most common secondary research uses of deidentified residual NBS bloodspots is for the development of new NBS tests by public health laboratories. Because the conditions involved are usually extremely rare, it may be necessary to access millions of bloodspots to develop and validate a new screening test. It is our understanding that the NPRM would require broad consent for this secondary use of bloodspots, meaning that such research could only take place in the future with consented specimens. This raises a number of concerns for our organizations.

Viability of future test development: Given that the development of new newborn screening tests requires access to very large numbers of deidentified samples with specific characteristics, it is possible that it may no longer be possible to conduct certain types of research and test validation. As a result, the viability of such test development may be in jeopardy, or at least delayed years beyond when it otherwise would have been able to take place.

Refinement of existing tests: Existing newborn screening tests are continually being refined, such as through the adjustment of cutoffs for levels that indicate a positive or negative result. While the NPRM is not clear on whether this type of activity is covered, it is our belief that it should not be, since this process involves the creation of a reference range for one population and one lab. This activity should be excluded explicitly as a quality assurance/quality control effort.

Legislative mandates for testing: In the recent past, some state legislatures have passed laws adding conditions to their state newborn screening panels for which no test or only an experimental test existed. As a result, state public health laboratories have been required to develop a new test from scratch or adapt an existing one for large-scale use on short timeframes. If such research can only take place using consented samples, the development of such tests may not be possible without violating the legislative mandate and its timeframe. The NPRM may need to consider providing an exclusion for research that takes place under a legislative mandate to allow for the use of unconsented biospecimens.

Other Types of Research

Deidentified newborn screening residual bloodspots have been used in the past for important research in a variety of fields that may no longer be possible if broad consent is required before use. In particular, newborn screening bloodspots have been valuable for research that requires a large representative sample of the newborn population. Examples of such research includes prevalence studies of newborn lead and mercury levels, as well as antibody levels in newborns whose mothers have received vaccinations. Such studies may no longer be able to produce viable, dependable, actionable results if only consented bloodspots can be used, since they would not represent the population as a whole.

As noted above, we remain deeply concerned that some states may simply end all secondary research using newborn bloodspots, rather than incur the cost and burden of establishing and enforcing a consent process and the associated systems.

Penalties for Re-Identification of Biospecimens

Our organizations believe strongly that the wrongful attempt by any person to re-identify an individual on the basis of either a biospecimen or any medical information should be viewed as a serious violation of law with appropriate penalties. The NPRM does not, however, address this issue. We urge HHS to use an appropriate vehicle to describe the criminal and civil statutes that would be violated by such an act, and the associated penalties that would be incurred. The existence of clear rules and strict penalties would help reassure patients that re-identification is unlikely to occur because the consequences would be severe.

In conclusion, our organizations appreciate the opportunity to share with you our concerns about the potential implications of the proposed changes to the Common Rule contained in the NPRM for secondary research involving residual newborn screening biospecimens. If we may provide additional

information, please contact Cynthia Pellegrini, Senior Vice President for Public Policy and Government Affairs at the March of Dimes at 202/659-1800.

Sincerely,

American Association for Clinical Chemistry
American Congress of Obstetricians and Gynecologists
Association of Maternal and Child Health Programs
Association of Obstetric, Women's Health and Neonatal Nurses
Association of Public Health Laboratories
Association of State and Territorial Health Officials
Immune Deficiency Foundation
March of Dimes
Muscular Dystrophy Association
National Organization for Rare Disorders
Parent Project Muscular Dystrophy
Save Babies Through Screening Foundation