



January 6, 2016

Jeffrey Menikoff, Director
Office for Human Research Protections (OHRP)
Department of Health and Human Services
1101 Wootton Parkway, Suite 200
Rockville, MD 20852

RE: Comment on HHS-OPHS-2015-0008-0001 (“Federal Policy for the Protection of Human Subjects”)

Dear Dr. Menikoff:

On behalf of the 30 million Americans with one of the approximately 7,000 known rare diseases, the National Organization for Rare Disorders (NORD) would like to thank the Office for Human Research Protections (OHRP) for the opportunity to provide comments on the notice of proposed rulemaking (NPRM) titled, “Federal Policy for the Protection of Human Subjects.”

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research, and patient services.

NORD’s central policy and advocacy mission is to foster the innovation, development, and delivery of life-changing and often life-saving therapies for rare disease patients. However, with only close to 475 orphan therapies treating approximately 360 rare diseases, over 95% of rare diseases do not have an FDA-approved treatment. For these patients, hope of a treatment for their disease rests upon the initial research that can later lead to a treatment or cure.

It is for this reason that NORD takes a particular interest in this NPRM and the impacts it may have on the rare disease research environment, and we commend and thank OHRP for undertaking the incredibly arduous and difficult task of updating the Common Rule.

The following comments are not exhaustive and do not cover the full extent of the proposal put forth in OHRP’s NPRM. This is at least partially due to the short amount of time given to the public to digest and comment on such a lengthy and complex NPRM. We are thankful for the additional thirty days afforded us to comment, but still believe the comment period is too short.

Overall we share many of the same concerns the stakeholder community has on the NPRM. We also echo many of the Secretary’s Advisory Committee on Human Research Protections’ (SACHRP) sentiments. We agree that “the proposals are virtually impenetrable due to opaque language, unclear concepts, the overlapping nature of various elements, and the intricate relationships of elements to one another”.¹

The following comments address three key areas of the NPRM:

- 1) The proposed requirement of broad informed consent for the use of biospecimens in secondary research
- 2) The implications of this NPRM on newborn screening
- 3) Mandatory single IRB review for multi-site studies

1) Broad informed consent for the use of biospecimens in secondary research:

NORD thanks OHRP for its dedication to protecting patients in potentially harmful research endeavors, and commends OHRP's diligence in updating the Common Rule to reflect the changing technological environment.

With the patients at the core of our mission, we are always supportive of efforts that further guarantee their safety and improve their experience. However, we have various concerns with several aspects of OHRP's proposed informed consent changes as they may have a disproportionately deleterious effect on rare disease research.

Rare disease research is inherently difficult to conduct due to small and dispersed populations. Adding additional layers of requirements on rare disease researchers may have several harmful impacts, such as the closing of studies due to the lack of biospecimens, new studies not occurring due to the lack of a representative sample of biospecimens, and the overall slowing of rare disease research.

We understand the concern that deidentified biospecimens are never truly deidentified as, given the right technology, they can be reidentified using the DNA within the biospecimen. However, the potential reidentification by individuals acting unethically and illegally should not be reason enough to potentially impair the entire rare disease research ecosystem.

NORD believes 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 a criminal act with severe penalties, including a potential prison sentence. The NPRM does not, however, address this issue. We urge OHRP 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 addition to these overall concerns with the proposal, we echo SACHRP's statement that, "The risks that are associated with research with biospecimens largely flow from the information about the subject that is derived from specimen analysis. What sense is there in providing greater restrictions for research with a biospecimen than for research using an individual's full genome sequence derived from that specimen? Implementing different regulatory approaches to these two forms of research resources is not logical or defensible."²

SACHRP's recommendations on replacing broad informed consent with notices of research practices and opportunities for opt-out processes is, while not ideal, likely much more feasible in implementation and practice than obtaining broad informed consent.

Finally, we ask OHRP to consider the unique perspective individuals with rare diseases have on the risks and benefits of participating in biomedical research. Most patients with a rare disease have little to no research attention being paid towards their disease, and are therefore often willing to incur a much higher risk in order to facilitate research into their disease. The Food and Drug Administration (FDA) recognizes the additional risk rare disease patients are willing to incur because there are no alternatives, and we ask OHRP to consider the same perspective as it weighs patient protection with the robustness of the rare disease research environment.

2) Implications of the NPRM on newborn screening:

NORD joins a coalition of partners interested in the sustainability and viability of newborn screening programs. Much of the below are arguments taken from joint comments submitted on January 6th.³

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 rare conditions that, if left untreated, can cause disabilities, developmental delays, illnesses or even death. 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 newborn screening (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 the 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 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.

We 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 insight into the rates of various conditions and their temporal, geographic and other variation.

Broad Consent for Secondary Research Using Newborn Bloodspots

Much like our concerns regarding the requirement of broad consent for all biospecimens, we similarly 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.

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. The rare disease community can point to numerous benefits from such research. 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 biospecimens collected in a public health context.

Development of New Newborn Screening Tests

One of the most common secondary 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 test development could only take place in the future with consented specimens. This raises a number of serious concerns.

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 test development and 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. The net effect could be that placing additional childhood diseases on newborn screening panels across the country would become extremely difficult if at all possible even when effective treatments for those additional diseases have been approved but would consequently not be available to those affected infants until years later when it might well be too late.

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 activities 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 such activities that take place under a legislative mandate to allow for the use of unconsented biospecimens.

In sum, we strongly urge that HHS exclude the activities essential for newborn screening test development, validation and refinement from any restrictions on the use of deidentified bloodspots for secondary research.

3) Mandated use of single IRBs for multi-site cooperative research

We thank OHRP for its efforts to further streamline multi-site research by mandating the use of single IRBs with certain exceptions. This is particularly important for rare disease research, as rare disease patients that are eligible to participate in research are few and far between, and are usually scattered across the United States.

Under current practice and regulations (such as The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) Section 520(g) (21 U.S.C. 360j(g)), all consent forms must be reviewed, modified, and approved by a local Institutional Review Board before a collaborative study can be conducted at that institution. This results in a very large time delay in starting any study, a large cost burden to the study's sponsor or investigators, confusion with multiple documents with the same purpose (i.e. local version for each institution), and frustration by the research community.

It can also be a safety risk in that there is a significant reluctance and effort barrier to making potentially helpful modifications to consent documents due to the need for review at all sites. For rare diseases, which often require dozens of sites with one to two patients at each, this is a prohibitive cost and effort barrier. For patients who receive care at smaller sites this is a barrier to participation in research as these sites often lack the resources to create and review informed consent forms.

It is costly for institutions to maintain large Institutional Review Board (IRB) committees and it diverts resources that could be better spent on the research itself. Currently, there is no incentive for an institution to accept the IRB from another site and the attendant legal risk. A recent example for a small study enrolling under 50 patients but needing over 20 sites to do so was the 2 year timeframe it took to emplace the IRB at each site for a 1 year study. This issue significantly delays the delivery of new therapies to patients.

For these reasons, we are heartened by OHRP's proposal to streamline the IRB process. However, we would also urge caution in its structuring and implementation due to the complexity of the current system. We echo SACHRP's requests for additional data on the U.S IRB environment, and ask that OHRP also include exception allowances for state, local, or tribal laws. We also echo SACHRP's request for a public forum on the use of single IRBs, and the investigation of cost structures for single IRBs instead of multiple local IRB reviews.

Finally, the NPRM does not include provisions that would hold harmless participating institutions that were mandated to accept the decision of another IRB. In order to avoid institutions declining to accept another IRB's materials, and thus not participating in the study, due to legal liability concerns, we recommend the creation of a national reliance agreement network (NRAN) that will indemnify and hold harmless any participating institution, clinical trial site or investigator who commits to using any consent form prepared under the NRAN for the quality or content of that IRB product. This indemnification would exclude the IRB of origin for those documents.

NORD thanks OHRP for the opportunity to comment, and we look forward to working with OHRP on ensuring both rare disease research and patient protections are strengthened. For questions regarding NORD or the above comments, please contact Martha Rinker, Vice President, Public Policy at mrinker@rarediseases.org or (202) 588-5700, ext. 102.

Sincerely,



Peter L. Saltonstall
President and CEO

¹The Secretary’s Advisory Committee on Human Research Protections’ Recommendations on the Notice of Proposed Rulemaking entitled “Federal Policy for the Protection of Human Subjects”. (2016, December 28). Retrieved January 6, 2016, from <http://www.regulations.gov#!documentDetail;D=HHS-OPHS-2015-0008-0570>

² Ibid

³ Joint Comments on the Implications of the Proposed Changes of the Common Rule for Universal Newborn Screening Programs. (2016, January 6). Retrieved January 6, 2016, from <http://rarediseases.org/assets/files/policy-statements/2016-01-06.Common-Rule-NBS-group-comments-final.pdf>