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

Dear Dr. Menikoff,

Re: OPHS-2011-0005; Human Subjects Research Protections: Enhancing Protections for Research Subjects and Reducing Burden, Delay and Ambiguity for Investigators

Dear Dr. Menikoff:

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) offers its comments on the advance notice of proposed rulemaking (ANPRM) issued by the Office for Human Research Protections (OHRP) concerning how current regulations for protecting human subjects who participate in research might be modernized and revised.

NASPGHAN represents more than 1,500 pediatric gastroenterologists and hepatologists, many of whom conduct research intended to cure disease and help improve the lives of children with chronic conditions. Many of our patients and their parents are also interested in helping us understand and cure disease and partnering with us to conduct clinical research studies.

We commend OHRP for trying to streamline aspects of the "Common Rule" and to clarify otherwise gray areas of clinical research. As OHRP considers changes to current human subjects regulations, we believe that every consideration must be given to implications of any changes on pediatric patients and research.

Our review of Section IV of the ANPRM, "Improving Informed Consent," has raised questions and concerns related to pediatric research that we believe must be adequately addressed as OHRP proceeds with rulemaking.

Under current regulations, if identifiers are removed, specimens and data that have been collected for purposes other than the proposed research can be used without any requirements for informed consent. When those identifiers have not been removed, investigators may be allowed in certain situations to obtain a general consent for future research with existing biospecimens and other

information stored in databases. Under the changes being considered by OHRP, written consent would be required for research of biospecimens, even those that have been striped of identifiers. The rule further suggests that consent could be obtained using a standard, short form by which a person could provide open-ended consent for most research uses of a variety of biospecimens.

While the ANPRM raises several specific questions for comment on this proposal, it does not consider how changes in consent requirements could impact pediatric patients and research.

Applicability of Parental Consent once a Patient Turns Age 18

The ANPRM does not consider how the change in consent under consideration would apply when parental consent has been obtained for a minor. If tissue is banked from a minor under parental informed consent, once that minor turns 18 years of age will reconsent by the young adult now be required in order for research to be conducted on the banked biospecimen? **We believe that any proposed change should recognize the consent previously granted by parents or legal guardian when a banked biospecimen is used for research after a minor turns 18 years of age.** If reconsent is required, the implications for pediatric research could be catastrophic. For example, if a child with Crohn's disease undergoes a colectomy at age three and the parents or guardian(s) agree that the biospecimen obtained from the patient can be used for genetic research, that biospecimen will be banked in a national tissue repository. Fifteen years later, once the child turns 18 years of age, will the investigator be required to discard the specimen, which has been preserved at significant cost, if he/she cannot obtain the patient's reconsent? Alternatively, will the investigator be obligated to continually update the patient's contact information, which would impose significant time and resource costs, until the patient turns 18 and reconsent can be obtained?

If reconsent is required, it could block patients for benefiting from therapeutic discoveries. For example, if a treatable infectious pathogen is discovered as a cause of a serious liver disease, physicians should be allowed to go through stored liver biopsies of their patients to determine who might be eligible for this new life-saving treatment. If patient reconsent is required, a physician may not be able to test stored tissue on a young adult to find out if the treatment is effective and subsequently contact the patient for potentially life-saving therapy.

Physicians, patient organizations and institutions invest millions of dollars in building and maintaining pediatric research repositories that could be impacted by the changes to consent under consideration.

One such repository important to the hepatic research community is the Pediatric Acute Liver Failure (PALF) Study, which is funded by the National Institutes of Health. PALF is the first pediatric consortium, involving 19 pediatric centers, aimed at identifying, characterizing, and developing management strategies for infants, children, and adolescents who present with acute liver failure. For the study, information from a patient's hospital record, as well as blood and tissue samples, when available, are used to study acute liver failure. Participation in the study is possible only with informed consent from the child's parents or legal guardian. No names are used at any time in the study. If changes in regulation require reconsent to continue research on biospecimens once the patient turns age

18, there will be unquestionable added costs to obtaining reconsent, with the real possibility that investigators will be unable to obtain reconsent. Acute liver failure is a rare and very serious condition for which a complete picture of causes and possible treatments is still needed. We urge OHRP to avoid any changes in consent regulation that could hinder continuation of this important study.

Another example is the Crohn's and Colitis Foundation of America Risk Stratification Initiative. The initiative involves hundreds of pediatric gastroenterologists and more than 1,000 pediatric patients. For the first time, biological samples from a large prospective patient population are being collected and banked at the time of inflammatory bowel disease (IBD) diagnosis before therapy is started. Data and banked biospecimens (DNA, blood serum, stool and tissue biopsies) will be used for research over the next 20-30 years. The goal is to take knowledge gained and translate it into new protocols for individualized approaches to treating IBD in children, based on their risks, thus preventing severe disease and its lifelong consequences. If reconsent is required when a minor turns age 18, the associated administrative and cost burdens will undoubtedly serve as a disincentive for these types of important research initiatives.

Improving Consent Forms

OHRP is considering a number of modifications to the regulations to improve consent forms. We agree that consent forms can be too long and hard to understand. When considering revisions about how consent forms should be written and what information they should contain, we ask OHRP to consider how pediatric consent would be covered in a standard "short form." The ANPRM seems to suggest that a brief general consent form could allow for broad future research use. **We believe that broad general consent granted by parents or legal guardians for children enrolled in research should remain valid when the patient reaches age 18. We believe that the consent form should make clear that consent granted by a parent for a minor would extend to when the child reaches adulthood.** However, if parents have the ability to select "no research" for their children, we believe the regulations should explicitly state that patients could be approached for consent at age 18.

Research on "Discarded" Biospecimens

Currently, it is common practice for researchers to store de-identified "discarded" biospecimens for future research. Under current regulations, biospecimens that do not contain personal identifiers can be classified as research that does not fall under the purview of an Institutional Review Board or may be considered exempt. While many biospecimen registries and repositories operate with the use of informed consent, many other types of research that use "discarded" clinical or pathology specimens are conducted under a waiver of consent.

The proposals under consideration in the ANPRM would classify all tissue as identifiable and would require written consent for use of any biospecimen, even those that have been stripped of identifiers. For a biospecimen to be identifiable using DNA, the biospecimen must have an identifiable reference and matching must take place. We believe that requiring consent for the use of "discarded" biospecimens could unintentionally limit the potential to perform important research on pediatric rare conditions and disease because there could be fewer samples with consent (versus without consent) available for research. **We do not**

believe that consent should be required for research on pediatric, de-identified "discarded" clinical or pathology specimens. We believe that requiring consent for "discarded" pediatric biospecimens would be overreaching, difficult and costly to administer, and unnecessary without convincing evidence that patient protections would otherwise be at risk.

Additionally, we believe that the ANPRM lacks clarity of whether informed consent will be required to conduct retrospective studies of pathologic specimens collected prior to any regulatory changes. Should samples that were previously classified as de-identified now be treated as identifiable via DNA analysis? **We believe that any regulatory changes should not apply in <u>any instance</u> to biospecimens collected before the effective date of the new rules.** For example, if a pathologist wants to review old pathology slides to determine the prevalence of dysplasia ulcerative colitis, he/she should be allowed to do so under the new rules.

Conclusion

Our patients and their parents partner with physicians because we maintain a shared goal – to advance knowledge and cure chronic illness. While we believe that some of the regulatory changes being considered will benefit research, other changes are well-intentioned but lacking adequate consideration of how they could impact advances in medical science that might help our youngest and most vulnerable patients. We strongly encourage the OHRP to consider our concerns and to work with the pediatric research community as it proceeds with rulemaking. Should you require additional information or have any questions, please contact Camille Bonta, NASPGHAN consultant, at (202) 320-3658 or cbonta@summithealthconsulting.com.

Sincerely,

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