SACHRP Recommendations Regarding Research Uses of Newborn Dried Bloodspots and the Newborn Screening Saves Lives Reauthorization Act of 2014

Summary of Recommendations

Specific recommendations include the following, the background and rationale for each of which is set forth in this SACHRP report:

- SACHRP recommends that OHRP rapidly disseminate guidance to the research community regarding the implementation of this law.

- SACHRP recommends that guidance make clear that the requirements of subsection (a) of the law only apply to research that is funded by HHS and does not impact research with other types of data or specimens. Any related OHRP-enforcement actions will be limited to HHS-funded research.

- SACHRP recommends that OHRP's existing 2008 *Guidance on Engagement of Institutions in Human Subjects Research* be revised to include scenarios for the collection of newborn dried blood spots.

- SACHRP recommends that OHRP guidance encourages that blood spots used for research be de-identified unless there is a clear justification otherwise.

- SACHRP recommends OHRP guidance reinforce that institutions should continue to assess proposed activities to determine whether or not they represent research.

- SACHRP recommends that OHRP guidance note that the expedited review categories may be used for HHS-funded research with newborn dried blood spots.

- SACHRP recommends that OHRP guidance emphasize that the consent process for research use of residual newborn dried blood spots would be simplified if one-time permission is sought for broad future research use.

- SACHRP recommends that OHRP consider developing an example document for broad consent to research use of newborn dried blood spots as part of its guidance.

- SACHRP further recommends that the guidance emphasizes the ability of IRBs to grant waivers of documentation of consent under §46.117(c)(2).

Background

SACHRP views newborn screening programs to be an important public health activity that has contributed substantially to the public good. SACHRP also supports research that is socially beneficial provided that the research honors all the ethical principles. The public's trust in the overall research enterprise is paramount, and is supported by the existence of a regulatory framework that includes a review of the ethical acceptability of proposed research by institutional review boards (IRBs).

IRBs provide review and oversight of research using data, documents, records and specimens that were collected for non-research purposes in the context of healthcare. When the regulations were developed, it was anticipated that there would be mechanisms needed to facilitate this research within the ethical framework described in the Belmont Report. The Belmont Report requires that respect for persons, beneficence and justice each be considered in the evaluation of proposed research with human subjects. However, it is accepted that there can be tension between these principles. In research with data and specimens that have been collected for non-research purposes, the regulations give IRBs the authority to determine when consent is required and when it can be waived in low or minimal risk research. The waivers of informed consent included in the Common Rule regulations provide the mechanism for IRBs to approve research in this way.

All states collect newborn dried blood spots in order to conduct mandatory screening for serious medical conditions. Many state newborn screening programs retain residual blood spots after the completion of screening. These residual samples have numerous uses that have been valuable to the health of children including laboratory quality assurance testing, program evaluation activities, and biomedical research. In general, these samples have been collected without specific consent to research, and institutional review boards (IRBs) have reviewed proposed activities and assigned them one of three classifications:

- Activities with de-identified samples that do not meet the regulatory definition of research involving human subjects (informed consent is neither required nor possible);

- Activities that meet one of the exempt research categories (informed consent not required for exempt research); or

- Activities that constitute non-exempt research (informed consent is required unless the IRB grants a waiver of informed consent in accordance with 45 CFR 46.116).

In recent years legitimate legal and ethical concerns have been raised about the practice of states to retain residual dried blood spots and use them for purposes unrelated to newborn screening programs. Individuals have objected to the storage and use of even de-identified blood spots for research purposes without the informed consent of parents and in the context of state-mandated programs. This issue represents a conflict between closely held values –

parental decision-making related to the use of samples obtained from their children versus the need to pursue research that contributes to the public good and may be conducted in the absence of informed consent. IRBs are charged with weighing the need to respect the autonomy of research subjects against the reasonably foreseeable risks of the research and the potential benefits to subjects, science and society.

The Newborn Screening Saves Lives Reauthorization Act of 2014

On December 18, 2014 the *Newborn Screening Saves Lives Reauthorization Act of 2014* (Public Law No: 113-240), an extension of the *Newborn Screening Saves Lives Act of 2008* was signed into law. The bill includes an amendment addressing research uses of newborn dried blood spots, requiring immediate new interpretations of the current Federal Policy for the Protection of Human Subjects effective 90 days from the enactment of the law. (Box 1) The amendment also requires HHS to promulgate proposed revisions to Federal Policy for the Protection of Human Subjects within six months and final regulations within two years.

The law includes two significant changes to the human subjects regulations as they apply to research with newborn dried blood spots. First, the law requires that all research funded pursuant to the Public Health Service Act using newborn dried spots be considered human subjects research regardless of whether the specimens are identifiable. This is contrary to established regulatory approaches in which biological specimens that are not linked to identifying information are not considered identifiable and therefore do not constitute "human subjects" as defined at 45 CFR 46.102(f). Second, the law eliminates the ability of the IRB to approve alterations or waivers of informed consent under 45 CFR 46.116(c) and 116(d) for research involving newborn dried blood spots. This is contrary to long-established IRB practices in which research involving stored identifiable clinical specimens and data could be carried out under a waiver of informed consent if the IRB determined that the ethical and regulatory requirements were satisfied.

Box 1

TEXT OF SEC. 12. INFORMED CONSENT FOR NEWBORN SCREENING RESEARCH.

(a) IN GENERAL.—Research on newborn dried blood spots shall be considered research carried out on human subjects meeting the definition of section 46.102(f)(2) of title 45, Code of Federal Regulations, for purposes of Federally funded research conducted pursuant to the Public Health Service Act until such time as updates to the Federal Policy for the Protection of Human Subjects (the Common Rule) are promulgated pursuant to subsection (c). For purposes of this subsection, sections 46.116(c) and 46.116(d) of title 45, Code of Federal Regulations, shall not apply.

(b) EFFECTIVE DATE.—Subsection (a) shall apply only to new- born dried blood spots used for purposes of Federally funded research that were collected not earlier than 90 days after the date of enactment of this Act.

(c) REGULATIONS.—Not later than 6 months after the date of enactment of this Act, the Secretary of Health and Human Services shall promulgate proposed regulations related to the updating of the Federal Policy for the Protection of Human Subjects (the Common Rule), particularly with respect to informed consent. Not later than 2 years after such date of enactment, the Secretary shall promulgate final regulations based on such proposed regulations.

General Comments

SACHRP supports the established approach to reviewing and approving research with data and specimens. This approach allows IRBs to consider how proposed activities fit within the ethical framework of the Belmont Report and to give appropriate weight to the ethical principles in order to resolve conflict among them. This traditional approach to evaluating research on residual clinical specimens has included balancing the promotion of the public's health through research with respect for persons through informed consent. As noted in the Belmont Report, "the extent of protection afforded should depend upon the risk of harm and the likelihood of benefit." Experience to date indicates that the risk of harm to newborns and families from research with newborn dried blood spots is minimal, while the potential benefits to science and society are substantial. Importantly, research using newborn dried blood spots has resulted in the development of new screening tests that have been added to the public health newborn screening program and thereby benefitted other current and future newborns suffering from certain conditions and their families. Further, the burdens and complexities of obtaining a meaningful informed consent for research on residual clinical specimens can be significant. SACHRP is concerned that the law will limit future acquisition of new knowledge.

SACHRP recommends that OHRP rapidly disseminate guidance to the research community regarding the implementation of this law. SACHRP is concerned that an overly broad interpretation of the law's coverage by IRBs and institutions may be driven by prevailing impulses to avoid regulatory risk. The result may well be that IRBs will be increasingly reluctant to waive consent in situations in which such waiver may be entirely appropriate, thus adding significant new costs on research using already-collected biospecimens and data.

SACHRP recommends that guidance make clear that the requirements of subsection (a) of the law only apply to research that is funded by HHS and does not impact research with other types of data or specimens. Any related OHRP-enforcement actions will be limited to HHS-funded research. All research activities conducted utilizing newborn dried bloodspots with non-HHS funding are not subject to the new restrictions. In addition, OHRP should be clear that any enforcement activities will focus on HHS-funded research. Those institutions that have voluntarily extended the applicability of the federal regulations via their Federalwide Assurance

(i.e., have checked the box) to non-HHS research will not be expected to apply this law to non-HHS funded research.[1]

SACHRP recommends that OHRP's existing 2008 *Guidance on Engagement of Institutions in Human Subjects Research* be revised to include scenarios for the collection of newborn dried blood spots. SACHRP is concerned that the law may create confusion regarding the engagement of healthcare institutions and their staff in research. Guidance must clarify that clinical staff whose involvement in research utilizing newborn dried blood spots is limited to the clinical collection of blood spots for the purpose of newborn screening or the provision of consent information and materials to parents should not be considered researchers, and their institutions should not be considered engaged in human subjects research. In the absence of such clarification, institutions may believe that they are required to obtain a Federalwide Assurance.

SACHRP recommends that OHRP guidance encourages that blood spots used for research be de-identified unless there is a clear justification otherwise. SACHRP is concerned that the law will have an unintended consequence that negatively impacts human subject protections. Currently, almost all research in this domain is done with anonymized specimens. Following these regulations, there is no longer a regulatory incentive to de-identify the bloodspots, even though de-identification can reduce the chances of a breach of confidentiality.

Finally, it is recognized that the reality of newborn screening programs and practices at the state level is varied and complex. Research needs to be consistent both with the regulations that OHRP enforces as well as with state law. Institutions need to know what local law applies to them and recognize that when state or local laws provide additional protections for human subjects they must be adhered to even when the research is also covered by 45 CFFR 46.

IRB Evaluation of Proposed Activities

When evaluating proposed activities institutions have applied the longstanding framework endorsed by OHRP for determining the regulatory status of proposed activities. Under this framework, individuals evaluating proposed activities are told to ask the following questions:

1. *Is the proposed activity research as defined by the regulations?*
2. *Does the activity involve human subjects?*
3. *Does the research fall under an exempt category?*
4. *Can the research be expedited?*

By following this progression of questions, IRBs are able to determine the proposed activity's regulatory status and assign a commensurate level of review that can range from no review required when the proposed activity is either not research or does not involve human subjects to review by the convened IRB or through expedited procedures.

[1] OHRP clarified this position in a public announcement published on 17 March 2015 (http://www.hhs.gov/ohrp/newsroom/announcements/2015.html#20150317)

Under the current regulatory framework, research protocols involving specimens that are not linked to identifiers are not typically considered human subjects research. As a result, numerous activities involving data, specimens, and records are routinely determined to be not human subjects research and IRB review and approval is not required.

Under the new law, research involving newborn dried blood spots must be evaluated using a modified framework. In the modified framework, the law has determined that newborn dried blood spots must be considered human subjects. Therefore, when a proposed activity is determined to be research, it must automatically be considered research involving human subjects, even when the blood spots are not linked to identifiers. The result is that many HHS-funded research activities involving newborn dried blood spots that would have previously been considered not human subjects research will now require IRB review.

Non-Research Use of Newborn Dried Bloodspots

SACHRP recommends OHRP guidance reinforce that institutions should continue to assess proposed activities to determine whether or not they represent research. As noted earlier, numerous non-research activities are performed using residual blood spots. These activities can include laboratory quality assurance[2], program evaluation, and public health practice. Following the OHRP framework, IRBs and institutions should continue to evaluate proposed activities to determine whether or not they are research. Research is defined by the Common Rule as "a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge." (§46.102(d)) Activities that do not meet this definition do not require IRB review and approval, even when they are HHS-funded.

Non-HHS Funded Research Use of Newborn Dried Bloodspots

Research activities involving newborn dried bloodspots that are not HHS-funded are not subject to the restrictions imposed by the law, and this demarcation should be reinforced in guidance from OHRP. IRBs that are reviewing such applications should continue to follow the current OHRP framework, including an assessment of whether or not any data or specimens should be considered human subjects. This framework is consistent with the regulations and the ethical demands of the Belmont Report.

HHS funded Research Use of Newborn Dried Bloodspots

Under the new law, HHS-funded research activities involving newborn dried blood spots will be automatically considered to involve human subjects. Under the modified framework, the next analysis by the institution or IRB is whether the research is exempt from IRB review or may be reviewed under the expedited categories or requires review by a convened IRB. The law requires that research with the bloodspots be considered to involve human subjects as defined

[2] The Office for Human Research Protections (OHRP) has addressed the issue of QA/QI versus research in a series of FAQs, available online at http://www.hhs.gov/ohrp/policy/faq/quality-improvement-activities/index.html.

at §46.102(f); however, the law does not prohibit the application of exempt or expedited categories by the IRB in its review of research.

Exempt Research

Exempt category 4 covers "[r]esearch involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or *if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects*." (§46.101(b)(4)) (emphasis added) Exempt category 4 was created to provide a regulatory pathway for research in which identifiable information would be accessed for the purpose of creating research data, but the research data itself would not retain identifiers thereby minimizing risks to subjects to the extent that IRB review would not provide additional meaningful protection. Also, under exempt category 4 the informed consent requirements at §46.116 do not apply.

Although the law does not prohibit IRBs from applying exempt category 4, the law is clearly concerned with the manner by which consent is obtained for research with residual newborn blood spots. SACHRP extensively discussed the issue of category 4 exemptions in the context of the requirements of the law. Given the law's deliberate elimination of waivers or alteration of informed consent, SACHRP would advise caution in the application of exempt category 4 to research involving these specimens.

Expedited Review of Proposed Research

SACHRP recommends that OHRP guidance note that the expedited review categories may be used for HHS-funded research with newborn dried blood spots. Non-exempt research activities will require review and approval by either an expedited reviewer or by the convened IRB. Expedited category 5 will frequently be applicable in this research, because the residual blood spots will have been originally collected for non-research purposes. Category 5 allows for expedited review of "research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis)." Newborn dried blood spots, which are collected for non-research purposes, clearly fall within the scope of expedited category 5. Research reviewed using expedited procedures must satisfy the requirements for informed consent at §46.116 and documentation of consent at §46.117.

Informed Consent for HHS funded Research Use of Newborn Dried Bloodspots

One of the most significant changes introduced by the law is the prohibition against the application of §46.116(c) and (d) which grants IRBs the authority to approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent, or waive the requirement to obtain informed consent. With this key piece of IRB flexibility eliminated, non-exempt HHS-funded research with residual blood spots will require

the prospective informed consent in the form of parental permission. The applicability of 46.116(c) for state projects that do not have HHS funding for the research is not changed under this law

Prospective informed consent for research use of such samples will present a significant challenge due to the wide range of healthcare facilities where births occur and the variable experience staff will have with obtaining consent to research procedures. This difficulty is potentially compounded in that blood spots currently are obtained for clinical purposes without consent, and almost all research use of the bloodspots will be unspecified and take place in the future. IRBs have traditionally considered research on such samples to involve minimal risk and impracticable without a waiver of informed consent.

SACHRP recommends that OHRP guidance emphasize that the consent process for research use of residual newborn dried blood spots would be simplified if one-time permission is sought for broad future research use. A broad consent form for future unspecified use is appropriate under §46.116, given that the sample is created as a result of a non-research procedure and because the foreseeable risk of the future research is minimal. There is also precedent in the research community for obtaining broad research consent to future use of leftover clinical specimens. The impracticability of obtaining informed consent for future research on a protocol by protocol basis compels OHRP to recognize the need for the use of broad research consent. Finally, SACHRP recommends that OHRP consider developing an example document for broad consent to research use of newborn dried blood spots as part of its guidance.

SACHRP further recommends that the guidance emphasizes the ability of IRBs to grant waivers of documentation of consent under §46.117(c)(2). Waivers of documentation would allow for a simplified consent process that can be more easily implemented at healthcare facilities that do not traditionally participate in research and are unfamiliar with the process of obtaining consent for research and maintaining documentation. When there is a desire to document consent for the purposes of managing the sample, IRBs are reminded that the regulations require that documentation must be a part of a written consent document that embodies the elements of informed consent required by §46.116. For newborn dried blood spots it may be appropriate to document consent on the blood spot card itself rather than within the consent document, and the recording of the choice may come from a parent or a staff member of the healthcare facility. In such cases, the IRB must grant a waiver of documentation of informed consent, as such documentation does not meet the §46.117 requirements.

Finally, there are a small number of states that require consent to research with newborn dried blood spots. SACHRP encourages OHRP to evaluate these state models and see if they might be useful at the national level.