What Constitutes Newborn Screening Research?

An evaluation of essential program activities for screening of current and new conditions.

Newborn Screening Programs Scenario Overview and Proposed Classifications

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Goal

- To review, discuss and refine the document ‘Uses of Residual Specimens and Associated Data in Newborn Screening Program Activities’

Overview

- NIH Meeting on Consent – March 9
  - Research vs. Not Research
  - Lack of consensus regarding most newborn screening activities.
  - Recognized need for better understanding and delineation of activities
- Starting point – Table 1 from TX NBS policy
- Discussions held among Newborn Screening Experts to further define and categorize program activities

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Disclaimers

- Document must still be fully vetted by FDA and OHRP
  - FDA has provided initial comments
  - OHRP has not provided comments

Overarching Issue

- Does research with data associated with NBS fall under this amendment?

➢ "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…"

➢ "Subsection (a) shall apply only to newborn 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."

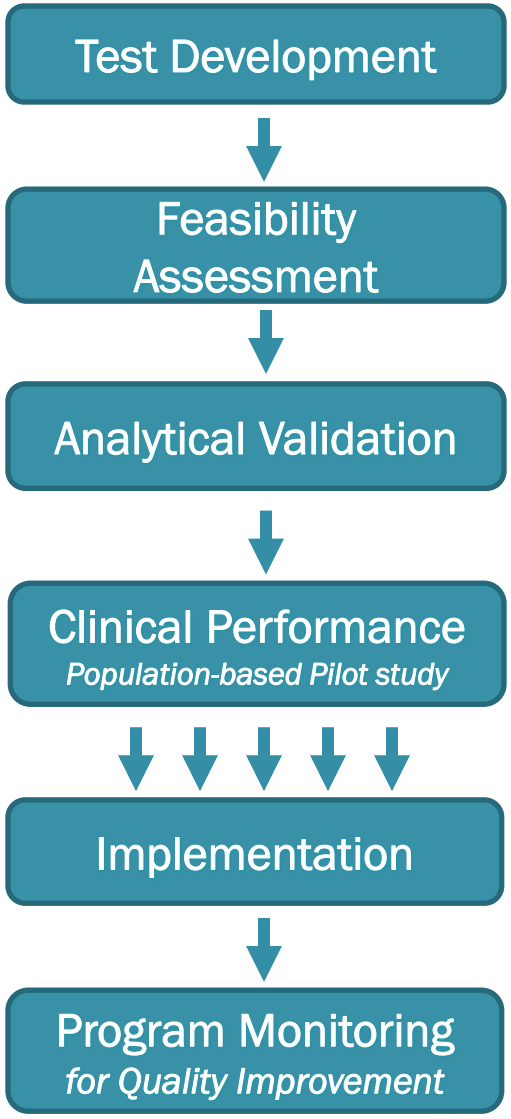
A 50,000 Foot View

- Sections 1, 2, 3 & 4 – ‘Not research’
  - QA/QC, training, and troubleshooting
- Sections 9, 10 & 11 – ‘Not research’
  - Program surveillance, reporting, COOP & other
- Sections 13 & 14 – ‘Research’
  - Research projects
- Sections 5 thru 8 – Test development & implementation

Critical Steps Leading to the Implementation of a New Condition

Stage	Description
Initial Development	To show proof of concept, to develop or to evaluate a biological marker, to determine optimal test conditions, test interferences or assess other performance.
Feasibility Assessment	To make modifications an existing (often published) research method to develop a robust, automated method with sufficient performance characteristics that would be appropriate for high-throughput screening in a public health environment. Question addressed is “Can I screen?”
Analytical Validation	Establishment of performance specifications of a new method as per CLIA/CAP requirements. E.g. Accuracy, precision, analytical sensitivity, reportable range, reference intervals
Clinical Performance	To determine whether the test is able to effectively screen for the specific condition. E.g. Clinical sensitivity and specificity; positive and negative predictive values; clinical utility. Question addressed is “Should I screen?”
Implementation	There is evidence that the test has met the threshold requirements from analytical validation and clinical performance studies. State-wide screening can be initiated.
Program Monitoring and Surveillance	To assess all components of the Newborn Screening system and provide information to ensure that program is achieving goals. To identify opportunities for quality improvement.

Systematic Investigation to Determine Whether or Not to Screen for a Condition



Intent of These Activities:

Collect sufficient evidence to determine whether or not to screen for a certain condition

Note: Program can decide at any point not to continue the process if analytical or clinical performance is not adequate.

This would be an early adopting state engaged in a pilot study … eg SCID pilot in WI or MA ~ 2008-9

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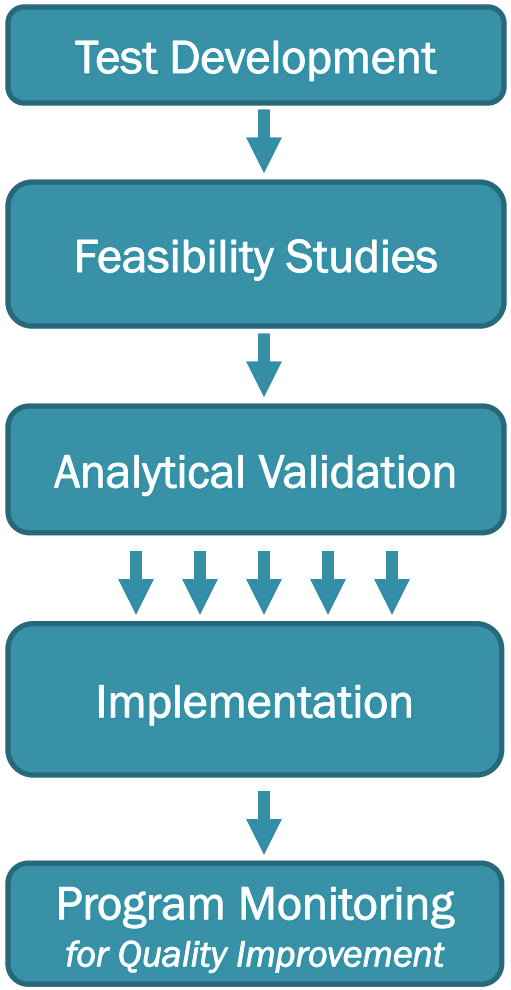
Implementation of a Screening Test with Well-Documented Clinical Performance



Intent of These Activities

Implement a test that has been shown to have appropriate analytical and clinical performance characteristics.

Note: In this case, pilot studies have already documented the clinical sensitivities/specificities; predictive values and clinical utility of the test.

This is where we currently are with SCID.

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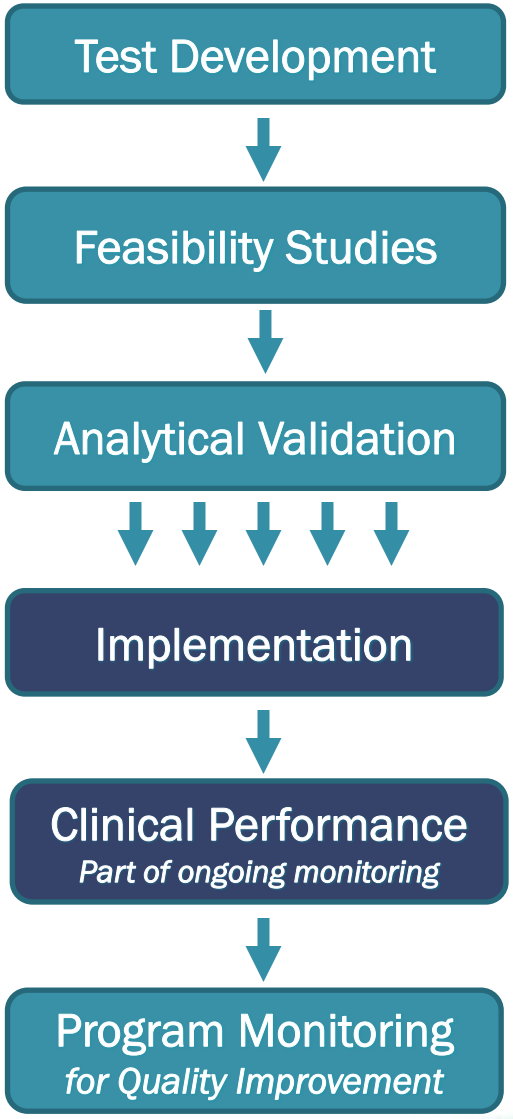
Implementation of a Mandated Screening Test Without Well-Documented Clinical Performance



Intent of These Activities

Comply with the mandate of a legislative authority and implement a test with appropriate analytical performance characteristics.

Note: Program does not have a choice about whether or not to implement screening. Both analytical and clinical performance metrics will be collected after implementation to inform the program about its performance.

Eg Krabbe and XALD in NY and LSDs in MO

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1. QUALITY ASSURANCE/QUALITY CONTROL (QA/QC) PERFORMED ON EXISTING NEWBORN SCREENING METHODS AND TEST SYSTEMS FOR *ROUTINE MAINTENANCE AND FUNCTION CHECKS*

These examples relate to the laboratory's current newborn screening activities and are necessary for maintaining laboratory certification under CLIA/CAP. ***Involves the use of identified and/or de-identified specimens and/or associated data within the state program itself. There is no sharing with external parties.***

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
1a	Perform routine maintenance and function checks as defined by manufacturer	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	
1b	Perform routine maintenance and function checks on in-house equipment, instruments or test systems as defined by maintenance protocol	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	
1c	Perform required calibration and calibration verification to ensure continued accuracy of test system, equipment and reagents	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	
1d	Use of residual blood spots as quality control material to monitor the accuracy, precision and validity of laboratory tests	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	
1e	Periodic updates of reference ranges	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	
1f	Assess equipment or test system performance characteristics after a major change within the lab that may affect safety and efficacy of test method	**OHRP Considerations:** Not research. CLIA/CAP requirement for laboratory quality management and is not designed to develop or contribute to generalizable knowledge	

2. QA/QC PERFORMED ON EXISTING NEWBORN SCREENING METHODS AND TEST SYSTEMS TO SATISFY PROFICIENCY TESTING REQUIREMENTS

These newborn screening activities are necessary for maintaining federal certification under CLIA/CAP.
Involves sharing of de-identified specimens and/or associated data with other state newborn screening laboratories as part of the required proficiency testing exchanges.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
2a	Inter-laboratory exchange for proficiency testing. Sending materials outside of your own laboratory to compare sample results.	**OHRP Considerations:** Not research. *CLIA requirement to participate in some form of proficiency testing for each specific laboratory test and is not designed to develop or contribute to generalizable knowledge*	
2b	Residual dried blood spot specimens may be sent to the CDC to assist in the development of proficiency testing material	**OHRP Considerations:** Not research. (1) Not a systematic investigation; (2) Designed to ensure that the quality of manufactured proficiency testing material is robust; Not designed to develop or contribute to generalizable knowledge	

3. *SHARING MATERIALS TO PROVIDE TRAINING AND TECHNICAL SUPPORT* ASSOCIATED WITH NEWBORN SCREENING METHODS AND TEST SYSTEMS

Involves sharing of de-identified specimens and/or associated data with other state programs to assist in training of new staff.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
3a	Residual dried blood spot specimens sent to other state programs or to the CDC to assist in hands-on laboratory training courses	**OHRP Considerations:** Not research. Intended to facilitate technical proficiency in testing and is not designed to develop or contribute to generalizable knowledge	

4. *TROUBLESHOOTING TECHNICAL ISSUES* ASSOCIATED WITH EXISTING NEWBORN SCREENING METHODS AND TEST SYSTEMS

These newborn screening activities are necessary for maintaining federal certification under CLIA/CAP.
Involves sharing of de-identified specimens and/or associated data with the newborn screening vendors who supply equipment and supplies or with other technical experts or with other state programs to troubleshoot issues that arise in the lab's screening processes or for training purposes.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
4a	Residual specimens may be used for the purpose of troubleshooting equipment, supplies, reagent issues, and specimen quality. This may occur at the lab or at location of the lab's equipment/supply/reagent vendor to resolve issues identified in the newborn screening process	**OHRP Considerations:** Not research. CLIA/CAP requirement and good laboratory practice; Not designed to develop or contribute to generalizable knowledge	
4b	Specimens shared for the purpose of re-validating, troubleshooting, and evaluating NBS laboratory tests at CDC or in another state's NBS Program. E.g. One state needs to validate an MSMS procedure for a disease and does not have any positive cases. State requests de-identified positive samples of another state. E.g. You have a new MSMS instrument and want to have true positives to validate an existing method on a new instrument.	**OHRP Considerations:** Not research. CLIA requirement and good quality laboratory practice; Not designed to develop or contribute to generalizable knowledge	

5. DEVELOPMENT OR MODIFICATION OF NEWBORN SCREENING METHOD OR TEST SYSTEMS FROM INITIAL CONCEPT TO A STABLE TEST.

This section maps out possible scenarios during the development of a stable screening method or test system. States may choose to develop an appropriate in-house method for screening a new condition. The lab reviews existing research methods, purchases equipment and reagents, and performs modifications to develop a robust, high-throughput test that would be appropriate within a public health environment. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
5a	**Initial Development of a Lab Test.** **These studies may be performed in a public health laboratory or in a research laboratory that is collaborating with a Public Health Program.** **Primary intent of studies:** To show "proof of concept", to develop or to evaluate a biological marker, to determine optimal test conditions, test interferences or assess other performance characteristics of a test. By definition, this study is investigational. Results are intended to be published in literature. **Samples used during study:** Testing is performed on consented specimens from affected individuals where the disease state is already known. Testing laboratory may also receive anonymized residual dried blood spot samples from individuals and results of this testing is not be returned.	**OHRP Considerations:** Research. Studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** Amendment does not apply. ***HHS funded activity:*** Amendment rules apply. **FDA considerations:** As written, the study appears to be exempt from the Investigational Device Exemptions (21 CFR 812). FDA has provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable.	

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This section maps out possible scenarios during the development of a stable screening method or test system. States may choose to develop an appropriate in-house method for screening a new condition. The lab reviews existing research methods, purchases equipment and reagents, and performs modifications to develop a robust, high-throughput test that would be appropriate within a public health environment. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
5b	**State Lab Feasibility Assessment I:** **Primary intent:** To perform an investigation to determine whether or not a specific condition can be added to a screening panel. Specific performance metrics will be evaluated to determine whether they achieve a certain threshold before such a decision is made. This addresses the question: "Can you do the test in a high throughput screening public health environment?" State lab will perform a feasibility assessment to make *modifications an existing (often published) research method* to develop a robust, automated method with sufficient performance characteristics that would be appropriate for high-throughput screening in a public health environment. **Samples used:** During laboratory development, testing performed on consented specimens from affected individuals where the disease state is already known. Testing may also be performed on laboratory created specimens* that mimic an affected sample. Testing laboratory may also receive anonymized residual dried blood spot samples from normal or affected individuals and results of this testing will not be returned. *CDC or the state may create such specimens.	**OHRP Considerations:** Research. The intent is to create generalizable knowledge. Data collected will be used to determine whether there is sufficient evidence to proceed with population-based testing. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply **FDA considerations:** FDA has generally provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable. (As written, it does not matter whether the testing system is an LDT or not. FDA is looking at the source of specimens.)	Intent is to create generalizable knowledge and to accumulate information about performance characteristics of the test. Nuance: Program has not been approved to go live with screening for this condition. End point of this stage is an established method that can be validated.

5. DEVELOPMENT OR MODIFICATION OF NEWBORN SCREENING METHOD OR TEST SYSTEMS FROM INITIAL CONCEPT TO A STABLE TEST.

This section maps out possible scenarios during the development of a stable screening method or test system. States may choose to develop an appropriate in-house method for screening a new condition. The lab reviews existing research methods, purchases equipment and reagents, and performs modifications to develop a robust, high-throughput test that would be appropriate within a public health environment. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
5c	**State Lab Feasibility Assessment II:** ***Primary intent:*** State has been given a mandate by a public health authority to implement a screening program for a specific condition. Primary intent is to take all necessary steps towards implementation and to comply with the required mandate. ***The primary intent is <u>not</u> to create generalizable knowledge.*** State lab performs a feasibility assessment to make *modifications an existing (often published) research method* into a robust, automated method with sufficient performance characteristics that would be appropriate for high-throughput screening in a public health environment. **Samples used:** During laboratory development, testing is usually performed on consented specimens from affected individuals where the disease state is already known. Testing may also be performed on laboratory created specimens* that mimic an affected sample. Testing laboratory may also receive anonymized residual dried blood spot samples from normal or affected individuals and results of this testing will not be returned. *CDC or the state may create such specimens.	**OHRP Considerations:** Not research. The intent of this activity is to modify an existing (often published) method to comply with the state-specific mandate for implementation of screening for the new disease. **FDA considerations:** FDA has generally provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable. (As written, it does not matter whether the testing system is an LDT or not. FDA is looking at the source of specimens.)	Intent is not to create generalizable knowledge but to determine the conditions needed for high-throughput testing within the state. Each state has its own challenges and these studies are not generalizable since they seek to determine algorithms necessary for implementation within the state system. Not considered research. End point of this stage is an established method that can be validated. NOTE: While this may be classified as not research some states may still run this through an IRB to review the process used to anonymize samples.

6. ANALYTICAL VALIDATION OF A DEVELOPED AND STABLE NEWBORN SCREENING METHOD OR TEST SYSTEM.

The state now has an available established method and needs to validate the test. During validation, specific newborn screening activities are necessary for complying with the establishment and verification of performance specifications of a new method under CLIA/CAP. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
6a	**Validation of new method on a test system that is a Laboratory Developed Test or Home Brew.** **Primary Intent:** Establish and document the performance specifications of a new method as per CLIA requirements. ***As per CLIA requirements:*** Residual dried blood spots may be used to establish performance specifications that may include (but not limited to) determination of accuracy, precision, analytical sensitivity, reportable range, reference intervals. Testing may be performed on consented specimens from affected individuals where the disease state is already known. Testing laboratory may also use anonymized residual dried blood spot samples from normal or affected individuals and results of this testing will not be returned.	**OHRP considerations:** Not research. This activity is meant to comply with CLIA regulatory requirements and not to contribute to generalizable knowledge. **FDA considerations:** FDA has provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable.	

6. ANALYTICAL VALIDATION OF A DEVELOPED AND STABLE NEWBORN SCREENING METHOD OR TEST SYSTEM.

The state now has an available established method and needs to validate the test. During validation, specific newborn screening activities are necessary for complying with the establishment and verification of performance specifications of a new method under CLIA/CAP. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
6b	**Validation of a new method on a test system is an unmodified FDA-cleared or approved test system** **Primary Intent:** Establishment of performance specifications of a new method as per CLIA requirements. *Verification of performance specifications:* Use of dried blood spots to establish of performance specifications comparable to those established by the manufacturer. E.g. A state uses residual DBS to validate a kit in compliance with CLIA/CAP before the test can be used in routine high-throughput testing	**OHRP considerations:** Not research. This activity is meant to comply with CLIA regulatory requirements and not to contribute to generalizable knowledge. **FDA considerations:** FDA has provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable.	

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The state now has an available established method and needs to validate the test. During validation, specific newborn screening activities are necessary for complying with the establishment and verification of performance specifications of a new method under CLIA/CAP. Results WILL NOT BE RETURNED to patients.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
6c	**Primary Intent:** Establishment of performance specifications of a new method as per CLIA requirements. E.g. Vendor has asked a state program to evaluate performance metrics of a kit that has already been developed. State will use residual blood spots to evaluate newborn screening test kits at the state lab. De-identified data will be submitted to FDA by the manufacturer, where FDA approval may lead to use of the test kits.	**OHRP considerations:** Not research. Test kits are already developed with a procedure in place. Testing is performed to establish performance specifications of test kit. **FDA considerations:** FDA has provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable.	
6d	**Primary Intent:** Establishment of performance specifications of a new method as per CLIA requirements. E.g. State has just purchased an instrument from a vendor and wants to validate a kit associated with the instrument for use within the state.	**OHRP considerations:** Not research. Test kits are already developed with a procedure in place. Testing is performed to ensure test kit performance is adequate. **FDA considerations:** FDA has provided enforcement discretion for the requirement of informed consent when using leftover human specimens that are not individually identifiable.	

7. DETERMINATION OF THE CLINICAL VALIDITY AND CLINICAL UTILITY OF AN ANALYTICALLY VALIDATED NEWBORN SCREENING METHOD OR TEST SYSTEM

Studies are performed within the intended population to determine whether the test is able to effectively screen for the specific condition and assessment includes determination of clinical sensitivity/specificity; positive and negative predictive values and clinical utility.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
7a	**Determination of the Clinical Validity and Clinical Utility of a test for a state that HAS NOT BEEN MANDATED to screen.** **Primary intent:** To perform a clinical investigation to determine whether or not the analytically validated test effectively screens for the condition with sufficient sensitivity and specificity. This study addresses the question: "Should you screen for this condition?" Parameters to identify include: clinical sensitivity and specificity; positive and negative predictive values; clinical utility. These parameters are not collected during the analytical validation. **Samples used:** Testing should be performed on a consented population.	**OHRP Considerations:** Research. The intent of this study is to create generalizable knowledge. Data collected will be used to determine whether there is sufficient evidence to demonstrate that the test performs as it is intended on the selected population. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	Results of this investigation will impact whether or not there is sufficient evidence to add this condition to a newborn screening panel. Based on the data, the state may or may not decide to move forward with mandating the addition of this condition to their newborn screening panel.

7. DETERMINATION OF THE CLINICAL VALIDITY AND CLINICAL UTILITY OF AN ANALYTICALLY VALIDATED NEWBORN SCREENING METHOD OR TEST SYSTEM

Studies are performed within the intended population to determine whether the test is able to effectively screen for the specific condition and assessment includes determination of clinical sensitivity/specificity; positive and negative predictive values and clinical utility.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
7b	**Monitor Clinical Validity and Clinical Utility of a screened condition that HAS BEEN MANDATED by the state.** **Primary intent:** The intent is to monitor clinical performance characteristics of a mandated newborn screening test.	**OHRP Considerations:** Not research. Data being monitored WILL NOT inform or have an impact on whether or not the test will be implemented since screening has already been mandated by the state. The intent is not to create generalizable knowledge but to monitor clinical performance as a necessary part of compliance with a state mandate to implement screening for a condition.	A state has been mandated to implement screening for a certain condition. Once the state has an analytically validated test, it moves forward with live implementation of screening for the required condition. Information on clinical validity and clinical utility will be collected and monitored after the implementation of a live test. This includes clinical sensitivity and specificity; positive and negative predictive values; clinical utility.

8. IMPLEMENTATION OF A VALIDATED METHOD OR TEST SYSTEM FOR A NEWBORN SCREENING CONDITION

During implementation, state-wide screening using the validated test will be initiated. State would have already been mandated by an appropriate public health authority to implement screening for the new condition. After implementation, it is expected that the state will perform surveillance activities to track performance metrics of the existing program. Ongoing monitoring is essential to identify areas of improvement for the system.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
8a	State has been mandated to implement a screening test for a specific condition. Implementation involves a validated test system that is a Laboratory Developed Test or Home Brew.	**OHRP Considerations:** Not research. Intent of this activity is to implement a validated test to address a state-specific mandate to screen for a new disease. FDA has exercised enforcement discretion for certain provisions including premarket notification (i.e. clearance or approval) under the FD&C Act for laboratory developed tests.	State will continue to collect information to monitor the performance of the screening test and to assess the program as a whole.
8b	State has been mandated to implement a screening test for a specific condition. Implementation involves a validated test system that is an unmodified FDA-cleared or approved test system	**OHRP Considerations:** Not research. Intent of this activity is to implement a validated FDA approved test to address a state-specific mandate to screen for a new disease. No FDA considerations.	

9. SURVEILLANCE, EPIDEMIOLOGICAL PURPOSES, STATISTICAL PURPOSES

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
9a	State has established registries to monitor the number of children diagnosed with disorders included in the state newborn screening panel. These include cases diagnosed through the NBS program, cases missed by screening, as well as cases that reside in the state and did not have screening by the State program.	**OHRP Considerations:** Not research. This activity is meant for State surveillance and is not *designed to develop or contribute to generalizable knowledge.*	
9b	Additional surveillance activities, such as surveillance for hemoglobinopathies has been funded by outside sources using external grant funding	**OHRP Considerations:** Not research. This activity is meant for State surveillance and is *not designed to develop or contribute to generalizable knowledge.*	
9c	Collection of information for purpose of evaluation of the availability and effectiveness of preventive follow-up interventions (i.e. long-term follow-up). May include collection of annual patients' summary data on diagnosed cases that are being seen for ongoing management and care at specialty care centers via survey or other mechanism to determine whether the child is still accessing care or is lost to follow-up, the health status of the child, health care utilization data including hospitalizations and emergency department visits, new treatments initiated, etc.	**OHRP Considerations:** Not research. This activity is meant for State surveillance and is *not designed to develop or contribute to generalizable knowledge.*	

9. SURVEILLANCE, EPIDEMIOLOGICAL PURPOSES, STATISTICAL PURPOSES

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
9d	Surveillance of consent or refusal information to determine patterns or possible barriers to obtaining informed consent	**OHRP Considerations:** Not research. This activity is meant for State surveillance and is *not designed to develop or contribute to generalizable knowledge.*	
9e	Responding to legislative requests for aggregate data such as number of infants diagnosed with a particular condition in a certain time period.	**OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	
9f	Responding to request for aggregate data through a FOIA	**OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	

10. EMERGENCE PREPAREDNESS / CONTINUITY OF OPERATIONS (COOP) / CLINICAL USES, FORENSICS AND OTHER IDENTIFICATION

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
10a	Stored DBS are used to make emergency preparedness/COOP drills as realistic as possible and to validate that the assisting laboratory can successfully obtain the same screening outcomes. The samples may not be de-identified in order to assess the ability to enter patient information into the assisting states' LIMS.	**OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	In the past, all of this was protected by the 13 articles of EMAC as long as the proper paperwork and approval process was followed. However there are concerns that it may not be anymore. *EMAC is a national interstate mutual aid agreement that enables states to share resources during times of disaster.*
10b	Parents or siblings of an individual who has passed away from a genetic disorder may request the deceased individual's dried blood spot for genetic testing to identify specific mutations so that they can undergo carrier screening.	**OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.* Note: While this is not research states may require consent for the use.	
10c	DNA from the dried blood spot may be used to help identify victims in the aftermath of a disaster. Use of forensics based on parental or coroner request or subpoena.	**OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.* Note: While this is not research, states may still consider this to require consent or statutory authority for the use	

11. SURVEILLANCE OF STATE NEWBORN SCREENING PROGRAM BY STATE PROGRAM FOR INTERNAL USE AND TO CONSIDER QUALITY IMPROVEMENT STRATEGIES.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
11a	Evaluating newborn screening system performance measures to identify areas in need of improvement (e.g. turnaround time and percentage of specimens unsatisfactory for testing).	States Programs need to evaluate their own performance and determine areas for improvement. **OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	
11b	Monitoring of other parts of the newborn screening system: • the number of lost to follow-up cases • number of families refusing newborn screening • time to treatment • time to diagnosis • health care services provided • tests ordered and results • health status of the child, including symptoms Internal NBS Program evaluation of existing processes for NBS internal review and quality assurance, involving identified or de-identified specimens and/or associated data.	States Programs need to evaluate their own performance and determine areas for improvement. The intent of this activity is primarily for local program review and utilization. Results are not state-specific and utilized for internal quality improvement. **OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	

12. INTERNAL NBS PROGRAM REPORTS DE-IDENTIFIED NEWBORN SCREENING DATA FOR FEDERAL INITIATIVES TO EVALUATE NATIONAL TRENDS RELATED TO NEWBORN SCREENING.

Participating states have access to the federal compilation of data which facilitates improvement of individual NBS Programs.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
12a	State reports de-identified data to Newborn Screening Technical Assistance and Evaluation Program (NewSTEPS) to compare the state's NBS Program to that of other state NBS programs.	Colorado IRB did not classify this as research. Documentation is available. **OHRP Considerations:** Not research. This activity is *not designed to develop or contribute to generalizable knowledge.*	The Newborn Screening Technical assistance and Evaluation Program (NewSTEPs), funded through a cooperative agreement to the Association of Public Health Laboratories (APHL) by the Genetic Services Branch of the Health Resources and Services Administration (HRSA), provides quality improvement initiatives, an innovative data repository and technical resources for newborn screening programs. Question: Are the requirements for handling blood spot specimens the same as the requirements for handling its associated de-identified data?

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Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
12b	State reports de-identified data and may release residual specimens to participants in the NBSTRN VRDBS project. This may include basic demographic characteristics of diagnosed cases as well as similar demographic characteristics on a six month sample of negative cases.	NBSTRN website indicates that VRDBS is compliant with new regulations of the amendment. **OHRP Considerations:** For further discussion.	The **NBSTRN Virtual Repository for Dried Blood Spots (funded by NIH)** is a centralized, web-based tool to access specimens for newborn screening related research and program development. This virtual repository presents information from participating states and provides a centralized, de-identified view of dried blood spots, allowing researchers to browse and query for specimens.
12c	States send de-identified Tandem Mass Spectrometry (MS/MS) and other test data on true positive cases to R4S at NBSTRN, along with population percentiles and performance metrics to assist in maintaining tools for specimen interpretation and laboratory comparison.	**OHRP Considerations:** For further discussion.	

13. PROJECTS INITIATED BY OTHER PUBLIC HEALTH PROGRAMS BEYOND NEWBORN SCREENING WITHIN THAT STATE.

These studies involve identified or de-identified specimens and/or associated data (e.g. study to test a hypothesis)

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
13a	Research to evaluate the link between prenatal lead exposure and infant blood lead levels. Funding Source: State	**OHRP Considerations:** Research. These studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	
13b	IRB approved research activities where data from their prenatal screening program (example, prenatal screening markers) is linked to newborn screening program data (pregnancy/birth outcomes/NBS analytes, etc.). NBS data is also linked to emergency department and emergency room databases maintained by the Office of Statewide Health Planning and Development and to the Vital Statistics Birth and Death records.	**OHRP Considerations:** Research. These studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	

14. JOINT PROJECTS BETWEEN THE STATE NBS PROGRAM AND AN EXTERNAL ENTITY FOR RESEARCH PURPOSES.

The identity of the individual is known at the state lab but specimens and/or associated data are de-identified prior to distribution to the external co-researcher.

Ref #	Examples of activity	Proposed Classification: OHRP definition of research or not research; other regulatory considerations	Comments or considerations
14a	Evaluation of the link between hydrocephalus and infection with Cytomegalovirus (CMV), Lymphocytic Choriomeningitis Virus (LCMV), and Toxoplasmosis gondii.	**OHRP Considerations:** Research. These studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	
14b	Collaborating with external partners to explore various aspects of the newborn screening process and birth outcomes. Studies are usually disease focused (example VLADD) and de-identified data is shared with partners after receiving IRB approval.	**OHRP Considerations:** Research. These studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	
14c	Development of a test to measure polyfluoroalkyl compounds in blood spots to determine perinatal exposure and its effects on newborns. Performed with IRB exemption.	**OHRP Considerations:** Research. These studies will contribute to generalizable knowledge. ***Non-HHS funded activity:*** The Amendment does not apply. ***HHS funded activity:*** Amendment rules apply	