Nominating a Condition for the Recommended Uniform Screening Panel for Newborn Screening

Frequently Asked Questions

and other guidance

Nominating a Condition for the Recommended Uniform Screening Panel for Newborn Screening:

Frequently Asked Questions (FAQs)

Contents

Frequently Asked Questions (FAQs)....2
Contents....2
Introduction....3
Process for Adding a Condition to the Recommended Uniform Screening Panel (RUSP)....3
Developing the Nomination Package....4
Completing the Nomination Form....5
The Nomination Team....5
Section I – Condition Information and Treatment....5
Section II – Evidence-Based Information....5
Section III- Key References....6
FAQ for Completing the Nomination Form....7
More Information about Newborn Screening....9

Introduction

This Frequently Asked Question (FAQ) document is intended to be a resource for individuals interested in learning more about how to develop a nomination package to have a condition considered and added to the Recommended Uniform Screening Panel.

Process for Adding a Condition to the Recommended Uniform Screening Panel (RUSP)

Q: How does a condition get added to the Recommended Uniform Screening Panel?

A: There are a number of steps to how a condition is added to the RUSP. It involves convening a multi-disciplinary team to develop and submit a nomination package, submitting the package to HRSA, and multiple phases of Committee review. An overview of the steps in this process can be found on the Committee's website.

Q: How long does that process take to get a condition added to the RUSP?

A: For conditions that have been added to the RUSP using this process, the time from when a nomination is first presented to the Committee, to when the Secretary of Health and Human Services adds the condition to the RUSP has ranged from 1 year and 9 months (21 months) to 10 years (120 months). Most have been around 3 to 4 years.

Many condition nomination packages have had to be resubmitted to provide the Committee with all the information needed to consider whether the nomination is ready for full review.

Q: What happens if a nomination is not accepted or is deemed incomplete or not ready for Committee review?

A: Before a nomination is accepted, HRSA conducts an administrative review of the nomination package and form. If the nomination package or form is missing any information, the Committee's Designated Federal Official (DFO) will return it to the nominator, identifying the components needing further information. It is important to reach out to the HRSA DFO early and often during development of the nomination package. They are available to answer questions about the process.

Q: What happens if the DFO accepts the nomination, but then it is returned before it is presented at a full Committee meeting for further consideration or review?

A: After HRSA determines that the nomination package is complete, a smaller Committee workgroup, called the Nomination and Prioritization Workgroup, carefully reviews the nomination package. The Nomination and Prioritization Workgroup's first step is to determine whether there is sufficient information in the package to answer key questions. If this Committee workgroup identifies any missing information in the nomination package, the Committee Chair may return the nomination package and request additional information from the nominators.

Q: What happens if the nomination is accepted and presented at a Committee meeting, but the Committee votes NOT to move it any further for evidence review?

A: If a condition nomination package is presented and discussed at a Committee meeting and the Committee votes NOT to move the nomination to evidence-based review, the Committee Chair will send a letter to the nominator. This letter will state why the nomination was not moved forward. The letter will also include what additional information or evidence is needed for the Committee to re-consider the nomination.

Q: What should the nominator be doing once the Committee accepts the nomination and moves it to evidence review?

A: Once the Committee requests a full evidence-based review of the condition, the role of the nominator and team shifts. The Evidence-Based Review Group (ERG) typically will invite one of the nomination team members to serve on the Technical Expert Panel, or TEP. The TEP helps to guide the review as it progresses, providing expert insight to help the ERG understand and identify all available evidence, particularly any unpublished or gray literature that is not in the library databases. The nomination team representative often has an in-depth knowledge of activities or evidence related to newborn screening for the condition and may be an important facilitator to help the ERG identify potential evidence not otherwise readily available.

Developing the Nomination Package

Q: What do I need to submit for the RUSP nomination package?

A: The nomination package that must be submitted to the Committee (via the HRSA Designated Federal Official) includes the following components:

- Cover letter from nominator identifying the nomination team members
- Letters of support (from multi-disciplinary team members), if applicable;
- Completed Conflict of Interest Disclosure Forms from all nomination team members;
- Completed Nomination Form; and
- Key scientific/clinical references and supporting data to substantiate responses in the Nomination Form.

Q: What are some tips for developing a nomination package?

1. Educate yourself about newborn screening, the condition, the nomination process, and how the Committee reviews the nomination and evidence on newborn screening for the condition.
2. Identify and assemble an expert team for the nomination. Make sure that you have expert members who can advise, develop the nomination package, write, review, edit, and re-write.
3. Develop a key list of references, evidence and data that support nomination form responses.
4. Communicate with the Advisory Committee's Designated Federal Official, let them know your timeframe for submission and ask them for technical assistance.

Q: Who can nominate a condition to the RUSP?

A: Most anyone can be part of the nomination team, though including researchers, clinicians, key stakeholders and experts will be important to gain their input. Generally, the conflict of interest disclosure formsare required for each team member. If a potential team member has a major conflict of interest (e.g., financial stake in treatment for newborns identified through screening), that must be disclosed. Also, members of the Evidence-Based Review Group, Advisory Committee, HRSA,or others directly involved in the evidence review or decision-making, will need to recuse themselves of participating. However, these individuals may be consulted for input about the process as you are developing your nomination package.

Completing the Nomination Form

The Nomination Team

This initial section asks for the name and affiliation of the primary nominator submitting the package, and of the other team members. The nomination team should be comprised of key stakeholders who have expertise in some aspect of newborn screening and treatment for the condition, including scientific/research, clinical care and treatment, state newborn screening/public health laboratories, experts in conducting pilot newborn screening, if needed, and parents and families of patients who understand living with the condition.

Section I – Condition Information and Treatment

Part A: This section requires detailed information about the condition and its treatment. The condition information that should be provided includes the type of disorder, screening gene, locus, other names for the condition, case definition (what constitutes a case of the disease), incidence, timing of clinical onset and severity of disease (including morbidity, disability, mortality, spectrum of severity. The level of condition information is needed to accurately categorize the condition that is nominated and to provide the scientific and clinical references for why this condition maybe a candidate for public health based newborn screening.

Part B: This section focuses on treatment for the condition. For a condition to be considered for newborn screening, there must be a standard or approved therapy(ies) or intervention(s) available with which to treat the newborn identified with the condition. To be recommended for newborn screening, early detection and initiation of treatment should bring improved outcomes compared with clinical detection and treatment. The treatment information should include the modality of treatment, urgency of beginning treatment, documented efficacy, availability, and harms of treatment. All of the data points help indicate if detection and follow-up of the condition is feasible in a public health setting.

Section II – Evidence-Based Information

For a nominated condition to be considered there are three core requirements: A) validation of laboratory test, B) widely available confirmatory testing, and C) prospective, population-based screening (pilot study or newborn screening program). Section II focuses on the specific evidence available for each of these core requirements.

Part A: Validation of Laboratory Tests

In this section, nominators must describe and provide references for the evidence about the screening methods to demonstrate use for detecting newborns at high risk for having the condition in a high-volume, high-throughput application. The screening test (e.g., assay or genetic test) must have evidence of validity (e.g., that it is reliable, accurate, and sensitive to detect the condition), when used in assessing high volumes of specimens. Other specific information requested about validation of screening methods includes modality of screening and the type of specimen used, components of the screening algorithm, clinical and analytical validation, consideration for screening and diagnostic testing including false positives, carrier detection, and others, and if there are potential secondary findings.

Part B: Availability of Confirmatory Testing

This section focuses on the confirmatory testing for the condition. Newborn screening laboratories conduct confirmatory testing of a newborn's specimen that is determined to be a positive screen. Newborn screens that are confirmed to be positive, are referred to clinical providers for diagnostic confirmation. While newborn screening is a screening program, the end goal is to detect babies with condition and provide them with beneficial treatment. For confirmatory diagnostic testing, the nominator must document the availability of confirmatory diagnostic testing, noting the type of test used, its analytic and clinical validity, U.S. Food and Drug Administration status, if applicable, and a listing of all CLIA labs offering the test in the United States (U.S.)

Part C: Population-Based Pilot Study

In this section, the nominator will focus on available evidence from current prospective population-based screening. The nominator is asked to describe the prospective pilot(s) or screening program implementing screening to detect the condition across an entire population. This information is key because newborn screening is a population-based, public health program and any condition added to the RUSP must be able to be applied in high volume testing. Details of the population-based screening program or pilot(s) required include the following: location, number of newborns screened, number of screen positives, false positive and false negative rates, number of confirmed diagnosis and method of diagnosis.

Section III- Key References

In this section, nominators are asked to list and provide references from scientific journals to support the statements made in Sections 1 and II. It is vital to include a listing and copies of references used in the nomination package to ensure those involved at different stages of the review process have access to the information presented in the Nomination Form.

Q: What is needed for the "case definition" of the disease?

A: For this purpose, case definition refers to both the screening target and clinical phenotype(s) of particular focus for screening. Specifying the screening target is important for the state public health laboratories to know the goal of screening is in terms of the laboratory result. For example, Spinal Muscular Atrophy (SMA) screening specifies that "SMA with homozygous deletion of exon 7" is the screening target, which accounts for over 95% of the disease. The clinical case definition may be important, particularly when the condition has a more severe, early-onset form of the condition that may be time-critical for identification and treatment initiation. Alternatively, the condition may have a phenotype that is less severe or later-onset which may be considered as secondary to a relatively more time-critical phenotype. It is important for the nominator to distinguish the screening and clinical aspects of the case definition for newborn screening.

FAQ for Completing the Nomination Form

Q: How are different phenotypes of the same condition viewed by the Committee?

A: This question relates to the above question about "case definition." Different phenotypes may potentially have different net benefit and harms associated with them, based on different ages of symptom onset, treatment indications, and prognosis. In such cases, the evidence would be reviewed and assessed differently.

Q: What are the accepted sources of data for the Nomination Form and what data will be considered by the Evidence-Based Review Group (ERG) and Committee?

A: The Committee is charged with making evidence-based decisions. To the extent possible nominators should submit peer-reviewed/published information about the nominated condition. The evidence considered by the evidence-based review and the Committee includes a range of types of reports, U.S. or international A critical element is that the report include original research data or analyses relevant to the newborn screening or early treatment for the condition. The ERG screens and reviews different types of evidence reports systematically.

Table 1 below gives some examples of different types of evidence reports which may be reviewed. Screening and treatment articles included in the evidence review are also assessed for quality of evidence.

Table 1. Examples of types of reports which may be screened or reviewed

Type of Evidence	Report or Documents
Published, peer-reviewed evidence	• Reports published in scientific, peer-reviewed journals • Reports published in scientific databases (e.g., PubMed, EMBASE, CINAHL, and Cochrane Reviews) • Abstracts from scientific or professional conferences or meetings.
Unpublished evidence	• Prospective newborn screening programs or pilots. • Registry studies (patient or clinical) not published or reviewed elsewhere.
Gray literature	• Conference or meeting abstracts *not* otherwise peer-reviewed or published (e.g., patient group meetings, presentations at other newborn screening meetings, public health meetings). • Clinicaltrials.gov listings of trials which may warrant further follow up or indicate the state of treatments in the 'pipeline.'

Q: What are the questions the Evidence-Based Review Group is trying to answer?

A: The evidence-based review for each condition has a set of key questions about the condition, incidence and prevalence, natural history, screening, treatment, and the public health impact.

The question specifics are tailored for each condition under review.

Q: What data need to be gathered from any pilot studies or population-based screening program?

A: Section II. Part C. has been expanded to list the specific information requested fromprograms conducting population-based screening, which includes the following:

- Location of program or pilot
- Screening methods and algorithm
- Total number of newborns screened (to date)
- Number of screen positive results
- False positive rate
- False negative rate (if known)
- Number of infants confirmed with diagnosis
- Key outcomes of treatment
- Program contacts

Q: In instances in which the approved intervention may have little clinical data (i.e. use ofa surrogate biomarker), is there specific longitudinal data that will help inform Committee decision-making within a nomination package?

A: When screening or treatment is known to impact an intermediate biomarker and evidence is available about changes in the biomarker from treatment, it is also important to show evidence that changes in the biomarker are associated with changes in disease progression or other outcomes. If that connection is established, the biomarker may be considered an intermediate outcome of interest.

More Information about Newborn Screening

Q: Where can I find more information about newborn screening?

A: Newborn Screening Information Center - https://newbornscreening.hrsa.gov/

To increase awareness, knowledge, and understanding of newborn screening, the Newborn Screening Information Center was developed to deliver general as well as state-specific and condition-specific newborn screening information. The site provides information about newborn screening and the newborn screening process in the U.S. and how that process relates to follow up, diagnosis, and treatment. The site also identifies conditions that states screen for as part of newborn screening, and connect parents, parents-to-be, and health care providers with newborn screening resources and updates.