Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for review of processes in use to inform the expansion of newborn bloodspot screening programmes

2 July 2021

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory authority established to promote safety and quality in the provision of health and social care services for the benefit of the health and welfare of the public.

HIQA's mandate to date extends across a wide range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children, Equality, Disability, Integration and Youth, HIQA has responsibility for the following:

- **Setting standards for health and social care services** — Developing person-centred standards and guidance, based on evidence and international best practice, for health and social care services in Ireland.
- **Regulating social care services** — The Chief Inspector within HIQA is responsible for registering and inspecting residential services for older people and people with a disability, and children's special care units.
- **Regulating health services —** Regulating medical exposure to ionising radiation.
- **Monitoring services** — Monitoring the safety and quality of health services and children's social services, and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health technology assessment** — Evaluating the clinical and cost-effectiveness of health programmes, policies, medicines, medical equipment, diagnostic and surgical techniques, health promotion and protection activities, and providing advice to enable the best use of resources and the best outcomes for people who use our health service.
- **Health information** — Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information on the delivery and performance of Ireland's health and social care services.
- **National Care Experience Programme** — Carrying out national service-user experience surveys across a range of health services, in conjunction with the Department of Health and the HSE.

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List of abbreviations used in this document

EEA	European Economic Area
EU	European Union
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment
MS/MS	tandem mass spectrometry
NBS	newborn bloodspot screening
NNBSP	National Neonatal Bloodspot Screening Programme
NSAC	National Screening Advisory Committee

Background to the HIQA/NSAC work programme

The 'Scally Report' (2018) recommended the establishment of a National Screening Committee to advise the Department of Health and the Minister on all new proposals for screening and on revisions to current programmes. Following this report, the National Screening Advisory Committee (NSAC) was established as an independent advisory committee to play a significant strategic role in the development and consideration of population-based screening programmes in Ireland. The Health Technology Assessment (HTA) directorate within the Health Information and Quality Authority (HIQA) has been commissioned to provide evidence synthesis support to the NSAC, under an agreed work programme.

The current NSAC/HIQA work programme includes two evidence synthesis work streams:

- evidence synthesis to inform methods and processes for national screening programme policy-making
- evidence synthesis to inform advice on the expansion of the National Newborn Bloodspot Screening Programme (NNBSP).

The present document provides the research protocol for the review of processes to inform advice on the expansion of the NNBSP.

For the purpose of this review, only processes relating to the expansion of conditions screened for in first-line newborn bloodspot screening will be considered; while genetic screening may be used in some cases for second-tier screening (e.g., for confirmatory diagnosis), whole exome or whole genome screening of bloodspot material are considered out of scope for this review.

Review aims:

To identify evidence relevant to how different countries formulate advice on the expansion of newborn bloodspot screening (NBS) programmes.

Review question and objectives:

Review question:

> "Describe evidence, at an individual country-level, for the following elements relevant to decision-making on the expansion of newborn bloodspot screening programmes."

The review question is structured as four objectives in order to clarify the scope of

the review and to identify the appropriate approach for each aspect. These are outlined as follows:

- what are the conditions that are screened for in existing newborn bloodspot screening (NBS) programmes?
- what is the process for topic (condition) proposal, prioritisation procedures, and the selection of topics for evidence review?
- what are the decision-making processes that lead to the inclusion of a condition in an individual country's (or region's) NBS programme?
- what is the role of emerging technology in programme expansion (e.g., the impact of adoption of tandem mass spectrometry, novel laboratory assays, on expansion)?

Note that outcomes of processes, for example, measures of performance of NBS screening programmes, are out of scope.

Purpose of the review

The present review will aim to identify information on processes relevant to decision-making on the expansion of NBS programmes. In particular, the review will present an up-to-date account of current international processes. The findings of this review will be provided to the NSAC to inform decision-making processes within the NNBSP.

Background to the review

Introduction

Newborn bloodspot screening (NBS) is performed to identify treatable metabolic disorders or other inherited disorders in infants. This screening does not act as a diagnosis, but rather serves to suggest that a newborn may be at higher risk of having one or more of the conditions screened for (that is, where the baby is described as being 'screen positive'). Screening is performed so that these disorders may be identified before the development of symptoms, thereby facilitating the use of interventions to prevent or mitigate adverse outcomes associated with these conditions. Where these disorders are left undiagnosed and untreated, they pose risks of developmental delay, severe disability, or premature death.

Over time, the concept of NBS has evolved from a simple screening test to a potential comprehensive screening system capable of detecting over 50 different conditions.[1] Technological advances include the implementation of tandem mass spectrometry (MS/MS), allowing for the simultaneous testing of many different biochemicals without substantially increasing the costs of performing the test or the time to result. However, increasing the number of conditions screened may have unintended consequences, such as, increasing the number of false positive cases, overdiagnosis, and overtreatment.[2, 3]

Potential harms of screening and the need for structured decision-making

The potential harms associated with screening in general are well-recognised, and may include the physical consequences of testing or treatment, or the psychological consequences of parents being told their child is at high risk of a particular diagnosis, especially where that information represents a 'false positive'. As such, decision-making on the introduction of screening programmes must be careful, comprehensive and transparent in order to ensure that the benefits of screening outweigh the potential harms.[4, 5]

Ireland's National Newborn Bloodspot Screening Programme (NNBSP)

In Ireland, NBS, otherwise known as the 'heel-prick' test, is offered for every newborn baby and is carried out when the infant is between 72 hours and 120 hours of age with the consent of the parents.[6] Following the test, parents are contacted only if the test results are abnormal, usually when the infant is one to two weeks old.[7] Screening cards, which hold the dried bloodspots, are currently stored securely for ten years following the test and are thereafter destroyed.[7]

The NNBSP currently tests the baby's blood for the presence of the following eight conditions:[8]

- phenylketonuria (PKU)
- homocystinuria
- maple syrup urine disease (MSUD)
- classic galactosaemia
- congenital hypothyroidism
- cystic fibrosis
- medium chain acyl-CoA dehydrogenase deficiency (MCADD)
- glutaric aciduria type 1 (GA1).

The NSAC approved the addition of ADA-SCID (adenosine deaminase deficiency-severe combined immunodeficiency) to the list of conditions screened under the NNBPS, in July 2020.[9] Following the positive recommendation from the NSAC, the Minister for Health accepted the recommendation, and as of February 2021, the HSE is making arrangements for inclusion of this condition in the programme.[10]

Participation in the NNBSP in Ireland has been stated in recent years to be at 99.9%[6, 7, 11] and has previously been acknowledged as one of the most successful national public health initiatives.[7] Each year, newborn bloodspot screening identifies about 110 babies in Ireland with one of the above conditions.[12]

Current decision-making processes for conditions included in the NNBSP

As of the publication in 2014 of the 'National Rare Disease Plan for Ireland 2014-2018', the HSE had established and implemented a governance structure for the NNBSP.[13] In part, the NNBPS Governance Group is responsible for providing multidisciplinary advice, to the Director of Childhood Screening, regarding strategic direction of the programme, and thereby considers proposals to expand the programme.[14]

The 2018 edition of 'A Practical Guide to Newborn Bloodspot Screening in Ireland',[14] published by the National Newborn Bloodspot Screening Laboratory, states that conditions which form part of the NNBSP have been selected because they all have a relatively high incidence within the Irish population and because they fulfil, in part or in full, the criteria which have been set out internationally for newborn screening.

These criteria are stated to include the following:[14]

- the conditions screened are treatable
- there is a test available which is easily applied to large population groups
- there are few false positive and false negative results, that is, the test is reliable

- the incidence of the conditions in the community is sufficiently high to warrant screening
- the cost of screening makes the process cost-effective.

International differences in conditions included in newborn bloodspot screening programmes

There is substantial variation between countries, and regionally within some countries, in the number of conditions included in NBS programmes. For example, in North America, programmes are delivered by individual states within the US and individual provinces, territories or regions within Canada, resulting in differences in the numbers of conditions screened.[1] Consequently, efforts have been made to develop national recommendations; in the US, the Secretary of the Department of Health and Human Services recommends a list of disorders to be included by all individual states as part of their universal newborn screening programmes.[1] This 'Recommended Uniform Screening Panel' currently includes 35 conditions.[15]

In European countries, NBS programmes are heterogeneous, with no consensus across countries as to what conditions should or should not be included.[1] Significant variation exists in the number of conditions included for screening, both between countries and between regions within individual countries. For example, the United Kingdom currently screens for nine conditions[16] while Italy recommends over 40 conditions be included in screening.[17] In countries such as Belgium and Spain, policy-making is decentralised to regions or provinces; this has been noted to result in <100% screening coverage for certain conditions within these countries overall.[1]

In reviews of international decision-making processes, it has been observed that, historically, the expansion of NBS programmes has occurred following *ad hoc* consideration of conditions rather than following a structured and transparent approach.[4] As a result, there is a need for robust national decision-making processes to minimise the risks associated with policy-making with respect to the NNBSP.[5, 18]

Methods

The present review will aim to identify information on processes relevant to decision-making on the expansion of NBS programmes.

Objective 1, '*What conditions are screened for in existing blood spot screening programmes?* may be considered to be an output of processes which inform advice on the expansion of NBS, while objectives 2 and 3 concern the processes themselves, which inform advice on the expansion of NBS. Objective 4, '*What is the role of emerging technology in programme expansion'* relates to how aspects of technology are considered within processes which inform advice on the expansion of NBS, and also to how technology is adopted within current NBS programmes.

In order to answer review objectives 1, 2, and 3, a review of international processes and international NBS programmes will be performed. Information will be gathered on processes for the expansion of NBS by reviewing a sample of countries and obtaining information from both grey literature and academic literature. This review will document, for this sample of countries, the panel of conditions screened for within NBS programmes and the processes informing the expansion of such programmes. Inputs or criteria considered within such processes will be detailed and a specific summary of the factor of 'emerging technologies' (objective 4) will be provided. It is anticipated that objective 4 will be completed in tandem with the other objectives within this review; that is, information will be gathered on the role that emerging technologies have in decision-making processes overall.

Given the scope and proposed methodology of the present review, it will not be possible to judge the relative merits of particular processes and no judgement will be made on the appropriateness of processes in place in individual countries. However, where assessments have been made by academic authors or national authorities of the appropriateness of processes (for example, with respect to factors such as timeliness of review or suitability for advancement of population health), and where these are captured within the below described search approach, these assessments will be noted. Furthermore, a general discussion of findings will be provided, with input from an EAG to be compiled by HIQA.

Methodological overview

The review will involve an international review of practices in place, including decision-making practices, in international NBS programmes, focusing on countries considered to be of particular relevance to the Irish public health decision-making context. The approach will draw on the methods applied by Jansen et al. in their

2017 review of international differences in the evaluation of conditions for NBS, which took the form of a review of both academic literature and policy documents.[5]

The following list of countries were identified by Jansen et al. as providing clear information on NBS decision-making processes and as having long-standing NBS programmes:[5] Australia, Canada, Denmark, Germany, the Netherlands, New Zealand, the United Kingdom (UK), and the United States of America (USA). As such, these countries will be selected as the minimum set of countries for individual review; grey literature associated with delivery of screening within each of these countries will be searched to identify documents describing NBS-related decision-making processes. Information will also be sought from policy documents and reports by EU-level committees associated with screening decision-making, in order to determine processes at EU-level.

To complement this grey literature search, a search of academic literature will be performed. This will aim to identify reviews of international NBS programme policy-making processes. These will be examined to identify countries within the EU or EEA that have recently (within the past ten years) expanded their NBS programmes, as well as Australia, New Zealand, Canada, the UK and the USA, as these countries are expected to be of most relevance to the Irish public health decision-making process. This approach may identify additional countries for targeted grey literature review. Reviews, such as that by Jansen et al., which discuss factors influencing NBS policy-making or decision-making processes, will also be included for the purpose of incorporating this academic analysis.

The academic literature search will additionally aim to identify or confirm descriptive information with respect to review objective 1 for the overall European region (panel of conditions included in current NBS programme and extent of recent expansion). Early scoping for this review has identified three reviews recently published, or due for publication shortly, which provide information on the current status of NBS programmes within European countries and beyond.[1, 17, 19] Descriptive results for review objective 1, obtained from reviews identified through the literature search, will be cross-checked against each other and against the results of the grey literature review. Where discrepancies are identified, information from national screening programme websites will be given precedence and representatives of international screening programmes will be contacted to confirm findings, where appropriate.

Search of relevant sources

Academic literature search

Search strategies for identifying academic literature will combine a search for NBS with a search for policy-making or decision-making and will be conducted within the databases Medline and Embase (see appendix table 1.1 for details). The search strategy will aim to specifically identify reviews, but will not be restricted by language. The search will be supplemented by searching the first five pages of Google and Google Scholar incorporating similar terms.

This academic search will be used to identify relevant academic literature which reviews decision-making processes with respect to expansion of national NBS programmes. Data from this review will be used to supplement the information obtained as part of the grey literature search. If detailed evidence applicable to the Irish content is identified with respect to decision-making processes in European countries not already included in the minimum list for individual review, these countries will be carried forward to the grey literature search

Grey literature search

A grey literature search will be used to retrieve relevant documents that represent national-level (or EU-level) statements on the decision-making processes, and current status (with respect to conditions screened and technological processes involved in screening), of expansion of NBS programmes. For each country, websites of national ministries of health, authorities with responsibility for screening, and national public health agencies will be specifically searched for information related to the review question components. Although language will not be an exclusion criterion initially, relevant non-English language reports, for which a reasonable English translation cannot be obtained, will be excluded.

Selection of publications

All titles and abstracts of returned citations will be screened independently by one reviewer. All records identified as potentially relevant will be translated, where necessary, and full text copies obtained (academic publications). Relevant non-English language studies for which a reasonable English translation cannot be obtained will be excluded. Full text documents and articles will be screened by one reviewer and any uncertainty cross-checked by a second reviewer in accordance with the criteria outlined in the Population Interest Context tables presented in Table 1.

Table 1: Population, Interest, Context tables representing inclusion and exclusion criteria for searches and identification of relevant data

Academic literature search	
Population	Newborn Bloodspot Screening (NBS) Programmes within countries considered to be of similar public health decision-making relevance to Ireland: ▪ Australia, Canada, New Zealand, USA, UK ▪ EEA and Switzerland.
Interest	**Specific topics of interest:** <u>Descriptive information on NBS programmes (objectives 1, 2 and 3):</u> ▪ Conditions screened for in existing NBS programmes ○ number of conditions ○ composition of screening panels. ▪ The process for topic (condition): ○ proposal ○ prioritisation ○ selection for formal assessment. ▪ The decision-making processes that lead to the inclusion of a condition in the individual country's (or region's) newborn bloodspot screening programme. <u>Detailing of factors influencing NBS programme policy-making or decision-making (objective 4):</u> Criteria of particular interest include: ▪ Consideration of the role of technology with respect to its influence on proposal, prioritisation and selection procedures or decision-making processes for expansion of NBS programmes, for example: ○ availability of new technologies (e.g., influence of recent availability of new tests on expansion or on urgency of decision-making processes) ○ efficiencies or feasibility of implementation associated with certain technologies or emerging tests

	○ expansion taking place for groups of conditions as opposed to individual conditions, and reasons for such approaches: ▪ importance of efficiency in programme expansion (e.g., validation processes). ▪ Consideration of the role of ethics in decision making, for example: ○ perspective regarding screening beneficiary (i.e., the individual or group of people who will benefit most as a result of screening, e.g., child/family/society). **Exclude:** ▪ Articles specifically focusing on clinical effectiveness, cost-effectiveness, budget impact or acceptability of expansion of programmes (as opposed to reviews of processes). ▪ Articles not concerned with expansion of NBS programmes ▪ Single-authored opinion pieces. ▪ Papers relating to developing countries for which public health services and health system overall differ significantly to that of Ireland. ▪ Neonatal, but not bloodspot tests (e.g., hearing test / hip test).
Context	Description or consideration of processes within NBS programmes which have undergone expansion, or which have considered expansion, within the years 2011 to 2021.
Targeted grey literature search	
Population	Newborn Bloodspot Screening (NBS) Programmes within the following countries: ▪ (Non-EU) Australia, Canada, New Zealand, USA, UK ▪ (EU) Denmark, Germany, Netherlands ▪ EU-level institutions (e.g. committees tasked with NBS expansion guidance). Information on additional countries will be included where such countries are highlighted in existing reviews of international processes as having clear processes for NBS programme expansion decision-making.
Interest	**Specific topics of interest:**

	Descriptive information on NBS programmes (objectives 1, 2 and 3): ▪ Conditions screened for in existing NBS screening programmes, and recent expansion of programme or removal of conditions from programme. ▪ Topic (condition) proposal, prioritisation and selection procedures ▪ Decision-making processes. Detailing of factors influencing NBS programme policy-making or decision-making (objective 4): Criteria of particular interest include: ▪ Consideration of the role of technology with respect to its influence on proposal, prioritisation and selection procedures or decision-making processes for expansion of NBS programmes, for example: ○ availability of new technologies (e.g., influence of recent availability of new tests on expansion or on urgency of decision-making processes) ○ efficiencies or feasibility of implementation associated with certain technologies or emerging tests ○ expansion taking place for groups of conditions as opposed to individual conditions, and reasons for such approaches: ▪ importance of efficiency in programme expansion (e.g., validation processes). ▪ Consideration of the role of ethics in decision making, for example: ○ perspective regarding screening beneficiary (i.e., the individual or group of people who will benefit most as a result of screening, e.g., child/family/society). **Exclude:** ▪ Documents not concerned with expansion of NBS programmes. ▪ Local/institutional-level documents. ▪ Neonatal tests not involving bloodspot (e.g., hearing test / hip test).
Context	NBS programmes which have undergone expansion, or which have considered expansion, within the years 2011 to 2021.

Eligibility criteria

Publications, reports and government websites ('documents') will be eligible for inclusion in this review if they contain a description of the process of policy-making or existing policy with respect to the expansion of a national NBS programme, as per Table 1.

In the interests of capturing information on processes relevant to recent developments in NBS (which underlie calls for expansion to programmes), the search will be restricted to documents published in the past ten years. As such, documents will be included if they were published or updated between 1 January 2011 and 1 April 2021.

Reporting of findings

A summary of the findings will be drafted with all extracted data presented in the report. Draft data extraction tables are presented in Appendix 2.

Quality assurance process

This review will be led by an experienced analyst. A minimum of one team member will be assigned to assist with the review. Second reviewers will be required to check that the report accurately reflects the guidance included. The report will be reviewed by a senior member of the team, to ensure processes are followed and quality maintained.

With respect to external oversight, the review approach may involve making contact with representatives of national NBS programmes to confirm that the information gathered in the report is an accurate reflection of processes in place. Furthermore, the evidence synthesis team will establish an expert advisory group to contribute feedback on the present review protocol and on the final review.

Timelines

Work will commence on 1 March and a final draft will be completed and circulated to the NSAC on 14 May 2021 for consideration at the NSAC meeting taking place on 20 May 2021. It is estimated that this review will require at least 10 weeks to complete. This timeline is dependent on available resources and the extent of the literature. It is expected that 1.5 experienced researchers will be available to work on this review

throughout the review timeline and others may be required at certain stages of the reviews. This timeline assumes scoping and the development of a search strategy prior to 1 March 2021.

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Appendices

Appendix 1: Search strategy

Table 1.1. Search strategy for Pubmed and Embase search

PUBMED	
A	#1 (bloodspot* OR blood spot*) AND (neonatal OR newborn OR new born) #2 "guthrie test" #3 "Guthrie card" #4 "heel prick" #5 "metabolic screening" #6 #1 OR #2 OR #3 OR #4 OR #5
B	#6 Policy making #7 Public Policy #8 Health Policy #9 Guideline #10 decision making #11 "health planning" #12 health planning technical assistance #13 "regional health planning" #14 "National Health Programs" #15 "Government Programs" #16"polic*"[tiab] OR "guideline*"[tiab] OR "framework"[tiab] OR "program*"[tiab] OR "strateg*"[tiab] OR "decision making*"[tiab] OR "decision-making*"[tiab] OR "process*"[tiab] OR "procedure*"[tiab] OR "plan*"[tiab] OR "recommend*"[tiab] OR "committee*"[tiab] OR "expan*"[tiab] OR "evaluation"[tiab] OR "implementation"[tiab] OR "assessment"[tiab]
	#6 OR #7 OR #8# OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
C	A AND B
	Limit from 2011 to 2021
EMBASE	
A	#1 (neonatal OR newborn OR 'new born') AND ('blood spot*' OR 'bloodspot*') #2 'guthrie test' #3 'guthrie card' #4 'heel prick' #5 'PKU':ti,ab #6 'metabolic screening':ti,ab #7 #1 OR #2 OR #3 OR #4 OR #5 OR #6
B	#8 'policy' #9 'health care policy'/exp #10 'hospital policy'/exp #11 'practice guideline'/exp #12 'health program'/exp #13 'decision making'

	#14 'process design' #15 'process development' #16 'process optimi?ation' #17 'procedures' #18 'health care planning' #19 'strategic planning' #20 'hospital planning' #21 'patient care planning' #22 'program development' #23 'polic*':ti,ab OR 'guideline*':ti,ab OR 'framework':ti,ab OR 'program*':ti,ab OR 'strateg*':ti,ab OR 'decision making*':ti,ab OR 'decision-making*':ti,ab OR 'process*':ti,ab OR 'procedure*':ti,ab OR 'plan*':ti,ab OR 'recommend*':ti,ab OR 'committee*':ti,ab OR 'expan*':ti,ab OR 'evaluation':ti,ab OR 'implementation' OR 'assessment':ti,ab #23 #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
C	A AND B Limit from 2011 to 2021 Embase unique hits only

Appendix 2: Draft data extraction tables

Table App2.1: Characteristics of policy making processes for individual countries included in review

Country Body responsible for delivering NBS Data source(s), URL and date of publication or date of last update	Number of conditions currently screened for Secondary screening in place?	Regional variation in conditions screened Regional variation in conditions screened	How technology has influenced decision making	Information on expansion of programme 2011-2021	Information on NBS programme participation rates

Table App2.2: Proposal, prioritisation and selection of topics for review

Country Data source (URL and date published or updated)	Perspective regarding screening beneficiary	Method of proposal of condition to be considered for addition	Prioritisation of review of conditions to be considered for addition	Selection of condition(s) for review

Table App1.3: Methodologies for review and synthesis of evidence on screening effectiveness

Country	Inclusion of stakeholders?	Review type?	Who conducts review?	How is evidence quality appraised?	Quality assurance of review and recommendation?

Table App1.4: Decision-making processes in place for screening recommendations

Country	Inclusion of stakeholders?	Decision-making/ recommendation-issuing authority?	Structured decision-making process described?	Criteria considered within decision-making process?	Decision-making process description	Is the recommendation qualified?

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