Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for a health technology assessment of the addition of congenital adrenal hyperplasia to the National Newborn Bloodspot Screening Programme

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Reporting to the Minister for Health and engaging with relevant government Ministers and departments, HIQA has responsibility for the following:

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- **Regulating social care services** — The Chief Inspector of Social Services 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 permanent international protection accommodation service centres, health services and children's social services against the national standards. Where necessary, HIQA investigates serious concerns about the health and welfare of people who use health services and children's social 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.
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Table of contents

List of abbreviations used in this report

17-OHP	17-hydroxyprogesterone
21-OHD	21-hydroxylase deficiency
CAH	congenital adrenal hyperplasia
CEA	cost-effectiveness analysis
EAG	Expert Advisory Group
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
HTA	health technology assessment
ICER	incremental cost-effectiveness ratio
ISPOR	The Professional Society for Health Economics and Outcomes Research
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LYG	life year gained
NBS	newborn bloodspot screening
NMB	net monetary benefit
NNBSP	National Newborn Bloodspot Screening Programme
NSAC	National Screening Advisory Committee
PICOS	population, intervention, comparator, outcome, study design
QALY	quality-adjusted life year
SCID	severe combined immunodeficiency
SMA	spinal muscular atrophy

1 Introduction

1.1 Background

The National Screening Advisory Committee (NSAC) was established in 2019 by the Minister for Health as an independent advisory committee to play a significant strategic role in developing and considering population-based screening programmes in Ireland.[1] At the request of the Department of Health, the Health Technology Assessment (HTA) directorate within the Health Information and Quality Authority (HIQA) undertakes evidence synthesis and provides evidence-based advice to NSAC on behalf of the Minister for Health. To date, at the request of NSAC, HIQA has undertaken evidence synthesis to inform the committee's recommendations to expand the National Newborn Bloodspot Screening Programme (NNBSP) to include screening for Severe Combined Immunodeficiency (SCID) and Spinal Muscular Atrophy (SMA).[2] Preparations to add SCID and SMA to the newborn bloodspot screening (NBS) panel are ongoing.[3]

Conditions included in the NNBSP must fulfil internationally accepted standards for NBS.[4, 5] The NNBSP in Ireland currently screens for nine rare but serious conditions, excluding SCID and SMA.[6] Participation in the NNBSP in Ireland is high, with an estimated uptake of 99.9%.[4, 7] Each year, the NNBSP identifies over 120 cases with one of the conditions included in the screening panel.[4]

In May 2025, at the request of NSAC, HIQA agreed to undertake a HTA to support decision-making regarding the addition of congenital adrenal hyperplasia (CAH) to the NNBSP. This protocol outlines the methodological approach that HIQA's evaluation team will adopt to synthesise the evidence and develop HIQA's advice to NSAC.

1.2 Congenital adrenal hyperplasia

CAH is a group of autosomal recessive conditions caused by genetic mutations that disrupt enzymes involved in adrenal steroidogenesis, including 21-hydroxylase deficiency (21-OHD), 11-beta-hydroxylase deficiency (11β-OHD), and other rarer enzyme deficiencies.[8] Over 95% of cases of CAH are caused by mutations in *CYP21A2*, the gene encoding 21-hydroxylase (21-OH).[8]

There are two main types of CAH caused by 21-OHD:[9, 10]

- Classic CAH presents anytime from birth to early childhood, depending on the sex of the patient and the clinical subtype, as described below. Classic CAH can be further subdivided into two forms: salt-wasting and simple-virilising,[9] although the use of these sub-divisions is decreasing given noted overlap in their clinical phenotypes.[11]

- Non-classic CAH is less severe and presents in late childhood or adolescence.[9]

The clinical presentation of classic CAH differs by sex, with females typically diagnosed earlier than males. Females with classic CAH (salt-wasting or simple-virilising) generally present with signs of excess androgen (that is, male sex hormones) exposure at birth, resulting in visibly atypical external genitalia. CAH is not clinically apparent at birth in males, and subtle signs of virilisation (such as scrotal hyperpigmentation) due to excess androgens may be missed. As a result, salt-wasting CAH is often undiagnosed in males until they develop severe adrenal insufficiency. For those with salt-wasting CAH, in both sexes, a salt-wasting crisis requiring urgent medical intervention can occur in the first two weeks of life in the absence of prompt identification and treatment.[12] Salt-wasting occurs due to a severe lack of the hormones aldosterone, which is essential for maintaining salt and water balance, and cortisol, essential to support the body's normal stress response. In simple-virilising CAH, cortisol production is impaired but aldosterone production is sufficient enough to prevent a salt-wasting crisis.[12] In males, simple-virilising CAH is often not identified until later in childhood when cases present with signs related to excess androgen production, such as accelerated bone maturation.[12]

Newborn screening tests detect elevated levels of 17-Hydroxyprogesterone (17-OHP), the substrate for the enzyme 21-OH. In non-classic CAH, 17-OHP levels are normal or only slightly elevated in the newborn period.[11, 13] Therefore, newborn screening tests are not sensitive enough to reliably detect non-classic CAH. Standard newborn screening tests are not available for other rare forms of CAH, such as CAH due to 11β-OHD.[14] The scope of the HTA will be limited to classic CAH due to 21-OHD only, hereafter referred to as CAH for simplicity.

In the absence of early diagnosis and treatment, infants with salt-wasting CAH may experience a life-threatening salt-wasting crisis in early life. Early diagnosis and treatment can prevent serious morbidity and mortality.[15] The Endocrine Society Clinical Practice Guideline recommends that all NBS programmes incorporate screening for CAH due to 21-OHD.[15] However, numerous factors contribute to uncertainty regarding the overall benefit-harm balance of NBS for CAH. These include, but are not limited to, the potential for many female cases to be identified clinically at birth in the absence of screening and concerns regarding test accuracy.[16] These and other factors will be considered in the evaluation of the overall benefit-harm balance as part of this assessment.

2 Evidence synthesis approach

HTA is a multidisciplinary process that summarises information about the medical, social, economic and ethical issues related to the use of a health technology in a

systematic, transparent, unbiased and robust manner.[17] HTAs are designed to inform safe and effective health policies that are both patient-focused and achieve the best value. The following domains will be considered in this HTA:

- Epidemiology and burden of disease
- Description of the technology, including available treatments and a review of international policy and practice
- Clinical effectiveness and safety, including test accuracy
- Economic aspects, including cost effectiveness and affordability
- Organisational considerations
- Ethical, patient, and social implications.

2.1 Aims and objectives

The specific objectives of this HTA, agreed with the Chair of NSAC on behalf of NSAC, are as follows:

- describe the epidemiology and burden of disease of CAH in Ireland
- describe the current care pathway for patients with CAH in Ireland, and the proposed screening care pathway
- review international guidelines, policy and practice on newborn screening for CAH
- review the test accuracy, clinical effectiveness and safety of newborn screening for CAH
- review published economic evaluations reporting on the cost effectiveness of newborn screening for CAH
- assess the potential economic and organisational implications associated with adding CAH to the NNBSP
- consider any ethical, patient or social implications that newborn screening for CAH may have for patients, families, the general public or the healthcare system in Ireland.

NSAC outlines 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme.[5] These criteria will be considered under the relevant HTA domains in order to inform consideration by NSAC regarding the extent to which NBS for CAH fulfils these criteria.

2.2 Stakeholder engagement

In line with HIQA guidelines for stakeholder engagement, an expert advisory group (EAG), will be convened to ensure that the HTA takes into account all relevant and important issues from the perspectives of multiple stakeholders (see section 2.2.1).[18]

2.2.1 Expert Advisory Group

An appropriately represented EAG will be convened as a source of expertise to inform the interpretation of the evidence and development of the advice to NSAC. This group will comprise nominees from a range of stakeholder organisations, including patient representation, public representation, healthcare providers, and clinical and public health experts.

2.2.2 Public and targeted consultation

A public and targeted consultation is not planned for this assessment. Additional stakeholders not represented on the EAG will be contacted to facilitate access to data and information, if appropriate.

3 Epidemiology

The purpose of this chapter will be to provide an overview of the epidemiology of CAH. The specific aims of this chapter will be to describe:

- CAH and its subtypes
- the aetiology, symptoms, and natural progression of CAH
- the disease burden (incidence, prevalence, morbidity, and mortality) associated with CAH.

Given the rarity of the condition, epidemiological data are expected to be limited. Irish data will be used where available, and supplemented with international evidence deemed broadly applicable to the Irish context, preferably from multi-centre studies or reviews.

4 Description of the technology

The technology under consideration, NBS for CAH, represents a modification to the NNBSP, one of the population-based screening programmes within the Health Service Executive (HSE) National Children's Screening Services.[4] This chapter will describe the current approach to diagnosis and management of CAH in the absence of screening, the proposed screening care pathway within the context of the NNBSP, and its potential integration with existing diagnostic and clinical pathways in the HSE. If identified, potential implications for current diagnostic or management pathways will be explored further in the organisational considerations of the HTA (section 6.3). The specific aims of this chapter will be to describe:

- the current diagnostic and management pathway for children with CAH (including follow-up) in Ireland
- the NBS pathway for CAH
- international policy, practice and guidelines on screening for CAH in newborns (see section 4.1).

4.1 Review of international guidelines, policy and practice

Current international screening guidelines, policies and practices will be reviewed. The overview will be informed by a search of the peer-reviewed literature and grey literature sources (for example, national public health organisations, the websites of government departments and relevant agencies) using scoping methodology. The specific objectives of this review will be to identify:

1. guidelines from professional societies or organisations in relation to NBS for CAH
2. international assessments of NBS for CAH
3. international practice in NBS for CAH.

In relation to the first objective, guidelines, position papers, recommendations and standards from professional societies or organisations reporting on NBS for CAH will be identified. Guidelines will be considered eligible for inclusion depending on their relevance to the context of this HTA. Preference will be given to international or European guidelines, if available. Guidelines developed for a specific country, region, or context (for example, national or low- or middle-income specific guidelines) may be considered if international evidence is unavailable or conflicting. The following exclusion criteria will be applied:

- guidelines that have been replaced, retired or updated (that is, where more than one guidance documented from a professional society is identified, only the most recent document will be included)
- guidelines specific to treatment of CAH.

Regarding objective two, international evidence syntheses evaluating NBS for CAH used to inform screening policy in a country or region will be included. Evidence syntheses outputs considering all or a subset of HTA domains will be considered. Only evidence synthesis outputs linked to decision-making will be included.

In relation to the third objective, existing evidence syntheses on international screening practices for CAH,[19] and NBS generally,[20, 21] will be used as a starting point, with country-level data updated where possible. The following information will be extracted, where reported:

- the status of the screening programme in each country (for example, under consideration, piloting, implemented or discontinued)
- level of implementation (for example, pilot, local, regional, or national).

Additional information will be extracted from a subset of countries deemed of greatest relevance to the Irish context. Selection will be based on country-level factors (such as, population size and decision-making context), newborn screening programme-specific factors (for example, structure and operation of the screening programme or timing of implementation), and pragmatic considerations (such as the availability of high-quality English language translations). For example, the timing of sample collection has been identified as a key factor affecting the reliability of screening test results for CAH due to changes in 17-OHP levels during the first week of life.[22] This may influence the applicability of screening practices in other countries to the Irish context. The following information may be extracted, where available:

- type of screening test and analyte measured (for example, 17-OHP immunoassay)
- cut-off values for a positive screening test result
- details of second-tier testing, if performed (for example, whether positive first-tier screening test results may be followed by second-tier testing using liquid chromatography-tandem mass spectrometry (LC-MS/MS))
- the care pathway from a positive screening test result to diagnosis
- other relevant characteristics identified during data extraction (for example, testing protocols for preterm or low birth weight infants).

5 Clinical effectiveness and safety

Preliminary scoping identified a number of rapid or narrative reviews investigating the clinical effectiveness of NBS for CAH.[23-27] More recent reviews have highlighted the evolution of testing methodologies over time, from single-tier immunoassays to multi-tier strategies to reduce false positive results. Improvements in the positive predictive value would improve the overall acceptability of the screening test and reduce the resources required for follow-up. As described in section 5.2, the applicability of screening algorithms to the current clinical context will need to be considered in the inclusion criteria for this review.

The optimal approach to newborn screening for CAH is an active area of research, with many published studies focusing on analytical method optimisation and validation prior to widespread clinical application. The aim of this review will be to focus on studies with patient-centred or accuracy outcomes from tests implemented in real-world clinical settings. Validation or analytical performance studies reporting

on technical assay development or laboratory optimisation only, without assessment of clinical outcomes or test accuracy, will be excluded.

5.1 Research question

The aim of this review is to assess the clinical effectiveness, potential harms and test accuracy of NBS for CAH. The specific research question for this review was formulated according to the Population, Intervention, Comparator, Outcome, Study design (PICOS) framework (Table 5.1). Data for subgroups of interest (for example, preterm or low birth weight neonates) will be extracted, if available.

Table 5.1 Review question for review of clinical effectiveness and safety

Population	Newborns Subgroups of interest may include: ▪ Preterm infants ▪ Low birth weight infants ▪ Males and females.†
Intervention	Population-based‡ newborn bloodspot screening for CAH
Comparator	▪ no comparator ▪ no screening or usual care (that is, clinical presentation or family history)
Outcomes	Single-arm population-based screening studies ▪ case characteristics (for example, age, sex, subtype and symptom status at diagnosis) ▪ detection rate (incidence of CAH) ▪ test accuracy (positive predictive value and false negatives) ▪ any potential harms (for example, incidental findings, parental anxiety or psychological distress). Comparative studies: ▪ case characteristics (for example, age, sex, subtype and symptom status at diagnosis) ▪ morbidity (for example, adrenal crisis and long-term health outcomes) ▪ mortality ▪ resource use (for example, emergency department attendances, hospitalisation, length of stay) ▪ pathway timings (for example, time to diagnosis, time to treatment) ▪ any potential harms (for example, false positives, incidental findings, anxiety or psychological distress).
Study design	▪ Test accuracy outcomes: Single-arm population-based screening studies ▪ Clinical effectiveness and harms: Any study design with a comparator group (for example, non-randomised controlled trial, cohort study or case-control study)

† For outcomes where sex-specific differences are biologically plausible (for example, fertility or bone health), data will be extracted separately for males and females.

‡ Population-based studies are defined as a group of individuals taken from the general population who share common characteristics, such as age, sex, or health conditions. Studies will be considered population-based if all eligible participants in a large, clearly defined geographic region (that is, entire counties, regions or countries internationally) were invited to participate. Studies using sampling methods or undertaken in a single healthcare centre, hospital, town, or subset of towns within a wider geographic region will not be included.

5.2 Search strategy and study selection

Electronic searches will be conducted in MEDLINE (EBSCOhost), CINAHL (EBSCOhost), PsycINFO (EBSCOhost), Embase (Elsevier), The Cochrane Library, the World Health Organization's (WHO) ICTRP portal and ClinicalTrials.gov supplemented by a grey literature search of national and international electronic sources. The electronic search strategy was developed by a librarian and was peer reviewed by a second librarian using the PRESS tool.[28] The complete electronic search strategy will be available on Zenodo.[29] The data limit for this search was informed by the emergence of two-tier screening protocols in clinical practice during the early 2000s.[30] The structured grey literature search will include the Turning Research into Practice (TRIP) database, International Network of Agencies for Health Technology Assessment (INAHTA) HTA database, LENUS (the Irish Health Research repository), websites of government and public health agencies, rare disease and screening networks or registries, evidence syntheses identified as part of the review of international guidelines, policy and practice (section 4.1), and dissertations or theses. A full list of grey literature sources is provided in the Appendix, Appendix

Table A1. Forward citation searching and examination of the reference lists of included studies will also be conducted.

A 2022 evidence review undertaken to support decision-making by the UK NSC reported that single-tier screening protocols may result in a relatively large number of false positive results.[24] The Endocrine Society Clinical Practice Guideline recommends that laboratories undertaking screening for CAH use a two-tier protocol (that is, an initial screening test (first-tier) is performed on all participating newborns, followed by a more specific test for those with a positive first-tier result (second-tier testing)) to improve the positive predictive value.[15] On this basis, only test accuracy studies using a two-tier screening protocol will be included in this review. Definitions of testing tiers may also vary between studies or screening programmes. As such, the applicability of studies will be assessed based on the description of the screening algorithm, rather than the labelling of testing tiers.

Given the expected limited evidence base for comparative effectiveness evidence,[23] studies using single- or two-tier screening protocols will be included for these outcomes (morbidity and mortality). Studies reporting potential harms of screening will be considered eligible for inclusion in accordance with a hierarchy of evidence.

Studies using two-tier strategies are considered most relevant to the context of this assessment, given that screening protocols may influence psychological outcomes related to the screening pathway. If no comparative studies using two-tier screening protocols are identified which report data on harms, evidence from studies using single-tier screening protocols will be included.

Single-arm test accuracy studies will only be considered eligible for inclusion if they are population-based, defined according to geographic region, age and sex. Additional outcomes, such as incidence and pathway timings, will be extracted from population-based, single-arm test accuracy studies, where reported. Comparative studies reporting outcomes for a subset of screened or unscreened participants from a larger population-based screening programme will be included.

The following exclusion criteria will be applied:

- studies investigating analytical performance (that is, the technical characteristics of the test including reproducibility, reliability, and ease of use)
- studies designed for analytical method optimisation and or validation (for example, investigating interference, sample stability or precision) prior to widespread clinical application
- epidemiological or descriptive studies reporting CAH incidence or case characteristics only (including age at diagnosis), without effectiveness, harms or test accuracy outcomes
- multi-condition analyses, unless disaggregated data are available
- test accuracy studies that do not report, at a minimum, the number of true positive and false positive cases
- comparative studies with extreme imbalance between groups and very small sample sizes, as reliable interpretation of between-group differences is not possible
- comparative studies in which the numerator and denominator for the outcome of interest are not reported for both groups (for example, between-group differences or event counts only)
- comparative healthcare utilisation data not linked to clinically relevant outcomes (for example, total number of appointments rather than appointments for adrenal crisis management)
- surveys or questionnaires without data verification due to the potential for recall bias
- papers for which an adequate English translation cannot be obtained
- letters, editorials, commentaries, preprints, and conference abstracts where a detailed description of the methods is not available
- studies published before 2000.

5.3 Data extraction and quality appraisal

Data will be extracted using a standardised, pre-piloted electronic data extraction form. In addition to the outcomes presented in Table 5.1, the following population and study characteristics will be extracted: country or region, sample size, loss to follow-up, uptake rate, screening test pathway, threshold for test positivity, timing of dried blood spot collection, and incidence of CAH. Potential factors that may influence test accuracy (for example, gestational age, types of CAH other than the screening test target or maternal steroid exposure) observed in the context of optimised, real-world screening algorithms will also be extracted, where reported.

The appropriate quality appraisal tool will depend on the study designs included, as outlined in Table 5.2. No validated quality appraisal tool tailored specifically to population-based non-comparative observational studies was identified. Unless a more appropriate tool is identified during the conduct of this HTA, key criteria for an effective screening programme set out by the WHO will be used to guide the assessment of the conduct and reporting of single-arm population-based screening studies.[31] Adaptation of these criteria to reflect the objectives of this review will be necessary.

Table 5.2 Quality appraisal tools according to study design

Study design	Quality appraisal tool
Randomised controlled trial	Risk of Bias 2.0[32]
Non-randomised studies of interventions	Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I)[33]
Single-arm observational studies of population-based screening effectiveness	No validated quality appraisal tool identified

5.4 Data synthesis

If data of sufficient quantity, quality, and homogeneity are identified, meta-analysis will be undertaken. If this is not the case, findings will be narratively synthesised, such as in a Synthesis Without Meta-Analysis (SWiM) approach.[34] A narrative synthesis will be structured by the outcomes of interest to the review and sectioned by study type (that is, non-comparative and comparative studies), where applicable.

6 Economic aspects

6.1 Review of cost effectiveness

A 2020 review of cost effectiveness identified four economic evaluations of NBS for CAH (including one unpublished Australian cost effectiveness analysis (CEA)).[35] In this review, the observed variability in cost-effectiveness estimates was reported to be influenced by limitations in the evidence base and concerns regarding the

robustness of modelling approaches used.[35] The majority of economic evaluations of NBS for CAH modelled only short-term health outcomes among infants with CAH.[35] The identified review was not designed to comprehensively assess all studies reporting on NBS for CAH, and did not include an assessment of methodological quality. Therefore, a de novo review is warranted.

6.1.1 Research question

The aim of the review of cost effectiveness is to synthesise and critically appraise the i) methods and ii) results of published CEA and cost-utility analyses reporting on the cost effectiveness of NBS for CAH. To facilitate the first objective, the primary information of interest to be extracted will include the:

- model structure (for example, health states, time horizon)
- approach to generation of key model inputs and structural assumptions (for example, health state valuation, assumptions regarding resource utilisation).

Of note, all model inputs will not be extracted from included studies. Extraction of specific model inputs will be dependent on their transferability to the Irish context. Parameters considered transferable or partially transferable to the Irish context may be used to inform the inputs to an Irish-specific economic model (see section 6.2 and 6.3).

For the second objective, the main outcome of interest will be the incremental cost-effectiveness ratio (ICER) or net monetary benefit (NMB). The specific research question is outlined in Table 6.1.

Table 6.1 Review question for review of cost effectiveness

Population	Newborns
Intervention	Population-based NBS for CAH
Comparator	No systematic screening (that is, clinical presentation or family history)
Outcomes	▪ ICER (for example, cost per life year gained or cost per quality-adjusted life year) ▪ NMB
Study design	▪ Full economic evaluations: ○ cost-utility analysis ○ cost-effectiveness analysis ○ cost-benefit analysis.

Key: CAH – congenital adrenal hyperplasia; ICER – incremental cost-effectiveness ratio; NMB – net monetary benefit.

6.1.2 Search strategy and study selection

Literature searching and screening for the reviews of clinical and cost effectiveness will be conducted simultaneously. See section 5.2 for a description of the search strategy. Cost effectiveness studies will be assessed for eligibility according to the criteria outlined in Table 6.1. The following exclusion criteria will be applied:

- partial economic evaluations[36]
- multi-condition analyses, unless disaggregated data are available
- commentaries, letters, and conference abstracts where a detailed description of the methods is not available
- papers for which an adequate English language translation cannot be identified.

6.1.3 Data extraction and critical appraisal

Study characteristics, methods and results will be extracted using a standardised, pre-piloted electronic data extraction form. The preferred cost-effectiveness outcome measure will be the cost per quality-adjusted life year (QALY) gained. Where QALYs are not used as the effect measure, other outcomes (for example, cost per life year gained (LYG) or cost per hospitalisation avoided) will be extracted.

Methodological quality will be assessed using the Consensus on Health Economics Criteria (CHEC)-list.[37] The ISPOR questionnaire will be used as a framework to guide the assessment of the transferability of economic evaluations to the Irish context.[38]

6.1.4 Data synthesis

In line with ISPOR best practice recommendations, the results of model-based (that is, parameters are based on multiple sources) and empirical evidence-based (that is, parameters are based on a single study such as a randomised controlled trial) economic evaluations will be synthesised separately.[36] To facilitate comparability of the results across countries and years, costs will be inflated, where appropriate, and adjusted to Irish Euro in accordance with national HTA guidelines.[39] Willingness-to-pay thresholds of €20,000 and €45,000 per QALY, commonly employed in Ireland and consistent with empirically-based thresholds in other high-income countries, will be adopted as reference points to guide interpretation of cost effectiveness.[40, 41] Unadjusted ICERs as reported by the included studies and context-specific willingness-to-pay thresholds will also be reported.

6.2 De novo cost-utility analysis

The feasibility of a de novo Irish-specific cost-utility analysis will be determined following formal appraisal of published economic evaluations (see section 6.1.3), and based on whether the evidence identified in Chapter 2 (Epidemiology), Chapter 4

(Description of the technology) and Chapter 5 (Clinical effectiveness and safety) can address identified limitations.

6.3 Organisational considerations and budget impact analysis

The assessment of organisational considerations will examine anticipated operational changes to the NNBSP and the follow-up care pathways for infants with a positive screening result. Context-specific operational considerations will be identified in consultation with key stakeholders on the EAG and, where appropriate, additional stakeholders with relevant expertise. Potential impacts on the wider healthcare system will be considered, where applicable.

A budget impact analysis will be undertaken to determine the additional investment required to include screening for CAH in the NNBSP over a five-year time horizon. The comparator will be current standard practice in Ireland. In line with national HTA guidelines,[42] the analysis will be undertaken from the perspective of the publicly-funded health and social care system in Ireland, the HSE. Only direct costs to the HSE will be considered. Indirect costs such as productivity losses and out-of-pocket expenses incurred by families attending healthcare services will not be considered. However, ethical, patient and social considerations will be assessed in the ethical analysis (section 7).

The structure of the budget impact model will be informed by the care pathway outlined in the description of the technology and organisational chapters. Where possible, model inputs will be informed by Irish data sources. In the absence of robust national data, international data considered generalisable to the Irish context may be used. Input from the EAG will be required to inform plausible values where empirical evidence is lacking or limited. In addition to the cost of screening tests and laboratory equipment, potential changes to organisational processes (for example, clinical pathways) resulting from the addition of CAH to the NNBSP will be considered. Potential cost offsets, such as prevention of or reduction in hospitalisation admissions for adrenal crisis, will also be considered, if appropriate.

Where plausible estimates of uncertainty are available, sensitivity analyses will be conducted to assess the impact of uncertainty in individual parameters on the budget impact analysis.

7 Ethical, patient and social issues

Ethical, patient and social considerations will be explored at a workshop attended by members of HIQA's evaluation team. The findings of the workshop will be

supplemented with evidence from the published literature and the perspectives of the EAG. Potential patient, social and ethical considerations may include:

- informed consent regarding the limitations of screening
- potential detection of cases that are not the intended target of the screening test (for example non-classic CAH)
- the potential implications of false positive results for test acceptability and healthcare resources
- whether early diagnosis can prevent or reduce the period of incorrect gender assignment in females
- whether early detection and treatment of those with salt-wasting CAH can potentially prevent adrenal crisis, and the associated clinical and psychosocial consequences for patients and their families
- uncertainty regarding the added value of screening in some cases (for example, females with classic CAH and atypical genitalia who may be identified clinically at birth without screening).

8 Anticipated timeline

The final assessment will be submitted to the Board of HIQA for approval. Subject to its approval, the final HTA including HIQA's advice to NSAC will be submitted to NSAC for consideration and published on the HIQA website. The anticipated completion date is Q3 2026.

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Appendix

Table A1 List of grey literature sources

Rare disease and newborn screening networks	
National Organization for Rare Diseases (NORD)	https://rarediseases.org/
EURORDIS	https://www.eurordis.org/
Genetic Alliance	https://geneticalliance.org/about/mission
Orphanet	https://www.orpha.net/
International society for newborn screening (ISNS)	https://www.isns-neoscreening.org/
Rare disease and screening registries	
I-CAH registry	https://sdmregistries.org/i-cah/
Government and public health agencies with dedicated screening websites	
Health Resources and Services Administration (HRSA) – Newborn Screening	https://newbornscreening.hrsa.gov
National Institutes of Health (NIH) / Genetic and Rare Diseases Information Center (GARD)	https://rarediseases.info.nih.gov/
Australian Government – Department of Health & Aged Care (Newborn Bloodspot Screening)	https://www.health.gov.au/our-work/newborn-bloodspot-screening
World Health Organization (Screening)	https://www.who.int/europe/teams/ncd-management/screening
Geneva Foundation for Medical Education and Research (Neonatal Screening)	https://gfmer.ch/Guidelines/Neonatology/Neonatal_screening.htm
Belgian Health Care Knowledge Centre (Preventative Medicine)	https://kce.fgov.be/en/publications/thematic-pages/focus-on-preventive-medicine
US Preventive Services Task Force (Type of Preventive Service: Screening)	https://uspreventiveservicestaskforce.org/

Evidence synthesis databases	
INAHTA database†	https://inahta.org
TRIP database	https://www.tripdatabase.com/
UpToDate	https://www.uptodate.com
Repositories	
Lenus	https://www.lenus.ie/
Open Access Theses and Dissertations	https://www.oatd.org/
ProQuest Dissertations and Theses	https://www.proquest.com/

† Evidence syntheses relating to newborn screening for CAH will be identified as part of the review of international guidelines, policy and practice (section 4.1). The list of included studies within any reviews of clinical or cost effectiveness conducted as part of any identified evidence syntheses will be examined to identify additional eligible studies.

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