Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for the Health Technology Assessment of the introduction of population-based screening for familial hypercholesterolaemia in children

23 February 2026

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent statutory body 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.

Reporting to the Minister for Health and engaging with relevant government Ministers and departments, 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 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.
- **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 and social care services, with the Department of Health and the HSE.

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List of abbreviations used in this report

ASCVD	atherosclerotic cardiovascular disease
CAD	coronary artery disease
CSO	Central Statistics Office
EAG	expert advisory group
FH	familial hypercholesterolemia
HIQA	Health Information and Quality Authority
HSE	Health Service Executive
INAHTA	International Network of Agencies for Health Technology Assessment
HTA	health technology assessment
NSAC	National Screening Advisory Committee
LDL	low-density lipoprotein
LDLR	lipoprotein receptor
LDL-C	low-density lipoprotein cholesterol
PICO	Population, Intervention, Comparator, Outcome
RCT	randomised controlled trial
ROBINS-I	Risk Of Bias In Non-randomised Studies-of Interventions
ROBIS	Risk Of Bias In Systematic reviews
TRIP	Turning Research into Practice

1 Introduction

1.1 Background

In 2019, the National Screening Advisory Committee (NSAC) was established by the Minister for Health as an independent advisory committee to play a significant strategic role in the development and consideration of population-based screening programmes in Ireland. 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.

NSAC requested HIQA to undertake a HTA to support decision-making regarding screening for familial hypercholestolaemia (FH) in children. This protocol outlines the methodological approach that will be adopted by HIQA's evaluation team to synthesise the evidence and develop HIQA's advice to NSAC.

1.2 Condition and screening technology

FH is an inherited condition characterised by very high lifelong levels of total cholesterol, and specifically, low-density lipoprotein (LDL) cholesterol (LDL-C).[1-3] When elevated, LDL-C is recognised as a principal driver (that is, a causative factor rather than an indicator of risk) in the development of atherosclerotic cardiovascular disease (ASCVD), which includes coronary artery disease (CAD), myocardial infarction (MI), ischaemic stroke, and peripheral artery disease (PAD).[4] LDL-C is a type of cholesterol which is attached to LDLs. LDLs are composed primarily of lipids and proteins and assist with cholesterol transportation through the body.[2, 5, 6] Efficient clearance of LDLs is necessary for normal lipid homeostasis.[6] LDLs are cleared primarily by the liver through a process where the particles bind to low-density lipoprotein receptors (LDLR). However, in those with FH, inefficient clearance of LDL particles by the liver leads to very high levels of LDL-C in the bloodstream.[2, 6-8]

FH is most commonly inherited in an autosomal dominant pattern.[1, 3] Autosomal dominant inheritance means that the pathogenic gene alteration occurs on one of the 22 non-sex chromosomes ('autosomal') of an affected parent, and a child is clinically affected when the child inherits one pathogenic alteration from a parent ('dominant'). Most cases of FH are caused by pathogenic alterations in one of three genes.[1-3, 7-9] Diagnosis of FH is generally based on a combination of clinical, biochemical, and or genetic features, with genetic testing considered to be the gold standard.[10] Unless detected by cascade testing or opportunistically, FH is often only identified after experiencing a cardiovascular event.[11] Once a case of FH is

identified, cascade testing is typically recommended, given the inheritance pattern of the condition.[3] Cascade testing involves offering testing to family members, usually first- and second-degree relatives, to identify further cases.

Population-based screening (or universal screening) may be defined as a programme aimed at a group of people who do not have any signs or symptoms of the condition. The focus of this HTA is population-based screening for FH in children.

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. It does so in a systematic, transparent, unbiased, and robust manner. HTAs are designed to inform safe and effective health policies that are both patient-focused and achieve the best value.

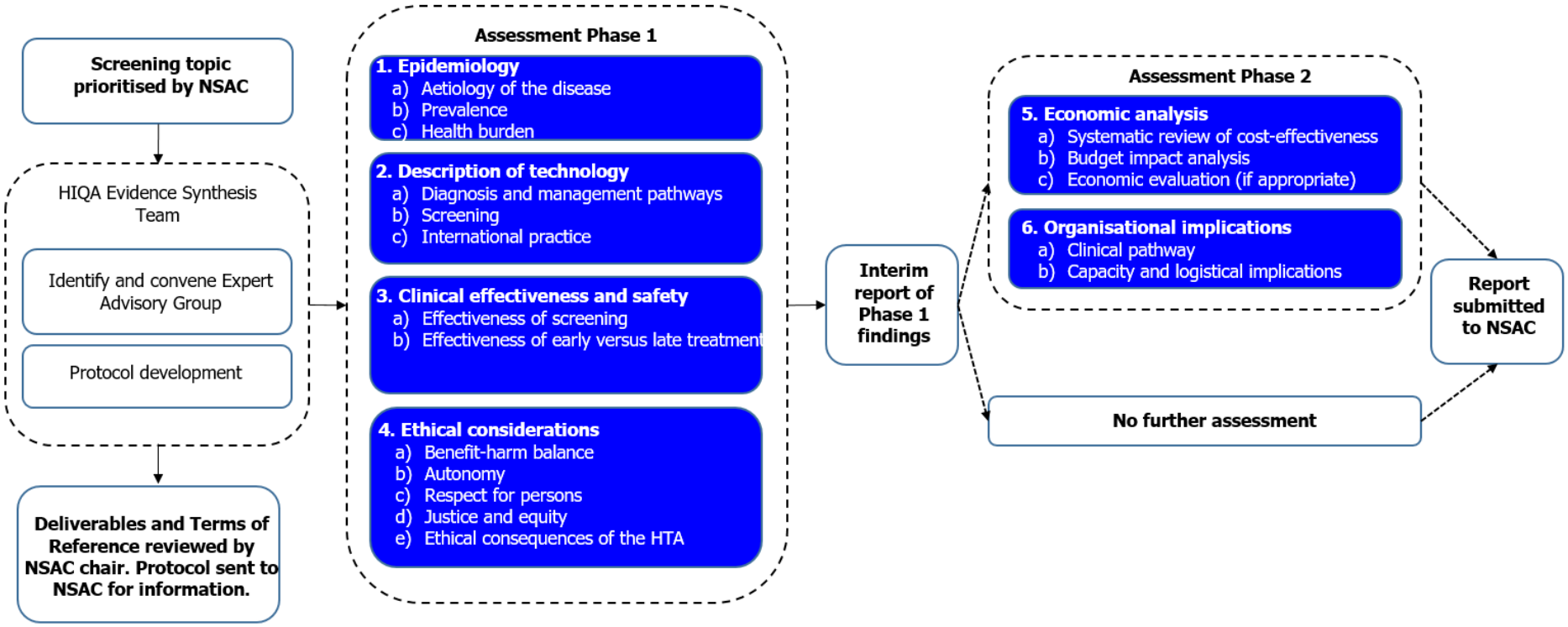
HIQA HTAs typically include the following domains:

- epidemiology and burden of disease
- description of the technology
- clinical effectiveness and safety
- costs and economic evaluation
- organisational considerations
- social and ethical implications.

Given the resource-intensive nature of HTA and the need for responsive evidence-based decision-making, the evidence synthesis approach adopted for this assessment will follow a stepwise (two-phase) process. An overview of this process is presented in Figure 2.1.

In the first phase, evidence synthesis underpinning FH screening in children will be conducted for the domains of the description of the technology, epidemiology, clinical effectiveness and safety, and social and ethical implications. The social and ethical implications will specifically be included in the first phase due to the noted challenges with screening for FH in children from other national screening committee reports.[12-14] Subject to the findings of these HTA domains, and recommendation by NSAC, a second phase may be undertaken to assess the economic and organisational implications of introducing FH screening in children in Ireland. The domain of social and ethical implications may be expanded to include considerations arising from the additional domains.

Figure 2.1 HTA process flow to inform NSAC advice on FH screening in children



Key: DoH – Department of Health; HTA – health technology assessment; NSAC – National Screening Advisory Committee.

2.1 Aims and objectives

NSAC outlines 20 criteria for appraising the viability, effectiveness and appropriateness of a screening programme.[15] These criteria will be explored in order to inform consideration by NSAC.

The terms of reference for the first phase of this HTA, agreed with the Chair of NSAC on behalf of the committee, are as follows:

- describe the epidemiology and burden of disease of FH in Ireland
- describe the current care pathway for patients with FH in Ireland, and the proposed care pathway for population-based screening in children
- conduct a review of international practice on the use of population-based screening for FH in children
- conduct a review of the clinical effectiveness of population-based screening for FH in children
- conduct a review of the clinical effectiveness of early treatment for FH (that is, before experiencing a cardiovascular event and or experiencing morbidity) compared with late treatment (that is, after experiencing a cardiovascular event and or experiencing morbidity)
- consider any ethical or social implications that a population-based screening programme for FH in children may have for individuals, families, the general public or the healthcare system in Ireland.

The focus of this HTA is population-based screening of FH in children. Screening in children has been proposed at various age points, often from ages one to nine years; however, the optimal age for screening remains uncertain.[10, 16] The first phase of this HTA will consider three potential age groups:

- Pre-school aged approximately one to two years
- School-aged group 1 approximately four to five years of age
- School-aged group 2 approximately eight to nine years of age

Where feasible and relevant, the evidence will be considered individually for each age group to enable consideration of the most appropriate screening strategy by NSAC.

2.2 Stakeholder engagement

An appropriately represented expert advisory group (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, healthcare providers, and clinical and public health experts.

3 Epidemiology

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

- the aetiology, symptoms and natural progression of FH
- the burden of FH (that is, prevalence, morbidity, and mortality).

Where available, national data and relevant international data on the morbidity and mortality associated with FH will be presented. Data on the size of the eligible population in Ireland will be sought from the Central Statistics Office (CSO).

If possible, the prevalence of FH in Ireland will be estimated from national registries of FH. If these data are not available, the prevalence will be estimated from international estimates deemed broadly applicable to the Irish context, preferably from multi-centre studies or reviews. Data will be sought from multiple sources, such as published audits of the outcomes, the CSO, and or the Hospitalised In-Patient Enquiry (HIPE) system.

4 Description of technology

The purpose of this chapter is to provide an overview of a screening programme for FH in children. The specific aims of this chapter will be to describe:

- international policy, assessments and guidelines in the use of screening for FH
- the current clinical care pathway for diagnosis and management of FH in Ireland
- the proposed method for population-based screening for FH in children
- the proposed care pathway associated with a screening programme for FH in children.

4.1 Review of international policy and guidelines

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

- guidelines from professional societies or organisations in relation to screening for FH in children
- international assessments of population-based screening for FH in children
- international policy and practice of screening for FH.

In relation to the first objective, a search for guidelines, position papers, recommendations and standards from professional societies or organisations reporting on screening for FH will be conducted. Guidelines will be considered eligible for inclusion depending on their relevance to the context of this HTA. Information of interest will include recommendations on the target population and the care pathway following a positive screening test result (for example, cholesterol threshold for intervention and or follow up, and cascade testing). The following exclusion criteria will be applied:

- guidelines that have been replaced by updated guidance (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 adults only
- guidelines specific to cascade testing for FH
- guidelines specific to treatment of FH
- context-specific guidelines (for example, an individual hospital or hospital group).

Regarding objective two, international evidence syntheses and HTAs evaluating population-based screening for FH in children in a country or region by recognised national bodies will be included (for example, the UK National Screening Committee, or the Australian Health Minister's Advisory Council's Standing Committee on Screening). Evidence synthesis 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, previous reviews of international practice in screening for FH,[17, 18] will be used as a starting point. Data for individual countries will be updated, where possible. The following information will be extracted, where available:

- the status of the screening programme (for example, under consideration, piloting, implemented)
- level of implementation (for example, local, regional, national)
- the population being screened (for example, age and or targeted screening)
- any other relevant characteristics identified during data extraction.

5 Clinical effectiveness and safety of screening

5.1 Research questions

The aim of this systematic review is to assess the clinical effectiveness and safety of population-based screening for FH in children compared with no systematic population-based screening. Initial scoping has indicated that there is a scarcity of studies comparing population-based screening for FH in children with no population-based screening. Therefore, as a proxy for the clinical effectiveness and safety of population-based screening, the clinical effectiveness and safety of early detection and or treatment for FH (that is, before experiencing a cardiovascular event and or experiencing morbidity) compared with late detection and or treatment (that is, later in life after opportunistic or cascade screening, or after experiencing a cardiovascular event and or experiencing morbidity) will also be considered. Accordingly, two research questions (RQ) have been formulated to review the clinical effectiveness and safety of population-based screening for FH in children:

- RQ 1 – What is the clinical effectiveness and safety of population-based screening for FH in children compared with no population-based screening?
- RQ 2 – What is the clinical effectiveness and safety of early detection and or treatment compared with late detection and or treatment for FH?

Table 5.1 PICO for Research Question 1 – review of clinical effectiveness and safety of population-based screening

Population	Asymptomatic children*
Intervention	Population-based screening for FH in children (including pilots)
Comparator	Comparative studies: ▪ No population-based screening for FH (patients presenting clinically with FH and or cascade testing only) Non-comparative studies: ▪ No comparator (outcomes of screening cohort only described)
Outcomes	▪ Case characteristics – Incidence/prevalence of screen-detected FH ▪ By pathogenic gene alteration, if available – Incidence/prevalence of cascade testing detected FH (following either population-based, opportunistic screening or clinical detection) ▪ Morbidity – Incidence/prevalence of ASCVD ▪ Surrogate markers – LDL-C – Carotid intima-media thickness ▪ Mortality – FH-related mortality – All-cause mortality ▪ Safety – Any screening related potential harms (for example, anxiety or psychological distress) ▪ Quality of life (for example, EQ5D or SF-36 measures) ▪ Health-resource utilisation (for example, FH-related GP or hospital visits) ▪ Pathway timings (for example, time from FH diagnosis to follow-up, time to FH treatment, where indicated)
Study design	▪ Randomised or non-randomised controlled trials (nRCT)† or comparative observational studies ▪ Population-based‡ non-comparative observational studies Exclude: ▪ Case studies, case series, letters, editorials, commentaries and conference abstracts

Key: ASCVD – atherosclerotic cardiovascular disease; FH – familial hypercholesterolaemia; GP – general practitioner; LDL-C – low-density lipoprotein cholesterol; nRCT – non-randomised controlled trials.
* Children defined as anyone under 18 years of age † As defined by the Cochrane Effective Practice and Organisation of Care, nRCTs are trials in which participants are allocated to different groups for comparison using a method that is not random (for example, chart number).[19]
‡ 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 participants were enrolled based on geographical location (e.g., an entire region or country), as opposed to healthcare setting (e.g., hospital-based enrolment).[20]

Table 5.2 PICO for Research Question 2 – review of clinical effectiveness and safety of early versus late treatment for FH

Population	Individuals with a confirmed diagnosis of FH (clinical or genetic)*
Intervention	Early detection and or treatment# for FH (that is, before experiencing a cardiovascular event and or experiencing morbidity)
Comparator	Late detection and or treatment# for FH (that is, treatment initiated later in life after opportunistic screening, or after experiencing a cardiovascular event and or experiencing morbidity)‡
Outcomes	▪ Morbidity – ASCVD prevalence/incidence ▪ Surrogate markers – LDL-C – Carotid intima-media thickness ▪ Mortality – FH-related mortality – All-cause mortality ▪ Safety – Any screening related potential harms (for example, anxiety or psychological distress) ▪ Quality of life (for example, EQ5D or SF-36 measures) ▪ Health-resource utilisation (for example, FH-related GP or hospital visits) ▪ Pathway timings (for example, time to pharmacological treatment for FH from diagnosis)
Study design	▪ Randomised or non-randomised controlled trials (nRCT)† or comparative observational studies Exclude: ▪ Non-comparative observational studies, case studies, case series, letters, editorials, commentaries and conference abstracts

Key: ASCVD – atherosclerotic cardiovascular disease; FH – familial hypercholesterolaemia; GP – general practitioner; LDL-C – low-density lipoprotein cholesterol; nRCT – non-randomised controlled trials.
* Including paediatric, adult and mixed populations to investigate the health benefits of treatment initiation after population-based screening in childhood compared with treatment later in life, for example after opportunistic screening or after a health event.
# Including non-pharmacological interventions such as diet or lifestyle and behavioural modification, and pharmacological interventions such as lipid-lowering treatments (LLT).
‡ Where a comparator is treatment initiated from a different screening programme, for example, opportunistic screening or cascade testing before a CVD event, and or at a later point in life, results will be treated as single arm trial results and reported accordingly.
† As defined by the Cochrane Effective Practice and Organisation of Care, nRCTs are trials in which participants are allocated to different groups for comparison using a method that is not random (for example, chart number).[19]

The reporting of the reviews will adhere to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria[21] and national guidelines[22].

5.2 Search strategy and study selection

Electronic searches will be conducted in MEDLINE (EBSCOhost), CINAHL (EBSCOhost), PsycINFO (EBSCOhost), Embase (Elsevier), The Cochrane Library, WHO's ICTRP portal and ClinicalTrials.gov supplemented by a grey literature search of national and international electronic sources. Searches will be considered from database inception to November 2025. The electronic search strategy will be developed in consultation with a librarian and will be peer reviewed by a second librarian using the PRESS tool.[23] The complete electronic search strategy for all databases will be available on Zenodo.[24] 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), and websites of HTA agencies. Forward citation searching and searching of the reference lists of included studies will also be undertaken.

Titles and abstracts of articles retrieved will be screened independently by two reviewers in Covidence. The full text of potentially eligible articles will be retrieved and independently assessed for eligibility by two reviewers according to the criteria that follows. A PRISMA flow diagram, outlining the study selection process, will be completed. Disagreements will be resolved through discussion, or if necessary, through involvement of a third reviewer.

Inclusion criteria

Studies will be considered eligible for inclusion in accordance with the hierarchy of evidence. Initial scoping did not identify any similar high-quality systematic review,

and it is not expected that systematic reviews with sufficiently similar research questions will be found. If systematic reviews are identified through searches, included studies will be cross-checked for eligibility for inclusion in this review. Eligible study designs will include randomised or non-randomised controlled trials (nRCT) or comparative observational studies. Population-based non-comparative observational studies (defined according to geographic region, age and or sex) will also be considered for studies investigating population-based screening in children (RQ1).

Exclusion criteria

The following exclusion criteria will be applied:

- studies testing for cholesterol in newborn cohorts, for example, bloodspot or cord testing
- studies undertaken in symptomatic populations, with known risk factors (that is, already displaying symptoms or lifestyle factors associated with high cholesterol), or population with a previous diagnosis of high cholesterol - RQ1 only
- observational single-arm studies that are not population-based
- case studies
- letters, editorials, commentaries and conference abstracts
- papers not available in English for which an adequate English translation cannot be obtained.

5.3 Data extraction and quality appraisal

Data extraction will be conducted independently by two reviewers using a standardised, pre-piloted electronic data extraction form in Microsoft Excel. Disagreements in data extraction will be resolved through discussion, or if necessary, a third reviewer. Where necessary, unclear data will be checked with the listed contact author by email.

In addition to the outcomes presented in **Error! Reference source not found.** and **Error! Reference source not found.**, the following study and population characteristics may be extracted as appropriate to the RQ:

- study characteristics (study author, year, study design, inclusion and exclusion criteria, funding sources, country, number of participants and loss to follow-up)

- intervention and comparator details
- acceptability measures (for example, uptake of screening)
- population characteristics (for example, age at screening, comorbidities, presence of physical symptoms such as xanthomas)
- care pathway timings (for example, timing of pharmacological intervention, timing of non-pharmacological or other treatment)
- health event details (for example age at first event)
- treatment regime (for example, type of intervention).

Two reviewers will independently assess the quality of included studies, and record appraisal decisions using a standardised form. 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. In the absence of a tailored quality appraisal tool, the JBI checklist for cross-sectional studies,[25] was deemed sufficient to meet the requirements of this review. Any adaptions to quality appraisal tools will be noted. Disagreements among reviewers will be resolved through discussion, or if necessary, a third reviewer. Results of the quality assessment will be summarised narratively.

Table 5.2 Quality appraisal tools according to study design

Study design	Quality appraisal tool
Randomised controlled trial	Risk of Bias 2.0[26]
Non-randomised studies of interventions	Newcastle Ottawa Scale for Cohort Studies[27]
Single arm observational studies	JBI Critical Appraisal Checklist for Analytical Cross Sectional Studies[25]

5.4 Data synthesis

Where appropriate, if sufficiently homogeneous data are available, meta-analysis will be used to generate a pooled effect estimate. Where meta-analysis is not considered appropriate, outcomes will be synthesised narratively.

6 Ethical and social issues

Key ethical considerations outlined in the EUnetHTA Core Model will be used to guide the ethical analysis of population-based screening for FH in children.[28] Potential ethical issues may include issues related to:

- the benefit-harm balance of the various ages for population-based screening, given a potential time delay between diagnosis and pharmacological

treatment eligibility, and the balance of the degree of cascade testing (that is, first-degree and second-degree relatives and so on)

- autonomy and informed consent, such as the autonomy of decision-making for a child and the rights of family members when considering elements such as cascade testing
- the potential trade-off between the benefits and harms of screening, such as reducing FH-related mortality and morbidity versus the potential for increasing anxiety and a potential time delay between diagnosis and pharmacological treatment eligibility
- the equity and justice of screening for FH in children only, such as ensuring fair access and distribution of resources and considerations for adults without children who would not benefit from potential cascade screening.

7 Anticipated timeline

It is expected that a draft report of the phase 1 deliverables of the HTA will be completed in Q2 2026. This timeline is dependent on available resources and the extent of the literature. The draft report will then be circulated and reviewed at a meeting of the EAG convened for this review. Necessary amendments and revisions to the draft report will be made following the meeting of the HIQA EAG before the final report is circulated to NSAC for consideration (expected delivery Q2 2026). Should the HTA proceed to phase 2, timelines will be estimated accordingly.

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Published by the Health Information and Quality Authority (HIQA).

For further information please contact:

Health Information and Quality Authority

George's Court

George's Lane

Smithfield

Dublin 7

D07 E98Y

+353 (0)1 8147400

info@hiqa.ie

www.hiqa.ie