Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Protocol for a health technology assessment of extending BowelScreen to those aged 50 to 54 years

31 July 2024

About the Health Information and Quality Authority (HIQA)

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 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 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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Table of contents

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. Since 2020, at the request of the Department of Health, the Health Technology Assessment (HTA) Directorate within the Health Information and Quality Authority (HIQA) has undertaken evidence synthesis and provided evidence-based advice to the NSAC on behalf of the Minister for Health.

1.2 Condition and screening programme

1.2.1 Colorectal cancer

Colorectal cancer, also called bowel cancer, refers to cancer that occurs in the lower part of the bowel, that is, the colon and rectum. Colorectal cancer usually develops from benign polyps (growths of tissue that commonly occur on the mucous membrane) in the lining of the colon or rectum. These polyps, or adenomas, may become cancerous over time. The progression of adenomas from benign to cancerous is referred to as the adenoma-carcinoma sequence. The removal of adenomas interrupts this sequence, and has the potential to impact the subsequent development of colorectal cancer.[1]

Globally, colorectal cancer is the third most commonly diagnosed cancer, accounting for approximately 10% of all cancers diagnosed in 2020, with over 1.8 million new cases.[2] In Ireland, colorectal cancer is the second most frequently occurring cancer (excluding non-melanoma skin cancer) in males and the third most common cancer in females, with an annual average of 2,562 new cases between 2018 and 2020. Similarly, colorectal cancer represents the third most common category of cancer deaths, accounting for an average of 1,001 deaths a year during the same period.[3] Risk factors for colorectal cancer include increasing age, male sex, a family or personal history of colorectal cancer, personal history of inflammatory bowel disease, sedentary lifestyle, obesity, a diet high in red and processed meats, smoking, and alcohol consumption.[4, 5]

1.2.2 The BowelScreen Programme

In January 2010, following due consideration of the evidence from two HIQA health technology assessments (HTAs),[6, 7] a decision was made to introduce a national population-based colorectal cancer screening programme. BowelScreen, the National Bowel Screening Programme, commenced in October 2012 with the aim of offering free screening to people aged 55 to 74 years on a two-yearly cycle. The first round

of screening (2012 to 2015) invited those aged 60 to 69. As of January 2024, BowelScreen invites people aged 59 to 69 years for screening. The National Cancer Strategy 2017-2026 and the 2020 Programme for Government outline a commitment to expand BowelScreen to those aged 55 to 74, as per the original aim of BowelScreen.[8, 9]

As its primary screening tool, the programme uses a faecal immunochemical test (FIT) to detect occult (hidden) blood in stool, with a screen-positive decision threshold of 45µg haemoglobin/g faeces (225ng haemoglobin/mL buffer). Screening participants with a positive FIT test result are referred for colonoscopy, or, in some cases, computed tomography (CT) colonography.

Extending BowelScreen to people aged 50 to 54 years

In response to submissions received as part of the 2021 and 2022 annual calls, at the request of the NSAC, HIQA agreed to undertake a HTA of extending the BowelScreen programme to people aged 50 to 54 years. This age extension would be in addition to that already committed to, that is, screening of all those aged 55 to 74. The scope of the HTA was agreed with the NSAC following preliminary scoping exercises, and is limited to consideration of this age extension; alternative testing modalities (for example, a primary screening tool other than FIT) or specifications (for example, an alternative FIT threshold for test positivity, or an alternative screening interval, other than every two years) will not be considered.

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 and 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.

The HTAs conducted by HIQA's HTA Directorate follow the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[10] As per the Core Model, HTAs conducted by HIQA's HTA Directorate commonly include the following domains:

- description of the technology
- epidemiology
- clinical effectiveness and safety
- costs and economic evaluation
- organisational, social, ethical and legal implications.

The mapping of these domains to the NSAC Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme is outlined in Appendix 1.

2.1 Aims and objectives

In the subsequent sections of this protocol, the scope and methods of the HTA are described according to the HTA domains that will be assessed. The aim of this HTA is to consider the benefits, harms and implications of extending the age of eligibility for the BowelScreen programme. The objectives are as follows:

- describe the existing BowelScreen programme and the proposed changes
- conduct a review of the international practice of colorectal cancer screening
- describe the epidemiology and burden of disease of colorectal cancer
- review the test accuracy of faecal immunochemical tests (FIT) in colorectal cancer screening in people aged 50 to 54 years
- describe the clinical effectiveness of screening for colorectal cancer
- assess the cost effectiveness, budget impact, and resource implications of extending the BowelScreen programme to those aged 50 to 54 years
- consider any wider organisational, ethical or societal implications that the extension of the colorectal cancer screening age range may have for patients, families, the general public or the healthcare system in Ireland.

2.2 Stakeholder engagement

In line with HIQA guidelines for stakeholder engagement, multiple engagement strategies, including convening an expert advisory group (EAG) and engaging in public consultation, will be employed to ensure that the HTA takes into account all relevant and important issues from the perspectives of multiple stakeholders.[11]

2.2.1 Establishment of the expert advisory group

HIQA will convene an appropriately represented multidisciplinary EAG as a source of expertise to advise the Evaluation Team and inform the interpretation of the evidence and development of the advice to the NSAC. The EAG will comprise nominees from a range of stakeholder organisations, including patient representation, healthcare providers, and clinical and public health experts. The role of the group is to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate.

2.2.2 Public and targeted consultation

A public and targeted consultation will be conducted to provide stakeholders not directly involved in the HTA with an opportunity to give feedback on a draft version of the report. The aim of the consultation will be to obtain feedback on any important issues that may not have been adequately addressed in the draft HTA and, based on the feedback received, to expand coverage of these issues in the final HTA report submitted to the NSAC, where appropriate. The feedback received during the consultation and HIQA's responses to the issues raised, including any changes made to the report as a result, will be published on the HIQA website in a Statement of Outcomes report alongside the final HTA.

3 Epidemiology

The purpose of this chapter within the HTA is to provide an overview of the epidemiology and natural history of colorectal cancer (CRC). The specific aims of this chapter will be to describe:

- the natural history of CRC
- the burden of CRC (that is, incidence, prevalence, morbidity and mortality)
- diagnosis and treatment of CRC.

Where available, national datasets will be used to estimate the burden of colorectal cancer in Ireland. Data on the size of the population affected by the potential age extension of the BowelScreen programme will be sought from the Central Statistics Office (CSO). Data on CRC incidence and mortality, patient characteristics such as mode of detection, cancer stage and treatment, and survival time will be requested from the National Cancer Registry Ireland (NCRI). National data will be supplemented with data from the international literature that is considered broadly applicable to the Irish context.

The epidemiological data from this chapter will inform the estimated resources required (sections 7.1 and 7.2) to extend the age of eligibility for the BowelScreen programme to people aged 50 to 54 years.

4 Description of technology

The purpose of this chapter is to provide an overview of colorectal cancer screening and the Irish population-based colorectal cancer screening programme, BowelScreen. The specific aims of this chapter will be to describe:

- screening for colorectal cancer in average-risk populations

- the existing BowelScreen programme in Ireland, including the screening pathway for those aged 59 to 69, and the planned expansion of the programme to people aged 55 to 74 years
- the proposed age extension of the BowelScreen programme to include people aged 50 to 54 years.

To inform the chapter, a review of relevant literature and publications from the BowelScreen programme will be conducted.

4.1 Review of international practice and guidelines

This section will provide an overview of international practice, describing the countries that currently have a colorectal cancer screening programme in place. The overview will be informed by reviewing grey literature sources (for example, national public health organisations, and the websites of governmental departments and relevant agencies), and recent peer-reviewed literature. The overview will focus on countries considered of most relevance to Ireland, including:

EU/EEA

- Austria
- Belgium
- Denmark
- Finland
- France
- Germany
- Italy
- Netherlands
- Norway
- Portugal
- Slovenia
- Spain
- Sweden
- Switzerland

Non-EU

- Australia
- Canada
- New Zealand
- England
- Scotland
- Wales
- Northern Ireland

As part of this review, specific information relating to existing screening programmes will be extracted. This will include, but is not limited to: the age at which screening commences and concludes; the method of screening (for example, FIT, colonoscopy etc.); the threshold used to designate a positive screening result for stool-based tests; and the interval at which screening is performed. Other noteworthy elements of each relevant programme will also be extracted.

Additionally, international guidelines relating to colorectal cancer screening will be examined. Guidelines intended for use in the European context or considered

transferable to the European context will be considered eligible for inclusion. Where possible, specific recommendations related to colorectal cancer screening will be extracted, such as FIT threshold(s), age range(s), interval(s), and screening method(s). Particular focus will be applied to guidelines that specify or include the age range under consideration in the HTA.

5 Clinical effectiveness of screening

5.1 Clinical effectiveness

Studies examining the clinical effectiveness of colorectal cancer (CRC) screening have considered a variety of screening modalities such as colonoscopy, flexible sigmoidoscopy and faecal occult blood tests, including guaiac-based faecal occult blood tests (gFOBT) and faecal immunochemical tests (FIT). These studies have either compared CRC screening to no screening, or have explored the comparative effectiveness of different screening modalities. While randomised controlled trial (RCT) evidence of the effectiveness of stool-based CRC screening is based on older gFOBTs, these have largely been replaced with newer, more sensitive FIT tests in screening programmes.[12]

Initial scoping indicated limited evidence of the effectiveness of FIT-based screening at younger starting ages compared to older starting ages. Given the variety of screening modalities considered and the dearth of studies specifically addressing the strategy of interest to this HTA, a broad Population, Intervention, Comparator, Outcomes and Study design (PICOS) framework will be applied to ensure a sufficient breadth of evidence is captured.

5.1.1 Review question

The review question was formulated according to the PICOS framework presented in Table 1. The review seeks to answer the following question:

- What is the clinical effectiveness of colorectal cancer screening with a starting age of 50 compared to a starting age of 55?

Table 1. Review question for assessing clinical effectiveness

Population	Average-risk, asymptomatic populations
Intervention	***Ideal intervention and comparator for HTA research question:*** *Colorectal cancer screening using FIT-based strategies at a starting age of 50 years (with screening age up to 74), compared to a starting age of 55.* **Range of evidence that will be considered:** Colorectal cancer screening using a range of modalities (colonoscopy, flexible sigmoidoscopy, guaiac-based faecal occult blood test (gFOBT), faecal immunochemical test (FIT), CT colonography), where the intervention eligibility age incorporates people aged between 50 and 54 years. All screening intervals (annual/every two years/longer) will be considered.
Comparator	Later starting age of screening, or no screening.
Outcomes	Colorectal cancer mortality and incidence, screening-related adverse events (for example, perforation, bleeding, death).
Study design	RCTs, non-randomised control trials, cohort studies, population-based case control studies.

5.1.2 Identification of studies

Preliminary scoping identified a number of systematic reviews investigating the clinical effectiveness of screening, including a 2021 systematic review from the US Preventive Services Task Force (USPSTF) and a 2024 evidence review by the European Commission.[13, 14] These reviews will be examined as potential key sources for identification of clinical effectiveness studies for the present review.

A de novo search for clinical effectiveness studies will be performed in Medline via EBSCOhost, Embase via Ovid, the Cochrane Library CENTRAL database and ClinicalTrials.gov to identify studies published since the conclusion of the aforementioned reviews. The electronic search strategy will be developed by a librarian and peer reviewed by a second librarian using the PRESS tool.[15] Reference lists of included studies will be searched for potentially relevant citations and forward citation searching of the USPSTF systematic review and of included studies will be performed in Google Scholar.

Study selection

Studies included within the USPSTF systematic review and or European Commission review will be examined for relevance to the present review according to the criteria outlined in Table 1. With respect to the search for additional studies, titles and

abstracts will be screened in duplicate by two reviewers. The full text of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 1, with any disagreements being resolved by discussion or a third reviewer, if required. Screening will be undertaken using Covidence software.

5.1.3 Data extraction and management

Data extraction will be performed by one reviewer using Microsoft Excel software. All data extracted will be reviewed by a second reviewer, with disagreements resolved by discussion. A standardised data extraction template will be developed prior to undertaking the review. At a minimum, the following information will be extracted for each study: publication year, authors, country/region, study design, details of the screening strategy (screening start and stop ages, screening modalities and intervals used, FIT thresholds), comparators, outcomes (including harms of screening).

Quality assessment

Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer. The quality of each study will be assessed with tools appropriate to the respective study designs.

Data synthesis

Given the anticipated range of screening strategies and age ranges, results will be synthesised narratively.

6 Test accuracy of FIT for detecting colorectal cancer

The faecal immunochemical test (FIT) is the primary screening tool for the BowelScreen programme, with a screen-positive decision threshold of 45µg Hb/g faeces (225ng haemoglobin/ml buffer). In order to inform decision-making by the National Screening Advisory Committee, it is necessary to consider whether the test accuracy of FIT for detecting colorectal cancer varies according to the age of the screened population. The aim of this section, therefore, is to review the test accuracy of FIT in colorectal cancer screening in people aged 50 to 54 years, and to determine if test accuracy varies by age.

6.1.1 Review question

Initial scoping indicated the existence of a variety of FIT types, with a range of thresholds reported in studies assessing their performance; most commonly, thresholds of 10 to 20µg Hb/g. Comparatively fewer studies have reported FIT test accuracy at higher thresholds, or have presented results stratified by age. This review seeks to answer the following question:

- Does test accuracy of FIT at a threshold of 45µg/g vary by age?

Given that information on FIT test accuracy has most commonly been reported at thresholds ≤20µg/g, it may also be necessary to consider the following broader questions:

- Does test accuracy of FIT (at any threshold) vary by age?
- What is the test accuracy of FIT at a threshold of 45µg/g?

The review questions were formulated according to the Population, Index test, Target condition (PIT) framework, presented in Table 2.

Table 2. Review questions for assessing test accuracy

Population	Average-risk population, stratified by age where available.
Index test	Faecal immunochemical test (FIT) at a threshold of 45µg Hb/g faeces (225 ng/mL buffer). A range of thresholds, as close to this threshold as possible, may also be considered.
Target condition	Adenoma, advanced adenoma, colorectal cancer.

Eligible studies

Table 3 outlines the inclusion and exclusion criteria for the review of FIT test accuracy. Eligible studies should include as a reference standard either a direct visualisation test (preferably colonoscopy) for all participants, or direct visualisation for FIT-positive participants in combination with at least one year of follow-up of participants with a negative FIT result using medical records or cancer registry.

Table 3. Inclusion and exclusion criteria for assessing test accuracy

	Inclusion criteria	Exclusion criteria
Population	Average-risk asymptomatic population, stratified by age where available	Symptomatic populations or those at high genetic risk of CRC, including Lynch syndrome (hereditary non-polyposis colorectal cancer (HNPCC)) and familial adenomatous polyposis
Index test	Quantitative FIT tests	Qualitative FIT tests, guaiac-based faecal occult blood tests (gFOBT)
Reference standard	Colonoscopy (or other direct visualisation test) for all participants, or colonoscopy (direct visualisation) for FIT-positive participants in combination with at least one year of follow-up of FIT-negative participants using medical records or cancer registry.	Colonoscopy/direct visualisation for FIT-positive participants only with no follow-up of FIT-negative participants.

6.1.2 Identification of studies

Initial scoping identified a number of systematic reviews of FIT test accuracy, including a 2021 USPSTF review[13] and a 2019 review by Selby et al.,[16] the latter of which specifically explored FIT test accuracy at different thresholds and according to age. These reviews were chosen as a key source for identification of test accuracy studies for the present review.

A de novo search for test accuracy studies will be performed in MEDLINE Complete via EBSCO, Embase via Ovid, the Cochrane Library and ClinicalTrials.gov from 1 May 2018 onwards to identify studies published since the 2019 systematic review by Selby et al. The electronic search strategy was developed by a librarian and peer reviewed by a second librarian using the PRESS tool.[15] The complete electronic search strategy for all databases is available on Zenodo.[17] Additional grey literature searches will be conducted in the INAHTA and TRIP databases. Reference lists of included studies will be searched for potentially relevant citations and forward citation searching of the Selby et al. systematic review and of included studies will be performed in Google Scholar.

Study selection

Studies included in the Selby et al. and USPSTF systematic reviews will be examined for relevance to the present review according to the criteria outlined in Tables 2 and 3. With respect to the search for additional studies, titles and abstracts will be screened in duplicate by two reviewers. The full text of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 3, with any disagreements being resolved by discussion or a third reviewer, if required. Screening will be undertaken using Covidence software.

6.1.3 Data extraction and management

Data extraction will be performed by one reviewer using Microsoft Excel software. All data extracted will be reviewed by a second person, with disagreements resolved by discussion. A standardised data extraction template will be developed prior to undertaking the review. At a minimum, the following data will be extracted for each study: publication year, authors, country/region and setting, sample size, details of the FIT test and reference standard (FIT brand and thresholds, type and timing of reference standard), target conditions, number of participants with each condition, true positives, false positives, true negatives, false negatives, sensitivity and specificity.

Quality assessment

Each study will be assessed by one reviewer, with the assessment cross-checked by a second reviewer. The quality of each study will be assessed using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2).[18]

Data synthesis

Results will be synthesised narratively. Additionally, depending on the available data, meta-analysis of test accuracy may be possible.

7 Assessment of cost effectiveness

In order to inform decision-making by the National Screening Advisory Committee, it is necessary to establish whether extension of BowelScreen to those aged 50 to 54 years is likely to be cost effective. Establishing this may be accomplished using two approaches:

- Reviewing existing published studies on cost effectiveness and relating the findings of such studies to the current Irish context
- Developing a model of cost effectiveness in the Irish setting.

Developing a model of cost effectiveness in the Irish setting would broadly involve the following steps: (1) Designing an appropriate model structure to represent the effect of BowelScreen; (2) Identifying relevant parameters to populate the model structure; (3) Running the analysis and presenting and interpreting the results. However, in order to inform the development of such a model, specifically in relation to steps (1) and (2), a review of existing published studies on cost effectiveness would likely be required. As such, the approach will in the first instance involve conducting a review of existing published studies on cost effectiveness and relating the findings of such studies to the Irish context.

Contingent on the findings of the review of published cost-effectiveness studies, development of a de novo model of cost effectiveness in the Irish setting may be considered necessary. This will be judged based on elements such as the applicability of international evidence to the Irish context, the availability of Irish data that may strengthen existing estimates, the potential for updates to the evidence base that may influence estimates of cost effectiveness, and the overall added value of performing such analysis in terms of informing decision-making.

7.1 Review of primary cost-effectiveness studies

Based on preliminary scoping, although there are published systematic reviews of cost-effectiveness analyses (CEAs) of colorectal cancer screening potentially relevant to this HTA, none were identified that are suited to the present question. For example, a systematic literature review of CEAs of stool-based colorectal cancer screening strategies was published in 2023 by Irish authors (Pokharel et al.).[19] While this paper considers the relevant starting age, the review aimed primarily to establish the extent to which existing CEAs considered the optimal screening interval and sought to identify an optimal screening strategy across a range of potential strategies. This paper also did not assess the relevance and credibility of the included studies to the Irish context, which is of particular importance to the present HTA. Therefore, it is considered that a review of the primary economic literature is necessary.

7.1.1 Review aim

The main aim of the review of cost-effectiveness studies is as follows:

- Examine relevant published CEAs and assess the extent to which they address the following research question:
    - For the Irish population at average risk of colorectal cancer, is FIT-based colorectal cancer screening every two years at a FIT threshold of 45µg/g, in persons aged from age 50 to 74 years, cost effective compared to screening in persons aged 55 to 74 years?

7.1.2 Findings of initial scoping work: impact on PICOS selection

Initial scoping indicated that a broad range of FIT-based colorectal cancer screening strategies have been examined in the primary economic evaluation literature, such as variations in screening eligibility starting and finishing ages, FIT thresholds, and screening intervals. Given the heterogeneity in these strategies and the dearth of studies specifically addressing the strategy of interest to this HTA, it is necessary to apply a broad PICOS to ensure a sufficient breadth of evidence.

Further, heterogeneity is expected in the parameters and parameter values used across the studies. Even where the research question addressed within the study is aligned with that of the present HTA, the methodologies applied, particularly the parameter values used, may not be appropriate or transferable to the Irish setting. As such, triangulation of study findings (for example, focusing on sensitivity analyses to identify whether these corroborate the findings of main analyses) will likely be required. Therefore, a broad PICOS was considered necessary for this review as per Table 4, 'Intervention and comparator'.

Study designs

Model-based studies that estimate the cost effectiveness of FIT-based colorectal cancer screening strategies published since 2014 will be eligible for inclusion (Table 4).

Exclusion criteria

Studies not reporting measures of cost effectiveness such as incremental cost-effectiveness ratios (ICERs), or not reporting both measures of costs and health benefits will be excluded (Table 4). Additionally, and consistent with the recent review published by Pokharel et al.,[19] only European studies will be included in this review, as these are most likely to be transferable to the Irish context.

Table 4. PICOS framework for review of cost-effectiveness studies

	Inclusion criteria	Exclusion criteria
Population	Average-risk populations in European countries	Studies in populations at high genetic risk
Intervention and comparator	***Ideal intervention and comparator for HTA research question****:* *Colorectal cancer screening using FIT-based strategies at a starting age of 50 (with screening age up to 74), compared to a starting age of 55.* **Range of evidence to be considered:** Colorectal cancer screening using FIT-based strategies with any screening interval (annual/every two years/longer), where the intervention eligibility age incorporates people aged between 50 and 54 years with any finishing age, compared to a later starting age of screening. Evidence for consideration may include varying FIT thresholds.	Studies for which the only comparator is no screening.
Outcome	Measures of cost effectiveness, for example, ICERs (cost per quality-adjusted life year) or measures of costs and health benefits expressed separately.	Studies not reporting measures of health benefits such as life years gained or ICERs, or not reporting both measures of costs and health benefits.
Study design	Full economic evaluations: - Cost-utility analyses - Cost-effectiveness analyses.	Studies published prior to 2014. Conference abstracts, comments and editorials.

Key: ICER – incremental cost-effectiveness ratio; FIT – faecal immunochemical test.

7.1.3 Identification of studies

The Pokharel et al. review[19] was identified as a recent systematic review that considered strategies of particular relevance to the present review. As such, this review was chosen as a key source for identification of cost-effectiveness studies for the present review.

A de novo search for cost-effectiveness studies will be performed in MEDLINE Complete via EBSCO, Embase via Ovid and the CEA registry from 1 September 2022 onwards to identify studies published since the Pokharel et al. review. The electronic search strategy was developed by a librarian and peer reviewed by a second librarian using the PRESS tool.[15] The complete electronic search strategy for all databases is available on Zenodo.[20] Electronic database searches will be supplemented by a search of grey literature (from 2013–2024) in TRIP database,

INAHTA database, and UptoDate. Reference lists of included studies will be searched for potentially relevant citations and forward citation searching of included studies will be performed in Google Scholar.

Study selection

Studies included within the Pokharel et al. systematic review will be examined for relevance to the present review according to the criteria outlined in Table 4. With respect to the search for additional studies, titles and abstracts will be screened in duplicate by two reviewers. The full text of potentially eligible studies will be retrieved and independently assessed for eligibility by two reviewers according to the criteria outlined in Table 4, with any disagreements resolved by discussion or with a third reviewer, if required.

7.1.4 Data extraction and management

A data extraction form will be developed in Microsoft Excel and piloted. Data will be extracted in duplicate with any disagreements resolved through discussion or a third reviewer where necessary. At a minimum, the following information will be extracted for each study: publication year, authors, country/countries of screening setting, details of relevant screening strategies (screening start and stop ages, intervals between screens, FIT thresholds), details of the comparator, screening uptake rates, source of disease data, estimated costs, health benefits gained from the intervention, cost-effectiveness threshold, reported cost-effectiveness ratio, time horizon applied, analysis perspective, discount rate applied.

Assessment of methodological quality and transferability

Assessment of the methodological quality of economic evaluations will be carried out using the Philips checklist.[21] The ISPOR questionnaire will be used to assess the transferability potential of economic evaluations to the Irish setting.[22] This will be performed by two people independently with any disagreement resolved through discussion or a third reviewer where necessary.

Data synthesis

General characteristics of the studies and screening programmes will be presented using tables. A narrative synthesis of the results of the included studies will be presented. Willingness-to-pay thresholds of €20,000 and €45,000 per quality-adjusted life year (QALY) gained are typically used in Ireland as reference points for decision-making regarding reimbursement. Therefore, where possible, results will be presented in the context of these thresholds to facilitate comparisons across studies in terms of the interpretation of the results from the cost-utility analyses (CUAs) for the Irish context. To facilitate comparability of the results across countries and

years, costs will be adjusted to the 2023 price year using country-specific consumer price indices and purchasing power parities in accordance with national HTA guidelines.[23]

De novo economic evaluation

Contingent on the findings of the review of cost-effectiveness studies described above, a de novo economic evaluation may be considered appropriate. This will be judged based on elements such as the applicability of international evidence to the Irish context, the availability of Irish data that may strengthen existing estimates, the potential for updates to the evidence base that may influence estimates of cost effectiveness and the overall added value of performing such analysis in terms of informing decision-making.

8 Budget impact analysis and organisational implications

8.1 Budget impact analysis

A budget impact analysis (BIA) will be carried out to enable assessment of the affordability and capacity required to extend the BowelScreen programme. The BIA will estimate the incremental direct costs and resources required by the HSE to extend BowelScreen to include people aged 50 to 54 years and will be conducted over at minimum a five-year time horizon. The analysis will be conducted in accordance with national HTA guidelines for the conduct of budget impact analysis of health technologies.[24]

The analysis will model and compare the costs and resources required, including cost and resource offsets (such as colonoscopies and treatments avoided through earlier screening) for the following comparisons:

i. commencing screening at age 50, with screening continuing every two years up to age 74

ii. commencing screening at age 55, with screening continuing every two years up to age 74 (that is, current policy for expansion of the BowelScreen programme, in addition to current practice of screening in those aged 59 to 69 years).

The following are examples of direct costs that will be considered within the BIA for each year of the programme:

- FIT testing (including purchase, postage and processing of tests)

- colonoscopy and CT colonography (including both diagnostic and surveillance testing)
- histopathology, radiology, treatment (chemotherapy, radiotherapy and surgery) and hospitalisation for those diagnosed with cancer.

In addition to unit costs, parameters that will be required for the analysis will include, for example: the number of individuals who would be in receipt of FIT testing; uptake rates for satisfactory return of samples; parameters relating to the natural history of colorectal cancer; rates of adenoma and cancer detection through screening; and expected demographic changes.

Resource use will be estimated based on the size of the eligible population with consideration of estimated screening uptake rates, and informed by data from the existing BowelScreen programme,[25] similar screening programmes internationally (section 4.1) and the input of the expert advisory group. Similarly, screening-related parameters will be informed by BowelScreen data,[25] similar international screening programmes and the expert advisory group. Demographic changes will be estimated using census data, while colorectal cancer natural history parameters will be identified through analysis of National Cancer Registry Ireland data (as per section 3).

8.2 Organisational considerations

Implementation of the proposed extension of the BowelScreen programme to include those aged 50 to 54 years will require consideration of the core principles and elements of a screening programme.[26, 27] The assessment of necessary organisational changes will be carried out in accordance with guidance specified in the EUnetHTA Core Model®.[28]

The analysis will consider the impact of extending the BowelScreen programme to people aged 50 to 54 years on human (that is, staff) and capital resources (such as equipment and facilities). Potential challenges associated with managing timely access to colonoscopy following a positive FIT result, in the context of existing endoscopy capacity constraints within the healthcare system, will also be considered.

9 Ethical and social considerations

Key ethical considerations outlined in the EUnetHTA Core Model will be used to guide the ethical analysis of extending the BowelScreen programme to people aged 50 to 54 years. Potential ethical considerations may include issues related to:

- **Balancing potential benefits and harms:** Lowering the screening age increases the number of individuals undergoing screening, which may lead to

earlier detection and potentially improved outcomes.[29] However, it also raises concerns about potential harms, such as false positives and unnecessary procedures, including colonoscopies.[29] Striking the right balance between potential benefits and risks is crucial, especially for younger individuals who may have a lower risk of developing colorectal cancer.

- **Equity and access:** Expanding screening to younger individuals may exacerbate existing disparities in access to healthcare.[30, 31] Ensuring equitable access to screening for all individuals, regardless of socioeconomic status, race, ethnicity, or geographic location, is an ethical imperative.[31]
- **Informed consent and shared decision-making:** Individuals considering screening should be fully informed about the potential benefits, risks, and limitations of screening, especially in the context of the lower screening age.[29] This includes providing information about the potential for over-diagnosis and unnecessary procedures.[30]
- **Resource allocation:** Lowering the screening age may strain healthcare resources, including financial resources, healthcare personnel, and screening infrastructure.[30] It is important to consider the ethical implications of diverting resources from other important healthcare needs and to ensure that the benefits of expanded screening justify the additional costs.[30]
- **Psychological impact:** Colorectal cancer screening can be invasive and anxiety-provoking;[30] this may be especially relevant for younger individuals who may not have experienced such procedures before. It is important to consider the potential psychological impact of screening on individuals and to provide appropriate support and counselling services to address any anxiety or distress.[32]

10 Anticipated timeline

The assessment will be submitted to the Board of HIQA for approval. Subject to its approval, the final HTA and associated Statement of Outcomes will be submitted to the NSAC for consideration and published on the HIQA website. The anticipated completion date is Q2 2025.

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Appendix 1 National Screening Advisory Committee (NSAC) criteria± by HTA domain

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
1	The Condition	The condition should be an important health problem. The epidemiology, incidence, prevalence and natural history of the condition should be understood, including development from latent to declared disease and or there should be robust evidence about the association between the risk or disease marker and serious or treatable disease.	Epidemiology
2		All the cost-effective primary prevention interventions should have been implemented as far as practicable.	Not applicable**
3		If the carriers of a mutation are identified as a result of screening, the natural history of people with this status should be understood. The psychological implications should be considered, and the necessary psychological supports should be in place.	Epidemiology, Ethical, social and legal issues
4	The Screening Method	The screening method should be, as far as is practicable: a) simple b) safe c) precise d) reliable e) validated.	Clinical effectiveness and safety, Organisational issues
5		The distribution of screening values in the target population should be assessed and suitable cut-off levels/measurements defined and agreed by the applicant.	Description of technology, Clinical effectiveness and safety, Organisational issues
6		The screening process should be acceptable to the target population.	Ethical, social and legal issues
7		There should be an agreed policy on the further diagnostic investigation of individuals with a positive screening result and on the choices available to those individuals.	Description of technology, Organisational issues
8		If screening is for a particular mutation(s) or set of genetic variants, the method for their selection should be kept under review.	Organisational issues

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
9	The Intervention	There should be an effective intervention for patients identified through screening, with evidence that intervention at a pre-symptomatic phase leads to better outcomes for the screened individual compared with usual care.	Description of technology, Clinical effectiveness and safety
10		There should be agreed evidence-based policies covering which individuals should be offered interventions and the appropriate intervention to be offered.	Description of technology, Organisational issues
11	The Screening Programme	Ideally there should be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity. Where screening is aimed solely at providing information to allow the person being screened to make an informed choice, there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.	Clinical effectiveness and safety, Ethical, social and legal issues
12		There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is acceptable and can be implemented.	Ethical, social and legal issues, Organisational issues
13		The benefit gained by populations and individuals from the screening programme should outweigh the harms. The public should be informed of these harms and of their associated undesirable physical and psychological consequences.	Ethical, social and legal issues, Organisational issues
14		The opportunity cost of the screening programme (including testing, diagnosis and treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (value for money). Assessment against these criteria should have regard to evidence from cost-benefit and/or cost-effectiveness analyses and have regard to the effective use of available resource.	Economic analysis
15	Implementation Criteria	Clinical management of the condition and patient outcomes should be in place before a screening programme is initiated.	Organisational issues

Criterion No.	NSAC Grouping	Criterion	HTA domain(s)*
16		Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.	Organisational issues
17		All other options for managing the condition should have been considered (such as improving treatment or providing other services), to ensure that no more cost-effective intervention could be introduced, or current interventions increased within the resources available.	Economic analysis, Ethical, social and legal issues
18		There should be a plan for managing and monitoring the screening programme against an agreed set of quality assurance standards. This should include monitoring performance against different sub-groupings in the population.	Organisational issues
19		The potential benefits and harms of screening, investigation, preventative intervention or treatment, should be made available and explained to the eligible participants to assist them in making an informed choice. There should be a clear system of communication incorporated into each screening programme to ensure patients are kept aware of any developments in their case.	Ethical, social and legal issues, Organisational issues
20		**Decisions about commencing, expanding or ceasing a programme should be based on scientifically validated evidence.**	**All**

Key: HTA – health technology assessment; NSAC – National Screening Advisory Committee. **Source of NSAC criteria**: Department of Health[33]
± NSAC Criteria for Appraising the Viability, Effectiveness and Appropriateness of a Screening Programme.
* A mapping exercise was conducted by the HIQA evaluation team to identify the relevant HTA domain for each of the individual NSAC criteria, based on the HTA Core Model® proposed by the European Network for Health Technology Assessment (EUnetHTA).[10] The mapping exercise aimed to clarify the extent to which a typical HTA addresses the NSAC criteria, and which HTA domain addresses which criterion/criteria.
** Considered outside the scope of a conventional HTA, unless the HTA is undertaken specifically to inform this criterion.

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