

Study ID: 7-A/26

**Title: European implementation study on
simultaneous screening for gastric and
colorectal cancers**

Acronym:

EUGastScreen

STUDY PROTOCOL

Version 3.2

24 September 2026

Status of the document

Document information		
Status	Revision date	Authors
First draft of v. 1.4 created by the coordination team	29.08.2024	Mārcis Leja, Linda Mežmale, Yelena Tarasenko
Draft v. 1.5 created by the coordination team after discussions with partners	29.09.2024	Mārcis Leja, Yelena Tarasenko
Draft v 1.5 circulated to all the partners asking for the country-specific feedback	29.09.2024	Mārcis Leja
Version 1.6 created by the coordination team after discussions with partners	18.11.2024	Mārcis Leja
Version 1.6 updated	25.11.2024	Yelena Tarasenko
Version 1.7 created by the coordination team after discussions with partners	03.01.2025	Mārcis Leja, Yelena Tarasenko
Version 1.8 created by the coordination team	29.01.2025	Mārcis Leja
Version 1.9 created by the coordination team following the feedback from partners	30.06.2025	Mārcis Leja

Version 1.9 circulated to all the partners	30.06.2025	Mārcis Leja
Version 2.0 created by the coordination team following the feedback from partners	25.11.2025	Mārcis Leja, Yelena Tarasenko
Version 2.0 circulated to all the partners	25.11.2025	Mārcis Leja
Version 2.1 created by the coordination team following the feedback from partners	01.02.2026	Mārcis Leja, Yelena Tarasenko
Version 2.1 circulated to all the partners	01.02.2026	Mārcis Leja
Version 2.2 created by the coordination team following the feedback from partners	15.04.2026	Mārcis Leja, Yelena Tarasenko
Version 2.2 circulated to all the partners	15.04.2026	Mārcis Leja
Version 2.2 updated following the feedback from all partners	30.04.2026	Kateryna Priadko, Yelena Tarasenko
Version 3.0 created by the coordination team	05.05.2026	Mārcis Leja, Kateryna Priadko
Version 3.0 circulated to all the partners	15.05.2026	Mārcis Leja
Version 3.0 updated following the feedback from all partners	10.06.2026	Kateryna Priadko, Yelena Tarasenko

Version 3.1 created by the coordination team	16.06.2026	Mārcis Leja, Kateryna Priadko
Version 3.1 sent for review to all the partners and the External Advisory Committee	17.06.2026	Mārcis Leja
Version 3.1 updated following the feedback from all partners and external Advisory Committee	05.07.2026	Yelena Tarasenko, Kateryna Priadko
Version 3.2 created by the coordination team	08.07.2026	Mārcis Leja
Version 3.2 finalized by involving all partners	28.07.2026	Kateryna Priadko
Updated protocol version (3.2) submitted for the Ethics Committee in Latvia (Riga East University Hospital Foundation)	30.07.2026	Mārcis Leja
Ethics approval received from the Ethics Committee of the Riga East University Hospital Foundation	20.08.2026	Mārcis Leja
Version 3.2 submitted for registration to the ClinicalTrials data base	24.09.2026	Kateryna Priadko
Final review		
Final version		

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Abbreviations

BID – *bis in die*, i.e., twice a day

CI – Confidence interval

CRC – Colorectal cancer

EEA – European Economic Area

EIA – Enzyme immunoassay

ELISA – Enzyme-Linked Immunosorbent Assay

EU – European Union

FAIR – Findable, Accessible, Interoperable, and Reusable

FIT – faecal immunochemical test

GDPR – General Data Protection Regulation

gFOBT – guaiac-based faecal occult blood test

GP – general practitioner (primary care physician)

H. pylori – *Helicobacter pylori*

IARC – International Agency for Research on Cancer

ITT – intention-to-treat

NNT – number needed to treat

PCAB – potassium-competitive acid blockers

PI – Principal Investigator

PP – per protocol

PPI – proton pump inhibitor

SAT – stool antigen test for *H. pylori*

Strategy – in the context of the current study, screen-and-treat strategy for *H. pylori* by SAT in individuals undergoing FIT screening for colorectal cancer

UBT – ¹³C-Urea breath test for *H. pylori*

WHO – World Health Organization

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Justification

Helicobacter pylori (*H. pylori*) is the primary causative factor for gastric cancer, with nearly 90% of non-cardia gastric cancer cases attributed to the infection ¹. Globally, this accounts for approximately 770 000 new cases annually, making *H. pylori* the leading infectious cause of cancer in countries with high and very high Human Development Index ². Additionally, *H. pylori* infection is a major aetiological factor for diffuse-type gastric cancer, including proximal gastric cancer and a subset of adenocarcinomas of the gastro-oesophageal junction³.

The prevalence of *H. pylori* varies significantly across the EU27 countries, ranging from 9.1% in Finland to 69.2% in Estonia ⁴. This variation may help explain the differences in gastric cancer incidence among these countries. Within individual countries, the prevalence of *H. pylori* also varies between different socioeconomic groups. For instance, first-generation immigrants to the Netherlands exhibit a significantly higher prevalence of *H. pylori* ⁵. A review by Morais *et al.* ⁶ indicates that migrants from high-risk areas are particularly vulnerable to *H. pylori* infection. Most studies suggest that the prevalence among migrants is generally comparable to or lower than that in their country of origin but remains higher than in their host country. Given the current socio-political landscape in Europe, migration is expected to increase prevalence of *H. pylori* in many European Union (EU) countries, particularly among vulnerable populations.

Globally, while the prevalence of *H. pylori* in adults remains high, it has declined significantly over the recent decades – from 52.6% (95% Confidence interval (CI): 49.6%–55.6%) in the 1990s to 43.9% (95% CI: 42.3%–45.5%) between 2015 and 2022 ⁴. However, this declining trend was not observed among children and adolescents. Over the past decade, the prevalence of *H. pylori* infection in Europe has been estimated at 46.7% (95% CI: 40.8%–52.7%), with notable differences among countries ⁴.

Eradicating *H. pylori* can substantially lower the risk of gastric cancer. A Cochrane review ⁷ based on studies conducted in Asia and Colombia found that the number needed to treat (NNT) to prevent one gastric cancer was 72, while the NNT to prevent one gastric cancer-related death is 135. A global implementation of the “screen-and-treat” strategy could yield 8.7 million disability-adjusted life-years ^{7, 8}. However, similar projections cannot yet be made for the European population due to the limited data available in Caucasian groups.

An international expert group organised by the International Agency for Research on Cancer (IARC) in 2025 has provided detailed evaluation of *H. pylori* eradication strategies in general population to prevent gastric cancer ⁹.

Basic principles for cancer screening in Europe

In Europe, only organised, properly governed, population-based, and quality-assured screening programmes are recommended ¹⁰. An international consensus, based on a blend of a systematic review and an online modified Delphi process conducted by the IARC/World Health Organisation

(WHO) ¹¹, established 16 essential and desirable criteria, which screening programmes would aspire to fulfil to be better-organised ¹². These criteria include, but are not limited to, the following:

a) protocol/guideline should be available; the document must define the target population, screening intervals, screening tests, referral pathways, and the management of positive cases; b) the target population should be clearly identifiable, and a systematic approach must be in place to invite eligible individuals for screening; c) key performance indicators should be defined, and the system's performance should be evaluated and audited against these benchmarks; d) proper governance structures and quality assurance measures must be in place. While most cancer screening programmes in Europe - such as those for breast, cervical, colorectal cancer (CRC) – adhere to these criteria, no such framework currently exists for gastric cancer screening. Significant knowledge gaps remain regarding the required indicators to develop evidence-based protocols or guidelines for an organised gastric cancer screening programme.

Traditionally, cancer screening has been considered a form of secondary prevention, aimed at detecting cancer or precancerous lesions within the target population. In the case of gastric cancer, screening strategies may involve both primary and/or secondary prevention, which can also be combined for greater effectiveness.

The *EUGastScreen* study is designed as a quality implementation study to explore gastric cancer screening strategies within organised cancer screening frameworks. The study is set to target individuals who are entering the age range for CRC screening, integrating gastric cancer screening into this existing structure.

Recommendations of the Council of the European Union

The Council of the EU ¹⁰ has recommended strategies for implementing quality-assured population-based, nationwide screening programmes across European Member States. These recommendations encompass CRC screening as well as strategies for gastric cancer prevention. Below are the specific guidelines for these two gastrointestinal cancers:

1. Colorectal cancer

Quantitative faecal immunochemical test (FIT) is the preferred screening method for individuals aged 50 to 74 years, serving as a basis for follow-up colonoscopies. Further research may enable the use of quantitative information from FIT results to develop risk-tailored strategies, incorporating thresholds adjusted by factors such as sex, age and prior test results. Upper endoscopy may also be adopted as a primary tool to facilitate integrated screening approaches ^{13, 14}.

2. Gastric cancer

Screen-and-treat strategies for *H. pylori*, including implementation studies, should be considered in those countries or regions inside countries with high gastric cancer incidence and death rates.

Screening should also address strategies for identification and surveillance of patients with precancerous stomach lesions unrelated to *H. pylori* infection.

European guidelines on screen-and-treat strategy for *H. pylori* as the primary tool to prevent gastric cancer (EC-GaC within EU GAINS project) are under development by an expert group coordinated by IARC and are anticipated to be finalized by the end of 2027.

EUGastScreen aims to integrate these recommendations, combining screening strategies for both gastric cancer and CRC into a unified approach.

Principles of implementation research

EUGastScreen will follow the principal steps of implementation research outlined in the WHO guide, “*A guide to implementation research in the prevention and control of noncommunicable diseases*”¹⁵. This guide defined four key steps for effective implementation research: 1) Identification: Recognizing the need for a policy or intervention; 2) Adaptation: Tailoring the policy or intervention to fit the specific context; 3) Evaluation: Assessing the policy or interventions effectiveness; and 4) Scaling-Up: Expanding the successful policy or intervention to a broader context (**Figure 1**).

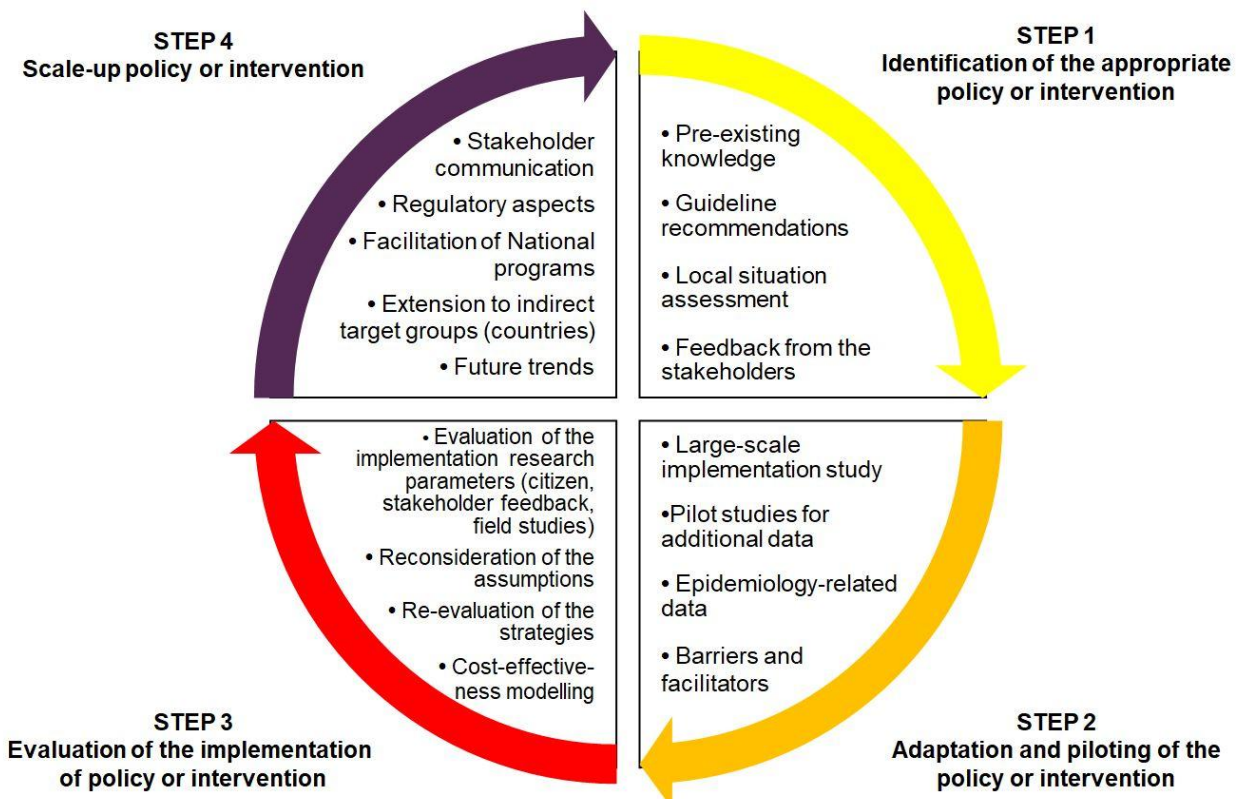


Figure 1. Implementation and the implementation research cycle (according to the WHO guide).

The *EUGastScreen* study will address Step 2 (Adaptation) and Step 3 (Evaluation) in the implementation research cycle.

The implementation outcome variables associated with these steps are outlined in **Table 1**.

Table 1. Implementation outcome variables.

Implementation outcome	Working definition	Related terms
Acceptability	The perception among stakeholders (for example, consumers, providers, managers, policymakers) that an intervention is agreeable	Factors related to acceptability (for example, comfort, relative advantage, credibility)
Adoption	The intention, initial decision, or action to try to employ a new intervention	Uptake, utilization, intention to try
Appropriateness	The perceived fit or relevance of the intervention in a particular setting or for a particular target audience (for example, provider or consumer) or problem	Relevance, perceived fit, compatibility, perceived usefulness or suitability
Feasibility	The extent to which an intervention can be carried out in a particular setting or organization	Practicality, actual fit, utility, trialability
Fidelity	The degree to which an intervention was implemented as it was designed in an original protocol, plan, or policy	Adherence, delivery as intended, integrity, quality of programme delivery, intensity, or dosage of delivery
Implementation Cost	The incremental cost of the implementation strategy (for example, how the services are delivered in a particular setting). The total cost of implementation would also include the cost of the intervention itself	Marginal cost, total cost

Coverage	The degree to which the population that is eligible to benefit from an intervention actually receives it	Reach, access, service spread or effective coverage (focusing on those who need an intervention and its delivery of sufficient quality, combining coverage and fidelity); penetration (focusing on the degree to which an intervention is integrated in a service setting)
Sustainability	The extent to which an intervention is maintained or institutionalized in a given setting	Maintenance, continuation, durability, institutionalization, routinization, integration, incorporation

***EUGastScreen* will address these outcome variables in the following way:**

Acceptability will be addressed either through its own activities or related activities in *EUCanScreen* and other projects, such as TOGAS and TOGAS Plus ¹⁶. *EUCanScreen* will establish a Governmental Advisory Board and a Stakeholder forum to gather perspectives and foster collaboration. TOGAS is currently collecting feedback from screening authorities, governmental decision-makers, and the target population directly involved in the screening process. *EUGastScreen* together with these activities will also reach out to medical professionals and disseminate information to the potential screening group to further enhance acceptability.

Adoption at the EU level was initiated with the 2022 Council Recommendation on screening, where all Member States expressed support for the guidance. *EUGastScreen* will focus on directly promoting adoption among the target groups. The project will analyse the uptake of various steps of intervention and address barriers to compliance.

Appropriateness will be addressed during various stages of the project. The results are expected to depend on epidemiological factors and the performance of different steps of intervention. The appropriateness of the intervention will be assessed based on its ability to meet contextual and population needs.

Feasibility will be evaluated through pilot studies conducted in several populations with varying gastric cancer incidence and *H. pylori* prevalence. Participating countries may differ also in their CRC screening programme setup and success rates. Differences in the registration status and availability of pharmaceuticals for eradication purposes, as well as the reimbursement status for diagnostic tests and medication, will also be considered. These factors will collectively inform the assessment of feasibility.

Fidelity will be a critical focus for *EUGastScreen*. Key indicators to be analysed include the following: outreach effectiveness across different countries and communication strategies,

response rate; test acceptance and return rates; proportion of correctly collected samples, adequate lab result, and compliance with treatment protocols; completion rates and success rates of first- and second-line treatments. These indicators will help ensure the intervention is implemented as intended.

Implementation cost of the intervention is expected to be analysed within other activities of *EUCanScreen*. Nevertheless, *EUGastScreen* will contribute valuable information to support this analysis.

Coverage is an important implementation outcome, reflecting the extent to which eligible individuals participate in the *EUGastScreen* intervention. Coverage will be assessed by examining participation among eligible individuals and, where feasible, the proportion of the target population reached. Where reliable denominator data are available from screening registries, healthcare databases, or participating general practitioners (GPs) practice lists, coverage will be estimated as the proportion of the eligible target population participating in *EUGastScreen*. Where such denominator data are unavailable, participation among invited individuals will be used as the primary measure of programme reach.

Sustainability of the programmes, in particular in the context of surveillance, is essential to maximizing the programme's impact. Efforts to address sustainability will be addressed during *EUCanScreen* and are expected to continue beyond the project's timeline.

Approaches to gastric cancer screening

Depending on the chosen approach, screening may target different stages of gastric carcinogenesis process or risk factors. Specifically, screening can focus on detecting cancer itself, identifying precancerous lesions, or assessing the primary causative risk factor – *H. pylori* infection¹⁷. The target lesions and corresponding screening modalities are illustrated in **Figure 2**.

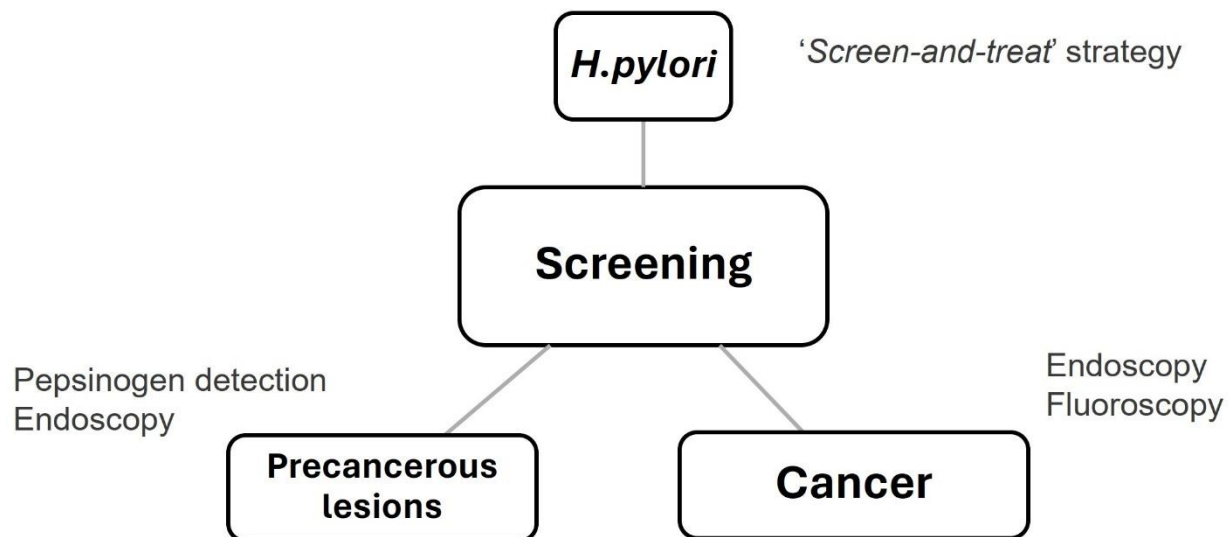


Figure 2. Approaches to gastric cancer screening.

The eradication of *H. pylori* infection is categorized as primary prevention of gastric cancer, whereas screening for cancer or precancerous lesions is considered secondary prevention ¹⁸.

EUGastScreen study will focus on the ‘screen-and-treat’ strategy, while elements involving invasive (endoscopic) identification and the surveillance of patients with precancerous lesions will also be included.

Screen-and-treat strategy

Screen-and-treat strategy – searching for *H. pylori* in general population, i.e. screening individuals without symptoms of the infection or previous related medical history (including family history) and treating those who tested positive for the infection ¹⁷.

The recommendation on the diagnosis, treatment, management, and prevention of *H. pylori* infection are presented in the Maastricht/Florence Consensus report, a series of evidence-based guidelines developed by an international panel of experts ³. According to the recommendations, diagnostic tests used to screen for *H. pylori* infection in screen-and-treat strategy should preferably be non-invasive (Maastricht VI, WG4 Statement 11) ³.

¹³C-urea breath test (UBT) remains a crucial tool for diagnosing *H. pylori* infection, both before and after eradication therapy (Maastricht VI, WG2 Statement 4) ³. While it can be an excellent tool in screen-and-treat strategy, certain limitations must be acknowledged. UBT requires either visiting a medical facility (such as a breath test laboratory) or submitting the breath sample to the laboratory via a courier. In the latter scenarios, the breath sample may be collected by the individual at home. However, there are indications that a significant proportion of the target population may find the test instructions for at-home sample collection challenging to understand and follow. Furthermore, this approach is expected to incur higher costs.

According to Maastricht VI, the **monoclonal stool antigen test (SAT)**, if properly validated, is considered an appropriate test for detecting *H. pylori* both before and after treatment (Maastricht VI, WG2 Statement 5) ³. Since the test uses stool material, it is expected to integrate seamlessly with CRC screening programmes that already utilize FIT.

Another non-invasive test is **serology** based on the detection of IgG group antibodies to *H. pylori* infection. However, its utility in screening programmes is limited due to its tendency to produce a significant number of false-positive results ¹⁹. Therefore, serology should not be used as stand-alone test for deciding on eradication therapy. If serology is employed for the initial stage of *H. pylori* screening, confirmation of an active infection through another test (e.g., UBT or SAT) is required before initiating treatment (Maastricht VI, WG4 Statement 12) ³. Additionally, serological testing requires the retrieval and handling of a blood sample, which is not currently part of CRC screening programmes in Europe.

The accuracy of UBT and SAT may be affected by the regular use of proton pump inhibitors (PPIs) and antibiotics, which can lead to false-negative results.

During short-term post-eradication follow-up (4–6 weeks), no antibiotics or bismuth should be used to permit optimum testing for *H. pylori*. PPIs must be discontinued at least 14 days before testing (Maastricht VI, WG2 Statement 10) ³.

Screen-and-treat for *H. pylori* at the time of initiating colorectal cancer screening

The EUGastScreen study approach is to integrate gastric cancer prevention through a screen-and-treat strategy for *H. pylori* into existing or planned FIT-based CRC screening programme.

According to the Maastricht VI recommendations ³, combining gastric cancer prevention modalities (non-invasive or endoscopic) with CRC screening represents a promising opportunity (WG4 Statement 18). However, testing for *H. pylori* during CRC screening remains controversial, as reflected by the borderline acceptance of this approach in the relevant statement in the Maastricht VI guidelines (Grade C2, Agreement 81%).

The primary challenge lies in the evidence that *H. pylori* eradication is most effective earlier in life before the development of gastric precancerous lesions. By the time individuals enter the target age for CRC screening, some may have already developed such lesions or progressed beyond the “point-of-no-return”. Despite this, there is no established method to define this threshold, and the Maastricht VI guidelines affirm that *H. pylori* eradication is effective at any age: *H. pylori* eradication offers the chance for gastric cancer prevention at any age in adulthood. The magnitude of the benefit decreases with age (WG4 Statement 9) ³.

The EUGastScreen study will evaluate the feasibility of the screen-and-treat strategy for *H. pylori* at the time of CRC screening. The target population will include individuals entering an organised CRC screening programme.

While the typical age of entry is 50 years, this may vary among participating countries based on their respective CRC programme initiation ages. In countries without an organised CRC screening programme, simultaneous pilot programmes for FIT-based CRC screening and *H. pylori* screen-and-treat could be an optimal solution. Emerging research highlights the importance of studying the effects of simultaneous invitations for screening or testing for multiple types of cancer to improve cancer screening rates in Europe ^{20, 21}.

Choosing the age group entering CRC screening programme is justified by two primary considerations: 1) to increase effectiveness of *H. pylori* eradication by targeting a relatively younger age group; 2) to minimize confusion among individuals who may have previously undergone single test for CRC screening.

To date, only one major study has investigated the combination of FIT for CRC screening and SAT for *H. pylori* screen-and-treat, conducted in Changhua County, Taiwan ²². A total of 152,503 participants aged 50-69 years were enrolled and divided into two groups: SAT+FIT or FIT alone. The participation rates were 49.6% for SAT+FIT group and 35.7% for FIT-alone group ²².

Treatment regimen selection in a population-based prevention programme

According to Maastricht VI, *H. pylori* eradication regimens should be tailored to account for local resistance patterns, particularly resistance to clarithromycin ³, which is still the most frequently used antibiotic in these regimens ²³.

If individual susceptibility testing is not available, bismuth quadruple therapy is the recommended first-line in regions with high (>15%) or unknown clarithromycin resistance. If bismuth quadruple therapy is unavailable, non-bismuth concomitant quadruple therapy may be considered (WG4 Statement 2)³. The treatment duration of bismuth quadruple therapy should be 14 days, unless 10-days regimens with proven effectiveness are available (WG4 Statement 3) ³.

After failure of bismuth-containing quadruple therapy, a fluoroquinolone-containing quadruple (or triple) therapy or the high-dose PPI-amoxicillin dual therapy may be used as the second-line treatment option (WG4 Statement 11) ³.

After failure of both the first-line treatment with bismuth quadruple and second-line treatment with fluoroquinolone-containing therapy, clarithromycin-based triple or quadruple therapy can be considered only in regions with low (<15%) clarithromycin resistance. In areas with high resistance, alternative regimens such as a high-dose PPI-amoxicillin dual therapy, a rifabutin-containing regimen, or bismuth combined with different antibiotics are recommended (WG4 Statement 16) ³.

These recommendations were primarily developed for managing symptomatic patients. In population-based prevention programmes, **antibiotic stewardship** must be a key consideration ²⁴ even more so than in treating symptomatic patients, as population-based interventions in high-risk areas may significantly increase antibiotic consumption at the population level ²⁵.

While conflicting data exist on whether clarithromycin- and levofloxacin-containing therapies contribute to the long-term development of the gut resistome ^{26, 27}, this potential risk, along with the associated public health costs, cannot be ignored. Therefore, the choice of antibiotic regimens for population-based *H. pylori* eradication may differ from those used for symptomatic individuals; the potential of inducing the gut resistome should be considered when making the choice ²⁸. Avoiding commonly used antibiotics, such as macrolides (clarithromycin) that are important for treating life-threatening diseases, is a rational approach.

Taking these considerations into account, bismuth quadruple therapy with a high-dose PPI (e.g., esomeprazole 40 mg twice a day, BID) is the preferred *H. pylori* regimen for the first-line treatment within the EUGastScreen study. The treatment duration would be 10 days if using a fixed one-capsule combination (e.g., Pylera[®]), otherwise – 14 days.

For the second-line therapy, a fluoroquinolone-containing quadruple (or triple) therapy for 14 days would be the chosen option. In areas with low (<15%) clarithromycin resistance, clarithromycin triple therapy may be considered.

Modifications to these regimens can be made in accordance with local guidelines and drug availability.

Key Considerations for Public Health

The potential for resistome (i.e., complete set of antimicrobial resistance genes in a microbial community) induction must be carefully assessed when developing population-based *H. pylori* eradication programmes¹⁹. Bismuth quadruple therapy is recommended as the first-line treatment due to its lower impact on critical antibiotic classes, making it the preferable option for large-scale use. Conversely, fluoroquinolone- and clarithromycin-containing regimens should be reserved for situations where local antibiotic resistance patterns justify their use. This approach reflects both the principles of antibiotic stewardship and the overarching goal of reducing gastric cancer risk without exacerbating antimicrobial resistance.

Referral for upper endoscopy

Considering that the target population comprises asymptomatic individuals with a low individual risk of gastric cancer and given that screening endoscopy is not recommended for the general population in Europe, referrals for upper endoscopy must adhere to relevant guideline recommendations.

According to Maastricht VI, upper GI endoscopy is required for dyspeptic patients aged over 50 years (Maastricht VI, WG2 Statement 2)³ with a special attention to be given to individuals presenting with alarm symptoms or newly developed dyspepsia.

Furthermore, endoscopy with biopsies is recommended for asymptomatic individuals aged 45 and above who have a family history of gastric cancer (excluding hereditary gastric cancer) (Maastricht VI, WG4 Statement 13)³.

In line with these recommendations, the *EUGastScreen* study will offer upper endoscopy to participants with positive family history and alarm symptoms if such are identified (SAT and FIT negative individuals may not undergo questioning for the presence of alarm symptoms), provided a quality-assured endoscopic procedure has not been performed recently.

Potential limitations and approaches to address them

1. International guidelines emphasize that *H. pylori* eradication is most effective at an earlier age, before the development of precancerous lesions. At the recommended age of CRC screening initiation in Europe (50 years)¹⁰, some individuals may have already progressed

beyond the so called “point-of-no-return”, where the risk of gastric cancer remains elevated even after successful eradication of *H. pylori*.

The solution. 1) *EUGastScreen* will target individuals at the age when they first enter the CRC screening programme; 2) The TOGAS project Pilot 2 will estimate the proportion of individuals with high-risk precancerous lesions at this age.

2. The choice of antibiotics to be used for *H. pylori* eradication regimens is made based on the following two considerations: 1) effective eradication of *H. pylori* requires regimen achieving a success rate of 90% or higher, but increasing antibiotics resistance (e.g., to clarithromycin and levofloxacin) poses a challenge to achieve the target eradication rate; 2) a population-based gastric cancer prevention strategy will likely increase antibiotic use, raising concerns about increasing antimicrobial resistance.

The solution. Use antibiotics that are infrequently prescribed to treat life-threatening conditions to minimize broader resistance risks and regimens allowing to achieve about 90% success rates. Bismuth quadruple therapy will be recommended as the first-line treatment where available.

3. A substantial proportion of the target population is likely to be on long-term therapy with potent acidity-lowering agents (PPIs or potassium-competitive acid blockers, PCABs). Discontinuing these medications for testing purposes may be unacceptable to some patients.

The solution. 1) Whenever possible, participants will be asked to discontinue PPIs or PCAB use for at least 14 days before performing SAT or UBT. The timing of the tests will be adjusted accordingly. 2) If discontinuation is not feasible, the use of these medications will be documented and factored into the data analysis.

4. Some CRC screening programmes engage GPs in delivering and/or collecting and analysing the FIT test results. However, involving only highly motivated and exceptionally well-trained GPs in the project may limit the generalizability of the results.

The solution. Pre-selecting GPs based on their motivation should be avoided as much as possible. Instead, regional piloting that includes all practices within a given area may offer a more representative approach.

The list of invitees should be optimally created from population or screening registries instead of GP registries to avoid preselection bias.

Objectives

The overall objective of *EUGastScreen* is to evaluate the feasibility and acceptability of implementing the *H. pylori* screen-and-treat Strategy within existing or planned FIT-based CRC screening pathways (thereafter referred to as the “Strategy”) across diverse European health

system contexts, and to identify contextual factors that facilitate or hinder successful implementation at the national or regional levels.

Specific objectives

Primary objectives

(addressing implementation outcomes)

1. To evaluate the feasibility of integrating the Strategy into existing or planned FIT-based CRC screening pathways across diverse European health system contexts, as measured by SAT participation rates among invited individuals in each participating country and site, ability to reach the target population, valid and analyzable sample return, and completion of key implementation steps.
2. To assess participant acceptance and adoption of the Strategy, as measured by participation in *H. pylori* testing, uptake of *H. pylori* eradication therapy among SAT-positive individuals and participant-reported reasons for participation, acceptance, or refusal.
3. To evaluate implementation fidelity across participating sites, including adherence to invitation procedures, sample collection and testing pathways, treatment delivery, referral completion, post-treatment confirmation testing, and achievement of successful *H. pylori* eradication.
4. To assess the appropriateness of the Strategy across diverse CRC screening settings by examining contextual fit, including *H. pylori* positivity and confirmed infection where available, together with variation in implementation outcomes, such as participation, treatment uptake, pathway completion, and follow-up across countries and delivery models.

Secondary objectives

(addressing screening, treatment, and safety outcomes)

5. To estimate the prevalence of *H. pylori* infection (SAT positivity) and FIT positivity in the study population across participating countries, and to monitor whether addition of SAT to the CRC screening invitation affects CRC screening participation rates.
6. To assess treatment uptake and completion, post-treatment confirmation of *H. pylori* eradication therapy, and to characterize reasons for treatment non-completion among participants who complete less than 90% of the prescribed treatment regimen, including self-reported adverse effects and other factors contributing to discontinuation.
7. To determine the proportion of participants meeting criteria for referral to upper gastrointestinal endoscopy based on potential alarm symptoms, newly developed dyspepsia, or first-degree family history of gastric cancer, and to assess participation rates and endoscopic and histological findings in this subgroup.

8. To assess participation in follow-up colonoscopy among participants with positive FIT results, stratified by country and referral pathway, and to characterize colonoscopy findings where available.

9. To assess the proportion of returned material for SAT that is not valid for testing, and the reasons for invalidity (e.g. late return, inappropriately collected material).

Exploratory objectives

(addressing implementation context, barriers, and facilitators, or optimization strategies)

10. To identify participant-reported barriers and facilitators of participation, treatment uptake, and pathway completion through structured feedback questionnaires and free-text responses.

11. To explore the influence of invitation strategies, including invitation delivery methods, reminder systems, and GP-mediated versus centralized approaches, on participation and pathway completion across participating sites.

Resource use and cost data collected incidentally during study implementation may be made available to the EUCanScreen economic evaluation team where feasible; however, formal economic evaluation is outside the scope of EUGastScreen. The implementation outcome domains were selected to address specific study objectives with their alignment summarised in **Table 2**.

Table 2. Alignment of study objectives and implementation outcome domains.

Specific objective	Implementation outcome domain	Priority
1. SAT participation rates	Feasibility, coverage	Primary
2. <i>H. pylori</i> eradication therapy uptake and participant-reported acceptance/refusal	Acceptability, adoption	Primary
3. Adherence to pathway procedures and successful <i>H. pylori</i> eradication	Fidelity	Primary
4. Variation in implementation outcomes across countries and delivery models	Appropriateness, feasibility	Primary
5. SAT positivity prevalence; FIT positivity prevalence, and monitoring of CRC screening participation	Coverage, feasibility, appropriateness	Secondary

6. Proportion of inappropriately returned material for SAT testing	Feasibility, fidelity	Secondary
7. Completion of treatment, acceptance of post-treatment eradication confirmation test, and reasons non-compliance	Adoption, fidelity, acceptability	Secondary
8. Upper gastrointestinal endoscopy referral, participation, and endoscopic/histological findings *	Coverage, fidelity	Secondary*
9. Participation in follow-up colonoscopy after positive FIT results *, and the relevant findings	Coverage, fidelity	Secondary*
10. Participant-reported barriers and facilitators of participation and implementation	Acceptability, appropriateness	Exploratory
11. Contribution of invitation strategy and reminder systems to participation and pathway completion	Feasibility, adoption	Exploratory

* Supporting clinical and pathway outcomes mapped to the implementation outcome framework

Design: Principles

EUGastScreen is a multicentre, prospective, pragmatic, single-arm implementation study conducted across five European countries (Estonia, Italy, Latvia, Lithuania, and Portugal), with two distinct sites participating from Italy (Marche Region and Emilia-Romagna Region).

In all participating countries, the Strategy is implemented within existing or planned FIT-based CRC screening pathways. However, the degree of integration varies according to national and regional screening infrastructures, including differences in invitation systems, GP involvement, sample distribution and collection, laboratory organization, and follow-up pathways. These variations are an inherent and deliberate feature of the study design, reflecting the real-world diversity of CRC screening systems across EU Member States.

The study operates across two complementary levels of evaluation.

Overall multinational design. At the multinational level, EUGastScreen evaluates the feasibility, acceptability, adoption, appropriateness, and fidelity of the Strategy across diverse European CRC screening settings. The study also explores implementation-related factors influencing participation, coverage, treatment uptake, pathway completion, and integration into existing healthcare systems.

This level of analysis addresses whether the Strategy can be feasibly and acceptably integrated into different health system settings and explores contextual factors associated with variation in implementation outcomes across participating sites. Cross-country comparisons are exploratory and hypothesis-generating rather than confirmatory, given the non-randomized nature of implementation and the intentional adaptation of delivery models to local screening infrastructures.

Country-level implementation models. At the country level, each participating site operates within a country-specific implementation model reflecting its CRC screening infrastructure, healthcare organization, and availability of comparator benchmark data (**Table 3**). Country-level estimates constitute the primary analytical unit. Pooled cross-country estimates may additionally be reported alongside measures of between-country variability and interpreted cautiously, reflecting differences in existing screening infrastructures, healthcare delivery systems, and locally adapted implementation pathways across participating sites.

Given its primary focus on implementation processes and outcomes, with clinical and pathway outcomes assessed secondarily, EUGastScreen most closely aligns with a Hybrid Type 3 implementation design.

Table 3. Overview of country-specific implementation models and comparator benchmark availability in EUGastScreen.

Country/Site	Implementation model	Comparator data availability	Key implementation features
Estonia	Prospective single-arm implementation within organised CRC screening	Historical benchmark available through the Cancer Screening Registry	Registry-based recruitment and follow-up integrated with national CRC screening infrastructure
Italy (Marche)	Prospective single-arm implementation within organised regional CRC screening	Concurrent benchmark available from ongoing FIT-only screening programme	Established regional CRC screening infrastructure with study centre-based test distribution
Italy (Bologna)	Prospective single-arm implementation within organised regional CRC screening	Concurrent benchmark available from ongoing FIT-only screening programme	Established regional CRC screening infrastructure with study centre-based test distribution

Latvia	Prospective implementation pilot linked to CRC screening-age population	Concurrent benchmark potentially available through participating GP-managed screening programme	Simultaneous piloting of organised FIT invitation and <i>H. pylori</i> screening
Portugal	Prospective single-arm implementation within regional CRC screening pathways	Historical benchmark partially available through national screening databases	FIT and <i>H. pylori</i> simultaneous screening invitations using a regional CRC screening database of eligible citizens.
Lithuania	Prospective single-arm implementation linked to GP-based CRC screening pathways	Concurrent benchmark potentially available within participating GP-based CRC screening settings	GP-mediated recruitment and screening delivery using qualitative FIT for CRC screening

Comparator Data

EUGastScreen is a single-arm study. There is no randomized or formally allocated control group. However, where available, comparator benchmark data from existing CRC screening programmes will be used to contextualize implementation findings, particularly participation rates.

The use of comparator benchmark data serves two specific and limited purposes:

1. To provide a baseline against which SAT participation rates can be interpreted (i.e., to understand the level of engagement the target population already demonstrates with cancer screening before the Strategy is added);
2. To monitor whether addition of SAT to the FIT screening invitation influences participation in established CRC screening pathways, ensuring that implementation of the Strategy does not inadvertently reduce uptake of existing CRC screening programmes. This represents a safeguard for the existing screening programme rather than a primary outcome comparison.

The nature of comparator benchmark data available varies by country as follows:

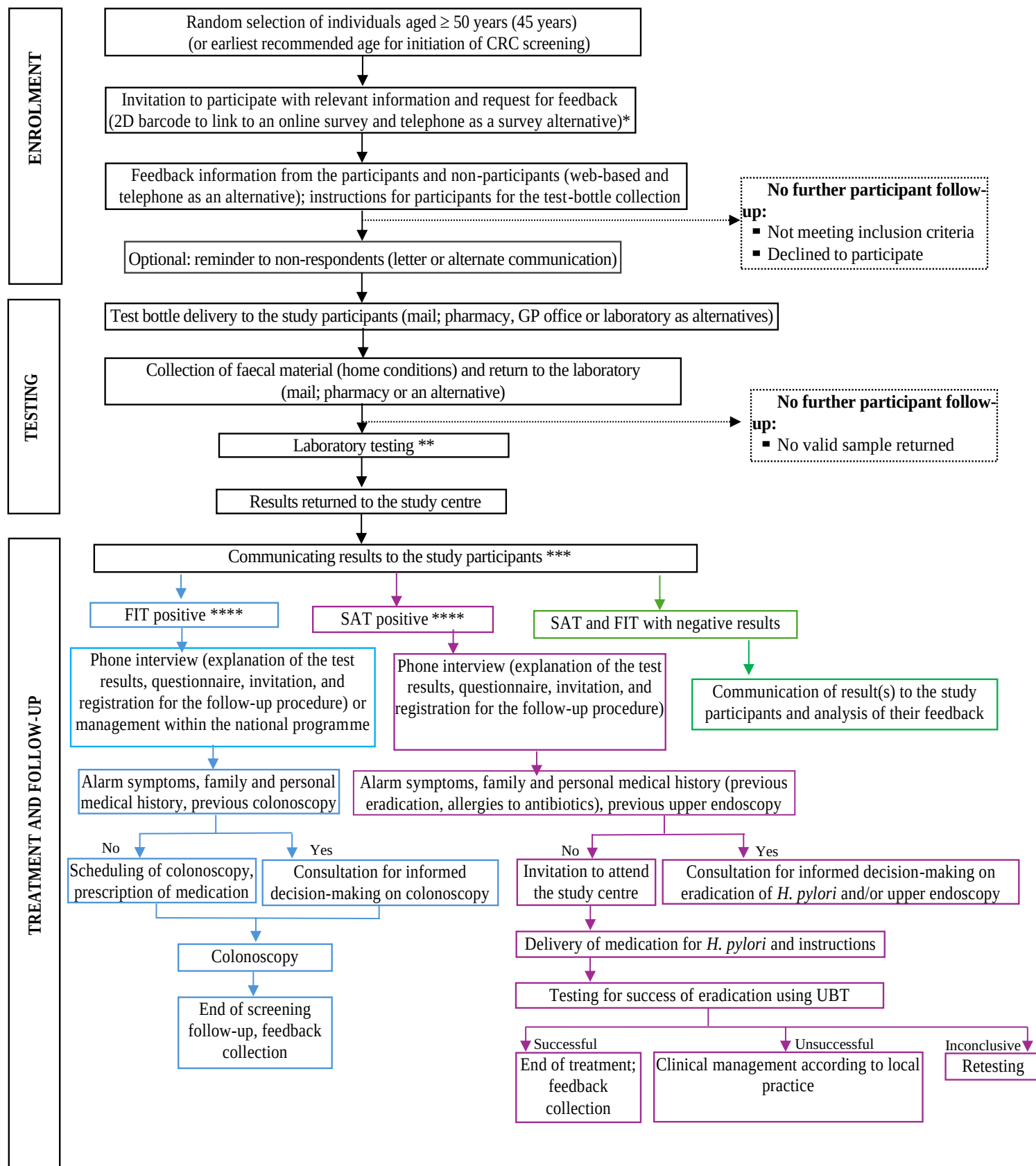
- historical benchmark: Estonia and Portugal will use registry data from preceding CRC screening rounds in the same eligible population as a historical reference point for participation rates. These data will enable within-country contextualization of SAT participation rates and assessment of any change in FIT participation associated with the dual-test invitation;
- concurrent benchmark: Italy (Marche and Emilia-Romagna) and Lithuania will reference participation data from ongoing FIT-based CRC screening pathways operating in the same

region during the study period. These data will provide a contemporaneous benchmark under similar implementation conditions;

- potential concurrent benchmark: Latvia may be able to reference participation data from participating GP-managed screening programmes (data available from the national screening database)

In all countries, comparator benchmark data are intended solely for contextualization and benchmarking. No formal comparative or inferential statistical analysis between the Strategy and existing CRC screening programmes is planned as a primary study objective. Any such analyses will be considered exploratory and interpreted cautiously, acknowledging that observed differences may reflect factors other than the intervention itself, including temporal trends, population differences, and variation in invitation conditions.

The study design chart



**Eligible individuals will receive a single integrated invitation to participate in EUGastScreen, offering both FIT-based CRC screening and H. pylori screening by SAT. Participants will not receive separate study invitations for FIT and SAT; however, kit distribution and follow-up procedures may vary according to country-specific implementation pathways.*

*** In case of inconclusive SAT results, one repeat SAT is recommended where feasible and consistent with local laboratory capacity and clinical practice. Site-specific retesting procedures will be documented. Initial inconclusive rates, repeat testing rates, and final valid/analyzable SAT rates will be reported separately.*

**** Where feasible, communication of results and follow-up recommendations should be coordinated to avoid duplicate or conflicting contacts. The communication method may include telephone contact, GP consultation, electronic notification, or other established mechanisms and will be documented for each site. Study-relevant follow-up data, including colonoscopy participation and findings where available, will be collected for EUGastScreen analyses.*

***** FIT-positive participants will be managed according to existing national or regional CRC screening pathways where applicable. Follow-up may be coordinated by the study team or the standard CRC screening programme, depending on country-specific implementation arrangements. Participants positive for both FIT and SAT will proceed through both the CRC screening pathway and the H. pylori management pathway.*

General principles

The study has been initiated by the *EUCanScreen* consortium members with a limited number of pilot study sites. Increasing the number of study participants at these and additional sites is expected to enhance the value of the study findings. Therefore, other *EUCanScreen* partners, as well as collaborators outside the consortium, are encouraged to join the study, provided the study protocol is followed and the minimum recruitment requirements per site are met. National implementation studies are also encouraged and may be eligible for funding through national healthcare budgets.

The initial population estimates for this study aim to provide preliminary insights into the feasibility of integrating gastric cancer prevention with CRC screening. However, further implementation studies will be necessary to conduct more detailed analyses and refine the approach.

Design: description of the steps

1. Study sites

The original study sites are selected following the tasks within the *EUCanScreen* Joint action and are represented by countries with one of the highest CRC and gastric cancer age-standardised incidences (**Table 4**)²⁹.

Table 4. Age-standardised incidence rates (World) per 100,000 of CRC and gastric cancer in the original and additional pilot countries ²⁹.

Country	Gastric cancer incidence per 100 000	CRC incidence per 100 000
Estonia	13.1	31.8
Portugal	12.8	37.8
Latvia	12.1	23.5
Lithuania	11.7	21.8
Italy	6.8	30.6

As the protocol is open for other sites to join, the latter are listed as “Additional pilot sites”. Those are planned to provide more generalizable study results. Additional pilot sites are expected to participate according to their possibilities, nevertheless they are required to follow the protocol. The list of those sites is still open for new candidates also following the completion of the protocol.

The study population will generally be selected from a pre-defined geographical area to ensure access to necessary study facilities. These facilities include invitation and test distribution, laboratory testing, a study centre for medication distribution, and resources for UBT and endoscopic testing. The following regions have been identified as initial study centres:

Original pilot sites

Estonia – Tallinn city and Harjumaa municipality;

Italy (Marche) – Marche Region – Macerata District;

Latvia – Riga city, Jēkabpils region and Aizkraukle, Madona, Varakļāni, Līvāni municipalities;

Portugal – North of Portugal, Santo Tirso (Medio Ave Local Health Unit; Barcelos-Esposende Local Health Unit).

Additional pilot sites

Italy (Bologna) - Emilia-Romagna Region – Bologna District;

Lithuania – Vilnius city municipality.

2. Study population identification

The study will target a non-selected population of individuals at the initial age of CRC screening in their respective country (i.e., commonly 50 years in the EU). Efforts should be made to achieve an equal distribution between males and females. Special consideration should be given to the inclusion of potentially vulnerable populations (e.g., lower socioeconomic groups, immigrants).

It is recognized that the starting age for CRC screening varies between countries. The study will aim to recruit participants during their first round of CRC screening. For the initially participating countries, the target age groups will be defined as follows:

Original pilot sites

Estonia – 56 years (or 54 years if the age limit for CRC screening will be lowered further in 2027);

Italy (Marche) – 50 years;

Latvia – 50 years;

Portugal – 50 years.

Additional pilot sites

Italy (Bologna) - 50 years;

Lithuania – 50 years.

The study will examine regions with both high and low prevalence of *H. pylori* and varying incidence of gastric cancer, with a particular focus on high-risk areas. Existing data on the prevalence of *H. pylori* and the incidence of gastric cancer will be thoroughly analysed as part of the study.

3. The principles of study subject selection

National healthcare screening databases should be utilized for selecting study participants. Ideally, the same database used for CRC programme invitations should be employed. The selection and invitation processes must follow the principles of an organised cancer screening programme.

The following databases are planned for use in selecting study subject populations in the pilot countries:

Original pilot sites

Estonia – screening target population managed by Cancer Screening Registry;

Italy (Marche) – screening database held by the Marche Regional Health Services;

Latvia – screening database held by the National Health Services;

Portugal – screening database held by the National Health Services.

Additional pilot sites

Lithuania – screening database held by the National Health Services;

Italy (Bologna) – screening database held by the Local Health Authority of Bologna (Azienda USL di Bologna), Emilia Romagna Region.

Random (pre)selection of invitees from the general database should be utilized to ensure the target population meets the established criteria. This process will be carried out as follows:

Original pilot sites

Latvia:

Step 1. Create a list of eligible individuals for CRC screening aged 50 years old. Individuals having performed FIT testing will be excluded whenever this will be possible to identify. The data will be extracted from the screening database of the National Health Service, covering Riga and Jēkabpils regions (Aizkraukle, Madona, Varakļāni, Līvāni municipalities).

Step 2. Perform a random selection of the target population, ensuring an equal distribution between the sexes. The selection will aim to account for a minimum return rate of 30% for the tests. A 'reserve list' will be created and used in case of low participation rates;

Estonia:

Cancer Screening Registry will create a list of eligible individuals: the youngest cohort invited for the first time to CRC screening (either 56 or 54 years); included in the patient list of selected GP practices. GP practices will be selected to ensure representation of the population (e.g. covering different regions in the city and surrounding county);

Italy (Marche):

Step 1. Create a list of the eligible individuals for CRC screening aged 50 years. This includes individuals expected to begin their first screening round. The data will be extracted from the screening database of the Marche Region Health Service.

Step 2. Perform a random selection of the target population, ensuring an equal distribution between the sexes. The selection will aim to account for a minimum 30% for the returned tests;

Portugal:

A similar approach will be applied as in the current population-based CRC screening. However, instead of undergoing the current screening process, a random sample will participate in this pilot programme: A list of eligible individuals for 1st time CRC screening aged 50-51 years will be randomly selected from the regional screening database. The recruitment strategy will account for a minimum 30% of returned tests and a FIT positivity of 6%.

Additional pilot sites

Lithuania:

Step 1. Create a list of ambulatory polyclinics and GPs for patient screening and invitation for the screening.

Step 2. Perform a random selection of the target population, ensuring an equal distribution between the sexes. The selection will aim to account for a minimum 30% for the returned tests;

Italy (Bologna):

Step 1. Create a list of the eligible individuals for CRC screening aged 50 years. This includes individuals expected to begin their first screening round. The data will be extracted from the screening database of the Local Health Authority of Bologna (Azienda USL di Bologna), Emilia Romagna Region.

Step 2. Perform a random selection of the target population, ensuring an equal distribution between the sexes. The selection will aim to account for a minimum 30% for the returned tests.

The information retrieved from the databases for selected individuals will include mailing addresses, alternate contact information (e.g., telephone numbers and email addresses), age, sex, and information about their GP. To account for potential nonresponses (e.g., refusals, undelivered or lost mail), the sample sizes for participants returning valid tests, as noted in the *EUCanScreen* grant application, will need to be increased.

If potential study participants are known to have a **personal history of gastric cancer or CRC**, they should not be invited to participate in *EUGastScreen*. However, this information may not always be known to study personnel prior to the invitation process. Efforts should be made to identify individuals with a prior history of gastric or CRC using the National Cancer Registry or other relevant databases. Is this scenario anticipated by the respective pilot site, and what methods are planned to identify target individuals?

Original pilot sites

Estonia – YES, Estonian Cancer Registry;

Italy (Marche) – YES, Marche Cancer Registry;

Latvia – No;

Portugal – YES, ICPC-2 classification, records by GP.

Additional pilot sites

Italy (Bologna) – No;

Lithuania – YES.

4. Invitation strategy

The invitation process is predominantly planned via mailed or e-mailed letters, though alternative approaches may also be considered. The invitation letter will provide information on the burden of gastric cancer, its relation to *H. pylori* infection, the benefits and harms for *H. pylori* eradication along with information on CRC screening.

The invitation letter will request recipients to provide feedback on their willingness to participate in the study, where applicable. Feedback will be primarily collected through a web-based system,

where the bar-code on the invitation letter links to a personalised registration portal. Telephone-based response as well as in-person registration at a study centre will also be available.

A 2D code will be prominently included in the invitation letter, linking to a webpage with the questionnaire and additional information. As an alternative, a telephone number will be provided for responses and survey data collection.

For individuals unwilling to participate, the feedback will include questions about the reasons for non-participation.

For individuals willing to participate, questions will address potential alarm symptoms, personal and family history of gastric cancer and CRC, as well as whether and when previous upper endoscopies and colonoscopies have been performed.

Some questions (e.g. on family history) may overlap between the two groups.

For participants scheduled for testing without further consultation, instructions will be included on how to collect sampling bottles. Centres may offer multiple options for sampling bottle collection, such as mail delivery, collection at a laboratory or GP office.

The planned invitation delivery will be as follows:

Original pilot sites

Estonia – invitation by e-mail (or mail if no email address) and SMS;

Italy (Marche) – mail;

Latvia – mail;

Portugal – mail.

Additional pilot sites

Italy (Bologna) – mail or digital invitation via the Electronic Health Record (Fascicolo Sanitario Elettronico);

Lithuania – SMS and phone call from GP offices.

5. Feedback collection

Feedback request on acceptance or refusal to participate in the project will be collected from all invitees. A link to the web-based feedback questions will be provided via the 2D code included in the invitation letter. Alternatively, feedback may be collected through a telephone interview, with the invitation letter also providing the relevant telephone number.

For individuals who agree to participate, the following key responses will be gathered:

- 1) Preferred methods for collecting sampling bottles (if multiple options are available);
- 2) History of previous *H. pylori* eradication therapy, if applicable;
- 3) Personal or first-degree family history of gastric cancer or CRC;
- 4) Information on the previous upper endoscopy and colonoscopy (whether and when the investigations have been performed).

For the respondents unwilling to participate, the question on the reason for unwillingness to participate (collected in a structured format) will be addressed.

6. Reminder for individuals who agree to participate

A reminder (via letter, SMS, or phone call) is expected to increase participation rates³⁰. However, for this study, sending a reminder after shipment of the collection kits will be considered optional.

The planned implementation of reminders is as follows:

Original pilot sites

Estonia – YES, reminders will be sent via e-mail, SMS and/or phone call;

Italy (Marche) – optimally YES, reminders will be sent through an additional mailed letter;

Latvia – YES, first reminder will be sent through an additional mailed letter-or SMS;

Portugal – YES, reminder phone calls will be performed after a non-enrolment in the Engage platform within two weeks after receiving the invitation letter.

Additional pilot sites

Italy (Bologna) – YES if possible, reminders will be sent through an additional mailed letter, SMS or phone calls;

Lithuania – YES, reminders will be sent through an additional SMS.

Up to two reminders may be sent: a first reminder 7-14 days after kit distribution and a second reminder 10–21 days after kit distribution, using locally appropriate methods (SMS, phone, or mail).

Otherwise, reminders can remain site-specific and documented as part of implementation evaluation.

Participants will be considered non-completers for the screening step if no valid stool sample is returned within 30 days of kit distribution, despite at least one reminder. This timeline could be left to country/site discretion based on local logistics.

7. Delivery of sampling bottles and the relevant instructions

The planned delivery mechanisms of the sampling bottles and the relevant information are as follows:

Original pilot sites

Estonia – sampling bottles for both SAT and FIT will be distributed through GP offices;

Italy (Marche) – sampling bottles for both SAT and FIT will be available at the laboratory of the study Centre. Sampling bottles for FIT may also be available at pharmacies;

Latvia – sampling bottles for SAT and FIT will be delivered via mail with a pre-paid return delivery note;

Portugal – sampling bottles for SAT and FIT will be sent to subjects by mail together with a pre-paid envelope, for sample shipment to the centralized lab. In case participants do not adhere to the digital pathway, they will have the opportunity to enroll non-digitally, via mailed paper format. The instructions will be provided together with the sample collection tubes and a prepaid return envelope and should be returned together to the laboratory.

Additional pilot sites

Italy (Bologna) – sampling bottles for both SAT and FIT will be available at the laboratory of the study Centre. Sampling bottles for the FIT may also be available at pharmacies;

Lithuania – sampling bottles for both SAT and FIT will be distributed through GP offices.

[Note: delivery at primary care facilities could introduce selection bias if only a limited number of facilities are utilized for this step.](#)

Participants will be instructed to return stool samples as soon as possible after collection (preferably within 24 hours). Each site will define acceptable return methods and timelines consistent with local logistics and laboratory requirements, ensuring SAT testing within the manufacturer-specified ambient stability window.

8. Sample collection

The planned sample collection mechanisms are as follows:

Original pilot sites

Estonia – mail or delivery services to laboratory;

Italy (Marche) – delivery to the laboratory of the study Centre by the study participant. Sampling bottles for the FIT may also be delivered to pharmacies;

Latvia – prepaid delivery services to laboratory;

Portugal – delivery via post office or postal mailbox in a prepaid envelope addressed to the centralized lab.

Additional pilot sites

Italy (Bologna) – delivery to the laboratory of the study Centre by the study participant. Sampling bottles for the FIT may also be delivered to pharmacies;

Lithuania – delivery to the primary healthcare centre by the study participant.

9. FIT testing

Ideally, FIT testing for the study has to be incorporated into the national screening programme. Centralized reading of the FIT result is a prerequisite.

The test-system used for the project is as follows:

Original pilot sites

Estonia – SENTiFIT® FOB Gold® latex Wide (Sentinel Diagnostics);

Italy (Marche) – OC-Sensor;

Latvia – OC-Sensor;

Portugal – OC-Auto Sampling Bottle 3.

Additional pilot sites

Italy (Bologna) – OC-Sensor;

Lithuania – AQ4 PolyCheck® (Veda Lab, France), IFOB® (SureScreen Diagnostics Ltd., UK), MediSmart® (Lobeck Medical Ltd., Switzerland) (qualitative tests will be used).

The laboratory instrument to be used for the FIT testing is as follows:

Original pilot sites

Estonia – SENTiFIT®270 (Sentinel Diagnostics);

Italy (Marche) – OC-Sensor Pledia;

Latvia – OC-Sensor Pledia;

Portugal – OC-Sensor Pledia.

Additional pilot sites

Italy (Bologna) – OC-Sensor Pledia;

Lithuania – OC-Sensor Pledia.

The cut-off values to be used will get pre-defined by the respective CRC screening programme.

The cut-off for a positive FIT result is as follows:

Original pilot sites

Estonia – $\geq 100\text{ng Hb/mL buffer} = 20\text{ }\mu\text{g/g faeces}$;

Latvia – $\geq 75\text{ ng Hb/mL buffer} = 15\text{ }\mu\text{g/g faeces}$;

Italy (Marche) – $\geq 100\text{ng Hb/mL buffer} = 20\text{ }\mu\text{g/g faeces}$;

Portugal – $\geq 100\text{ng Hb/mL buffer} = 20\text{ }\mu\text{g/g faeces}$.

Additional pilot sites

Italy (Bologna) – $\geq 100\text{ng Hb/mL buffer} = 20\text{ }\mu\text{g/g faeces}$;

Lithuania – ≥ 47 ng Hb/mL buffer = 9.4 µg/g faeces.

Centralized reading of the FIT result by qualified laboratory personnel is a prerequisite.

10. Stool antigen testing for *H. pylori*

Monoclonal SAT, following local validation, should be used. Infrastructure should be designed to ensure that samples are analysed within the manufacturer-specified stability period for the selected assay. Where this permits, testing within 72 hours of collection is recommended.

The optimal choice for SAT testing would be laboratory-based Enzyme-Linked Immunosorbent Assay (ELISA) monoclonal SAT.

Alternatively, an immunoassay for *H. pylori* stool antigen can be utilized with an automated analyser readout.

If available, systems routinely used for the purpose that meets the above criteria should be used. The current availability of such laboratory services is as follows (if applicable, please specify the manufacturer and brand of the tests).

Original pilot sites

Estonia – Sentifit 270 by Sentinel Diagnostics[®] analyser;

Italy (Marche) – STANDARD[®] *H. pylori* Ag fluorescence immunoassay analyser;

Latvia – GEMINI[®] Compact microplate processor (DIATRON MI ZRT);

Portugal – automated ELISA analyser Mindray[®] MR-96A.

Additional pilot sites

Italy (Bologna) – LIAISON XL[®] analyser by DiaSorin (Saluggia, Italy);

Lithuania – automated ELISA analyser.

The following reagents will be used for SAT testing:

Original pilot sites

Estonia – PyliaGold by Sentinel Diagnostics[®];

Italy (Marche) – chemilluminescence Immunoassay *H. pylori* SAT (LIAISON[®] *H. pylori* Diagnostic Solution);

Latvia – monoclonal automated ELISA test-system Premier Platinum HpSA PLUS (Meridian Bioscience[®]);

Portugal – laboratory-based monoclonal ELISA/ Enzyme Immunoassay (EIA) and rapid lateral flow immunoassays (immunochromatography) are utilized, with monoclonal tests preferred for higher accuracy (Meridian Bioscience[®] or alternative);

Additional pilot sites

Italy (Bologna) – LIAISON[®] Meridian *H. pylori* SA (Chemiluminescent immunoassay);
Lithuania – laboratory-based monoclonal ELISA/EIA and rapid lateral flow immunoassays (immunochromatography) are utilized, with monoclonal tests preferred for higher accuracy (Meridian Bioscience[®] or alternative).

11. Planned 1st line eradication medication

The recommended approach is bismuth quadruple therapy for 10-14 days, combined with a high-dose PPI BID.

The planned 1st line eradication regimen would be as follows:

Original pilot sites

Estonia – Concomitant therapy (Clarithromycin, Amoxicillin, Metronidazole, and omeprazole) for 14 days;

Italy (Marche) – PYLERA[®] + PPI 10 days;

Latvia – PYLERA[®] or a generic if available + esomeprazole 40 BID for 10 days;

Portugal – PYLERA[®] + PPI 10 days.

Additional pilot sites

Italy (Bologna) – PYLERA[®] + PPI 10 days;

Lithuania – Concomitant therapy (Clarithromycin, Amoxicillin, Metronidazole, and omeprazole) for 14 days.

Note: PYLERA[®] is not registered/available in Latvia and Lithuania.

12. Planned 2nd line eradication medication

Levofloxacin-based quadruple/triple for 14 days plus high-dose PPI BID should be the recommended approach.

The planned 2nd line eradication regimen would be as follows:

Original pilot sites

Estonia – PYLERA[®] + esomeprazole for 14 days;

Italy (Marche) – Levofloxacin-based triple therapy + PPI BID for 14 days;

Latvia – Levofloxacin-based triple therapy + esomeprazole 40 BID for 14 days (the limitation is that levofloxacin is not registered in Latvia);

Portugal – Levofloxacin-based triple therapy + esomeprazole 40 BID for 14 days.

Additional pilot sites

Italy (Bologna) – Levofloxacin-based triple therapy + PPI BID for 14 days.

Lithuania – Levofloxacin-based triple therapy + PPI BID for 14 days.

13. Control for the success of eradication by using ^{13}C -urea breath test

The availability of ^{13}C -UBT for controlling the success of eradication:

Original pilot sites

Estonia – YES;

Italy (Marche) – YES;

Latvia – YES;

Portugal – YES, UBT or SAT.

Additional pilot sites

Italy (Bologna) – YES;

Lithuania – YES.

Upper endoscopy is performed only when clinically indicated and is not intended as routine test-of-cure. Eradication success will be confirmed using at least one validated method at least 4 weeks after therapy termination. Non-invasive (^{13}C -UBT or SAT) remains the preferred and scalable approach; however, when gastroscopy with biopsies is performed for independent clinical indications after eradication therapy, histology-based *H. pylori* status may be accepted to document eradication success, and an additional ^{13}C -UBT would not normally be required.

14. Planned invitation strategy for colonoscopy in FIT-positive cases

The planned invitation strategy for colonoscopy in FIT-positive cases will be managed as follows:

Original pilot sites

Estonia – standard approach: FIT positive patients are consulted by GP office, and a colonoscopy appointment is scheduled with designated service providers;

Italy (Marche) – through phone interview. In subjects with questionable indications, following a specialist or a GP consultation;

Latvia – through phone interview. In subjects with questionable indications, following a specialist or a GP consultation;

Portugal – A FIT-positive notification will prompt an online appointment with their GP so that patients can be informed of the test result. After the research team phone interview, patients will be summoned to attend their primary healthcare centre and invited to undergo colonoscopy.

Additional pilot sites

Italy (Bologna) – through phone interview. In subjects with questionable indications, following a specialist consultation;

Lithuania – FIT positive patients are consulted by GP office, receive the referral to colonoscopy, which can be done in a few centres (the patient either registers by themselves or is registered by GP's team).

Participants with positive results will be contacted or referred for follow-up within approximately 3–5 working days after result availability, or according to national CRC screening timelines.

The pathway of subject referral following a positive FIT result will be implemented according to national CRC screening pathways. In countries with GP-led referral (e.g., Estonia), communication and referral to colonoscopy are performed by the GP; the study team records referral and completion outcomes only.

15. Planned invitation strategy for upper endoscopy in the eligible cases

Upper endoscopy could be indicated in a subset of cases, e.g. relatives of 1st degree gastric cancer patients without previous endoscopic investigations as well as subjects with newly onset symptoms or alarm symptoms (Vomiting or hematemesis; Black, tarry stools; Difficulty swallowing food or liquids; Recurrent nausea or vomiting; Loss of appetite; Increasing weakness or fatigue; Unexplained weight loss (>5% over the past 12 months); Recent change in bowel habits; Blood in stool).

The planned invitation strategy for upper endoscopy for eligible cases would be as follows:

Original pilot sites

Estonia – phone contact by clinical study centre (East-Tallinn Central Hospital);

Italy (Marche) – phone interview (in person for cases attending the study centre). In subjects with questionable indications, following a specialist or a GP consultation;

Latvia – phone interview in case of specific red flag symptoms are present or positive first-degree relative history (in person for cases attending the study centre). In subjects with questionable indications, following a specialist or a GP consultation;

Portugal – phone contact by clinical study centre in case specific red flag symptoms are present or positive first-degree relative history.

Additional pilot sites

Italy (Bologna) – phone interview (in person for cases attending the study centre). In subjects with questionable indications, following a specialist or a GP consultation;

Lithuania – phone interview (in person for cases attending the study centre). In subjects with questionable indications, following a specialist or a GP consultation.

Information on National guidelines related to *H. pylori* detection and management

Are national guidelines on *H. pylori* detection and management available in the target country?

Original pilot sites

Latvia – No;

Estonia – Available, but outdated;

Italy (Marche) – YES;

Portugal – No.

Additional pilot sites

Italy (Bologna) – YES;

Lithuania – No.

If yes, please provide a reference:

Original pilot sites

Latvia – N/A;

Estonia – N/A;

Italy (Marche) – Romano M, Gravina A, Eusebi L, et al. Management of *Helicobacter pylori* infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). *Dig Liv Dis*. 2022;54:1153-1161; “*Trattamento dell’infezione da Helicobacter Pylori in Italia*” – Treatment of *Helicobacter pylori* infection in Italy. Available on line: iss.it/-/snlg-trattamento-infezione-helicobacter-pylori;

Portugal – N/A.

Additional pilot sites

Italy (Bologna) – Romano M, Gravina A, Eusebi L, et al. Management of *Helicobacter pylori* infection: Guidelines of the Italian Society of Gastroenterology (SIGE) and the Italian Society of Digestive Endoscopy (SIED). *Dig Liv Dis* 2022;54:1153-1161; “*Trattamento dell’infezione da Helicobacter Pylori in Italia*” – Treatment of *Helicobacter pylori* infection in Italy. Available on line: iss.it/-/snlg-trattamento-infezione-helicobacter-pylori;

Lithuania – N/A.

Current participation rates in an organised FIT screening programme (in the relevant region)

Participation rates within a current organised FIT screening programme (with personalised invitations) are presented in the **Table 5**:

Table 5. Current FIT screening participation rates.

Country	Participation rate
Estonia	62% in whole Estonia, 58% in the planned pilot region
Italy	Marche Region: 36% Italy: 34.1%
Italy	Emilia-Romagna Region: Overall: 53% Among individuals invited for the first time: 37%–38%
Latvia	Invitations are not mailed, tests delivered by GPs; ~25% participation of the overall eligible population
Portugal	35-40%
Lithuania	50%

Details and sources of information:

Original pilot sites

Estonia – National Cancer Screening Registry; official organised screening statistics;

Italy – Database of National Screening Observatory; regional screening programme database for Marche region;

Latvia – no organised programme by mailing invitations is ongoing, FIT tests are delivered by GPs;

Portugal – Data Base of National Screening Programme.

Additional pilot sites

Italy (Bologna) – Database of the Local Health Authority (LHA) of Bologna (Azienda USL di Bologna), Emilia Romagna Region;

Lithuania – organised programme, FIT test are delivered by GPs.

Estimated participation rates

The following participation rates in the Strategy (estimates as number of tests returned from the total number of invitations sent) is estimated as follows (**Table 6**):

Table 6. Estimated Strategy participation rates.

Country	Expected participation rate
Estonia	60%

Italy (Marche)	30-35%
Italy (Emilia Romagna)	30-50%
Latvia	30%
Portugal	30%
Lithuania	30%

Justification (please provide also references):

Original pilot sites

Estonia – Participation in CRC screening has steadily increased over recent years, rising from 54% in 2019 to 55% in 2022 and 60% in 2023 and 62% in 2024. Further improvements in CRC screening participation are expected, with the added benefit of offering an additional *H. pylori* test;

Italy – Participation in CRC rate is stable during the years, 50%;

Latvia – there is currently no organised programme for mailing invitations. A pilot study using mailed invitations for FIT screening achieved a 45% response rate ³⁰. However, an intense reminder strategy was used in this pilot study, which will not be applied in *EUGastScreen*. As a result, a lower participation rate has been estimated for this study;

Portugal – Participation in CRC screening has been steady over the past years at around 34%.

Additional pilot sites

Italy (Bologna) – Although the overall participation rate in the CRC screening program has been around 50%, the uptake among individuals invited for the first time is only approximately 37%–38%;

Lithuania – invitations managed by GPs. Participation reported in the range of 16-18.1% per year resulting in 49.5% coverage within a 5-year period (2014-2018) ³¹.

Assumptions for *H. pylori* positivity

The following *H. pylori*-positivity is anticipated among the target group and presented in the **Table 7**.

Table 7. Anticipated *H. pylori* positivity rate.

Country	<i>H. pylori</i> positivity rate
Estonia	55%
Italy (Marche)	30%
Italy Emilia Romagna	30%

Latvia	50%
Portugal	50%
Lithuania	>50%

Source of information:

Original pilot sites

Estonia – Sebnova N, Stsepelova J, Sillakivi T, et al. The Prevalence of *Helicobacter pylori* in Estonian Bariatric Surgery Patients. Int J Mol Sci 2018;19(2); *H. pylori* prevalence judged on histology (55.9%) data from patients planned for bariatric surgery whereas PCR method revealed 64.7% positivity³²;

Italy (Marche) – Chen YC, Malfertheiner P, Yu HT, et al. Global prevalence of *Helicobacter pylori* infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology 2024; 166:605-619⁴;

Latvia – GISTAR study, data on file, 2023;

Portugal – Morais S, Ferro A, Bastos A, et al. Trends in gastric cancer mortality and in the prevalence of *Helicobacter pylori* infection in Portugal. Eur J Cancer Prev 2016 Jul;25(4):275-81. doi: 10.1097/CEJ.0000000000000183.

Additional pilot sites

Italy (Bologna) – Chen YC, Malfertheiner P, Yu HT, et al. Global prevalence of *Helicobacter pylori* infection and incidence of gastric cancer between 1980 and 2022. Gastroenterology 2024; 166:605-619⁴;

Lithuania – Jonaitis P, Kupcinskas J, Nyssen OP, et al. Evaluation of the Effectiveness of *Helicobacter pylori* Eradication Regimens in Lithuania during the Years 2013-2020: Data from the European Registry on *Helicobacter pylori* Management (Hp-EuReg). Medicina (Kaunas). 2021 Jun 23;57(7):642. doi: 10.3390/medicina57070642.

Sample size considerations

The sample size calculations are guided by the expected participation rates, defined as the proportion of invited individuals who return the screening test(s), and by the study's implementation-focused objective. As EUGastScreen is designed to evaluate feasibility and implementation rather than to provide policy-defining effectiveness estimates, a precision level of approximately ± 3 –5 percentage points is considered acceptable.

Participation rates are anticipated to vary across participating countries, largely influenced by the knowledge levels of the target population and the previous experiences with cancer screening. This variability underscores the importance of collecting feedback data. The insights gathered may inform the modification of strategies during the full-scale implementation phase to ensure equity across the EU, as mandated by the Beating Cancer Plan.

Other variabilities are also expected, including differences in the prevalence of *H. pylori* infection and the levels of antibiotic resistance, which may lead to variable success rates of eradication therapy. This information will be used in cost-effectiveness analysis conducted as part of the *EUCanScreen* project (outside the scope of the current protocol).

Comparison between the countries is limited by the fact that different strategies for test delivery and collection will be implemented. However, this variability will provide an opportunity to compare the strategies.

Limited data are expected on the comparison of invitation letter delivery strategies at the GP offices vs. by mail, in particular, because these strategies will target different populations and are unlikely to cover entire countries. However, test collection preferences (e.g., by mail, at GP offices or laboratories) may be analysed if offered as alternatives to the same target groups. The added value of reminders will also be a key aspect for *EUGastScreen* to address, even though the means used (e.g., mail, e-mail, SMS, or telephone call) may vary across sites. Furthermore, pilot study sites may employ different tools for the initial invitation and reminder Strategy (e.g., phone calls or SMS following an unanswered mail invitations), allowing for comparisons between these approaches.

Estimates of the invited individuals based on anticipated participation rates

In Latvia, for example, assuming an expected participation rate between 30% and 60%, the required number of individuals to be invited was estimated to achieve the desired precision around the participation estimate. These estimates refer to the number of invited individuals (i.e., the denominator for estimating participation), not the number of returned tests.

For example, if the true participation rate is 45%, inviting approximately 1,057 individuals would allow the participation rate to be estimated with a margin of error of ± 3 percentage points (95% confidence), while inviting approximately 595 individuals would provide a margin of error of ± 4 percentage points (**Table 8**).

The expected number of returned tests can be obtained by multiplying the number of invited individuals by the anticipated participation rate. For example, inviting 1,057 individuals with an expected participation rate of 45% would yield approximately 476 returned tests.

Table 8. Estimated number of invited individuals required to estimate participation rates with specific precision (95% confidence).

Expected participation rate (returned tests)	$\pm 1\%$	$\pm 2\%$	$\pm 3\%$	$\pm 4\%$	$\pm 5\%$
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among invited individuals)					
30%	8068	2017	897	505	323
45%	9508	2377	1057	595	381
60%	9220	2305	1025	577	369
65%	8740	2185	972	547	350

Based on the 2011 Latvian FIT screening pilot ³⁰, participation among adults aged 50–54 years was 35.3%, which was the lowest response rate among the five age groups reported. This estimate supports the assumption that participation in Latvia may plausibly fall within the 30–45% range, depending on the invitation strategy and implementation conditions.

For Estonia, for example, assuming an expected participation rate of 60-65%, approximately 1,025–972 invited individuals would be required to estimate participation with a margin of error of approximately ± 3 percentage points, while approximately 577–547 invited individuals would be sufficient for a margin of error of ± 4 percentage points.

Target sample sizes

The target sample sizes (**Table 9**) are based on the expected number of returned tests available for analysis, while recognizing that the number of individuals invited will need to be larger depending on the anticipated participation rate at each site.

Table 9. Minimal and optimal target number of returned tests available for analysis.

Country/Site	Minimal target	Optimal target
Estonia	600	1000
Italy (Marche)	500	1000
Italy- Emilia Romagna	500	1000
Latvia	1000	3000
Portugal	500	1000
Lithuania	1000	1000
TOTAL:	4100	8000

Ethical considerations

The study will be conducted in accordance with the principles of the Declaration of Helsinki, applicable national regulations, and relevant European legislation governing research involving human participants. Participation in EUGastScreen will be voluntary, and informed consent will be obtained from all participants before enrolment and data collection. In case questions are raised in regard to participation, and for all individuals who gave their consent, the participation will be assisted by study staff or healthcare personnel authorized by them. Participants may withdraw from the study at any time without consequences for their healthcare or participation in existing screening programmes.

The study involves procedures that are already established within routine clinical practice, including FIT-based colorectal cancer screening, *H. pylori* testing, eradication therapy, and clinically indicated diagnostic follow-up procedures. Risks associated with screening procedures are considered minimal and primarily relate to potential discomfort associated with sample collection. Risks associated with eradication therapy, including antibiotic-related side effects and the possibility of treatment failure, will be fully disclosed to participants prior to treatment initiation. Where participants are asked to temporarily discontinue PPIs or PCABs for testing purposes, this will be clearly communicated as part of the informed consent process, and the clinical appropriateness of discontinuation will be assessed on an individual basis.

Given that EUGastScreen involves population-scale antibiotic administration, participants will be informed not only of individual treatment risks and benefits but also of the broader public health rationale underpinning the selection of the eradication regimen. Specifically, participants will be made aware that bismuth quadruple therapy has been chosen as the preferred first-line regimen partly to minimise the risk of inducing resistance to antibiotic classes critical for treating life-threatening infections. This reflects the unique ethical responsibility associated with population-based antimicrobial interventions and ensures that consent is meaningful and appropriately contextualised.

The study includes procedures for referring participants for upper gastrointestinal endoscopy or colonoscopy where clinically indicated. Participants will be informed that these investigations may reveal findings beyond the scope of the study. A clear pathway will be in place at each site to ensure that incidental clinical findings are communicated to participants and their general practitioners in a timely manner, and that appropriate follow-up is arranged through existing healthcare systems.

The study will actively seek to include potentially vulnerable populations, including individuals from lower socioeconomic groups and first-generation immigrants, who may carry a disproportionate burden of *H. pylori* infection. Inclusion of these groups is considered both scientifically important and ethically appropriate given the study's public health aims. Invitation materials and informed consent documentation will be made accessible and, where feasible, culturally and linguistically appropriate to support equitable participation. Specific safeguards will be provided to ensure that recruitment of vulnerable individuals is conducted with appropriate care and without coercion.

Feedback will also be collected from individuals who decline participation, namely information on reasons for non-participation. As these individuals are not formally enrolled in the study, this data will be collected on an opt-out basis or, where required by national regulations, with explicit consent. The basis for data collection from non-participants will be clearly documented in site-specific consent and information materials.

Where participants provide consent for data linkage, study data may be shared in pseudonymised form with authorized partners within the EUCanScreen consortium for related activities. Participants will be informed of the scope of any such data sharing prior to enrolment. Personal data will be collected, processed, and stored in accordance with the General Data Protection Regulation (GDPR; EU 2016/679) and applicable national legislation. Additional details regarding data handling and participant confidentiality are provided in the Data Management section.

Ethics approval

- Centralized ethical approval was obtained in Latvia from Ethics Committee of the Riga East University Hospital Support Foundation (approval No 7-A/26) and is shared with all partners. An update of the approval will be sought following an updated version of the protocol.
- If additional national ethical approvals are required in specific countries, it will be the responsibility of the respective national partners to secure them (e.g., Estonia requires national ethics approval).

Data management

All study data will be collected, processed, and stored in accordance with the EU General Data Protection Regulation (GDPR) (EU 2016/679), the Personal Data Processing Law of Latvia, and the EUCanScreen Data Management Plan. Data will be captured electronically using a secure, GDPR-compliant digital platform (Longenesis Engage), with access restricted to authorized users through secure authentication methods.

The study will collect personal, demographic, and health-related data, including contact details, age, sex, national identification number (for secure data linkage), questionnaire responses, screening test results (FIT and SAT), and follow-up diagnostic outcomes (e.g., colonoscopy, upper endoscopy, breath test). Personal identifiers will be used only where necessary (e.g., for follow-up or data linkage) and will be replaced with unique coded identifiers (pseudonymization) for analysis. Identifiable data and re-identification keys will be stored separately and securely by the data controller, University of Latvia.

With participant consent, study data may be securely linked to national health databases, including the National Health Service, the National Cancer Registry, and hospital records, for research and follow-up purposes. Data processing will be carried out by the study team at the University of Latvia, authorized data processors (including Longenesis), and relevant healthcare institutions involved in screening and diagnostic procedures.

Data will be stored on secure institutional servers or EU/ European Economic Area (EEA)-based cloud infrastructure, with appropriate technical and organizational safeguards, including encryption, role-based access control, and regular backups. Access to identifiable data will be limited to authorized personnel bound by confidentiality obligations.

For analysis and reporting, data will be used in pseudonymized or anonymized form wherever possible. De-identified data may be shared with authorized research partners within the EU/EEA under secure and compliant conditions and may be deposited in secure EU-based research repositories for verification or related analyses. No identifiable personal data will be included in publications or reports. No personal data will be transferred outside the EU/EEA unless appropriate safeguards are in place (e.g., EU Standard Contractual Clauses).

Data will be retained for up to 10 years after study conclusion in accordance with project requirements and applicable institutional policies. Where national or institutional regulations require shorter retention periods (e.g., 7 years), data will be retained for the minimum period required, after which they will be anonymized or securely deleted.

Participants retain all rights under GDPR, including the right to access, correct, or withdraw their data at any time without consequences for their participation or healthcare.

Data management procedures follow FAIR principles (Findable, Accessible, Interoperable, Reusable) and are supported by a defined governance structure, including designated Data Stewards and institutional Data Protection Officers, ensuring data quality, security, and compliance throughout the study lifecycle. Site-specific implementation adaptations or changes occurring during the study will be documented in an implementation change log, including the affected pathway step, planned procedure, actual procedure, date of change, reason for change, and expected impact on implementation outcomes.

Statistical Analysis

All analyses will be performed at the country/site level, with country-specific estimates constituting the primary analytical unit. Pooled cross-country estimates may additionally be reported alongside measures of between-country variability and interpreted with caution, as implementation was intentionally adapted to existing national and regional CRC screening infrastructures across participating sites.

The primary analytical focus of EUGastScreen is implementation evaluation rather than formal hypothesis testing of clinical effectiveness. Accordingly, analyses will emphasize descriptive estimates of implementation outcomes, including feasibility, acceptability, adoption, appropriateness, coverage (where feasible), fidelity, and pathway completion.

Primary implementation outcomes, including SAT participation rates, coverage indicators, uptake of *H. pylori* eradication therapy among SAT-positive participants, adherence to predefined implementation procedures, completion of key pathway components (including treatment completion, referral completion, and post-treatment eradication confirmation testing), and successful *H. pylori* eradication, will be summarized as proportions with 95% CIs calculated using the Wilson score method.

Participation rates will be calculated as the proportion of invited individuals who return a screening sample. The proportions of valid, analyzable, and inadequate/unsatisfactory tests will be reported separately. Coverage measures will be calculated where reliable denominator data for the eligible target population are available from screening registries, healthcare databases, or participating GP practice lists. Where such denominator data are unavailable, participation among invited individuals will be reported instead.

Variation in implementation outcomes across countries and implementation models will be summarized descriptively to assess appropriateness and adaptability of the Strategy across diverse CRC screening settings.

Participation rates in the Strategy will be contextualized against available benchmark data from existing CRC screening programmes within each country. These comparisons are intended for descriptive and contextual interpretation only and will not be treated as formal comparative effectiveness analyses.

Secondary outcomes, including SAT positivity rate, FIT positivity rate, treatment completion, reasons for treatment non-completion, colonoscopy participation and completion rates, upper gastrointestinal endoscopy referral and completion rates, and endoscopic and histological findings where available, will be reported as proportions with 95% CIs at the country/site level and, where appropriate, in aggregate.

Eradication success rates will be calculated using both intention-to-treat (ITT) and per-protocol (PP) approaches. ITT analyses will include all SAT-positive participants offered eradication therapy, regardless of treatment completion or availability of post-treatment confirmation testing. PP analyses will include participants who complete at least 90% of the prescribed medication regimen and undergo post-treatment eradication confirmation testing.

Continuous variables will be summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Categorical variables will be summarized using frequencies and percentages.

Exploratory subgroup analyses may be performed according to:

- country/site;
- sex;
- age group;
- invitation strategy;
- reminder use; and
- GP-mediated versus centralized invitation pathways.

Where appropriate, chi-squared tests or Fisher's exact tests will be used for categorical variables, and Student's t-test or Mann-Whitney U test for continuous variables. Given the exploratory

nature of subgroup analyses and the heterogeneity of implementation settings, p-values will be interpreted cautiously and in conjunction with effect estimates and confidence intervals.

Multivariable logistic regression may be used to explore factors independently associated with participation in the Strategy, uptake of eradication therapy, pathway completion, and successful eradication confirmation. Potential covariates may include age, sex, country/site, invitation strategy, reminder use, and *H. pylori* positivity status.

Participant-reported barriers and facilitators related to participation in the Strategy will be collected through structured feedback questionnaires administered to invited individuals and study participants, including those declining participation where feasible. Structured questionnaire responses will be summarized descriptively using frequencies and proportions. Free-text responses, where available, will be reviewed, coded, and grouped into recurring themes related to participation, treatment uptake, and pathway completion. Qualitative findings will be used to contextualize quantitative implementation outcomes and support interpretation of cross-country variation in participation and uptake.

Missing data will be summarized descriptively. No formal imputation is planned for primary implementation outcomes. Denominators used for each analysis will be clearly reported.

No formal non-inferiority testing between the integrated Strategy and existing CRC screening participation rates is planned, as comparator benchmark data are not derived from randomized or equivalent implementation settings. Any comparisons with existing CRC screening participation rates will therefore be considered exploratory and contextual.

All statistical analyses will be performed using Stata (StataCorp), R, or equivalent statistical software. Reporting will follow relevant STROBE and StaRI recommendations where applicable.

Trial registration

The study will be registered in the ClinicalTrials.gov registry by the University of Latvia.

Database

A centralized online database for capturing study data will be developed by the University of Latvia (development of the database will be subcontracted to Longenesis, SIA).

Timelines

- 2024 – protocol development, coordination with the national PIs; development and agreement on the surveys

- 2025-2026 – finalization of the protocol, development of the study infrastructure, including data capture system, Ethics and other legal approvals, study registration, contracts, establishment of the study facilities
- 2026-2027 – selection of the relevant study population from the relevant registries, field study, collection of the study results
- 2027 – final analysis of the data, presentation of the data, reports and publications

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Appendices

Table S1. Description of CRC Screening Programmes in the Four Original Study Sites (based on the European Health Interview Survey 2018-2020, EHIS-3³³ and OECD data)

Countries (alphabetical order)	Structure of CRC screening programme	Year of programme initiation	Age group	Type of screening	Screening interval	Category according to gFOBT/FIT offer
Estonia	Organised (roll-out)	2016-2019	60-68	FIT	2 yrs	B
	Organised	2020	60-68	FIT	2 yrs	A
Italy	Organised	1982-1996	50-69	gFOBT	2 yrs	B
	Organised	1996	50-70/74	FIT		B

Italy (Piedmont and Veneto regions)	Organised	2003/2004	58-60-69	Flexible sigmoidoscopy	Once only	B
Latvia	Opportunistic	2005	50-74	gFOBT	1 yr	C
	Opportunistic	2019	50-74	FIT	2 yrs	C
Portugal	Opportunistic	NR	50-74	FIT/colonoscopy	1 yr/10 yrs	B
Portugal (Alentejo and Central regions)		2009-2018	50-70	gFOBT	2 yrs	B
Portugal (Northern region)	Organised (pilot)	2016-2018	50-74	FIT		B
	Organised	2018				B

Note: Category A, countries with nationwide organised screening fully implemented using fecal tests; Category B, countries with organised programmes with fecal tests partially rolled out or with regional coverage only; Category C, countries with opportunistic programmes with fecal test; category D, countries with no programme with fecal tests or a small-scale pilot programme only.

Table S2. Screening-related data to be collected and measures to be calculated (adopted from Chapter 8 by Lee et al.²²)

Required data to be collected	Measures to be calculated ^b	Definitions of measures ^c
Screening quality characteristics		
(1) Number of invitations to testing (2) Number of SAT and FIT eligible people	Invitation rate	Proportion of individuals who receive an invitation among eligible people
(1) Number of participants in SAT (2) Number of invited people	SAT participation rate ^a	Proportion of participants among invited people
(1) Number of participants in FIT (2) Number of invited people	FIT participation rate ^a	Proportion of participants among invited people
1) Number of test positives for <i>H. pylori</i> (2) Number of participants	SAT positivity rate	Proportion of test positives among participants
(1) Number of FIT tests with positive results (2) Number of participants	FIT positivity rate	Proportion of test positives among participants

(1) Number of inadequate SAT results (2) Number of tests for <i>H. pylori</i>	Inadequate/unsatisfactory SAT rate	Proportion of unsatisfactory test results among participants
(1) Number of inadequate results of FIT (2) Number of FIT	Inadequate/unsatisfactory FIT rate	Proportion of unsatisfactory test results among participants
(1) Number of referrals to treatment for <i>H. pylori</i> (2) Number of test positives for <i>H. pylori</i>	Referral to treatment rate	Proportion of <i>H. pylori</i> positive referred for treatment
(1) Number of referrals to undergo colonoscopy (2) Number of FIT with positive results	Referral to treatment rate	Proportion of FIT with positive results referred for colonoscopy
(1) Number of referrals to treatment (2) Number of taking <i>H. pylori</i> treatment	Treatment rate	Proportion of <i>H. pylori</i> positive taking treatment
(1) Number of referrals to undergo colonoscopy (2) Number who underwent colonoscopy	Treatment rate	Proportion of FIT with positive results referred for colonoscopy
(1) Number who has successful eradication (2) Number of taking <i>H. pylori</i> treatment	Eradication rate	Proportion of successful eradication among participants taking treatment
(1) Number of (serious) adverse events (2) Number of participants treated for <i>H. pylori</i>	Adverse event rate	Proportion of (serious) adverse events among treated participants
(1) Number of stopping treatment due to adverse events (2) Number of participants treated for <i>H. pylori</i>	Rate of stopping treatment due to adverse events	Proportion of stopping treatment due to adverse events among treated participants
(1) Number of participants in SAT (2) Number of eligible people	Coverage rate	Proportion of individuals who participate in testing among eligible people
(1) Number of participants in FIT (2) Number of eligible people	Coverage rate	Proportion of individuals who participate in testing among eligible people
(1) Number of <i>H. pylori</i> infected people (2) Number of eligible people	<i>H. pylori</i> prevalence rate	Proportion of <i>H. pylori</i> infected people among eligible people

^a These rates may differ if participants choose to participate in one screening modality only (e.g., in FIT as part of the ongoing organised population-based CRC screening).

^b The numerator is (1) and the denominators are (2) or (2) × (3).

^c The definition is equal to (1) divided by (2), or (1) divided by (2) × (3) when follow-up time is required.

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