EUROPEAN COMMISSION
JOINT RESEARCH CENTRE
Directorate F – Health and Food
Disease Prevention

ECICC - EUROPEAN COMMISSION INITIATIVE ON COLORECTAL CANCER

European guidelines on colorectal cancer prevention, screening and diagnosis:

Draft systematic review protocols on invitation strategies to organised, population-based colorectal cancer screening programmes

Purpose of the document: for stakeholders' consultation

Date: October 2024

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Specific protocol 1

Healthcare Question	**Should an invitation strategy involving General Practitioners vs. not involving General Practitioners be used for inviting asymptomatic adults to an organised, population-based, colorectal cancer screening programme?**
	The European guidelines on cancer screening are developed in the context of organised, population-based cancer screening programmes. Thus, a centralised call/recall system for screening participation will be considered as starting point for further recommendations.
Objective	To assess the relative effectiveness of different strategies for involving general practitioners (GPs) in the invitations to organised, population-based colorectal cancer screening programmes.
Eligibility criteria	**Population:** Asymptomatic individuals at average risk of developing cancer eligible for participating in a colorectal cancer screening programme. Studies reporting results from other populations will only be included if a separated analysis is available for colorectal screening population.
	Intervention(s): Intervention: Engagement of GP in the organisation of centralised call/recall system for participation in screening. We will consider GP's engagement as: – GP in charge of sending invitations. – GP in charge of sending reminders (written and/or phone calls) – Invitation letter including a GP's signature.
	Comparator: – GP is not engaged in the organisation of centralised call/recall system for participation in screening. – Any intervention above
	Subgroups: The following sub-populations will be separately evaluated (if possible): – First participation in screening (prevalent screening)

	– Subsequent participation in screening (incident screening) Although the following sub-populations will NOT be separately evaluated we will identify the following characteristics in the included studies: Age, sex, socially disadvantaged groups, non-native speakers, individuals with disabilities, individuals with obesity, individuals from the LGBTQI+ community, and certain religions who do not accept colonoscopy.
	Outcome(s): – Participation in screening – Awareness of information – Accessibility to information – Informed decision making – Confidence with decision making – Satisfaction with decision making
	Study design: We will include randomised clinical trials or observational evidence, including but not limited to: standalone randomised clinical trials, nested randomised trials in large cohorts, cohort studies, before-after studies, single-arm add-on studies. Most updated systematic reviews of randomised clinical trials or observational evidence will be used as source of evidence if no flaws in the items that have been identified as critical are detected (or are unjustified) (Shea 2017). Non-comparative studies and studies reported only as (conference) abstracts will be excluded.
Search strategy	A protocol for the systematic identification of research evidence on invitation strategies for different cancer screening programmes has been already issued and published elsewhere (see above).
Study selection, evidence appraisal, and synthesis	**Data collection:** One reviewer will extract relevant data from eligible studies on their main characteristics. We will describe in a table the reasons that led to the decision to exclude a study and describe in tables the main characteristics of the included studies, outcomes of interest and their main effect estimates. A different reviewer will cross check the data extracted for accuracy.

	Risk of bias: We will assess risk of bias in randomized controlled trials using the Cochrane Risk of Bias 2 tool (Sterne 2019), risk of bias in observational studies using the ROBINS-I tool (Sterne 2016) and AMSTAR for systematic reviews (Shea 2007).
	Strategy for data synthesis: We will report the estimates stratified by type of study design for each outcome on which we decided to include other kinds of studies apart from RCTs. We will perform all analyses in Stata and/or RevMan. <u>Randomized control trials</u> We will estimate the relative effects of the screening tests, pooling appropriate measures of effect (i.e. risk ratios) for the outcomes of interest with random-effects pairwise meta-analyses. We will assess the presence of heterogeneity between studies by visual inspection of forest plots for all outcomes and complemented by the assessment of inter-study heterogeneity by I2 index (Deeks 2023). Heterogeneity of 0% to 40% will be considered as "minor heterogeneity," 30% to 60% as "moderate heterogeneity," 50% to 90% as "substantial heterogeneity," and 75% to 100% as "considerable heterogeneity." Noteworthy, overlapping categories convey that there are no strict cut-offs for interpreting heterogeneity, and categorization depends on the magnitude and direction of effects. <u>Observational studies</u> We will pool effect sizes (i.e. relative risks, hazard ratios) for effectiveness using a random effects model with the Mantel-Haenzel or inverse variance method. We will prioritize the adjusted estimations. We will assess the presence of heterogeneity between studies by visual inspection of forest plots for all outcomes and complemented by the assessment of the I2 parameters for relative effects following the methods described above (Deeks 2023)
Summary of findings, and assessment of the certainty of evidence	We will rate the certainty of evidence across studies and for each outcome following the GRADE approach as high, moderate, low or very low, depending on several factors including; risk of bias, imprecision, inconsistency, indirectness and publication bias (Schünemann 2013) We will develop a GRADE evidence profiles and summary of findings (SoF) tables, summarizing the evidence for a list of selected outcomes related to benefits and harms, the relative and absolute effects of the

	intervention and the volume and certainty of evidence.
References	– Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. – Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. – Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from www.guidelinedevelopment.org/handbook. – Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. – Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M,et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919. – Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.

Specific protocol 2

Healthcare Question	**Should a letter including the self-sampling stool-based test vs. a letter alone (with instructions on how to obtain the kit) be used for inviting asymptomatic adults to an organised, population-based, colorectal cancer screening programme?**
	The European guidelines on cancer screening are developed in the context of organised, population-based cancer screening programmes. Thus, a centralised call/recall system for screening participation will be considered as starting point for further recommendations.
Objective	To assess the relative effectiveness of two organised colorectal cancer screening invitation strategies addressed to the general population: invitation letter with/without self-sampling kit for stool-based tests.
Eligibility criteria	**Population:** Asymptomatic individuals at average risk of developing cancer eligible for participating in a colorectal cancer screening programme. Studies reporting results from other populations will only be included if a separated analysis is available for colorectal screening population.
	Intervention(s): Invitation letter including a self-sampling kit for stool-based sampling Enhanced information such as digital video discs (DVD) or videos available from public/restricted websites, website-based information or downloadable software, programme, booklets etc. will be excluded. Similarly face-to-face counselling or delivered through telephone will be also excluded.
	Comparator: Invitation letter (may include instructions to pick up a self-sampling kit elsewhere)
	Subgroups: The following sub-populations will be separately evaluated (if possible): – First participation in screening (prevalent screening) – Subsequent participation in screening (incident screening)

	– Invitation letter along with self-sampling kit including an advanced notification letter Although the following sub-populations will NOT be separately evaluated we will identify the following characteristics in the included studies: Age, sex, socially disadvantaged groups, non-native speakers, individuals with disabilities, individuals with obesity, individuals from the LGBTQI+ community, and certain religions who do not accept colonoscopy.
	Outcome(s): – Participation in screening – Awareness of information – Accessibility to information – Informed decision making – Confidence with decision making – Satisfaction with decision making
	Study design: We will include randomised clinical trials or observational evidence, including but not limited to: standalone randomised clinical trials, nested randomised trials in large cohorts, cohort studies, before-after studies, single-arm add-on studies. Most updated systematic reviews of randomised clinical trials or observational evidence will be used as source of evidence if no flaws in the items that have been identified as critical are detected (or are unjustified) (Shea 2017). Non-comparative studies and studies reported only as (conference) abstracts will be excluded.
Search strategy	A protocol for the systematic identification of research evidence on invitation strategies for different cancer screening programmes has been already issued and published elsewhere (see above).
Study selection, evidence appraisal, and synthesis	**Data collection:** One reviewer will extract relevant data from eligible studies on their main characteristics. We will describe in a table the reasons that led to the decision to exclude a study and describe in tables the main characteristics of the included studies, outcomes of interest and their main effect estimates. A different reviewer will cross check the data extracted for accuracy.

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	Strategy for data synthesis: We will report the estimates stratified by type of study design for each outcome on which we decided to include other kinds of studies apart from RCTs. We will perform all analyses in Stata and/or RevMan. Randomized control trials We will estimate the relative effects of the screening tests, pooling appropriate measures of effect (i.e. risk ratios) for the outcomes of interest with random-effects pairwise meta-analyses. We will assess the presence of heterogeneity between studies by visual inspection of forest plots for all outcomes and complemented by the assessment of inter-study heterogeneity by I2 index (Deeks 2023). Heterogeneity of 0% to 40% will be considered as "minor heterogeneity," 30% to 60% as "moderate heterogeneity," 50% to 90% as "substantial heterogeneity," and 75% to 100% as "considerable heterogeneity." Noteworthy, overlapping categories convey that there are no strict cut-offs for interpreting heterogeneity, and categorization depends on the magnitude and direction of effects. Observational studies We will pool effect sizes (i.e. relative risks, hazard ratios) for effectiveness using a random effects model with the Mantel-Haenzel or inverse variance method. We will prioritize the adjusted estimations. We will assess the presence of heterogeneity between studies by visual inspection of forest plots for all outcomes and complemented by the assessment of the I2 parameters for relative effects following the methods described above (Deeks 2023)
Summary of findings, and assessment of the certainty of evidence	We will rate the certainty of evidence across studies and for each outcome following the GRADE approach as high, moderate, low or very low, depending on several factors including; risk of bias, imprecision, inconsistency, indirectness and publication bias (Schünemann 2013) We will develop a GRADE evidence profiles and summary of findings (SoF) tables, summarizing the evidence for a list of selected outcomes related to benefits and harms, the relative and absolute effects of the

	intervention and the volume and certainty of evidence.
References	– Deeks JJ, Higgins JPT, Altman DG (editors). Chapter 10: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Cochrane, 2023. Available from www.training.cochrane.org/handbook. – Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ 2021;372:n160. – Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. Updated October 2013. The GRADE Working Group, 2013. Available from www.guidelinedevelopment.org/handbook. – Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. BMJ. 2017 Sep 21;358:j4008. – Sterne JAC, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M,et al. ROBINS-I: a tool for assessing risk of bias in non-randomized studies of interventions. BMJ 2016; 355; i4919; doi: 10.1136/bmj.i4919. – Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019; 366: l4898.