PREcision ScrEeniNg for ColoRectal Cancer: a randomized non-inferiority trial (PRESENT-CRC)

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	The trial will be registered at https://clinicaltrials.gov and on the Swiss National Clinical Trials Portal (SNCTP) at https://www.humanforschung-schweiz.ch/.

Sponsor and coordinating investigator for French-speaking centers

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Investigated Intervention:	Risk-based colorectal screening recommendations vs standard of care (no specific recommendations for screening) in the general population aged 50-69 years
Protocol ID	PRESENT-CRC
Version and Date:	Version 3.0 (dated 04/08/2025)

PROTOCOL SIGNATURE FORM

Study Title	Precision Screening for Colorectal Cancer: a randomized non-inferiority trial
Study ID	PRESENT-CRC

The Sponsor-Investigator, the (co)-coordinating investigators and the trial statistician have approved the protocol version 3.0 (dated 04.08.2025) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor-coordinating investigator for French-speaking centers:

Name: Dr. Kevin Selby, Unisanté, Route de Berne 113, 1010 Lausanne

Date: 06. Oct. 2025 Signature: _____

Coordinating investigator for German-speaking centers:

Name: Prof. Viviane Hess, University Hospital Basel

Date: 29. Sep. 2025 Signature: _____

Trial statistician

Name: Aziz Chaouch, MSc

Date: _____ Signature: _____

PROTOCOL SIGNATURE FORM

Study Title	Precision Screening for Colorectal Cancer: a randomized non-inferiority trial
Study ID	PRESENT-CRC

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Sponsor-coordinating investigator for French-speaking centers:

Name: Dr. Kevin Selby, Unisanté, Route de Berne 113, 1010 Lausanne

Date: _____ Signature: _____

Coordinating investigator for German-speaking centers:

Name: Prof. Viviane Hess, University Hospital Basel

Date: _____ Signature: _____

Trial statistician

Name: Aziz Chaouch, MSc

Date: 29.09.2025 Signature: _____

PROTOCOL SIGN-OFF PAGE FOR THE (LOCAL) PRINCIPAL INVESTIGATOR
PROTOCOL VERSION 3.0:

Study Title:	Precision Screening for Colorectal Cancer: a randomized non-Inferiority trial
Study ID:	PRESENT-CRC
Site name:	Vaud screening program
Site address:	Route de Berne 113 1010 Lausanne, Switzerland
Principal Investigator:	Dr. Romain Freund

Having read and understood protocol version 3.0 (04.08.2025), I agree to conduct the trial as specified in the protocol.

Date: 01/10/25 Signature: _____

PROTOCOL SIGN-OFF PAGE FOR THE (LOCAL) PRINCIPAL INVESTIGATOR
PROTOCOL VERSION 3.0:

Study Title:	Precision Screening for Colorectal Cancer: a randomized non-Inferiority trial (PRESENT-CRC)
Study ID:	PRESENT-CRC
Site name:	Screening programs of the canton of Berne, and of the cantons Basel-City and Basel-Country
Site address:	Krebsliga beider Basel Petersplatz 12 4051 Basel, Switzerland
Principal Investigator:	Dr. Simone Dertschnig

Having read and understood protocol version 3.0 (04.08.2025), I agree to conduct the trial as specified in the protocol.

Date: 29.9.2025 Signature: Simone Dertschnig

PROTOCOL SIGN-OFF PAGE FOR THE (LOCAL) PRINCIPAL INVESTIGATOR
PROTOCOL VERSION 3.0:

Study Title:	Precision Screening for Colorectal Cancer: a randomized non-Inferiority trial (PRESENT-CRC)
Study ID:	PRESENT-CRC
Site name:	Geneva screening program
Site address:	Fondation genevois pour le dépistage du cancer Boulevard de la Cluse 43 1205 Genève
Principal Investigator:	Dr. Ania Wisniak

Having read and understood protocol version 3.0 (04.08.2025), I agree to conduct the trial as specified in the protocol.

Date: 01/10/2025 Signature: _____

PROTOCOL SIGN-OFF PAGE FOR THE (LOCAL) PRINCIPAL INVESTIGATOR
PROTOCOL VERSION 3.0:

Study Title:	Precision Screening for Colorectal Cancer: a randomized non-Inferiority trial (PRESENT-CRC)
Study ID:	PRESENT-CRC
Site name:	Fribourg screening program
Site address:	Ligue fribourgeois contre le cancer Rte St-Nicolas-de Flüe 2 1701 Fribourg, Switezrland
Principal Investigator:	Prof. Daniel Betticher

Having read and understood protocol version 3.0 (04.08.2025), I agree to conduct the trial as specified in the protocol.

Date: October 2, 2025 Signature: _____

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
BASEC	*Business Administration System for Ethical Committees*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
eCRF	*electronic Case Report Form*
FOPH	*Federal Office of Public Health*
GCP	*Good Clinical Practice*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
SAE	*Serious Adverse Event*
CRC	*Colorectal cancer*
FIT	*Fecal immunochemical test*
MC-SIS	*Multi-Cancer Screening Information System*
MISCAN	*Microsimulation Screening Analysis model*
NNS	*Number needed to scope*

1. STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Sponsor-Investigator: Kevin Selby Unisanté, University Center for Primary Care and Public Health Route de Berne 113, 1010 Lausanne Kevin.Selby@unisante.ch
Study Title	Precision Screening for Colorectal Cancer: a randomized non-inferiority trial (PRESENT-CRC)
Short Title / Study ID	PRESENT-CRC
Protocol Version and Date	Version 3.0 (dated 04.08.2025)
Study Registration	This study will be registered on ClinicalTrials.gov after feedback from the Ethics Committee but prior to including participants.
Study Category and Rationale	Category “Other clinical trials” and Category A. The study intervention is a change in the information provided to persons invited for routine colorectal cancer (CRC) screening. The two screening tests recommended by the intervention and control materials, colonoscopy and faecal immunochemical tests (FIT), are the current standard of care in Switzerland. The intervention will orient participants to one or the other test.
Background and Rationale	CRC incidence and mortality can be effectively prevented through screening with FIT or colonoscopy. While colonoscopy is more sensitive for detecting advanced neoplasia, it is expensive, burdensome, and requires trained specialists. Risk factors for CRC include advanced adenomas, quantitative FIT results (higher hemoglobin concentrations in stool), increasing age, male sex, environmental factors, and lifestyle. CRC risk can be estimated by entering information about risk factors into validated models. Screening programs could use individual risk for CRC to optimize colonoscopy use and achieve the same public health impact while performing fewer colonoscopies. However, the effect of risk-based screening on the detection of advanced neoplasia is still unclear. Moreover, Swiss screening programs report low participation rates in screening. Mailing FIT kits and offering patient navigation for colonoscopy are efficient methods to increase CRC screening uptake. However, their impact on participation and cost-effectiveness in Switzerland are unknown.
Risk / Benefit Assessment	We do not anticipate serious adverse events linked to the study intervention, which will orient participants towards FIT or colonoscopy according to their CRC risk. We do not consider serious adverse events from colonoscopies to be a direct result of our intervention. A potential adverse event related to the intervention is anxiety that can be experienced by the participants at high-risk. To mitigate anxiety, we will provide recommendations for screening and an information flyer to facilitate communication with a GP or pharmacist if needed. The main benefit for the intervention group is a better balance of risks and benefits of screening tests (non-invasive test for low-risk individuals, colonoscopy for high-risk). The benefit for future screening programs is an improved use of resources.

Objective(s)	**Primary objective:** Assess the non-inferiority of personalized screening recommendations for FIT or colonoscopy compared to usual care (no specific recommendations) for the detection of advanced neoplasia after 3-year follow-up. **Secondary objectives:** • To assess whether mailed FIT increases FIT completion among participants at lower risk at 1-year follow-up. • To assess whether participant navigation increases colonoscopy completion among participants at higher risk at 1-year follow-up. • To assess the effect of risk-based screening on overall screening participation (for both FIT and colonoscopy) as compared to usual care at 1-year follow-up. • To assess whether risk-based screening has a different effect on overall screening participation depending on participants' estimated socioeconomic (SEP) position, we will stratify analyses for participation at 1-year follow-up by SEP. • To compare the number needed to scope, which is the number of colonoscopies needed to find one advanced neoplasia, between risk-based screening and usual care at 3-year follow-up. The trial contains two **sub-projects** with the following objectives: • Cost-effectiveness study: Assess whether risk-based CRC screening is cost-effective compared to usual care, from a healthcare system perspective. Both a within-trial analysis using a time horizon of 3 years, as well as a long-term analysis using a life-time horizon, will be conducted. • Process evaluation study: Assess to what degree planned trial interventions were implemented as intended, and how they were perceived by study stakeholders.
Endpoint(s)	**Primary endpoint:** The proportion of participants diagnosed with advanced neoplasia up to 3-year follow-up, defined as • Adenoma > 1cm; • Adenoma of any size with high-grade dysplasia; • Adenoma with villous or tubulovillous histology (≥25% villous) • Serrated lesion > 1cm; • Serrated lesion of any size with high-grade dysplasia; • Traditional serrated adenoma (any size); • Adenocarcinoma; **Secondary endpoints:** • FIT completion among low-risk participants who received a mailed FIT (Intervention 2) and low-risk participants who did not receive a mailed FIT (Intervention 1) at 1-year follow-up; • Colonoscopy completion among high-risk participants offered navigation (Intervention 2) and among high-risk patients not offered navigation (Intervention 1) at 1-year follow-up; • Overall screening participation at 1-year follow-up;

	• Overall screening participation between the Intervention arms 1 and 2 and the control arm, stratified by socioeconomic position at 1-year follow-up; • Number needed to scope to detect one advanced neoplasia at 3-year follow-up. We will also collect information about participants' age, canton of residence, sex, socio-economic position, family history of CRC, and baseline screening preferences. **Endpoints for the Cost-effectiveness sub-study**: Cost per quality-adjusted life-year (QALY) gained, from a healthcare system perspective during the trial period. Cost per QALY gained, from a healthcare system perspective, with a lifetime horizon.
Study Design	This is a multicenter, parallel group, non-inferiority, randomized, controlled trial with 3 groups (control, Intervention 1, and Intervention 2) with a 2:1:1 allocation ratio. In addition to personalized screening recommendations (Intervention 1), Intervention 2 includes targeted interventions to increase screening completion (mailed FIT for participants at lower risk or patient navigation for colonoscopy for those at higher risk). The trial will include five organized CRC screening programs (screening centers) from the cantons of Geneva, Vaud, Fribourg, Bern, and Basel-City/Basel-Country. The sponsor will be Unisanté. We will stratify randomization based on risk level (calculated prior to randomization) and screening center, using a varying block size of 4 or 8. Study participants will be blinded. The investigators, screening centers and study statistician will not be blinded.
Inclusion- / Exclusion Criteria	Recruitment will be conducted by the screening centers. Our inclusion criteria are: • being aged between 50 and 74 years old; • residing in a canton whose screening center is recruiting for the trial; • having provided informed consent. People at very high risk of CRC or already up to date with screening are excluded. Specifically, those: • with current symptoms suspicious for colorectal cancer (i.e. rectal bleeding, unusual weight loss, etc.); • with a medical condition requiring colonoscopy surveillance at a shorter than 10-year interval; • having had a colonoscopy within 9.5 years or a FIT within 1.5 years. We will work with sex as defined administratively in Switzerland (male/female). As recruitment will be conducted using mailed invitations, we will not be able to ensure sex and gender balance. Nevertheless, based on our pilot data (final study sample of 515 participants included 51% of women and 49% of men) we expect similar participation among both sexes.

Number of Participants with Rationale	The sample size was calculated based on the primary outcome. We expect a detection rate of advanced neoplasia of 31.5 cases per 1000 participants in both the intervention and control arms. With 7'244 participants we have 80% power to exclude a difference in favor of the control group of more than 11.5 cases per 1000 (relative decrease of 37%) based on the upper limit of a one-sided 97.5% confidence interval. Assuming 10% of screening occurs outside of the organized program (missing data), we need 8'050 participants at the start of the trial.
Study Interventions	**Intervention 1** will consist of a brochure communicating to participants their risk for CRC and orienting them to a risk-appropriate screening test. **Intervention 2** will consist of providing the same brochures as Intervention 1 with additional interventions to increase screening completion: We will mail FIT to participants at lower risk and we will offer telephone-based patient navigation to those at higher risk to help organize a colonoscopy if no colonoscopy has been done after 4 months post-randomization. CRC risk will be calculated using the QCancer-colorectal 15-year risk score calculator. This tool uses risk factors such as age, sex, life-style factors, and pre-existing diseases to predict an individual's 15-year risk of CRC. We will increase its predictive power by including participants' screening history, when available. Participants will be divided into lower risk (1-3% absolute risk) and higher-risk groups (4-7+% absolute risk). People at very high risk (symptoms or certain conditions) are excluded as they need colonoscopy surveillance.
Control Intervention	Participants of the control group will receive the standard invitation letter and brochure used by the participating screening programs. Control materials do not provide personalized risk information or specific recommendations for FIT or colonoscopy.
Study procedures	**Recruitment.** Approximately 73'720 invitations will be mailed to individuals potentially eligible for screening. Recruitment materials will provide access to a secure REDCap platform containing the information sheet and the consent form. Potential participants can request paper copies. Participants will access the recruitment questionnaire immediately after providing consent. Non-responders will receive a reminder 4-6 weeks after the invitation. Those who do not respond within 6 weeks of the reminder will receive a standard invitation to screening (excluding them from the study). **Randomization and intervention.** Randomization will be stratified based on screening center and risk level. Participants will be randomized to one of 3 groups (control, Intervention 1, Intervention 2) with allocation ratio 2:1:1. The two intervention groups will be pooled when analyzing the primary outcome. Intervention and control materials will be mailed to participants after group assignment. **Follow-up.** Follow-up starts at the date when the invitation letter to screening is generated in MC-SIS and will last three years. Participants who have completed a FIT or who have not completed any test will be reinvited for screening two years later. Participants choosing colonoscopy will not receive further invitations within this trial. Participants at higher risk randomized to Intervention 2 who have

	not been included for colonoscopy 4 months after randomization will be contacted for participant navigation. Information about screening test completion and clinical outcomes will be collected by the screening programs using routine procedures and the existing software 'MC-SIS'. Given the potential for opportunistic screening, a random, 10% subsample of lower-risk and 20% subsample of higher-risk participants will complete a brief questionnaire 3 years after randomization asking about screening tests done outside of the screening programs.
Study Duration and Schedule	The follow-up period of the trial is 3 years, starting on the day of mailing the intervention or control materials. We plan to start recruiting in September 2025 and to start mailing intervention/control materials in November 2025. Recruitment will not start before approval of the protocol by the ethics committees of all involved cantons. Planned October 2025 of First-Participant-In Planned May 2029 of Last-Participant-Out of intervention period Planned long-term follow-up with tumor registry until 2045
Investigator(s)	**Sponsor and Coordinating Investigator for French-speaking sites:** Kevin Selby, Unisanté. **Coordinating Investigator for German-speaking sites:** Viviane Hess, University of Basel. **Local Principal Investigators:** • Vaud Screening center: Romain Freund • Geneva Screening center: Ania Wisniak • Fribourg Screening center: Daniel Betticher • Bern and Basel-City/Basel-Country Screening centers: Simone Dertschnig Approximately 14 **co-investigators** will participate in the trial. Delegation of study staff by the coordinating investigators or local principal investigators will be documented locally through delegation and contact lists.
Study Center(s) and Partners	**Sponsor:** The Sponsor is Unisanté. Address: Route de Berne 113, 1010 Lausanne, Switzerland. **Study centers:** • Vaud screening program. Address: Route de Berne 113, 1010 Lausanne, Switzerland. • Geneva screening program. Address: Bd de la Cluse 43, 1205 Geneva, Switzerland. • Fribourg screening program. Address: Route St-Nicolas-de-Flüe 2, 1701 Fribourg, Switzerland.

	• Bern screening program. Address: Petersplatz 12, 4051 Basel, Switzerland. • Basel-City and Basel-Country screening program. Address: Petersplatz 12, 4051 Basel, Switzerland. **Coordinating investigators:** • Coordinating investigator for the French-speaking centers: Unisanté, Kevin Selby, Route de Berne 113, 1010 Lausanne, Switzerland. • Coordinating investigator for the German-speaking centers: University of Basel, Viviane Hess, Petersplatz 12, 4051 Basel, Switzerland. **Study partners:** • University of Zurich: the process evaluation study. Address: Universitätstrasse 84, 8006 Zürich, Switzerland. • University of Basel: the cost-effectiveness study. Address: Petersplatz 12, 4051 Basel, Switzerland. • Erasmus University Medical Center: the cost-effectiveness study. Address: Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
Statistical Considerations:	The primary outcome (difference in the proportion of advanced neoplasia between the control and intervention groups) will be analyzed using the Mantel-Haenszel estimator for the risk difference, accounting for the stratified design. This estimator will also be used to estimate binary secondary outcomes. Additionally, logistic regression models adjusted for the screening center and risk level as well as potential additional predictors (e.g. previous screening participation) will be used to obtain adjusted estimates. Baseline participant characteristics will be summarized by randomization group and by risk level. **Additional analyses.** We will compare screening participation stratified by socio-economic position. Other subgroup analyses will be descriptive only and will be conducted for age groups, canton of residence, sex, family history of CRC, and baseline screening preferences. **Cost-effectiveness study.** Health economic assessment will be within-trial and beyond trial with a lifetime horizon. Within trial health economic assessment will be based on the comparison of healthcare resource use, healthcare costs, and QALYs between the intervention and comparator arms. The beyond trial economic assessment will be based on the MISCAN-Colon model. The primary outcomes of the trial (findings of screening and appropriate screening uptake), and cost and quality of life estimates will be incorporated into the model.
Data privacy	Only authorized study team members will have access to the collected data to fulfil their duties within the scope of the study. There will be two participant identification lists allowing us to link identifying information to study IDs. The list of the German-speaking participants will be stored on the University Hospital Basel server and the list of the French-speaking participants on the Unisanté server. Access to the lists will be granted to the coordinating PIs and delegated staff.

Ethical consideration	Risk-based cancer screening has been widely promoted as a mean of improving screening for participants (improved balance between benefits-risks) and programs (better allocation of resources). Risk-based CRC screening has not been implemented due to concerns it could diminish the population-level impact of screening programs by lowering participation and decreasing the number of colonoscopies performed. Our study can answer this question with minimal additional risks to participants. Independent of screening recommendations delivered in the context of this study, all participants still have a free choice between FIT and colonoscopy and will be able to discuss screening options with their family doctor if needed. We expect study results to be generalizable to the eligible Swiss population and other screening settings with heavy colonoscopy use.
GCP Statement	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the HRA as well as other locally relevant legal and regulatory requirements.

2. BACKGROUND AND RATIONALE

Colorectal cancer (CRC) is the third most common cancer in men and second most common in women, causing approximately 930'000 deaths worldwide every year [1]. The long pre-clinical development of the disease allows for screening to reduce CRC mortality [2].

There are multiple risk factors for CRC. Whereas age and advanced adenoma are the most important of them, many other factors related to environment, lifestyle, personal history of several diseases, and heredity also contribute to CRC incidence [3, 4]. Thus, risk to develop CRC varies significantly among individuals [4], which provides an opportunity to implement personalized screening recommendations and offer screening options with a reasonable risk-benefit balance.

Presently, in Switzerland both fecal immunochemical test (FIT) and colonoscopy are reimbursed for CRC screening. Colonoscopy is the most accurate test for early detection of cancerous and precancerous lesions [5, 6], but it is related to risks of bleeding and perforation (1-2 events/1000 colonoscopies) [7, 8]. Moreover, colonoscopy requires onerous bowel preparation and can be embarrassing for patients. FIT provides an estimation of hemoglobin concentration in feces. This test is less costly, can be done at home without preparation, and has good acceptance among patients [5, 9].

Currently, in Switzerland organized CRC screening programs are operating or are planned in 14 cantons, 12 of which offer a choice of colonoscopy and FIT [10]. On the 2017 Swiss Health Survey, 48% of the population aged 50 to 75 years was up-to-date with screening, and 43% of individuals in that age range had had a screening or diagnostic colonoscopy [11]. However, there is no direct evidence for the superiority of colonoscopy compared FIT in an organized screening setting to detect CRC [5] and reduce CRC mortality [2], especially among individuals at low or average risk.

Overuse of colonoscopy represents a significant economic, environmental, and personal burden. Firstly, there is a limited number of specialist gastroenterologists who can perform colonoscopy, which leads to longer waiting time for people at higher risk. Secondly, colonoscopy requires onerous bowel preparations and in general one day off work. And thirdly, it has important environmental consequences. For instance, in the United States endoscopy is the third largest contributor to healthcare's carbon footprint [12].

Risk-based screening recommendations could decrease colonoscopy overuse among low-risk individuals. The risk score can be calculated by means of the QCancer-colorectal 15-year risk calculator (https://qcancer.org/15yr/colorectal/) [13]. This open-source tool was developed and validated in the United Kingdom. An external validation study showed that it assigns individuals aged 40 to 69 years old to the correct risk group 66-70% of the time, which ranks QCancer among tools with the highest discriminative power [13-16]. The QCancer calculator was successfully used in our pilot trial. In the current study, we will augment its predictive power with the screening history of the participants (when available), which has been shown to be a strong predictor for CRC risk [17]

Thus, it is possible to identify individuals at low risk and provide them with recommendations for FIT as a screening test. Those at high risk should be recommended colonoscopy. Giving screening recommendations in addition to CRC risk seems to be necessary to reorient people to risk-appropriate screening test and maintain overall screening participation. Indeed, in one randomized controlled trial conducted by Steckelberg and colleagues, communication of CRC risk without screening recommendation resulted in low and unchanged participation [18]. The other trial conducted by Smith and colleagues [19] showed a substantial decrease in screening participation (59% vs 75% participation, p=0.001). These trials, and a Cochrane review [20], showed that decision support and risk information, without screening recommendations, is unlikely to improve screening efficiency.

We tested the efficacy of risk-based screening recommendations in our pilot randomized controlled trial. This study showed that participants who received the intervention were 14% more

likely to complete risk-appropriated screening test compared to participants in the control group [21]. However, the efficacy of risk-based screening to detect advanced neoplasia is still unclear.

Another difficulty that organized screening programs are facing is low participation rates. Cantons are reluctant to adopt interventions developed abroad, like mailed FIT and participant navigation, due to concerns about waste, lack of cost-effectiveness information, and fear of missing high-risk individuals who could benefit from colonoscopy. Several countries face similar challenges [22].

In this context, our primary aim is to study whether risk-based CRC screening can work as well as the current approach for the detection of advanced neoplasia. The cost effectiveness of this approach will also be assessed. Finally, it will be assessed whether the research team and organized program staff applied the risk-based screening processes as intended. The study's results can potentially revolutionize CRC screening in Switzerland and abroad, moving from a generic approach to a more precise, risk-based strategy. This change could lead to comparable or better clinical results, lower costs, and more equitable use of resources.

3. STUDY OBJECTIVES, HYPOTHESES AND STUDY DESIGN

3.1. Hypothesis and primary objective

Primary objective: Assess whether risk-based screening recommendations for FIT or colonoscopy based on predicted CRC 15-year risk are non-inferior to standard invitations offering FIT and colonoscopy without specific recommendations (usual care) for the detection of advanced neoplasia after 3-years follow-up.

Primary hypothesis: We expect communicating CRC risk and screening recommendations to be non-inferior for the detection of advanced neoplasia as compared to usual care.

Secondary objectives and hypotheses:

1. Objective: To assess whether mailed FIT increases FIT completion among participants at low risk.
   Hypothesis: We expect that mailed FIT will give an absolute increase in FIT completion in low-risk participants by 10%, accompanied by a drop in colonoscopy in this group.
2. Objective: To assess whether participant navigation increases colonoscopy completion among participants at high risk.
   Hypothesis: We expect that participant navigation will give an absolute increase of 10% in colonoscopy completion in high-risk participants.
3. Objective: To assess the effect of risk-based screening alone (Intervention 1) on overall screening participation (for both FIT and colonoscopy) as compared to usual care.
   Hypothesis: We expect that overall screening participation (FIT and colonoscopy combined) will be similar in the Intervention arm 1 compared to the control arm.
4. Objective: To assess whether risk-based screening does not decrease overall screening participation among participants with a lower estimated socioeconomic position.

   Hypothesis: We expect the overall screening participation to be equal in the intervention and the control arms after stratifying by socioeconomic position using the Swiss-SEP.
5. Objective: To compare the number needed to scope (NNS), which is the number of colonoscopies needed to find one advanced neoplasia, between risk-based screening and usual care.
   Hypothesis: We expect that the NNS will be lower in the intervention arm, as participants at low risk in this arm would prefer FIT to colonoscopy, which should reduce the number of unnecessary colonoscopies.

This study includes two sub-projects (cost-effectiveness of risk-based screening and implementation evaluation) whose objectives, endpoints and methods are detailed in chapter 6.

3.2. Primary and secondary endpoints

Many primary and secondary outcomes will be collected via Multi-Cancer Screening Information System (MC-SIS) which is a platform used by the Swiss organized cancer screening programs to invite potentially eligible individuals for screening and collect data about completed screening tests, clinical outcomes and complications. Information about colonoscopies (such as the date of the examination, clinical results, and complications) are entered into MC-SIS directly by gastroenterologists who conduct the examinations. Polyp type (dysplasia, villous architecture, serrated lesion, etc.) is entered by pathologists. The results of FITs are entered by the partner laboratories conducting the fecal analyses. The data collected via MC-SIS are considered reliable by the cancer screening programs.

Our **primary endpoint** (non-inferiority of risk-based screening) is the diagnosis of advanced neoplasia of colon or rectum, defined as either of the following at the 3-year follow up. The advanced neoplasia is defined as:

- Adenoma > 1cm;
- Adenoma of any size with high-grade dysplasia;
- Adenoma with villous or tubulovillous histology (≥25% villous)
- Serrated lesion > 1cm;
- Serrated lesion of any size with high-grade dysplasia;
- Traditional serrated adenoma (any size) [23];
- Adenocarcinoma;

This outcome will be collected by means of MC-SIS, meaning that the clinical results of colonoscopies will be directly registered in MC-SIS.

We chose advanced neoplasia because the time frame is too short to capture CRC mortality and interval cancers would require too many participants as it is a rare outcome. Advanced neoplasia is a commonly used and valid surrogate endpoint in CRC-screening-trials: The greater the number of advanced neoplasia detected, the greater the number of cancers and cancer-deaths prevented [24]. This is because approximately 25% of advanced adenomas progress to cancer over 10 years [25], and most CRCs are believed to be clinically significant. A much smaller portion (~5%) of non-advanced adenomas are believed to progress to cancer and the detection of additional adenomas can lead to unnecessary colonoscopy surveillance.

Secondary endpoints

1. FIT completion among lower-risk participants (1-3% risk of CRC) who received a mailed FIT (Intervention 2) and lower-risk participants who did not receive a mailed FIT (Intervention 1) at 1-year follow-up: The number of completed FITs, collected via MC-SIS, will be used to assess this outcome. Among participants at lower risk, each completed FIT will be coded as 1. A completed colonoscopy will be coded as 0. Missing values (no record in the MC-SIS) will be considered as screening refusal and coded as 0 as well.

2. Colonoscopy completion among higher-risk (4-7% risk of CRC) participants offered navigation (Intervention 2) and among higher-risk patients not offered navigation (Intervention 1) at 1-year follow-up: The number of completed primary colonoscopies collected via MC-SIS will be used for this outcome. Among participant at higher risk, each completed primary colonoscopy will be coded as 1. No record in the MC-SIS or a completed FIT will be coded as 0. Participants who completed a secondary colonoscopy (after a positive FIT) will be excluded from the analysis.

3. Overall screening participation at 1-year follow-up: The number of completed FITs and primary colonoscopies will be used for calculating overall screening participation. This will be

the proportion of participants who agreed to participate in the trial and those who completed any screening test. A completed FIT or primary colonoscopy will be coded as 1. No record in the MC-SIS will be coded as 0. Secondary colonoscopies will not be considered for this outcome.

4. Overall screening participation between the Intervention arms 1 and 2 and the control arm, stratified by socioeconomic position at 1-year follow-up: This outcome will be calculated in the same way as overall screening participation. However, the comparison will be stratified by socioeconomic position using the Swiss-SEP in deciles to ensure that the effect of the intervention(s) on participation does not differ by socioeconomic position.

5. Number needed to scope (NNS) to detect one advanced neoplasia at 3-year follow-up: The NNS is the proportion of individuals who had ≥1 colonoscopy (primary or secondary) divided by the proportion who had an advanced neoplasia. The number of primary and secondary colonoscopies completed by the trial's participants will allow us to compare the proportion of who had a colonoscopy.

Baseline participants factors that may be associated with the primary endpoint

Parameters that will be collected from participants at recruitment include parameters necessary to:

- Identify eligible individuals: genetic risks or medical conditions that can cause a CRC, CRC symptoms, regular medical follow-up using colonoscopy, screening history.
- Calculate the CRC risk score: age, sex, height and weight, screening history, tobacco and alcohols consumption.
- Parameters known or hypothesized to affect screening uptake or choice of screening method: nationality, health literacy, education level, mastery of French or German, living alone or with others, intention for screening and preferences for a screening test, socioeconomic position.

These variables, summarized in Supplementary Table 1, will be compared between arms to ensure adequate randomization and allow stratified analyses of the primary and secondary outcomes.

The majority of these variables will be collected using the recruitment questionnaire. Socioeconomic position will be calculated using the Swiss neighborhood index of socioeconomic position (Swiss-SEP 3) [26]. The Swiss-SEP is a database allowing calculating neighborhood index based on income, education, occupation, and number of people living in a household. An R script will be used to calculate the socioeconomic position from the participants' address.

3.3. Study design, randomization and blinding

Study design

This is a multicenter, parallel group, non-inferiority randomized controlled trial with blinded participants. The investigators, screening centers and the trial statistician will not be blinded.

The trial will include five screening centers, two coordinating centers and three study partners:

- Sponsor-Investigator center: Unisanté.
- Study screening centers: Organized screening programs in the cantons of Geneva, Vaud, Fribourg, Bern, and Basel-City/Basel-Country.
- Lausanne and Basel coordinating centers: Lausanne coordinating center will coordinate screening centers in the cantons of Geneva, Vaud and Fribourg; Basel coordinating center will coordinate screening center in the cantons of Bern and Basel.

- Study partners: University of Zurich, University of Basel, and Erasmus University Medical Center. Study partners will carry out sub-studies on cost-effectiveness and process evaluation.

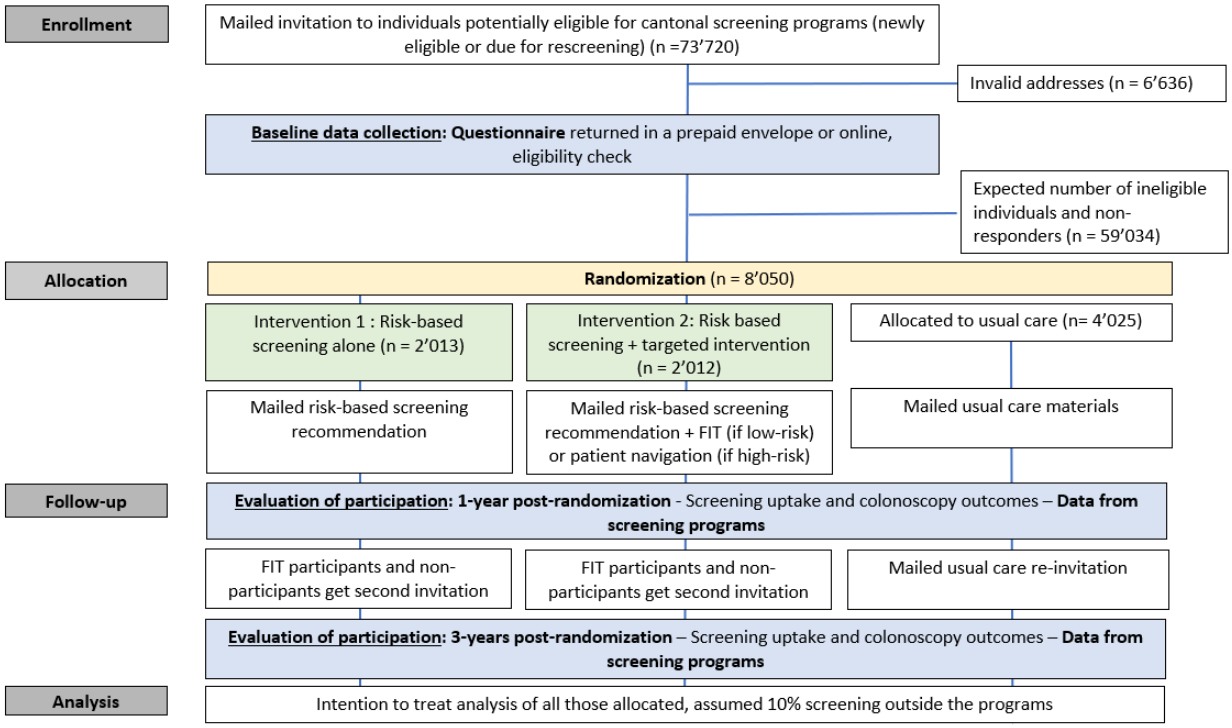
Randomization

Randomization will be stratified by cantonal program and risk level. A block randomization strategy will be applied within each stratum with a varying block size of 4 or 8 to prevent predictability in the group assignment and ensure approximately equal number of participants in each group in each stratum. The trial statistician will calculate a randomization plan and program the REDCap randomization module.

Participants will be randomized into 3 arms (control, Intervention 1, Intervention 2) with allocation ratio 2:1:1 (see Figure 1).

Randomization will be completed by clicking on the button “Randomize” in REDCap. Once a randomization arm has been assigned to a participant, it cannot be changed.

Figure 1. Planned CONSORT



Blinding

Study participants will be blinded, but not the screening centers, trial statistician or investigators. Participants will be told that the trial compares two slightly varying brochures about CRC screening options without disclosing the nature of the intervention. According to the article 18 of the HRA, in exceptional cases, participants may be partially informed of certain aspects of a research project before it begins, if it is necessary for methodological reasons and the risks and constraints inherent in the research project are minimal. In this study, the risk of being partially informed is minimal for participants, as participants in both groups still have access to both screening tests available in their canton. Moreover, we don’t plan to inform the participants in the

control group a posteriori about their risk level to avoid that this information engenders confusion or anxiety.

The first-time invitees will not realize to which group they are randomized, as they are not familiar with the screening programs' documentation. Those who were previously invited for screening and who will be randomized into one of the intervention arms may notice that the mailed documentation changed. However, as programs may modify their information brochure for many different reasons, we don't expect that participants will be able to identify that they received our intervention. Finally, individuals who were previously invited and who are randomized into the control arm may notice that they receive the same documentation as previously and thus conclude that they are in the control arm. We should take this into consideration when interpreting our results. However, as they receive the invitation and the brochure once in two years (if previous test was FIT) or once in ten years (if it was colonoscopy), we expect that they would have vague memories of this documentation and would not be able to correctly identify to which arm they are randomized.

Research and screening centers' staff will not be blinded, as they will assign participants to groups, perform mailings and answer questions. One important bias related to the single-blind design is the potential for differential cointerventions and biased assessment of outcomes. However, the risk of these biases is low because the investigators will have few personal contacts with the participants and will communicate with them via letters and electronic messages designed before the beginning of the trial most of the time.

The statistician performing the primary outcome analyses will not be blinded to group assignments, as he develops the randomization plan. However, although the statistician is associated with the research team, he is not subordinate to the PI of the trial and doesn't have financial interests to confirm the study hypotheses.

Other potential biases

Differences between cantonal screening programs in how participants access screening tests will be carefully documented and tolerated. The most important differences are documented in Table 1.

Table 1: Primary means of screening test access in each participating screening program

Canton	Basel City/County	Bern	Fribourg	Geneva	Vaud
FIT	Initial: online order, GPs. Repeat: mailed.	Initial: online order, pharmacy, GPs. Repeat: mailed.	Initial & repeat: online order, pharmacy, GPs.	Initial: pharmacy, GPs. Repeat: mailed.	Initial & repeat: pharmacy, GPs.
Colonoscopy	Visit GP for referral.	Visit GP for referral.	Visit GP for referral.	Visit GP for referral.	Visit GP for referral.

Another source of concomitant care is from participants' GPs and pharmacists, who vary in their recommendations and preferred test. We will inform GPs and pharmacists about the study and risk-based approach to screening via their cantonal professional associations. Moreover, participants in the intervention arms will receive an information sheet explaining to GPs and

pharmacists the risk-based approach to screening and the patient's personal risk for CRC. Further, many participants could take their decision about the screening test and get FIT in pharmacies or on-line without a specific consultation.

Finally, the Vaud screening program mails a 1-page flyer promoting FIT and explaining how to obtain it and how to complete it at home. In this canton, we expect a higher preference for FIT among the participants in the control arm. This particularity of the Vaud screening program will be considered during data analyses and interpretation.

Quality control and patient and public involvement

The trial will be monitored by the monitoring teams of Unisanté and the Department of Clinical Research (DKF) of the University of Basel. The Unisanté monitoring team is a monitoring coordinator who will monitor the coordinating center in Lausanne and the screening programs in French-speaking cantons. DKF will monitor the coordinating center in Basel and the programs of the German-speaking cantons.

The Steering Committee of the trial includes epidemiologists, gastroenterologists, psychologists, and a general practitioner from Switzerland, the Netherlands, and the US. The directors of the involved screening programs are also part of the Steering Committee.

A citizen advisory group of five women and men, who speak French, German, and English and are aged between 45 and 69 years participate in the co-development of documents for study participants and the study procedure. One of them is also part of the Steering Committee. The citizen advisory group will also participate in the procedure testing (for instance, test the feasibility of connection to the study website and the REDCap, test the online consent and questionnaire). One member of the group will be available to respond to the participants' questions about her experience related to cancer screening. At the end of the study, the group will be invited to give its feedback on the study results.

3.4. Study intervention

Choice of comparators

We will compare risk-based CRC screening recommendations to the standard screening invitations used by the participating screening programs, which offers a choice between FIT and colonoscopy. Standard screening invitations are an appropriate comparator because, while invitations vary between the programs, they result in approximately 50% of participants receiving FIT and 50% colonoscopy across screening programs, with little difference based on age and sex [27]. Standard invitations are an active control, as participants will nonetheless receive carefully conceived and established materials based on consensus documents from Swiss cancer screening encouraging them to participate in CRC screening.

CRC risk calculation

CRC risk will be calculated using the QCancer-colorectal 15-year risk score calculator [13], augmented to include previous quantitative FIT results and screening status. This open-source tool developed and validated in the United Kingdom assigns individuals aged 40 to 69 years old to the correct risk group 66-70% of the time, which ranks QCancer among tools with the highest discriminative power [13-16]. The QCancer score uses risk factors such as age, sex, several life-style factors, and pre-existing diseases to predict an individual's 15-year risk of CRC. To increase its predictive power, previous screening participation will be included in risk prediction, as this is associated with a lower risk of CRC. Moreover, for participants who had a negative FIT test before, the fecal hemoglobin concentration value of this test will be included in risk prediction [17]. During the consent process, participants will be informed that their screening history will be

requested from the screening program of their canton. The obtained score will be dichotomizedusing the cut-off of 4%, which will allow us to assign participants to low-risk group (1-3%) or high-risk group (4-7%).

All individuals with a strong family history (i.e. one first-degree relative diagnosed ≤60 years-old or two first-degree relatives at any age) will be considered as being at high risk and will receive recommendations to complete a colonoscopy [28].

Based on the pilot study and modelling results, we expect ~12% of participants to be at high risk based on their QCancer result alone and 2% because they have a high-risk family history. A further 6% will be judged high-risk because of their QCancer score enhanced with fecal hemoglobin concentration result, either due to a FIT before the trial, during the first round of screening, or due to increasing age between screening rounds. As such, over two rounds of screening, approximately 20% of participants allocated to risk-based screening will receive a recommendation for screening colonoscopy. We will not enquire about changes in behaviors or family history prior to the second round of screening.

Intervention

The intervention aims at communicating to participants their risk for CRC and orient them towards the risk-appropriate screening test (see Figure 1).

The intervention brochure is built on our pilot trial brochure which was co-created with a citizen advisory group, then evaluated with a series of 12 qualitative interviews and a short questionnaire [29]. This brochure was deemed usable and acceptable by pilot trial participants. The intervention brochure is written in plain language, includes a graphical display of CRC risk, and is available in French, German and English.

Intervention 1: Risk-based screening recommendations alone

Our mailed information materials will communicate to each participant their 15-year CRC risk category (based on QCancer score) and corresponding screening recommendations. Participants at higher risk (4-7% risk) will receive recommendations for colonoscopy and those at lower risk (1-3% risk) will receive recommendations for FIT. This is justified because FIT provides similar decreases in CRC mortality as colonoscopy over multiple rounds of screening among participants at lower risk. However, colonoscopy is appropriate for higher-risk individuals, despite being more burdensome, because of its higher sensitivity [30]. Those at very high risk due to symptoms or conditions are excluded from the study. People at very high risk cannot participate in organized screening in Switzerland and are followed by their physician.

Intervention 2: Interventions to enhance screening participation

In addition to risk-based screening recommendations, this group will receive mailed FIT (if at lower risk) or participant navigation for colonoscopy (if at higher risk), strategies that have been shown in other settings to increase participation in screening [31, 32].

a. Mailed FIT kits. Participants at lower risk will receive a mailed FIT kit at home. The FIT kit is likely to facilitate FIT completion by avoiding additional steps, such as ordering the test online, obtaining it in a pharmacy, or discussing the FIT with a general practitioner.

   Each canton has its own FIT instructions and pre-paid return envelopes towards a central lab. The screening centers in Vaud and Geneva, will mail FIT kits with the invitation to screening to the participants at lower risk randomized to the Intervention 2. In Bern and Basel, FIT are mailed directly by partner laboratories of the organized screening programs. Therefore, the Basel coordinating center will collaborate with these laboratories to ensure that study participants receive FIT kits at home a few days after the invitation for screening. If the control group participants are eligible to receive a FIT kit, they will receive it according to the routine process of the corresponding screening site. The

Fribourg screening center is unable to process mailed FIT kits and will not offer this intervention.

b. Participant navigation. The participants at higher risk who have not been included for a colonoscopy at 4 months after the intervention will receive a navigation phone call from a trained screening center staff member. The staff member will enquire about any steps the participant has already taken towards getting a colonoscopy (i.e. meeting their primary care physician or getting an appointment). If no steps have been completed, the staff member will explore potential barriers to getting a colonoscopy, both at the individual and structural level. Individual barriers include misunderstanding the indications for screening, or fear of colonoscopy preparation and the procedure. Structural barriers include finding a primary care doctor and getting information in a language they can understand. Staff will offer 1 or 2 follow-up calls to see how the participant is progressing.

   Bern and Basel screening centers cannot see inclusions for colonoscopy, only the information about a completed test is available for them.

   The Geneva screening center generally mails FIT kits with reinvitations to screening. During the study invitation period, FIT kits will not be mailed to the reinvited participants to whom colonoscopy is recommended. However, if a participant refuses colonoscopy and requests a FIT, a FIT kit will be mailed and patient navigation for colonoscopy will not be delivered.

   We will use the approach proposed by Kaiser Permanente [33]. Screening centers' staff members will receive a one-day course that includes role-playing and standard scripts explaining how to provide reminders to participants, as well as how to communicate basic information about CRC screening and explain the access options to screening in each canton [34]. We will build on the experience screening programs have verifying that participants with positive FIT have access to colonoscopy. Senior program staff, including practicing physicians, will be available in case of questions.

Control arm: Usual care materials

Participants of the control arm will receive standard invitations for screening and the brochure currently used by the screening programs. Control materials of all participating programs except for Vaud contain information about benefits and risks related to both tests and instructions on how to undertake FIT at home or how to prepare one's bowel for colonoscopy. These two tests are presented as equal options. Control materials do not include either personalized risk score or screening recommendations. The participants in the control arm will thus have no reference helping them to choose the screening test appropriate to their CRC risk. This suggests that in the control arm the screening tests will be chosen rather by provider or patient preferences than in accordance with the participant's risk level.

The Vaud screening program mails a 1-page flyer promoting FIT and explaining how to obtain it and how to complete it at home. The flyer does not contain personal risk for CRC. FIT is recommended to all eligible participants regardless their CRC risk.

4. STUDY POPULATION AND STUDY PROCEDURES

4.1. Inclusion and exclusion criteria, justification of study population

Recruitment will be conducted by the screening programs involved in the trial. We will use the same eligibility criteria as the recruiting screening programs.

Our inclusion criteria are:

- being aged between 50 and 74 years old;
- being a resident of a canton, whose screening program is recruiting for the trial;

- having provided informed consent.

Additional criterion for Geneva and Vaud screening centers: people living at the French border who currently work or worked in the past in Geneva or Vaud cantons and have a Swiss health insurance or a health insurance of several international organizations based in Geneva.

People at very high risk of CRC or already up to date with screening are excluded. Specifically, those:

- With current symptoms suspicious for colorectal cancer (i.e. rectal bleeding, unusual weight loss, etc.);
- With a medical condition requiring colonoscopy surveillance at a shorter interval than the 10-year interval approved for screening (for example, personal history of CRC, advanced adenoma or inflammatory bowel disease);
- Having done colonoscopy within 9.5 years or having done FIT within 1.5 years. Participants will be mailed materials at least 10 years after their previous colonoscopy or 2 years after their previous FIT but can be recruited to the study during the period immediately prior.

Additional exclusion criteria for the Fribourg screening center: individuals with body mass index of 35 or over, as for them the risk/benefit ratio is very high if a colonoscopy is performed, thus FIT test is the first exam proposed by the Fribourg screening center.

An additional exclusion criterion for Bern and Basel-City/Basel-Country screening centers will be repeated FIT at the second round of screening. In Bern and Basel-City/Basel-Country screening centers, repeated FIT is mailed by the partner laboratories and important technical and procedural modification to their routine work are needed to cancel the programmed mailing of repeated FITs.

In this study we will work with sex as defined administratively in Switzerland (male/female). To ensure sex balance between the intervention and the control arms, a randomization stratified by sex will be applied. Based on our pilot trial, which final sample included 51% of women and 49% of men, we expect to achieve similar participation among both sexes. However, as recruitment will be conducted using mailed invitations, we will not be able to ensure sex balance.

4.2. Recruitment, screening and informed consent procedure

Recruitment plan

Recruitment will be conducted by the screening centers of the cantons of Geneva, Vaud, Bern, Basel-City/Basel-Country, and Fribourg. Potentially eligible participants will be identified in each screening center's database (using MC-SIS), which draw from cantonal registers with all inhabitants aged 50 to 69 years. Due to changes in the federal law for basic insurance effective July 1, 2025, they may soon begin inviting people aged 70 to 74 years. Each program will draw a sample of people who have not yet been invited or are due for screening in 2025 or 2026.

Residents are newly eligible for screening because they:

- Have not yet had been invited because they live in a canton that has not completed inviting all their population in 2025 (Bern and Basel-Country/Basel-City),
- Have recently arrived in the canton,
- Have recently turned 50.

Residents can be due for screening because they completed a FIT within the program ≥ 1.5 years prior or having done a colonoscopy ≥9.5 years prior. Only the Vaud program will reinvite colonoscopy participants in 2025, having begun including participants in 2015.

Based on pilot data, we estimate we need 73'720 initial invitations. After selection of potential participants, the screening programs will assign to each of them a unique study identifier (study ID) previously generated by the coordinating center in Lausanne.

The screening center of the canton of Vaud will print invitations in-house, whereas the other screening centers will use their usual outside mail services to print and mail invitations. To optimize the recruitment process, it is planned to mail as many invitations as possible within 3 months; this period may be extended until 8 months if needed. Non-respondents will receive a reminder (a postal letter) six weeks (±2 weeks) after the invitation. There will be a break during the Christmas period and the invitations and reminders will not be mailed between the 17th December 2025 and the 5th January 2026. Participants can take up to 10 weeks after the invitation to consider participating and respond. For practical reasons, responses after that period will not be included in the study and these individuals will receive a standard invitation to screening. Potential participants who are ineligible for the trial are generally also ineligible for the screening program. They will receive an information letter (by email or a postal letter) suggesting they discuss their screening or diagnostic options with their GP.

Non-responders will be identified by cross-referencing data from MC-SIS and REDCap. The participants' study IDs and the date of the invitation to the trial will be entered into MC-SIS, and the participants responses to the informed consent and the questionnaire will be entered to the REDCap. Once a week, the coordinating center in Lausanne will extract the IDs of the individuals who have responded to the invitation from REDCap and transfer them to the screening centers. The trained screening centers' staff will upload this data into MC-SIS and thus will be able to identify non-respondents (see Supplementary Figure 1 for data flow).

The invitation to the trial will include:

- An invitation letter with the participant's study ID,
- A QR code allowing the access to study information, online consent form and the recruitment questionnaire programmed in REDCap (a paper version of the study information, consent form and questionnaire will only be mailed on demand for ecological reasons), and
- A flyer summarizing key information about the study (study summary).

For more information about documents provided to participants at each phase of the trial, see Supplementary Table 2.

Informed consent procedure

When mailing the invitations, we will promote the online consent and questionnaire in REDCap. To facilitate access to REDCap, a user-friendly interface available in three languages (French, German and English) will be created by the Unisanté information technology team. To access online documentation, participants will be asked to enter their study ID and their year of birth. This participant identification system will prevent potential participants from entering the wrong study ID. If their individually assigned study ID does not correspond with their year of birth, an error message will be displayed. This system will also prevent the participation of non-invited individuals in the study.

When developing user-friendly interface, the coordinating center in Lausanne will request a list of the study IDs with the corresponding year of birth of all potential participants from the screening programs. This information will be shared before the participants consent for the trial. This procedure is necessary to improve the quality of data collection. Moreover, year of birth alone is insufficient to identify potential participants given the number of invitations mailed each month.

The study materials will be written in plain language and reviewed by a citizen advisory group to ensure that the materials are easy to understand for an average person and include all important information for making an informed decision. Thus, the materials will explain the nature of the trial, its purpose, the procedures, expected duration, potential risks and benefits and any discomfort it may entail. Contact information of the recruiting screening programs as well as the coordinating centers in Lausanne and Basel will also be provided. Trained staff members will be available to respond to any questions the potential participants may have. As in this trial

information for participants, consent, and recruitment questionnaire will not be mailed with the invitation letter, study staff will provide assistance by telephone hotline for individuals who have difficulty accessing the documents online. Our research team has tested such procedure in a pilot project on the lung cancer screening that was conducted in 2024 in Vaud on the population of the same age (50-69 years old). About 2/3 of participants of this pilot project were able to access the online documents without assistance from the research team. The others completed paper questionnaires mailed on request.

Participants interested in taking part in the study will be asked to give their paper or online consent. In the paper consent, participants will be asked to sign and date the form and to return it to the coordinating centers in Lausanne or Basel (depending on their language) using the pre-paid return envelope. In the online version, they will be asked to confirm their agreement by clicking on the “Yes/No” button. Participants will have the possibility to download the completed consent from REDCap in a PDF format. The consent form (either paper or online) will be retained as part of the study records and will be kept for 20 years after the termination of the trial at the corresponding coordinating center.

The formal consent of a participant, using the approved consent form, will be obtained before the participant is submitted to any study procedure. Participants will be informed that their medical records may be examined by authorized individuals other than their treating physician. Further, each participant will be informed that participation in the study is voluntary and that they may withdraw from the study at any time. They will also be informed that screening uptake is not mandatory, and that withdrawal of consent will not affect their subsequent participation in organized screening.

Participants who accept to participate in the study will be asked to directly complete the recruitment questionnaire. The questionnaire will be designed in such a way that individuals ineligible for the study will not have to respond to all the questions. Individuals who are at particularly high risk for CRC will be advised to discuss with their family doctor or a participating pharmacist if they have no doctor. See details in the schedule of assessments (Supplementary Table 3).

The identifying information collected during the consent process and using the recruitment questionnaire will be stored in a separate project in REDCap labeled “Identifying data”. This information will be used to recontact the participants, for instance for mailing the invitations for screening and the intervention/control materials.

4.3. Study procedures

Participants’ eligibility will be assessed using their answers to the recruitment questionnaire. Eligibility will be calculated automatically using a programming code integrated into REDCap. The results of the eligibility evaluation and the reasons for ineligibility will be shown in specific fields (see eCRFs, administrative data). Eligible individuals will be invited to screening within the trial. Ineligible individuals will be informed as such immediately after completing the recruitment questionnaire. Ineligible individuals will also receive a message by email (or a postal letter if their email is unknown) from the Lausanne or Basel coordinating center (depending on their language) explaining the reason of their exclusion from the study and suggesting discussing their symptoms or screening options with their doctor.

For all eligible participants, their CRC risk score will be automatically calculated using the QCancer algorithm integrated into REDCap. The calculated CRC risk score will automatically appear in a specific field in the admin data (see eCRFs). The CRC risk level (lower or higher risk) will also be automatically identified from the QCancer score and recorded in the admin data. Then, participants will be randomized on an ongoing basis using the REDCap randomization module previously programmed by the trial statistician. Thus, participants will be randomized to the control arm, to Intervention 1 (risk-based recommendations alone) or Intervention 2 (risk-based recommendations + mailed FIT or patient navigation) (Figure 2). Study participants will receive

the intervention or control materials from their screening program within four weeks after the completion of the recruitment questionnaire, or as soon as they are eligible (for those about to turn 50 years old or have 2 years since their last FIT). First, the invitations to screening will be generated via MC-SIS and the date when the letter was generated will be communicated to the Lausanne coordinating center.

The Unisanté coordinating center will import the date invitation to screening letter was generated into REDCap. The 3-year follow-up starts individually for each participant on the date of letter generation in MC-SIS.

The staff members at screening and coordinating centers will be trained to export and import data. In case of difficulties, a member of the Unisanté IT-team will be available to assist on this procedure. Data import will be conducted using the unique study identifiers (study IDs) assigned to each participant via MC-SIS before recruitment. Data import using unique study identifiers is an automated process that prevents human errors and ensures accurate data uploading. Shared data will not contain participants' identifying information. The data shared during the recruitment period (such as invitations dates, eligibility, or group allocation), will be transferred by professional email. The follow-up data containing more sensitive information will be transferred using a secured system, such as FileCare.

Three months (±2 weeks) after randomization, the screening centers will check in MC-SIS whether participants completed a FIT or are included for colonoscopy (Bern and Basel can only have information about completed colonoscopies). Those who have not taken any action will receive a reminder. All reminders will be mailed by the screening programs and dates imported in REDCap by coordinating site staff.

Four months post-randomization, participants at higher risk who have not been included for colonoscopy will be contacted for patient navigation. These participants will be identified using MC-SIS. Navigators will be staff members of the screening centers who will be trained by the Lausanne coordinating center on the navigation procedure. The navigator will explore potential barriers to screening and suggest solutions to getting a colonoscopy; if the participant refuses colonoscopy but accepts FIT, a FIT kit will be mailed.

The navigator will make up to 4 telephone attempts at different times of day. Non-responders to the 1st call will receive an email containing the purpose of the call and a demand to contact the research team. In case of non-response after the 4th call, the navigator will leave a voice message referring to the email previously sent and another demand to contact the research team for navigation.

Two years post-randomization, the participants eligible for FIT will be re-invited for the second round of screening. Participants will become eligible for the 2nd round of screening 2 years after having a previous negative FIT. Those not having completed any screening test will also be reinvited (the date of their eligibility for screening will be defined as 2 years after the invitation to the 1st round of screening). Participants after a positive FIT will also be reinvited if they have not completed colonoscopy, as this reflects current practices of the programs.

Participant risk scores and risk levels will be recalculated by adjusting for their age and the results of their previous FIT, if available. The risk score and the risk level will be estimated automatically using a specific script integrated into REDCap. The results of these estimations will be shown in a specific folders (see eCRFs). It is possible that several participants will become at higher risk for CRC because of increasing age or fecal hemoglobin concentration in their previous FIT. All participants in Intervention 1 and Intervention 2 arms will receive the screening recommendations according to their risk level. Differences in the routine work of each screening center will be carefully identified and documented in a separate document. Next, a detailed procedure for each screening center will be developed in order to allow the screening centers to keep as closely as possible their routine work.

All test information and clinical outcomes will be collected by the screening centers using routine processes. However, given the potential for opportunistic screening, we will ask a random, 10%

subsample of low-risk and 20% subsample of high-risk participants to complete a brief questionnaire about screening tests done outside of the screening programs. This questionnaire will be administrated via REDCap or mailed by post at 34-month post-randomization (± 2 months). If a participant had a colonoscopy, we would request permission to obtain the colonoscopy report from their doctor.

An additional optional consent form will be collected from participants to follow them for an additional 15 years after randomization in the cancer registry of their canton, that is until 2040. In order to automatize the search of the participants in the registry database, the participants' old-age and survivor's insurance (OASI) number will be required. The OASI number will be asked only to those who accepted the follow-up in the tumor registry and will be stored in the REDCap module "Identifying information". Participants are free to provide us or not with their OASI number.

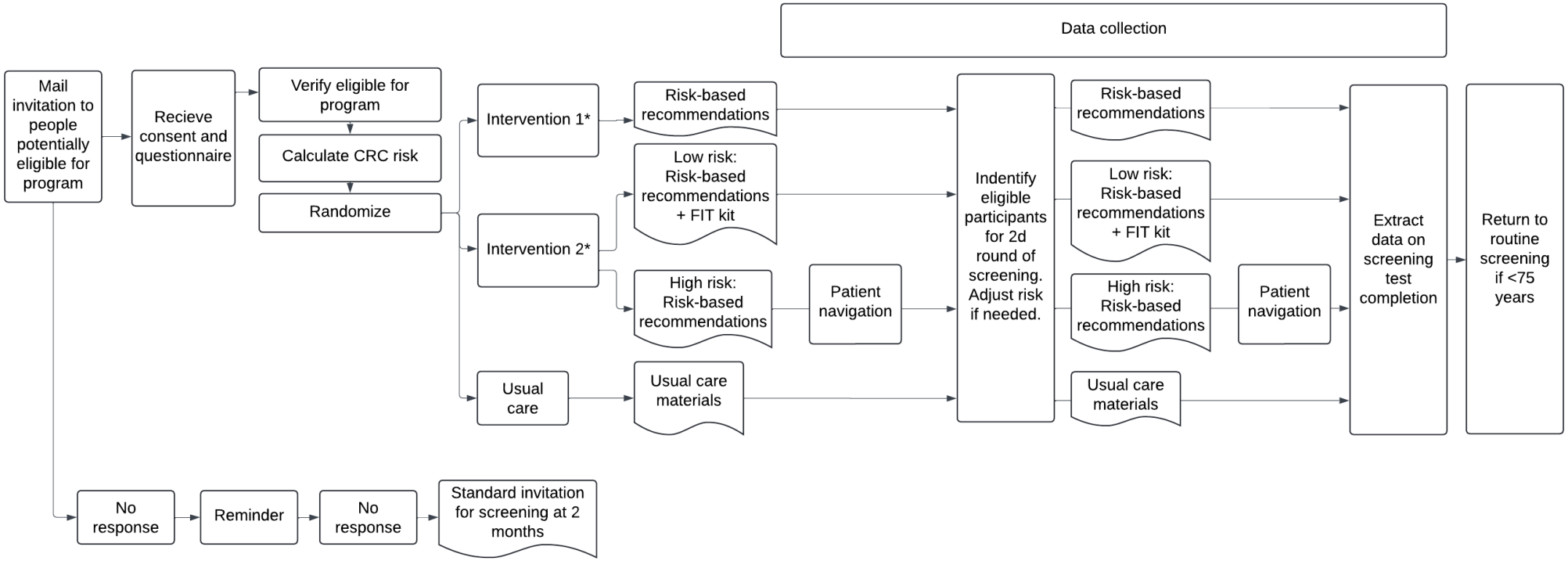


Figure 2. Detailed procedure of the trial.

* Intervention 1: Brochure containing the participant's CRC risk and recommendations for screening.

Intervention 2: Brochure containing the participant's CRC risk and recommendations for screening mailed along with a FIT kit (for participants at low risk) or patient navigation for colonoscopy (for those at high risk).

Potential biases

As for potential biases, it is possible that we will mostly recruit the individuals who are particularly interested in CRC screening and prevention (selection bias) and that participation rates will be low. People in poor health, disadvantaged populations, and individuals with poor health literacy are expected to be less likely to participate in the study. To deal with these biases we intend to use the following strategies:

- Explain the importance of screening;
- Write study materials in plain language to increase participation of people with poor French or German skills;
- Offer documentation in English;
- Insert the logos of Unisanté, the University of Basel in Basel cantons, and the Screening Programs on the envelope and in the study documents;
- Explain how confidential data will be protected and safely shared;
- Maintain telephone hotlines in German and French for people not comfortable with going online;
- Offer a choice between printed and on-line questionnaires;
- Sending reminders to non-responders.

4.4. Withdrawal and discontinuation

Participants can stop their participation at any time without providing any justification. They can inform the screening program of their canton or the coordinating centers in Lausanne or Basel about their decision to withdraw by sending an email or by calling the telephone number provided in the materials for participants.

If a participant withdraws his or her consent, all collected data until withdrawal date will be kept in a coded form and analyzed. If a withdrawing participant requests complete destruction of his or her data collected up-to-date, all these data will be removed from the REDCap.

No participant replacement will be done as 10% loss to follow-up is already included in the power calculation.

5. STATISTICAL ANALYSIS PLAN AND SAMPLE SIZE CALCULATION

5.1. Statistical analysis plan and sample size calculation

Sample size. The sample size was calculated for the primary objective. Intervention arms 1 and 2 will be combined for the comparison of risk-based screening to usual care (control). This is justified because the proportion of participants with an advanced neoplasia is expected to be similar between the two intervention groups; while mailed FIT is expected to increase FIT participation, it is also expected to lower colonoscopy use among low-risk participants. Overall, we anticipate 80% of individuals will be at lower risk of CRC and 20% at higher risk. Based on data from the Vaud screening program, 6% of individuals at lower risk and 14% of those at higher risk have advanced neoplasia (weighted average 7.5%) [10]. Moreover, based on the data from our pilot study, we assume that in the Intervention arm 1, 42% of individuals at lower risk will choose FIT (+14% from control group) versus 14% colonoscopy (-15% from control); 38% of those at higher risk will choose a colonoscopy (+10%) versus 18% FIT (-10%). In Intervention arm 2, 52% of those at lower risk will choose FIT and 48% of those at higher risk colonoscopy, which will increase overall participation but maintain a similar rate of advanced neoplasia detection. With these assumptions and considering a sensitivity of 95% and 50% for colonoscopy and 2 rounds of FIT, respectively, we anticipate that 3.15% of participants will have an advanced neoplasia within 3 years of follow-up, irrespective of the group. With 7,244 participants we have 80% power to exclude a difference in favor of the standard group of more than 1.15% (relative decrease of 37%) based on the upper limit of a one-sided 97.5% confidence interval. Assuming

10% of screening occurs outside of the organized program (missing data), we need 8,050 participants at the start of the trial. Assuming 12% of those receiving an invitation are eligible and sign a consent, we need 67,084 invitations. With 9% of addresses being invalid, we need to send out 73'720 invitations.

Moreover, we will evaluate the impact of the intervention aiming at enhancing participation in screening (mailed FIT and participant navigation for colonoscopy).

We expect that about 55% of participants receiving a risk-based recommendation alone will have completed a screening test (FIT or colonoscopy) 12 months after randomization, with similar overall participation between higher and lower risk. Based on our pilot data, we assume that after risk-based recommendations alone, 42% of participants at lower risk will choose FIT versus 14% colonoscopy, while 38% of those at higher risk will choose a colonoscopy versus 18% FIT (Intervention 1).

The low-risker participants will be mailed FIT. Results of randomized trials (where intervention was mailed FIT and control group was inactive) have shown an increase in FIT completion by 21% to 28% (RR 2.26 to 2.8) [31, 35] after intervention. In our trial, we expect a lower absolute increase because of our active control arm. With an alpha of 0.05, we expect to have >90% power to detect a 10-percentage point increase (RR 1.23).

The higher-risk participants will receive a patient navigation for colonoscopy. Randomized trials have shown an increase in colonoscopy uptake by as much as 18% (RR 2.01) [31] after a barriers-oriented intervention delivered by telephone. We expect to have 80% power to detect a 10-percentage point increase in colonoscopy completion (RR 1.26).

Statistical methods

For primary and secondary outcomes

The primary outcome (the proportion of participants with advanced neoplasia) will be compared using the Mantel-Haenszel estimator for the risk difference. Adjusted analyses on the primary outcome will be carried out using logistic regression. The secondary outcomes will be calculated separately for lower-risk (proportion completing FIT) and higher-risk participants (proportion completing colonoscopy) and analyzed using a similar model. All models will be controlled for the screening center (i.e. fixed center effects) and risk level, as our randomization is stratified by these factors. Data analysis will be performed using R statistical software [36] and/or Stata 18 software [37].

Baseline participant characteristics will be summarized across all participants by randomization arm and by risk level. Continuous and count variables will be summarized as mean (SD) or median (IQR) and categorical variables as number (percentage). Quality of the randomization will be assessed by examining the balance of baseline covariates in the different groups using standardized mean differences.

Secondary outcomes will be compared between randomization groups depending on the variable type. Treatment and analysis of cancer screening centers data, as well as production of secondary outcomes 1 to 5 will be performed by our experienced study epidemiologists.

For additional analyses

We are planning to perform stratified analyses of the primary outcome and secondary outcomes of participation by socio-economic position by deciles of the Swiss SEP-3 [26]. Other subgroup analyses will be descriptive only. Many typical subgroups are correlated with CRC risk and prevalence of advanced neoplasia. For instance, older age groups are at higher risk, more likely to be recommended colonoscopy and have advanced neoplasia. As such, the intervention will likely be superior to usual care among older participants and inferior for younger participants. Data for subgroups will be presented based on baseline regional characteristics (German- vs French-speaking, canton, and urban vs rural) and individual characteristics (sex, age group,

family history of CRC, and baseline screening preferences). We plan to perform sensitivity analyses such as: 1) a time-to-diagnosis of advanced neoplasia analysis incorporating competing risks such as death or becoming ineligible for screening and 2) using results about opportunistic screening from the random 10% sample to estimate the impact of opportunistic screening (see section 5.2).

Any deviation from the original statistical plan will be described and justified in the final trial report.

Interim analysis and stopping rules

Our recruitment period will last for up to 8 months and the intervention will be performed just after randomization. As such, our first data collection will take place after the end of recruitment and having given the main intervention. An interim analysis would therefore not stop recruitment early, nor would it prevent participants from receiving the intervention. We do plan to compare participation outcomes between intervention group 1 to intervention group 2 after 1-year follow-up. This analysis will not include a comparison with the control group, and we do not plan any rules for premature stopping.

5.2. Handling of missing data and drop-outs

We will perform intention-to-treat analyses including all participants who are randomized. There are no planned per-protocol analyses because we are not collecting individual data about the receipt of or actually reading written materials.

All individual-level follow-up will depend on routinely collected results of FIT and colonoscopies by the 5 screening centers. In our pilot study we had 91% follow-up of self-reported screening test completion using mailed questionnaires. Linkage with clinical data from the Vaud screening program provided more complete follow-up as it corroborated >95% of self-reported tests (little opportunistic screening) and 5% more tests among non-responders. All invitations and study materials will use the logos and letterheads of individual screening programs, and all instructions will encourage screening completion. We expect >90% of tests to happen in the organized programs. We expect few withdrawals as follow-up will be done passively (data will be collected using MC-SIS).

Opportunistic screening, notably colonoscopies performed outside of the screening, are thus a source of missing data. We will not know which individuals have colonoscopies done outside the program, except if the programs themselves actively seek this information (as done after positive FIT, for example). As such, we will collect self-reported screening information and colonoscopy reports from a random 10% sample at the 3-year mark. If opportunistic screening occurs differentially between study arms, a sensitivity analysis will be employed incorporating opportunistic colonoscopy outcomes into the model for the primary outcome.

6. SUB-PROJECTS

6.1. Cost-effectiveness evaluation study

Aim: Assess whether risk-based CRC screening, with or without an additional intervention to enhance participation, is cost-effective compared to usual care (standard screening invitation).

Specific objectives and hypotheses:

1. Objective: to evaluate the cost-effectiveness of risk-based screening compared to usual care. Cost-effectiveness will be measured in terms of costs per quality adjusted life year (QALY) gained. Health economic assessment will be within-trial with a time horizon equivalent to the trial observation period, and beyond trial with a lifetime horizon.

   Hypothesis: we expect that risk-based screening recommendations will decrease the cost

of screening with minimal loss in clinical effectiveness, resulting in improved cost-effectiveness compared to current screening practices.

2. Objective: to obtain current resource use and cost estimates for all important steps in the colorectal cancer lifecycle in Switzerland.

   Hypothesis: we expect that risk-based screening will decrease the overall costs of screening.

3. Objective: to estimate the average costs and QALY gained per study participants according to the different screening strategies (CRC risk and screening recommendations alone, CRC risk and screening recommendations along with mailed FIT or patient navigation, standard materials).

   Hypothesis: we expect that the intervention aiming to enhance participation will increase costs and QALY's gained as compared to risk-based screening recommendations alone, with an acceptable incremental cost-effectiveness ratio.

4. Objective: to obtain estimates for the environmental impact (carbon footprint) of all important steps in the CRC lifecycle.

   Hypothesis: we expect that risk-based screening will have a lower environmental impact than the current approach to screening in Switzerland.

5. Objective: to obtain baseline estimates concerning health-related quality of life of Swiss patients undergoing FIT or colonoscopy.

   No formal hypothesis was made. However, for the analyses it is important to have base case values for the Swiss population (instead of using international estimations).

6. Exploratory objective: to investigate the impact of the new tariff system TARDOC compared to the tariff system TARMED.

   Comment: The tariff structure for outpatient medical services TARMED, in force since 2004, will be replaced as of 1 January 2026 by the new TARDOC single service tariff structure and a tariff structure with flat rates. The aim of the new system is to simplify and optimize the billing of outpatient consultation. Whether this will result in a decrease of the ambulant costs is unclear.

7. Exploratory objective: to investigate the productivity loss due to CRC screening.

   No formal hypothesis was made. The inclusion of indirect costs related to productivity loss will allow additional economic analyses using a societal perspective.

Primary and secondary endpoints

The primary endpoint for objectives 1, 3, and 5, is cost per QALY gained, from a Swiss healthcare system perspective (i.e. including only direct medical costs), of risk-based screening compared to usual care. Primary endpoints for objective 2 are resources used and their costs, while the endpoint for objective 5 is health related quality of life.

In addition to information related to healthcare utilization, we will also investigate the productivity loss related to CRC screening. This will allow additional analyses using a societal perspective. Therefore, information on working status, employment rate, workdays lost due to screening or CRC treatment will be collected.

The primary endpoint for the evaluation of the environmental impact of the investigated interventions will be the carbon emissions related to performed colonoscopies as well as carbon emissions due to travelling by patients to and from the treating physician/center.

Procedure

Data necessary for the health economic analyses include:

- Screening organization costs, including organization of screening programs (infrastructure, personnel) and patient invitation;
- Risk-based screening costs, including risk assessment, patient navigation, mails, phone calls;
- Pre-screening consultations;
- Screening costs, including the number of FIT, colonoscopy, FIT + colonoscopy;
- Number of visits to physicians related to CRC;
- Number of complications and hospitalization days due to colonoscopy (e.g., bleeding, perforation);
- Number of hospitalizations and length of stay due to CRC;
- CRC treatment costs;
- Quality of life of patients undergoing CRC screening;
- Productivity loss in terms of workdays lost due to screening or CRC treatment;
- Distance from patient home to treating physician/center.

Information on resource use in terms of screening organization, patient invitation, risk-assessment and patient navigation, number of screening tests, number of complications, and number of hospitalization will be collected from screening programs during follow-up (T_1 and T_2). All these information should be directly available from the screening programs and directly imported into REDCap.

Due to the design of the study, collecting the number of CRC-related physician visits on an individual level was not deemed feasible or of high importance. On the one hand, retrospective collection of data at T_1 (1 year after enrolment, i.e. covering a period of 12 months) and at T_2 (2 years after T_1, i.e. covering 24 months) may lead to significant recall bias and an additional burden on the study participants. On the other hand, after screening, we do not expect significant differences in the number of physician visits (i.e., we expect that most persons undergoing FIT/colonoscopy will have a similar number of visits). In the economic analyses, the estimated number of physician visits per patient per year will be based on the published literature. This estimate will be stratified according to the adopted screening test (FIT or colonoscopy) as well as according to the screening results (subjects with positive screening test results will presumably have more physician visits).

To estimate quality of life in terms of utilities, all participants will be asked to fill in the EQ-5D questionnaire (5-level version) at recruitment (T_{-1}). A sub-sample of participants (random, 10% subsample of low-risk and 20% subsample of high-risk participants) will fill-up the questionnaire also at follow-up (T_2). The EQ-5D-5L is a validated questionnaire that is used to calculate a health status utility score for use in health economic analyses [38, 39]. There are two components to the EQ-5D-5L: a five-item health state profile that assesses mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, as well as a visual analog scale (VAS) that measures health state. The EQ-5D-5L is designed to capture the patient's current health status and takes approximately 5 minutes to complete.

For cancer treatment costs, we aim to collaborate with one or more Swiss hospitals (not necessarily actively participating in this study), to collect enough information to estimate treatment costs by cancer stage in Switzerland, outside the main trial.

As for the number of the physician visits, collecting detailed information on the loss of work due to CRC screening and CRC treatment during the entire trial period was not deemed feasible. As consequence, in the economic analyses, the estimated number workdays lost per patient per year

will mainly be based on the published literature. Nevertheless, information on productivity loss as well as the potential physician visits and hospitalizations related to CRC screening and treatment over a period of 12 months will be collected in a random, 10% subsample of low-risk and 20% subsample of high-risk participants at follow-up (T_2).

As already mentioned, the environmental impact of the investigated interventions will focus on the carbon emissions related to performed colonoscopies as well as carbon emissions due to travelling by patients to and from the treating physician/center. For carbon emissions, published estimates will be applied. Information on travel distance will be available from screening program. The number of kilometers (Km) travelled will be multiplied with published estimates (i.e. CO2 emissions per Km). Consent to participate in this sub-study will be asked in parallel to the consent for the main study (see Section 4.2.). All data collected through patient questionnaire as well as data from screening programs will be entered/imported in REDCap.

Planned analyses

Quality of life will be measured for all participants at T_{-1}. This measure will serve as baseline values. EQ-5D scores will be calculated by applying the EQ-5D-5L valuation algorithms for France [40] and Germany [41] to the EQ-5D questionnaire responses. In addition, in a random, quality of life will also be assessed in a 10% subsample of low-risk and 20% subsample of high-risk participants at follow-up (T_2). Quality of life decrement due to CRC screening procedures and treatment will be based on the published literature.

Health economic assessment will be within-trial with a time horizon equivalent to the trial observation period, and beyond trial with a lifetime horizon. Within trial, health economic assessment will be based on the comparison of healthcare resource use, healthcare costs, and QALYs between intervention and comparator including all time points. These results will be reported as estimated between-group differences with 2-sided 95% confidence intervals. Cost-effectiveness will be measured in terms of costs per quality adjusted life year (QALY) gained. This means that cost and quality of life differences between study groups will be combined to calculate incremental cost-effectiveness ratios (ICERs). Considering that the within-trial economic analyses will also include estimations extracted from the published literature (e.g. for the quality of life decrement due to CRC), sensitivity analyses will be conducted to deal with parameter uncertainty.

The beyond trial, economic assessment will be based on the Microsimulation Screening Analysis (MISCAN) model developed at the Erasmus Medical Centre in Rotterdam [42]. This well-established model has been used to inform CRC screening guidelines in countries throughout the world [43], and to evaluate the potential of risk-based screening in various settings [44-46]. Sex-specific MISCAN models have previously been developed for Switzerland by adjusting the Dutch version of MISCAN-Colon following an approach previously validated for Italy, Finland and Slovenia [16, 47]. For this analysis, the primary outcomes of the trial (findings of screening and appropriate screening uptake), and cost and QoL estimates will be incorporated in the model. As such, the trial is extrapolated to obtain lifetime outcomes and cost-effectiveness of the two screening interventions and the current standard of care. Moreover, the model will be used to compare the trial interventions with other potential (risk-based) screening approaches that arise during the trial. The estimates of lifetime costs and QoL are discounted at a rate of 3%. Combined analysis of uncertainty in the ICER resulting from stochastic uncertainty of trial data and uncertainty in external parameters (unit costs) will be conducted and scenario analyses may be added to further assess the robustness of the results.

A Health economic analysis plan will be developed before trial closure. A test data extraction from the study database will be used as basis for its development.

6.2. Process evaluation study

Research questions

Based on an overarching aim of assessing to what degree planned trial interventions were implemented as intended, and how they were perceived by study stakeholders, the process evaluation will be guided by the following research questions (RQs) and sub-questions:

RQ1: Did the research team apply the risk screening process and offer implementation strategies as intended?

What were the perceived barriers and/or facilitators that research team members experienced in using these implementation strategies?

RQ2: Did organized CRC screening program staff offer implementation strategies as intended, in particular patient-navigation for higher-risk participants?

In what way were these two implementation strategies designed and applied across participating programs in the trial?

What were the perceived barriers and/or facilitators that program staff experienced in using these implementation strategies?

RQ3: How did program participants in the intervention group (both lower and higher risk) perceive the risk screening process, and the implementation strategies attached to their respective screening modality?

The Medical Research Council (MRC) process evaluation framework will guide the process evaluation [48], focusing on investigating context, implementation, and mechanisms of impact.

Furthermore, at the beginning of the project, currently planned for spring 2025, two online workshops will be conducted with the research team to develop a PRESENT-CRC program theory that transparently summarizes the key assumptions guiding the intervention and the chosen implementation strategies. This program theory will inform all research activities and later be updated into a final program theory describing the knowledge about risk-based cancer screening and its implementation gained through the trial.

Participants

The process evaluation will involve research team members, organized CRC screening program staff, and organized CRC screening program participants, as listed in Table 3, describing the planned data collection approach for the process evaluation, structured by research question.

Table 3: Process evaluation data collection

Actors	Research question	Method	Time point	Sample
Research team	Did the research team apply the risk screening process as intended?	(1) Quantitative admin data as available (TBD) (2) Individual interviews with relevant research team members	(1) End of year 3 (2) End of year 1 or early year 2 and end of year 3	(1) All relevant available admin data (2) 5-6 individual interviews per round = 10-12 interviews in total
	What were the perceived barriers and/or facilitators that research team members experienced in using these implementation strategies?			
Organized CRC screening program staff	Did organized CRC screening program staff offer implementation strategies to both intervention groups as intended, i.e., mailed FIT to low-risk participants, and patient-navigation for high-risk participants?	(1) Quantitative survey (2) Focus groups	(1) End of year 1; mid-year 2; and early year 3 (2) End of year 2	(1) Minimum 3-4 program staff per program, including patient navigators = 15-24 respondents per survey round (2) 5-6 focus groups; 1 per organized CRC screening program, with program teams being interviewed together; 3-4 participants in each focus group, including the patient navigator
	In what way were these two implementation strategies designed and applied across participating programs in the trial?			
	What were the perceived barriers and/or facilitators that program staff experienced in using these implementation strategies?			
Organized CRC screening program participants	How did program participants in the intervention group (both low and high risk) perceive the risk screening process, and the implementation strategies attached to their respective screening modality?	(1) Individual interviews	(1) End of year 3	(1) 6 participants per program, representing the different intervention conditions (standard brochure; mailed FIT; patient navigation)

Measures

Three types of measures will be used during data collection for the process evaluation:

- Administrative data, as outlined in Supplementary Table 1, will be reviewed to determine the degree to which risk-based screening procedures were followed as intended.
- The pragmatic Context Assessment (pCAT) Tool will be administered with organized CRC screening program staff in three rounds to elicit information about how they, locally, experience the use of implementation strategies (with a focus on patient navigation) and the determinants that influence their use, including potential mechanisms that promote their (un-)successful application.
- Semi-structured interview guides for interviews with
    - Research team members

      An MRC framework-informed semi-structured interview guide will be used in individual interviews to elicit information from research team members about how they experience the use of implementation strategies (with a focus on mailed FIT and patient navigation) and the determinants that influence their use, including potential mechanisms that promote their (un-)successful application.
    - Program participants

      A simplified version of an MRC framework-informed semi-structured interview guide will be used in individual interviews with trial participants to elicit information about how they experienced program participation, especially the exposure to the two implementation strategies, i.e., mailed FIT and patient navigation. A broad range of actors challenging and/or facilitating participants' program participation will be of interest, including those of a structural, practical, social, or personal nature.
- Focus group guide for focus groups to be held with CRC screening program staff

  An MRC framework-informed topic guide will be used in focus groups to deepen the information retrieved through the first two survey rounds (see measure (2) above) and further the process evaluation team's understanding of local experience with the use of implementation strategies (focused on mailed FIT and patient navigation) and the determinants that influence this use, including potential mechanisms that promote their (un-)successful application. The collective experience and perspective of team members will be brought into play to especially examine mechanisms of successful strategy use and program implementation.

Procedures

Research team members and members of organized CRC screening program teams (including, e.g., clinical and/or administrative program leads, administrative staff, patient navigators, expert advisors, etc.) will be invited to participate in interviews and focus groups at the beginning of the study using a standardized process evaluation information sheet and consent form.

Data collection among research team members

The theory of change workshop with the research team will be held in two rounds, one in person on location of the lead organization of this trial and one online. Both meetings will last 60-90 minutes and be documented using notes and other written materials.

Two rounds of individual interviews with research team members (n= 5-6 team members per round) will be scheduled as online interviews at the end of trial year 1 (or early year 2) and 3. The communication platform Zoom will be used to hold and audio record interviews, which will be transcribed verbatim for later analysis. Interviews will be held in English, French, or German.

Data collection among organized CRC screening program staff

The quantitative survey will be administered using RedCap. Minimum 3-4 consenting CRC screening program staff members per program will be invited to participate in a total of three screening rounds, to be scheduled for the end of trial year 1, mid-year 2, and early year 3. Respondents will be asked to respond to the survey within a three-week time window and receive three reminders: one to be sent one week post invitation, the second two weeks post, and the final reminder three days before the survey closes.

Near the end of trial year 2, consenting CRC screening program staff will be invited to attend an in-person focus group meeting to be held at the location of the respective CRC screening program. One meeting per program with 3-4 attendees per focus group will be held. Meetings will last 90-120 minutes and be facilitated by one member of the process evaluation team, supported by a note-taker. Focus group meetings will be audio-recorded and transcribed verbatim. Focus group meetings will be held in English, French, or German. Participants will not be compensated for their time.

Data collection among CRC screening program participants

CRC screening program participants will be asked at baseline if they are willing to participate in an interview. Unisanté will select the required number of participants according to the eligibility criteria previously described by the University of Zurich research team. Specific consent will be collected from each individual willing to participate in the interview by contacting the individual by phone or e-mail, presenting the purpose of the process evaluation, agreeing on a time for the interview, and obtaining consent (in writing for face-to-face interviews, orally for online interviews) at the beginning of the interview.

Purposeful sampling of participants for interviews will be used to ensure that, for each program, different program participation conditions (standard brochure, mailed FIT, patient navigation) and sociodemographics (e.g., sex, age, urban vs. rural residency, etc.) are represented.

Individual interviews with consenting participants will be scheduled at a time and location convenient to the interviewee, i.e., by phone, online, or in person. Interviews will be audio recorded using communication platforms such as Zoom or MS Teams or an audio recording device. Interviews will be scheduled for 45 minutes, and audio recordings will be transcribed verbatim. Interviews will be held in English, French, or German. Following completed interviews, interviewees will be mailed a 50 CHF gift card for Payot, Coop or Migros.

Data management and analysis

Qualitative data will be stored for ten years in password-protected folders that only members of the process evaluation team will have access to. Transcripts of individual interviews and focus group conversations will be de-identified and assigned a unique identifier from a list that will be stored separately and only be available to members of the process evaluation team.

De-identified transcripts and focus group notes will be analysed based on the framework method [49], with matrix output being the characteristic feature allowing the process evaluation team to discuss and validate findings with the wider research team and CRC screening program representatives. Quantitative survey results will be integrated into the analytical work as relevant.

Quantitative data will be collected using the survey software Unipark and stored on servers located in Germany, meeting the security requirements of the ISO 27001 standard for IT risk management. The data will be gathered electronically and stored for ten years.

Data analysis

The process evaluation will be guided by the Medical Research Council (MRC) guidance for complex interventions [48]. It will focus on investigating context, implementation, and mechanisms

of impact. It will be analyzed based on the framework method [44], with matrix output being the characteristic feature that will allow the process evaluation team to discuss findings with the wider research team.

7. REGULATORY ASPECTS AND SAFETY

7.1. Local regulations / Declaration of Helsinki

This study is conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP, the Human Research Act (HRA), as well as other locally relevant legal and regulatory requirements.

7.2. (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation participant which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavorable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (

SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect.

Causality assessment: Both Investigator (local or coordinating investigators) and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines and adapted to this trial). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	Description
Definitely	Temporal relationship or other proof of intervention cause
Probably	Temporal relationship No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out

Severity assessment: Both Investigator (local or coordinating investigators) and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe.

- Mild means the complication is tolerable,
- Moderate means it interferes with daily activities,
- Severe means it renders daily activities impossible.

We will not actively collect SAEs. Our intervention aims at optimizing CRC screening. We will measure the efficacy of our printed materials (brochure containing CRC risk score and appropriate screening recommendations) and the additional intervention to enhance participation (mailed FIT or participant navigation) and not the efficacy of a specific therapy or medication. Moreover, both screening tests recommended in our materials (colonoscopy and FIT) are already approved for use and recommended as standard of care in Switzerland. FITs are administered by all the screening programs involved in the trial and processed with stringent quality controls. Colonoscopies, both screening and diagnostic, are performed by licensed gastroenterologists who assume final responsibility for test indication and adverse events.

A possible adverse event linked to receiving the intervention is that participants at higher risk, in particular, could have an increase in anxiety after learning that they are at increased risk for CRC. We attempt to attenuate their anxiety by providing information on the best means of decreasing their risk (colonoscopy within an organized program) and a specific flyer to help communicate this information with their primary care physician. Participants will have the choice of informing, or not, their GP that they are at higher risk. As such, their risk status does not need to become part of their health record and considered when applying for supplemental health or life insurance. Moreover, participants at higher risk randomized to the additional intervention to enhance participation will receive a patient navigation phone call to help decrease barriers to colonoscopy. Further, all participants will be informed through information and consent process that they can contact the coordinating investigator and/or local investigator in their canton and ask questions.

It is important to note that a Cochrane review of interventions providing screening participants their personal risk did not increase anxiety. In fact, there was a non-significant trend towards decreased anxiety with risk information (standard mean difference in anxiety -0.13 (95% CI -0.29 – 0.03) from 6 randomized trials) [20]. Our pilot study did not show increase in anxiety among study participants at low and moderate risk (we did not have participants at high risk in the pilot study, so we were not able to assess their emotional reaction to the intervention materials).

For all these reasons, the nature of this pragmatic trial and in derogation to ClinO Art. 63, only the spontaneous report of events fulfilling the above definition of a SAE through direct contact from the participant or relative with the coordinating investigator or local investigator will be documented. Coordinating investigator or local investigator (depending who will receive the contact) will document and assess all SAEs through completion of a study-specific SAE paper form to be archived in the investigator site file.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs documented as definitely, probably or possibly related to the intervention by the coordinating investigator or local investigator will be transmitted to Sponsor-investigator by email (etude-colon@unisante.ch) within a maximum of 24 hours following the contact with the participant or relative and copy to coordinating investigator, if applicable.

Sponsor-investigator will assess the event and transmit his evaluation of the event to the coordinating investigator and/or local investigator by sending back the SAE form by email.

These events (independently of the causality evaluation by the Sponsor-investigator) will be reported to the lead and the local ethics committees through BASEC by the Sponsor-investigator within 15 days and will be entered in the study database (REDCap) by the Sponsor-investigator.

Follow up of (Serious) Adverse Events

All SAE will be followed by the local investigator or coordinating investigator (depending who received the contact from the participant or relative) until they have abated, or until a stable situation has been reached. Depending on the event, follow-up may require referral to a general physician or a medical specialist.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the Sponsor-investigator notifies the lead and all local ethics committees of these measures, and of the circumstances necessitating them, within 7 days through BASEC platform.

7.3. Periodic reporting of safety and general progress of the clinical trial.

Once a year, the Sponsor-investigator submits to the lead and local Ethics Committees a list of the safety events including the severity of the events, their causality to the intervention and the safety of the study participants. The Sponsor-investigator also informs the Ethics Committee about the general progress of the clinical trial (ClinO, Art. 43).

7.4. Radiation

Non-applicable.

7.5. Pregnancy

Since one of the inclusion criteria is to be 50 years of age or more, the probability is extremely low that our sample will include pregnant women.

Reporting of pregnancies is not necessary within this trial. Following the pragmatic trial design, pregnancy and consequences on concomitant therapy will be handled according to local standards.

7.6. Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of participants may proceed without prior approval of the

Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the safety report / general study progress report.

7.7. Notification and reporting upon completion, discontinuation or interruption of the study

Upon regular study completion, the Ethics Committee is notified via BASEC within 30 days (ClinO, Art. 38). The end of the trial is planned 39 months post-randomization.

The Sponsor-Investigator may terminate the study prematurely according to certain circumstances, e.g.

- Ethical concerns,
- Insufficient participant recruitment,
- When the safety of the participants is doubtful or at risk (e.g. when the benefit-risk assessment is no longer positive),
- Alterations in accepted clinical practice that make the continuation of the study unwise, or
- Early evidence of harm or benefit of the experimental intervention.

Insufficient participant recruitment will be defined as the inability to recruit 8,050 participants. This could occur either because of low response to mailings, lower eligibility than expected among those who respond, or some combination of the two. If needed number of participants is not achieved during 8 months, recruitment will be stopped.

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (Article 38 ClinO).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38).

7.8. Insurance

In the event of study-related damage or injuries, the liability of the institution Unisanté - Policlinique Médicale Universitaire provides compensation, except for claims that arise from misconduct or gross negligence.

8 FURTHER ASPECTS

8.1. Overall ethical considerations

Organized screening programs can decrease population-level CRC mortality by 30% to 50%. Currently many organized screening programs offer all participants a choice of FIT and colonoscopy but are facing challenges in ensuring adequate colonoscopy resources. Further, participants at low and high risk are not made aware of their risk level, which could allow them to

make better decisions. Our intervention has the potential of optimizing overall colonoscopy usage and improving access to colonoscopy for those who need it most. Our pilot study showed that 14% of individuals at low risk chose FIT after receiving risk-based screening recommendations. The present trial aims at assessing whether risk-based screening is efficient (i) to detect advanced neoplasia and (ii) to encourage people to complete screening test appropriate to their CRC risk level.

We will be careful to put all needed information in the trial's documentation for participants to help potential participants to make their decision about participation in the trial. They also will be informed at the time of recruitment that they are free to refuse participating in the trial and that in that case, they will receive a usual invitation to the screening in about two months.

An important methodological aspect is that there is no established norm for cut-offs to define a lower-risk or higher-risk population. The screening programs to date have distinguished between 'average risk' and 'high-risk' populations, with high-risk persons being those with CRC symptoms, with a genetic syndrome, having family history of CRC, or being under surveillance after a high-risk polyp. We will calculate the risk using QCancer augmented with previous quantitative FIT results and screening history, and we will also consider people with a strong family history as being at higher risk. The trial participants will be divided into two groups, people at lower risk for CRC and those at higher risk and will suggest them risk-appropriate screening. Individuals who are ineligible for the study because of very high risk are generally followed by a gastroenterologist and are not part of screening programs. Moreover, all participants will have choice between FIT and colonoscopy and will be able to discuss with their family doctor screening options if needed.

We expect that the study results could be generalized on all Swiss population due to CRC screening because this trial will be conducted in five cantons and include French- and German-speaking cantons. No preselection except for eligibility for CRC screening program will be done, which means that we will include all eligible population regardless of their socio-economic status, sex, nationality and so on. As investigators will not be in direct contact with participants, they will not be able to ensure equal number of participants with different socio-demographic characteristics. However, we believe that if at recruitment process to this study a bias occurs, it will be the same that at recruitment conducted by screening programs.

8.2. Risk-benefit assessment

Potential risks for participants, as described in 7.2, are being mitigated and are expected to be minor. We are providing information to minimize anxiety among participants informed they are at higher risk (suggestion to complete screening, a sheet to discuss with a health professional, contact information of the screening centers and the Sponsor-investigator). We are also encouraging participants informed they are at lower risk to complete screening.

Currently all citizens of the cantons participating in the trial aged between 50 and 69 years are invited with a choice of FIT and colonoscopy and no personalized risk information. As such, potential benefits to participation will primarily be for those in the intervention arm, as the test recommended would better match their balance of risks and benefits. Moreover, participants randomized to the additional intervention to enhance participation will receive mailed FIT or participant navigation for colonoscopy, which could facilitate screening uptake.

The results of the study will inform screening programs in Switzerland and abroad about efficacy of personalized screening. If the study has negative results, it will prevent screening programs from investing in risk-based screening without benefitting participants. If the study has positive results, screening programs would implement some elements of risk-based screening in practice.

9 QUALITY CONTROL AND DATA PROTECTION

9.1 Quality measures

The staff of the Lausanne and Basel coordinating centers and of screening centers will dispose of the precise guidelines for inclusion/exclusion criteria, data collection, and handling missing values.

Before recruitment, the screening center staff will be trained on all trial procedures by the coordinating centers in Lausanne and Basel, at the latest during the respective site initiation visit organized by the monitors.

For data collection, we will use validated questionnaires or questionnaires pre-tested in previous studies. To facilitate the use of the online consent and questionnaire, a user-friendly interface will be elaborated by the Unisanté information technology team. All study materials including questionnaires will be reviewed and approved by the citizen advisory group in French and German, two main languages of the study.

For the quantitative measures, participants will be offered a choice between paper and online questionnaires. All answers received in paper format will be entered into REDCap and a quality check will be conducted at the beginning of the data collection to ensure accuracy. The quality check will be done by a trained study staff member in Lausanne and in Basel coordinating centers. The paper questionnaires will be kept in the investigator site files in coordinating centers (Lausanne or Basel) and will be available in case of doubt of the correctness of the data entry. Once data are in REDCap, its validity, coherence, and completeness will be assessed at several steps. First, control rules will be implemented in the data entry software (REDCap). Second, coherence of study plan and data collection will be regularly assessed by the coordinating investigators and delegated trial managers throughout the study and discussed during supervision sessions. Risk-based monitoring will also be performed (see chapter 10).

Exports form MC-SIS and imports into REDCap will be conducted by trained members of the study staff. A member of the Unisanté IT-team will assist with the import procedure at the beginning of the data collection and will be available if needed at the later stages. After the development of the MC-SIS module related to the trial's data collection, tests will be performed, and a detailed procedure of data import and export will be developed. Next, the staff members in each screening center and at the Lausanne and Basel coordinating centers will be trained on the export and import procedure.

For quality assurance the Sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

9.2 Data recording and source data

The data will be collected through REDCap, which will ensure restricted data access and audit trail. REDCap is hosted on a secure infrastructure, provided by DSI-CHUV and managed by Unisanté, with a safety back-up system. Identifying data will be kept separately from the research related data during the study and beyond in two distinct REDCap projects, labelled "Identifying Data" and "Research Data", respectively. The ID codes for the participants will be generated by the Unisanté IT-team and a check will be done to ensure that the study identifiers are unique.

Source data will be both paper (when questionnaires and consent form are received in returned envelop) and electronic (when questionnaires and consent form are directly completed in REDCap). Data on participants' participation in screening and results of screening tests collected by the screening centers will exist only in electronic form. This data will be exported every 2 months (±2 weeks) from MC-SIS by a trained member of the screening centers and transfered to Lausanne coordinating center for further data cleaning and uploading into REDCap.

During the study, paper source documents (signed consent forms, questionnaires) will be stored in the investigator files in the Lausanne and Basel coordinating centers. The completed SAE forms will be stored in the Lausanne and Basel investigator files or in screening center, depending on the entity reporting the SAE. Patient navigation delivery will be documented in a specific form in REDCap and stored in the investigator files at the screening centers. After the end of the study, paper source documents will be archived by the respective centers.

All electronic and paper documents will be stored for 20 years after completion of the trial or its premature termination.

9.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and will be accessible only to authorized personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number (study ID).

Only designated study members and scientific collaborators will have access to data. The Lausanne coordinating center will grant access rights to study staff members in accordance with their role in the data collection and data analysis process. All information about rights granted to access data will be in the Delegation logs. Most of the study staff members will have access for reading and entering data, and only a restricted number will be allowed to download data. After database lock, the access to the final dataset on the Unisanté server will be granted to the study statistician and designated members of the Lausanne coordinating center. This data will be protected by a password. Data stored on the Unisanté server are regularly backed up.

The other researchers participating in the project could ask for a copy of the coded data. Requested data will be transferred via a secured file transfer system (for instance, FileCare) after a signature of collaboration contracts with the study partners.

In REDCap, the participants' identifying information and answers to questionnaires will be separated. There will be two participant identification lists allowing to link identifying information to patient study code. The list of the German-speaking participants will be stored on the Basel University server and the list of the French-speaking participants on the Unisanté server.

Coded data and participant identification lists will be stored separately. Identification code lists will be stored following institutional standard operating procedures away from coded study datasets.

For data flow diagram, see Supplementary Figure 1.

9.4 Retention and destruction of study data and biological material

All study data are archived for 20 years after study termination or premature termination. To comply with the SNSF funder regulations that the collected data be available for further projects, coded data of participants having specifically consented for this reuse will be shared at the end of the study through the Unisanté data repository (data.unisante.ch). Access will be restricted and granted to external teams only upon ethical approval and signed transfer agreements.

10 MONITORING AND REGISTRATION

This study examines the efficacy of a behavioral intervention with minimal risks. The monitoring will be coordinated by the Research support unit of Unisanté with a delegation to the Department of Clinical Research of the University of Basel for monitoring of the German-speaking centers. Please see the monitoring plan for full details. The monitoring will follow the Swiss Clinical Trial Organization (SCTO) Guidelines for risk-based monitoring and internal Standard Operating Procedures (SOPs). Given the results of the analysis, a low-risk monitoring strategy will be

conducted with one initiation visit prior to the study start and 3 routine monitoring visits during the trial. Such monitoring visits will be conducted in all local (screening programs) and coordinating centers. The extent and nature of monitoring activities based on the objective and design of the study is defined in a study specific monitoring plan.

All source data and documents will be accessible to the monitor. The members of the coordinating and local centers will answer all the monitor questions.

No trial audit is planned. However, in case of audit and/or inspection by the responsible ethics committee, the study documentation and the source data/documents will be accessible to auditors/inspectors and questions will be answered during inspections by all study staff. All involved parties will keep the participant data strictly confidential.

The study will be registered in the Swiss National Clinical trial Portal (SNCTP) via BASEC in the national language of Switzerland in which recruitment is intended.

After the Ethics committee approval, the trial will be registered on ClinicalTrials.gov.

11. FUNDING / PUBLICATION / DECLARATION OF INTEREST

The study is funded by the Swiss National Science Foundation (project number 221652) for the period of January 1, 2025 and December 31, 2029.

Marie-Anne Durand has contributed to the development of Option Grid patient decision aids. EBSCO Information Services sells subscription access to Option Grid patient decision aids. She receives consulting income from EBSCO Health, and royalties. No other competing interests declared from her or the other investigators.

The sponsor enters and publishes a summary of the trial results in a public register in accordance with ClinO Art. 65a within one year of completion or discontinuation of the trial. An interruption lasting more than two years is considered a discontinuation of the trial.

For the purpose of publication in the public register the Sponsor also ensures that a lay summary of the trial results is entered in BASEC within one year of completion or discontinuation of the trial. The entry is made at least in the national languages of Switzerland in which the study participants were recruited.

The investigator will provide each study participant with the lay summary of the trial results at the end of the study, directly. The investigator should ensure that study participants are adequately informed about this in the patient information document and that they are informed where the lay summary of the study results will be published online. All clinical results collected in this study (advance precancerous lesions, adenocarcinomas) are communicated to participants by their treating clinicians. We do not anticipate the need for the research team to communicate results.

We plan at least 5 open-access publications in international journals based on the trial's data. Publishing contracts will be reviewed carefully before signing them to make sure that self-archiving and OA in a repository are permitted. After publication of the primary results, the data that support the findings of this study will be shared on the Unisanté data repository under a restricted access. Only the data for which a signed consent was obtained will be shared. Identifiable data (e.g., name, date of birth, contact information) will not be shared. Participants will provide consent for the reuse of their data in a coded form. To ensure data protection, data will be curated by the documentation and data unit of Unisanté before sharing.

Suggestions for oral communications and publications, as well as names of authors will be discussed during the meetings of the steering committee. The Sponsor-Investigator should be considered for the role of lead author for the primary results. Disputes regarding authorship will be settled by the principal investigator and the steering committee.

Details on collaboration with stakeholders are available in the contracts.

12. REFERENCES

1. Morgan, E., et al., *Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN.* Gut, 2023. **72**(2): p. 338-344.
2. Lauby-Secretan, B., et al., *The IARC Perspective on Colorectal Cancer Screening.* N Engl J Med, 2018. **378**(18): p. 1734-1740.
3. Robertson, D.J. and U. Ladabaum, *Opportunities and Challenges in Moving From Current Guidelines to Personalized Colorectal Cancer Screening.* Gastroenterology, 2019. **156**(4): p. 904-917.
4. Helsingen, L.M., et al., *Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a clinical practice guideline.* BMJ, 2019. **367**: p. l5515.
5. Quintero, E., et al., *Colonoscopy versus Fecal Immunochemical Testing in Colorectal-Cancer Screening.* New England Journal of Medicine, 2012. **366**(8): p. 697-706.
6. Kahi, C.J., et al., *Effect of screening colonoscopy on colorectal cancer incidence and mortality.* Clin Gastroenterol Hepatol, 2009. **7**(7): p. 770-5; quiz 711.
7. Panteris, V., J. Haringsma, and E.J. Kuipers, *Colonoscopy perforation rate, mechanisms and outcome: from diagnostic to therapeutic colonoscopy.* Endoscopy, 2009. **41**(11): p. 941-51.
8. Adeyemo, A., et al., *Does sedation type affect colonoscopy perforation rates?* Dis Colon Rectum, 2014. **57**(1): p. 110-4.
9. Grobbee, E.J., et al., *Diagnostic Yield of One-Time Colonoscopy vs One-Time Flexible Sigmoidoscopy vs Multiple Rounds of Mailed Fecal Immunohistochemical Tests in Colorectal Cancer Screening.* Clinical Gastroenterology and Hepatology, 2020. **18**(3): p. 667-675.e1.
10. Brändle, K. and J.-L. Bulliard, *First epidemiological evaluation of the Vaud colorectal cancer screening program.* Revue Medicale Suisse, 2022. **18**(803): p. 2108-2111.
11. Schneider, R., et al., *Ten-year changes in colorectal cancer screening in Switzerland: The Swiss Health Interview Survey 2007, 2012 and 2017.* Prev Med Rep, 2022. **27**: p. 101815.
12. Siau, K., B.H. Hayee, and S. Gayam, *Endoscopy's current carbon footprint.* Techniques and Innovations in Gastrointestinal Endoscopy, 2021. **23**(4): p. 344-352.
13. Hippisley-Cox, J. and C. Coupland, *Development and validation of risk prediction algorithms to estimate future risk of common cancers in men and women: prospective cohort study.* BMJ Open, 2015. **5**(3): p. e007825.
14. Usher-Smith, J.A., et al., *Risk Prediction Models for Colorectal Cancer: A Systematic Review.* Cancer Prev Res (Phila), 2016. **9**(1): p. 13-26.
15. Usher-Smith, J.A., et al., *External validation of risk prediction models for incident colorectal cancer using UK Biobank.* British Journal of Cancer, 2018. **118**(5): p. 750-759.
16. van Duuren, L.A., et al., *Population-level impact of the BMJ Rapid Recommendation for colorectal cancer screening: a microsimulation analysis.* BMJ Open Gastroenterol, 2024. **11**(1).
17. van den Berg, D.M.N., et al., *Fecal Hemoglobin Levels in Prior Negative Screening and Detection of Colorectal Neoplasia: A Dose-Response Meta-Analysis.* Gastroenterology, 2025. **168**(3): p. 587-597.
18. Steckelberg, A., et al., *Effect of evidence based risk information on "informed choice" in colorectal cancer screening: randomised controlled trial.* BMJ, 2011. **342**: p. d3193.

19. Smith, S.K., et al., *A decision aid to support informed choices about bowel cancer screening among adults with low education: randomised controlled trial.* BMJ, 2010. **341**: p. c5370.
20. Edwards, A.G., et al., *Personalised risk communication for informed decision making about taking screening tests.* Cochrane Database Syst Rev, 2013(2): p. CD001865.
21. Plys, E., et al., *Colorectal cancer screening based on predicted risk: a randomized controlled trial.* Official journal of the American College of Gastroenterology| ACG, 2025: p. 10.14309.
22. Cardoso, R., et al., *Utilisation of Colorectal Cancer Screening Tests in European Countries by Type of Screening Offer: Results from the European Health Interview Survey.* Cancers (Basel), 2020. **12**(6).
23. K. Truninger, A.L., D. Köberle, *Nachsorge nach koloskopischer Polypektomie und Therapie des kolorektalen Karzinoms.* Swiss Mecical Forum, 2022(22(21-22)): p. 349-355.
24. Winawer, S.J. and A.G. Zauber, *The advanced adenoma as the primary target of screening.* Gastrointest Endosc Clin N Am, 2002. **12**(1): p. 1-9, v.
25. Brenner, H., et al., *Risk of progression of advanced adenomas to colorectal cancer by age and sex: estimates based on 840,149 screening colonoscopies.* Gut, 2007. **56**(11): p. 1585-9.
26. Panczak, R., et al., *The Swiss neighbourhood index of socioeconomic position: update and re-validation.* Swiss Med Wkly, 2023. **153**: p. 40028.
27. Brandle;, K., et al., *Première évaluation du programme vaudois de dépistage du cancer colorectal, 2015-2020*, in *Raisons de santé*. 2022, Unisanté – Centre universitaire de médecine générale et santé publique: Lausanne.
28. *Les standards nationaux de qualité pour le dépistage du cancer du côlon en Suisse. Stratégie nationale contre le cancer 2014-2020.*; Available from: https://www.swisscancerscreening.ch/fileadmin/user_upload/Documents/SwissCancerScreening/WWW/Editors/Downloads/Darmkrebs/QS_Dickdarmkrebsvorsorge_FR_210126_secure_.pdf.
29. Plys, E., et al., *Colorectal cancer screening decision based on predicted risk: protocol for a pilot randomized controlled trial.* JMIR research protocols, 2023. **12**(1): p. e46865.
30. Buskermolen, M., et al., *Colorectal cancer screening with faecal immunochemical testing, sigmoidoscopy or colonoscopy: a microsimulation modelling study.* BMJ, 2019. **367**: p. l5383.
31. Dougherty, M., et al., *Evaluation of Interventions Intended to Increase Colorectal Cancer Screening Rates in the United States: A Systematic Review and Meta-analysis.* JAMA Intern Med, 2018.
32. Senore, C., et al., *Optimising colorectal cancer screening acceptance: a review.* Gut, 2015. **64**(7): p. 1158-77.
33. Coronado, G.D., et al., *Patient Navigation to Improve Colonoscopy Completion After an Abnormal Stool Test Result : A Randomized Controlled Trial.* Ann Intern Med, 2025.
34. Selby, K., et al., *Program Components and Results From an Organized Colorectal Cancer Screening Program Using Annual Fecal Immunochemical Testing.* Clin Gastroenterol Hepatol, 2020.
35. Jager, M., et al., *Mailed Outreach Is Superior to Usual Care Alone for Colorectal Cancer Screening in the USA: A Systematic Review and Meta-analysis.* Dig Dis Sci, 2019. **64**(9): p. 2489-2496.

36. *R Core Team. R: A language and environment for statistical computing [computer program]. Vienna, Austria: R Foundation for Statistical Computing, 2020. Available from: https://www.R-project.org/.*
37. *StataCorp. Stata Statistical Software, Release 16 [computer software]. College Station, Texas: StataCorp LLC 2019.* .
38. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Qual Life Res, 2011. **20**(10): p. 1727-36.
39. Janssen, M.F., et al., *Measurement properties of the EQ-5D-5L compared to the EQ-5D-3L across eight patient groups: a multi-country study.* Qual Life Res, 2013. **22**(7): p. 1717-27.
40. Andrade, L.F., et al., *A French Value Set for the EQ-5D-5L.* Pharmacoeconomics, 2020. **38**(4): p. 413-425.
41. Ludwig, K., J.M. Graf von der Schulenburg, and W. Greiner, *German Value Set for the EQ-5D-5L.* Pharmacoeconomics, 2018. **36**(6): p. 663-674.
42. Loeve, F., et al., *The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening.* Comput Biomed Res, 1999. **32**(1): p. 13-33.
43. van Hees, F., et al., *The value of models in informing resource allocation in colorectal cancer screening: the case of The Netherlands.* Gut, 2015. **64**(12): p. 1985-97.
44. van den Puttelaar, R., et al., *Risk-Stratified Screening for Colorectal Cancer Using Genetic and Environmental Risk Factors: A Cost-Effectiveness Analysis Based on Real-World Data.* Clin Gastroenterol Hepatol, 2023. **21**(13): p. 3415-3423.e29.
45. Naber, S.K., et al., *Cost-Effectiveness of Risk-Stratified Colorectal Cancer Screening Based on Polygenic Risk: Current Status and Future Potential.* JNCI Cancer Spectr, 2020. **4**(1): p. pkz086.
46. Cenin, D.R., et al., *Cost-Effectiveness of Personalized Screening for Colorectal Cancer Based on Polygenic Risk and Family History.* Cancer Epidemiol Biomarkers Prev, 2020. **29**(1): p. 10-21.
47. Gini, A., et al., *Development and Validation of Three Regional Microsimulation Models for Predicting Colorectal Cancer Screening Benefits in Europe.* MDM Policy Pract, 2021. **6**(1): p. 2381468320984974.
48. Moore, G.F., et al., *Process evaluation of complex interventions: Medical Research Council guidance.* Bmj, 2015. **350**: p. h1258.
49. Gale, N.K., et al., *Using the framework method for the analysis of qualitative data in multi-disciplinary health research.* BMC Med Res Methodol, 2013. **13**: p. 117.

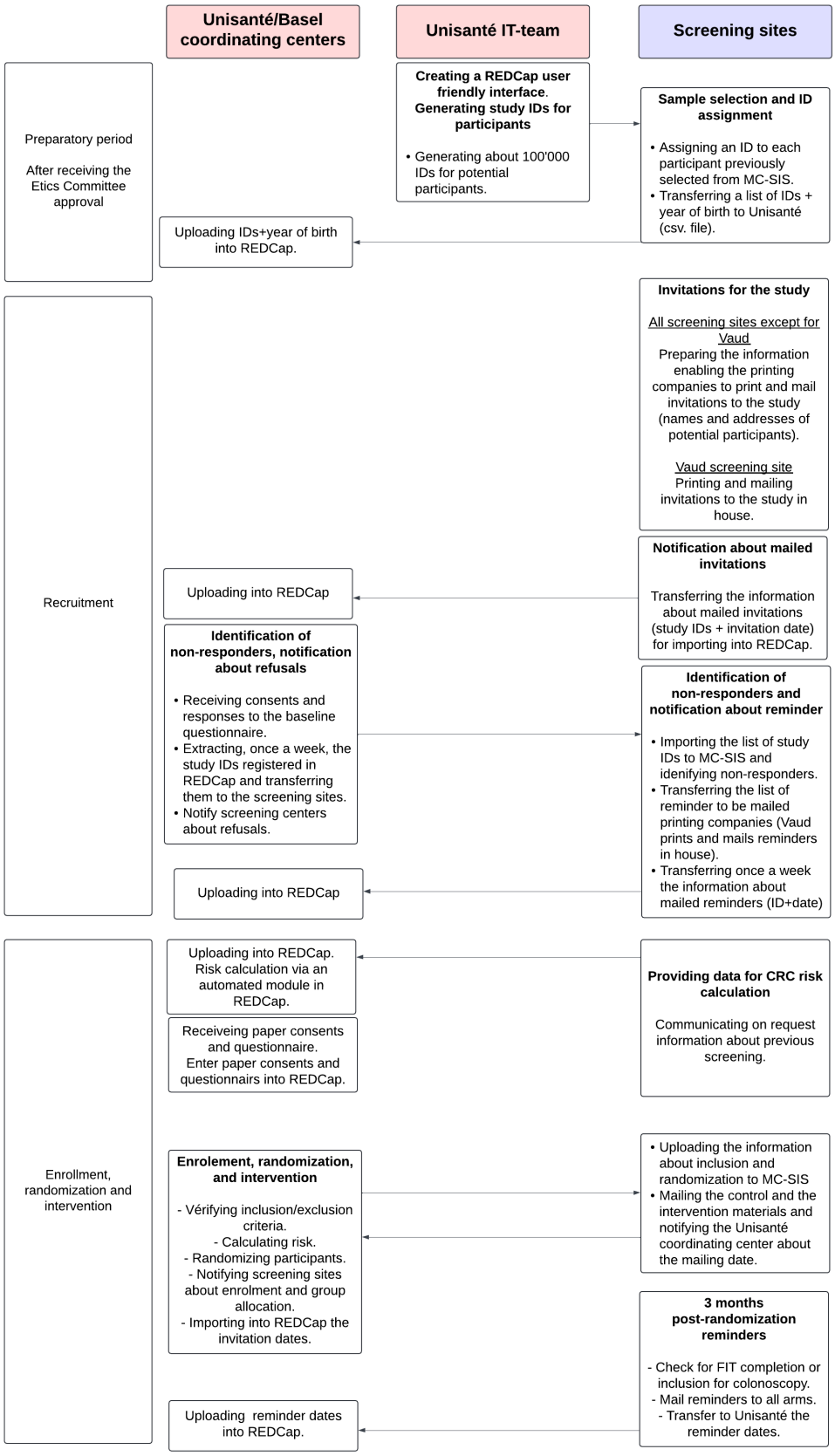
Appendix 1. Supplementary tables and figures

Supplementary Table 1: Baseline variables collected from participants and related to the primary endpoint

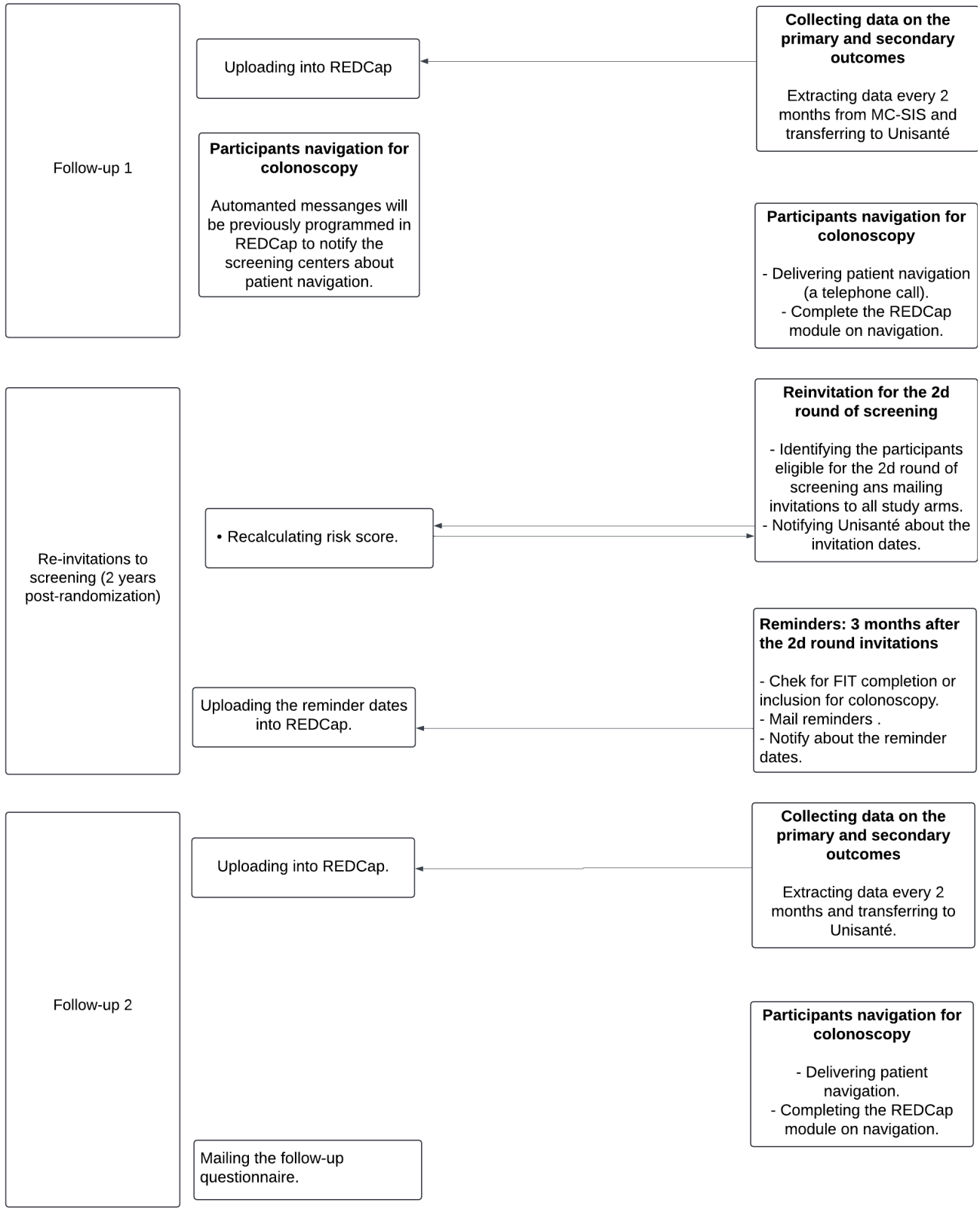
Patient characteristics	**Collected information**	**Variable type**
Age	Birth year	Continuous
Sex	Administrative Sex	Binary (male / female)
Nationality	Nationality	Categorical
Health Literacy	Comfortable completing medical form	Categorical
Education level	Level of education completed	Categorical
Height	Height in cm	Continuous
Weight	Weight in kg	Continuous
Mastery of French/German	Mastery of French or German (depending on the canton's language).	Categorical
Living alone or with others	Living alone, with a partner, with other family members or sharing apartment	Categorical
Genetic risks or medical conditions that can cause a CRC	Having genetic risks (e.g., Lynch syndrome) Having an inflammatory bowel disease (e.g., Crohn disease) Personal history of CRC Personal history of other cancers Family history of CRC or polyps Personal history of diabetes	Binary (yes / no)
CRC symptoms	Having one or more CRC symptoms	Binary (yes / no)
Regular medical follow-up using colonoscopy	Having surveillance colonoscopies after polyp removal	Binary (yes / no)
Screening history	Having had a colonoscopy within 9 years or a FIT within 1,5 years	Binary (yes / no)
Intention for screening	Intention for screening	Ordinal
Preferences for screening test	Baseline preferences for screening test	Categorical

Tobacco consumption	Number of cigarettes consumed per day	Categorical
Alcohol consumption	Number of standard units consumed per day	Categorical
Capacity to participate in screening	Having a major disease that can prevent participating in screening	Binary (yes / no)

Supplementary Figure 1. Data flow.



Supplementary Figure 1. Data flow (continued)



Supplementary Table 2. List of material provided to participants at each phase of the study.

	Timeline			
	Information and eligibility assessment	Randomization and 1st round of screening	2nd round of screening	Follow-up
Invitation letter	+			
Information about the study and consent form	+			
Key study information (flyer)	+			
Recruitment questionnaire	+			
Reminder (about the study)	+			
Message explaining the reasons why the person cannot be included to the study	+			
Message informing that the response was received after the end of recruitment	+			
Invitation for screening		+	+	
Intervention / control brochure		+	+	
Information sheet for GPs about the study (intervention group only)		+	+	
Mailed FIT kit (participants randomized to the Intervention 2 only)		+	+	
Reminder (about screening)		+	+	
Patient navigation for colonoscopy (participants randomized to the Intervention 2 only)		+	+	
Cover letter for the follow-up questionnaire				+
Follow-up questionnaire (10-20% sub-sample)				+

Supplementary Table 3. Schedule of assessments

	Study Period				
	Invitation, screening and enrolment	Randomisation and intervention	Follow-up		
Timeframe			1 year post randomisation	2 years post randomisation	3 years post randomisation
Sample selection by local screening centres	X				
Mail study invitation	X				
Mail study reminder *(approx. 4 weeks after invitation)*	X				
Informed consent procedure	X				
Baseline questionnaire	X				
Eligibility screen	X				
CRC risk calculation	X			X	
Randomisation		X			
Mail invitation screening and brochure*		X			
Mail reminder screening and brochure* *(approx. 3 months after invitation to screening)*		X			
Mail FIT-kit *(Intervention 2, participants at low risk only)*		X			
Patient navigation for colonoscopy *(Intervention 2, participants at high risk only, delivered approx. 6 months after the invitation for screening)*		X			
Oncological outcomes			*continuously collected*		
FIT and colonoscopy completion			*continuously collected*		
Colonoscopy complications *(participants with colonoscopy only)*			*continuously collected*		
Serious adverse events			*continuously collected*		

	Study Period				
	Invitation, screening and enrolment	Randomisation and intervention	Follow-up		
Timeframe			1 year post randomisation	2 years post randomisation	3 years post randomisation
Evaluation of participation: Screening uptake and colonoscopy outcomes			X		
Mail re-invitation for screening (2nd round) and brochure (*FIT participants and non-completers only*)				X	
Reminder for re-invitation to screening (2nd round) and brochure (reminders are sent according to the programme's standard of care processes)				X	
Mail FIT kit *(Intervention 2, participants at low risk only or according to the programme's standard of care processes, if applicable)*				X	
Screening completed outside of screening programs					X
Barriers for screening					X
Loss of productivity assessment					X

* Control group: standard brochure, intervention group: new brochure