Colorectal cancer screening in the average-risk population: a pragmatic, multicentre, randomised, controlled trial comparing colonoscopy and faecal immunochemical testing (COLONPREV Study)

ClinicalTrials.gov NCT00906997

Grupo Cooperativo para el Cribado del Cáncer Colorrectal en España

Study Protocol

Date: January 24th, 2024

INDEX

1. EXECUTIVE SUMMARY

Introduction

Colorectal cancer (CRC) is one of the most common malignancies in Western nations, and the second most common in Spain after lung cancer in men and breast cancer in women. Its incidence is estimated at 25,000 new cases per year, and it is the second leading cause of cancer death.

Although the efficacy of CRC screening in the prevention of this cancer is well established, the most appropriate procedure for screening has not yet been identified.

Primary objective

To measure CRC-specific mortality at 10 years after screening using biennial faecal immunochemical testing (FIT) compared to screening by one-time colonoscopy in an average-risk population (asymptomatic individuals aged 50-69 years with no personal or family history of CRC).

Study design

A pragmatic, non-inferiority, multicentre, randomised, controlled trial in eight Autonomous Regions of Spain (Aragon, Canary Islands, Catalonia, Galicia, Madrid, Murcia, Basque Country, and Valencia).

Methodology

Inclusion criteria: Asymptomatic men and women between the ages of 50 and 69.

Exclusion criteria: 1) Having previously undergone CRC screening within the prescribed period; 2) Belonging to high-risk groups due to family history (hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, other hereditary polyposis syndromes, first-degree relatives with CRC) or personal history (inflammatory bowel disease, adenoma, or prior CRC); 3) Symptoms suggestive of colorectal disease; 4) Having undergone a total colectomy; or 5) Individuals suffering from a serious illness.

Study groups

Group 1: Screening using biennial FIT (latex agglutination, OC-Sensor®, cut-off point: 75 ng Hb/ml), and performance of colonoscopy in patients with a positive result.

Group 2: Screening using one-time colonoscopy.

The study design allowed for cross-over between both screening strategies.

Sample size calculation

With an alpha risk of 0.025 and a beta risk of 0.20, using one-sided test of proportions, 27,749 subjects are required in each trial arm (total: 55,498) accepting a non-inferiority condition if the absolute difference was below 1.6‰ in the CRC-specific mortality rate at 10 years according to the intention to screen analysis (primary objective of the study).

2. BACKGROUND AND CURRENT STATUS OF THE ISSUE

Colorectal cancer (CRC) is the second most common cause of cancer death in Spain, accounting for more than 11,000 deaths annually. Its rate of incidence makes it the second most common cancer after lung cancer in men and breast cancer in women, but it is the most common cancer if figures for both genders are combined, with more than 25,000 new cases detected each year (1).

The mean survival rate for CRC in Spain is only 48% at 5 years after diagnosis (2). This may be because diagnosis is made late, in most cases as a result of a lack of screening programmes.

Several prestigious medical societies and clinical guidelines based on scientific evidence recommend screening for all individuals over the age of 50 even if no additional risk factors are present, as well as for members of high-risk population groups (hereditary CRC syndromes, individuals with first-degree relatives with CRC, and patients suffering from inflammatory bowel disease) (3-12). For screening in high-risk populations, the strategy of choice is colonoscopy, performed at various intervals depending on the clinical situation (6,12). However, it is not known which screening method (annual or biennial faecal occult blood testing [FOBT], sigmoidoscopy every 5 years, or colonoscopy every 10 years) is the most suitable for the average-risk population.

Of all the possible strategies, the most evaluated to date is annual or biennial FOBT screening. Several randomised controlled trials have shown that FOBT screening with a chemical test (guaiac) reduced mortality from CRC by approximately 15-30% (13-15) and also reduced its incidence (16).However, this method has been disputed because of its low sensitivity, with a detection rate of 30-50% in a single round of screening for CRC (15.17), and of less than 20% for advanced adenoma (18,19). Other disadvantages of screening with the guaiac-based FOBT method are that it needs to be repeated every 1-2 years, that it requires dietary restrictions to ensure the reliability of the test, and that three consecutive samples must be collected, thereby greatly reducing compliance. On the other hand, there are faecal immunochemical tests (FIT) that are more sensitive than chemical methods (20). Such methods specifically detect human haemoglobin, and therefore do not require dietary restrictions and only need a single sample to be taken. However, they have been insufficiently tested in Western countries, and there are no studies on the cost-effectiveness of CRC screening using this procedure.

In the past 15 years several pilot studies have been carried out in Spain for early detection of CRC in average-risk populations (21-25). Most of them used the chemical FOBT method as a screening test, followed by colonoscopy in individuals with a positive result. In total, these studies included more than 12,000 participants, with an average participation rate of 56% and an average detection rate of early stage CRC of 80%. Although these studies are not comparable from the methodological point of view, and were performed at different times, the results suggest an acceptable level of participation in the Spanish population, and high efficacy in the early detection of CRC. However, no studies have been conducted in Spain assessing the efficacy of screening in terms of mortality or incidence over the long-term.

In a recent study conducted in Tenerife (25), the acceptance, efficacy, and cost-effectiveness of a new FIT (latex agglutination, OC-Light®) was compared to the hemoFEC® chemical test for the detection of advanced adenoma and CRC. The study showed that the immunological method is more sensitive than the chemical test for detection of advanced adenoma (51% vs. 18%), CRC (100% vs. 52%) or both (57% vs. 22%). Specificity with the immunological method was 97% for advanced adenoma, 93% for CRC, and 95% for both, while with the chemical test it was 97% for

either advanced adenoma or CRC, and 98% for both. This study also showed that the probability of detecting advanced cancers (advanced adenoma or CRC) in individuals with a positive immunological test (OR: 13; 95% CI: 6.1-27.7) was four times higher than that for those in whom the chemical test was positive (OR: 3.17; 95% CI: 1.98-5.07). The immunological method was also more cost-effective than the chemical test in the detection of CRC or advanced adenoma. The chemical FOBT test achieved a cost-effectiveness ratio of € 3.573/QALY gained, reducing CRC-caused mortality by 20%, while for the immunological test the ratio was € 2,224/QALY gained, with a reduction in mortality of 52%. These data suggest that the FIT should replace the chemical method in future CRC screening campaigns in average-risk population.

Colonoscopy is the most accurate method that exists for the early detection and prevention of CRC. Although studies evaluating the effect of screening with this test on CRC-caused mortality in average-risk populations have not yet been published, its implementation is recommended based on the following evidence: 1) studies have demonstrated that colonoscopy with polypectomy reduces the incidence of CRC by 40-90% (27,28); 2) At least two case-control studies suggest that screening by flexible sigmoidoscopy significantly reduces the risk of death from distal CRC (29,30), an effect that lasts for more than 5 years (30) which has enabled extrapolation of its effectiveness to colonoscopy; 3) The prevalence of adenomas in cross-sectional studies of screening by colonoscopy is twice that observed for sigmoidoscopy (18,19,31,32), with colonoscopy also found to be more sensitive than the barium enema or virtual colonoscopy for detecting polyps and CRC (26); 4) Approximately two out of three patients with advanced cancers of the proximal colon do not show neoplasia distal to the splenic flexure, meaning that it would not be detectable in screening by sigmoidoscopy (33,34). This is particularly relevant if one considers that 40% of CRCs are located proximal to the splenic flexure (35).

An additional benefit of colonoscopy every 10 years compared to other screening strategies in an average-risk population is that it allows a long period of protection, which can help improve compliance in the population. It also facilitates diagnosis and treatment in one session, which decreases the risk of the loss of patients to follow-up that occurs with tests that are purely diagnostic.

The primary limiting factors for the use of colonoscopy in screening an average-risk population are its invasive nature, including a possible risk of potentially serious complications such as perforation or post-polypectomy bleeding (1-2 per 2,000 examinations), and a higher cost than other screening methods such as the FOBT test.

Despite the proven beneficial effect of secondary prevention on morbidity and mortality from CRC, there are significant obstacles that hinder the implementation of large-scale CRC screening programmes. First, there is still no agreement as to what constitutes an optimal screening strategy. Secondly, there is little compliance with them by the target population. This is due mainly to a significant lack of information among the target population, and among healthcare managers and staff themselves (36-38). Finally, the organisation and resources needed to ensure the safety and efficacy of a programme of this nature are not currently available.

An essential requirement for the implementation of any population screening programme for a particular disease is to be cost-effective. Several studies have confirmed that CRC screening is cost-effective regardless of the strategy applied (39-41), with the cost in terms of quality-adjusted life years (QALY) being lower than screening for other cancers such as breast or cervical cancer (40). These findings were corroborated in a recent analysis by the Evaluation and Planning Unit of the Canary Islands Health Service (unpublished data), which found that the costs of CRC screening using FIT or colonoscopy every 10 years would be significantly lower

(€ 2,500/QALY and € 2,300/QALY, respectively) than screening for breast (€ 18,489/QALY), cervical (€ 18,646/QALY) or prostate cancers (€ 12,647/QALY). It is worth noting that the National Institute for Health and Clinical Excellence (NICE) has recently established that any health intervention that costs less than € 30,000/QALY should be considered to be very acceptable from the standpoint of cost-effectiveness (42) and has, therefore, recommended its implementation.

Given that CRC is a high-priority health issue, and that sufficient evidence exists to show that it is a preventable disease with reasonable economic costs if diagnosed early, the Council of the European Union established guidelines in 2003 (43) so that population screening for CRC would be included as a priority in the health plans of member states. For that reason, the national health plan of the Spanish Ministry of Health and Consumer Affairs includes population screening for CRC as a priority as part of its comprehensive cancer plan (PICA), which is to be implemented before 2007 (43).

The Spanish Association of Gastroenterology (AEG) believes that, in order to reduce the mortality and incidence of CRC in Spain, various actions must be taken, among which are publicising the CCR prevention strategies, promotion of their implementation, establishment of mechanisms for assessment, improvement of the efficiency and quality of care levels involved and promotion of comprehensive care for patients with this cancer. This Association, therefore, proposes to conduct a multicentre, controlled study with a scope that covers several Autonomous Regions to establish the efficacy and efficiency of the two principal screening options in the average-risk population.

3. OBJECTIVES

3.1. Primary objective

- To assess CRC-specific mortality at 10 years after screening using a FIT method biennially compared to screening by one-time colonoscopy in an average-risk population (asymptomatic individuals aged 50-69 with no personal or family history of CRC).

3.2. Secondary objectives

- To compare diagnostic yield and detection rate of CRC and/or advanced adenomas in each screening strategy at the completion of the first round.
- To compare the participation rate in each screening strategy at the completion of the first round, and identify the factors influencing it (i.e. demographics, personal and familial characteristics, socio-economic status, etc.).
- To compare overall diagnostic yield and detection rate of CRC and/or advanced adenomas in each screening strategy at 10 years.
- To compare the overall adherence rate in each screening strategy at 10 years, and identify the factors influencing it.
- To assess the cost-effectiveness of each screening strategy.
- To assess the rate of serious complications in each screening strategy, both at the completion of the first round and overall at 10 years.
- To compare CRC incidence in each screening strategy at 15 years.

3.3. Additional objectives

Each Autonomous Region, hospital, and/or health centre participating in the study can propose additional objectives to be performed in its individual data sets. Any proposal should be approved by the Executive Committee of the COLONPREV study.

4. STUDY METHODOLOGY

4.1. Study type

Pragmatic, non-inferiority, multicentre, randomised and controlled.

4.2. Scope

The study will be conducted in eight Autonomous Regions: Aragon, Canary Islands, Catalonia, Valencia, Galicia, Madrid, Murcia and Basque Country.

The following centres will participate: Hospital Clínico Lozano Blesa (Zaragoza), Hospital Universitario de Canarias (Tenerife),Hospital Clinic de Barcelona, Hospital del Mar (Barcelona), Consorcio Hospitalario de Castelló, Hospital la Fe (Valencia), Complexo Hospitalario Universitario de Vigo, Complexo Hospitalario Universitario de Ourense, Hospital 12 de Octubre (Madrid), Hospital de la Princesa (Madrid), Hospital Puerta de Hierro (Madrid), Hospital Fundación de Alcorcón, Hospital Clínico San Carlos (Madrid), Hospital Universitario Virgen de la Arrixaca (Murcia), Hospital Reina Sofía (Murcia), Hospital de Donostia (San Sebastian), and Instituto Oncológico, Obra Social Kutxa, San Sebastián.

4.3. Target population

Inclusion criteria: Asymptomatic men and women between 50 and 69 years of age. This cutoff of age is the recommended by the Spanish Screening Network for the implementation phase of the Spanish CRC screening program. Thereafter, it is planned to increase this age cutoff to 74 years when the screening program will be extended to the whole country (unfortunately, this stage has not been accomplished at the end of COLONPREV study).

Permanent exclusion criteria: All individuals who meet any of the following conditions will be permanently excluded:

- Personal history of inflammatory bowel disease, colorectal polyps, colorectal adenoma or CRC.
- Family history of familial adenomatous polyposis syndromes or other hereditary polyposis syndromes, hereditary nonpolyposis colorectal cancer (diagnosed by the presence of germline mutation in DNA repair genes and/or meeting the Amsterdam II criteria), 2 or more first-degree relatives with CRC or 1 first-degree relative with CRC diagnosed before the age of 60.
- Severe comorbidity that involves a poor short-term prognosis (disease with a mean life expectancy of less than 5 years) or chronic disease that involves major limitation of physical activity (performance status ≥ 2).
- Individuals who have had a total colectomy.

Temporary exclusion criteria: All individuals who meet any of the following conditions will be temporarily excluded:

- Those who have undergone any of the examinations used in CRC screening, regardless of the reason, within the periods specified: history of FOBT screening in the past 2 years, or sigmoidoscopy or colonoscopy within the past 5 years (as long as its validity is documented) (to avoid this eventuality we will seek to conduct the study in a healthcare setting in which the population has not been screened previously). Such individuals may enter the study after the time periods mentioned have expired.

- Those showing symptoms suggestive of colorectal disease (rectal bleeding, altered frequency of bowel movements, constitutional symptoms, anaemia). These individuals may enter the study once their condition has been studied and a colorectal cancer or other pathology that would constitute a cause of permanent disqualification has been excluded, and if any of the above-mentioned tests were performed, once the periods mentioned in the previous section have expired.

4.4. Study groups, randomisation, and stratification

Asymptomatic men and women aged 50 to 69 years from each participating Autonomous Region will be identified through the corresponding Community Health Registry (CHR) for enrolment into this study. Randomisation will be carried out prior to invitation, with computer-generated lists in blocks of 4 (block randomisation) from the list of health cards, after having previously grouped individuals by household (specified by street address, floor, and apartment number) (see Processes of selecting and inviting the population to be screened section).

All eligible patients will be randomised (1:1 ratio) to the two study groups:

Group 1: Screening by biennial FIT (latex agglutination, OC-Sensor®, cut-off point: 75 ng Hb/ml, corresponding to 15 μg Hb/g of feces), and colonoscopy (after no more than 1 month) for patients with a positive result. Determination of FIT will be made using a single faecal sample, without dietary restriction or interruption of normal treatment of the individual, although the habitual use (>1 month) or recent use (last 7-15 days) of NSAIDs, aspirin, anti-platelet drugs and anticoagulants will be recorded. The above-mentioned cut-off point was used in the baseline round; in subsequent rounds, we decided to modify the cut-off to 20 μg Hb/g of feces since it is the one accepted in the Spanish population-based CRC screening program.

Group 2: Screening by one-time colonoscopy. The ongoing use (>1 month) or recent use (last 7-15 days) of NSAIDs, aspirin, anti-platelet drugs and anticoagulants will also be recorded.

Individuals in Group 1 or Group 2 who do not agree to the type of testing assigned to them may require receiving the alternative test and must still be followed up in order to carry out efficacy analysis according to the intention to screen analysis. The choice of the alternate test will not be actively offered to individuals invited to the study and, accordingly, COLONPREV is not considered a study of sequential screening test offers.

Information on the long-term status of individuals in Group 1 or Group 2 who do not agree to participate in the study will be obtained through population-based registries at the completion of the trial in order to assess efficacy according to the intention to screen analysis.

4.5. Sample size calculation

Considerations for calculation of the sample

Since there are no study examining the effect of screening with the strategies proposed in our trial on CRC-caused mortality, the calculation of the sample in this case must be based on hypothetical studies of cost-effectiveness that analyse the expected reduction in risk of mortality with biennial FIT or colonoscopy every 10 years. Furthermore, the calculation should be adjusted, when possible, to the local conditions where the strategies are to be implemented. In that sense, it is important to note that no study on this subject have yet been published in Spain.

Recently, the Evaluation and Planning Unit of the Canary Islands Health Service has conducted a study of this type based on real data for sensitivity and specificity of the tests in our setting. For a hypothetical population of 100,000 asymptomatic individuals aged 50, the estimated mortality reduction brought about by FIT is 51% and involves a cost of € 2,101/QALY. For the strategy of colonoscopy, the estimate is a reduction in mortality of 75% at a cost of € 2,188/QALY.

With an alpha risk of 0.025 and a beta risk of 0.10 using one-sided test of proportions, 27,749 subjects are required in each arm of the clinical trial (total: 55,498) accepting a non-inferiority condition if the absolute difference was below 1.6‰ in the CRC-specific mortality rate at 10 years according to the intention to screen analysis and with an expected overall compliance of 30%.

Estimates of recruitment by Autonomous Region

According to the established sample size, the number of individuals to be recruited in each Autonomous Region is 6,937.

4.6. Processes of selecting and inviting the population to be screened

In each Autonomous Region, randomisation will be done prior to sending the invitation letter (Zelen's design) in order to properly assess the participation in each screening group and perform the intention to screen analysis of the results.

The selection process will be the same as the one used in the Nottingham study (14), in which compliance with the programme reached 60%. Briefly, target population will be identified from the Community Health Registry (CHR) of each Autonomous Region. The CHR is based on the population registry, and includes unique identification for each person, such as name, date of birth, social security number, and contact address, and it is updated regularly to account for population migration, deaths and changes in personal details. This list will be refined using cancer registries or other sources of information (primary care medical records, hospital databases, etc.) in order to eliminate individuals who meet exclusion criteria (i.e. CRC and colorectal adenoma) or who have died. Prior to randomisation, individuals will be clustered by household. With such an approach, it is hoped to ensure that all individuals in one household will be assigned to the same study group.

All individuals will receive an initial, pre-invitation letter by mail (which may be signed by their primary care doctor or an area specialist, or the person responsible for the Autonomous Regions screening programme) with information regarding the relevance of CRC as a health problem, the possibility of preventing it by means of screening, and the impending start up of a pilot programme (**presentation letter**), along with an informative leaflet which explains existing measures for CRC prevention. They will later be sent a second letter (also signed by their primary care doctor or area specialist, or the person responsible for the Autonomous Regions screening programme) in which they are invited to participate in the study (**invitation letter**) and includes an appointment to the Local Screening Office (LSO) and a contact telephone number. In the invitation letter, individuals will also be informed of the screening option that applies to them, the characteristics of the test and its possible adverse effects. This whole process will be performed by the LSO (who may be assisted by staff of the project data manager).

Individuals who do not respond will receive a **reminding letter** at 3-4 months after sending of the introduction letter. Individuals who do not respond to it will receive a second reminding letter 2 months later.

The content of the two letters will be identical in all Autonomous Regions. However, translation into official languages and the use of logos, institutional images or letterheads of each Autonomous Regions is permitted.

The frequency of sending invitation letters will be adapted to the capacity of each LSO to attend individuals wishing to participate in order to diminish the lag time between randomisation and participation to less than 3 weeks.

At the Health Centre, the functions of staff responsible for the study (including physicians and nurses of the centre and the data-collector in charge of the study) will be: 1) To track selected individuals in the sample who do not respond or who do not come to the appointment; 2) For those who come to the appointment, to confirm their suitability to participate in the study (compliance with inclusion/exclusion criteria); 3) To provide more detailed and exhaustive information about the study objective and the strategy they have been assigned in order to facilitate their participation; 4) To identify high-risk individuals, and assign them an appointment for a high-risk clinic of the reference hospital or the corresponding genetic counselling unit (see below); 5) To obtain written informed consent for participation in the study; 6) To complete the questionnaire with the data of all individuals contacted and include them in the project database; and 7) To provide a FIT kit (Group 1) or formalise the appointment at the hospital CRC prevention unit assigned to perform the colonoscopy (Group 2). In the event that an attending individual refuses to participate in the study, the baseline questionnaire will be completed and the reasons for the refusal of the invitation will be recorded. They will also be informed that even if they are not examined during screening, they will be contacted periodically in order to monitor the state of their health.

4.7. Determination of faecal occult blood

Reading of the FIT tests will be done in a centralised manner in each Autonomous Regions.

At the baseline round, individuals participating in the FIT arm will be advised of returning the completed kit to the LSO within 5 working days and maintaining it in their refrigerator until such a moment. From the LSO to the centralized laboratory kits will be transported in insulated cooler bags once a day. On subsequent screening rounds, logistics for delivering and returning FIT kits will be adapted to the one employed in each Autonomous Region (i.e. in person on primary care centres or pharmacies without previous appointment, or by mail).

4.8. Technical characteristics of colonoscopies

All colonoscopies performed in a screening programme must be of the highest quality to avoid false negative results and to minimize potential complications. Results of colonoscopy will determine the interval until next endoscopic examination, which is 10 years if no neoplastic lesions are detected, according to current recommendations. Colonoscopies will be performed by experienced staff in the centres involved in the study, which should be able to make correct diagnoses and carry out proper treatment of different types of neoplastic lesions. In addition, these examinations will be performed in specific work modules with sufficient resources to offer the quality required. In that sense, it is important to keep in mind that more than half of the examinations performed to confirm a positive FIT are associated with a therapeutic procedure, most often polypectomy.

The period of time between acceptance to participate and performance of colonoscopy in individuals allocated to colonoscopy (Group 2) or between a positive

FIT result and performance of colonoscopy in individuals allocated to FIT (Group 1) will be established in less than one month.

Endoscopic procedures will be recorded in the appropriate databases, including high quality digital photographs of all lesions detected. The report should contain the parameters for quality assessment (caecal intubation, insertion and withdrawal times, quality of cleanliness for each colorectal segment, number of polyps identified, removed and recovered for histological examination, retroflexion manoeuvre in the rectum, immediate complications, etc.).

Proper cleansing should be another pillar of colonoscopy in the screening programme. Whichever method is used, part of the preparation should be administered a few hours before the procedure, since in various studies this pattern has resulted in, not only better quality cleansing, but also a greater proportion of patients with polyps detected. Any of the commercially available methods can be used (polyethylene glycol [Bohm® solution] or disodium hydrogen phosphate [Fosfosoda®]), whether combined or not with bisacodyl (Dulco Laxo®), taking care to provide the last dose for cleansing as close to the time of the colonoscopy as possible.

All colonoscopies will be performed under sedation.

In patients treated with anti-platelet agents, both for those in Group 1 with a positive FIT test (positive predictive value for colorectal neoplasia greater than 40%) and in Group 2 (positive predictive value of 5-7%), withdrawal or changes in medication will be assessed 7-10 days before testing. However, it is important to note that, according to current scientific recommendations, it is not necessary to discontinue anti-platelet agents to perform a polypectomy. Anti-coagulated patients (dicoumarol) should be changed, when possible, to subcutaneous administration of LMW heparin. Finally, the usefulness of metal clips has been described for the prophylaxis and treatment of post-polypectomy bleeding in at-risk groups, including in anti-coagulated patients.

The American Heart Association does not recommend the use of antibiotics prior to completion of endoscopic procedures (including colonoscopy and polypectomy) for prophylaxis of infectious endocarditis (http://circ.ahajournals.org/cgi/reprint/CIRCULATIONAHA.106.183095).

Biopsy of the polyp will be sought before polypectomy, especially for patients in whom it is anticipated that it will be difficult to obtain after the procedure. This measure aims to reduce the number of polyps not histologically studied.

In cases where colon cleansing is not adequate, the colonoscopy will be repeated.

In cases of failure to achieve complete colonoscopy, the procedure will be repeated or a CT-colonography will be offered.

Quality standards will be established for all the above requirements according to the recommendations made by the Quality Assurance Task Group of the National Colorectal Cancer Roundtable (44), which shall be subject to internal auditing during the course of the study. This will be the responsibility of the Quality Committee created specifically for this purpose (see below).

4.9. Quality assurance programme

A specific program will be designed to assure the quality of the whole process. It will include the following measures:

- A communication plan based in a comprehensive informative campaign designed and launched by the Spanish Alliance for CRC Prevention involving national and local media.
- Data will be registered in a centralized, safe database accessible online (www.coloncrib.org).
- Quality of FIT measurements will be assured by daily calibration at each reference laboratory, and external validation with samples provided by the manufacturer every 6 months.
- Colonoscopy quality will be ensured following the guidelines of the Spanish Gastroenterological Association and the Spanish Society for Digestive Endoscopy.

A specific **Quality Committee** will be created to oversee the quality assurance programme all over the study. This committee will meet in a periodical basis and will monitor by means of periodic audits the three main phases of the study (recruitment process, FIT determinations and colonoscopy).

5. DEVELOPMENT OF THE STUDY

This research project is included within the population-based screening programme of each Autonomous Region. This screening programme will ensure the recall of individuals for appointments in successive rounds of screening, while also continuing the strategy assigned to them during the randomisation of the study. The investigators will also be responsible to electronically or manually transfer to the LSO the information derived from the study that is of interest to the population screening programme.

Each Autonomous Region is committed with recruiting the same number of individuals regardless of the number of participating health centres or hospitals in each region.

The dynamics of the study are summarised as follow:

- Participants in Group 1 with a negative FIT will remain in their assigned group and will be offered the next round of screening at 2-year intervals until the age of 69. All of them will be sent a letter informing them of the test result and the date of the next round of screening. Individuals who enter the study at the age of 68 or 69 will undergo a single round of screening.
- Participants in Group 1 with a positive FIT will be contacted by phone and sent a letter informing them of the test result and the date of their appointment with the primary care physician (or specialist) or the person responsible for the screening programme, depending on the Autonomous Region They may be assisted in this task by the project staff. During the visit they will be informed about the colonoscopy procedure and will be scheduled for this procedure.
- Participants in Group 1 with a positive FIT but who have normal colonoscopies or in whom only non-neoplastic disease is detected will remain in the FIT arm and will be offered the next round of screening using the biennial FOBT test at 10 years after performance of the colonoscopy.
- Participants in Group 2 who are found to be negative in colonoscopy or in whom only non-neoplastic disease is detected, will remain in the colonoscopy arm and will be offered a new colonoscopy at 10 years after performance of the baseline colonoscopy.

Surveillance colonoscopy for patients with adenomas will be carried out according to the Joint Guideline from the *US Multi-Society Task Force (USMTF)* (45).

- Participants in either Group 1 or Group 2 in whom only 1 or 2 non-advanced adenomas (low-risk adenomas) are detected, will be included in a surveillance programme and offered a new colonoscopy at 5 years.
- Participants in either Group 1 or Group 2 in whom 3 or more non-advanced adenomas or 1 or more advanced adenomas (high-risk adenomas) are detected will be included in a surveillance programme and offered a new colonoscopy after 3 years.
- Participants in either Group 1 or Group 2 in whom >10 adenomas are detected in a single examination will be scheduled for surveillance colonoscopy in less than 3 years.
- Participants in either Group 1 or Group 2 in whom a large sessile adenoma is detected and removed by piecemeal resection will undergo a colonoscopy in 2-6 months to verify complete removal.

- The interval between subsequent surveillance colonoscopies will depend on the findings of the earlier examinations. In general, if a neoplastic lesion is detected, the above-mentioned criteria will be applied. On the other hand, if the examination is normal or if only non-neoplastic disease is detected, the next colonoscopy will be performed 5 years later.
- For participants in either Group 1 or Group 2 in whom a malignant polyp is detected (pT1N0M0) and for whom endoscopic polypectomy is deemed sufficient (see criteria below), a new colonoscopy will be performed with biopsy of the resected area within a period of no more than 2-3 months to confirm that complete resection of the lesion was achieved. Subsequently, new colonoscopies will be performed after 1 and 3 years.
- Participants in either Group 1 or Group 2 in whom an invasive CRC is detected will be treated and followed up according to the specific protocol of each centre, but always including a colonoscopy 1 year after the resection, and every 3 years thereafter.

Any individual may refuse the screening examination assigned and request an alternative method. Any such individual will be assessed according to the group to which he/she was randomised for the "intention to screen" analysis, and according to the procedure actually performed in the "as-screened" analysis. These same criteria will be applied when any screening examination is performed (FOBT, colonoscopy, CT-colonography, or colonic capsule) and that is not foreseen in the study, regardless of the reason.

All randomised subjects, whether the appropriate screening strategies have been performed or not, will be followed up for the purpose of tracking changes in the state of their health.

Individuals who are not contacted will be registered for calculation of the invited population.

For subsequent screening rounds, the same system of invitation will be used and according to each Autonomous Region policy.

The CRC prevention units will ensure the performance of colonoscopies no more than 4 weeks after the procedure is indicated. Patients in whom any neoplastic colorectal lesion is detected will be treated and followed up properly.

The treatment of lesions detected in any screening examination will be conducted according to the specific protocol of each centre.

5.1. Screening phases

Phase 1:

- It begins when the presentation letter, containing information on the CRC screening programme and the rationale of the study, is sent.
- Four weeks later, the invitation letter indicating in which screening strategy the individual has been allocated, is sent.
- It ends with receipt of the FIT test results (and performance of colonoscopy in those individuals with a positive result) (Group 1), or after completion of colonoscopy (Group 2).

Phase 2 (individuals who require retesting):

- In Group 1, it begins with repetition of the FIT test in patients for whom the previous test was invalid and ends when it is delivered and properly read.
- In Group 2, it begins with repetition of colonoscopy in cases in which the bowel preparation was inadequate, or repetition of colonoscopy or performance of CT-colonography when the colonoscopy was incomplete.

Phase 3: includes all Group 1 respondents for phases I and II who are included in the subsequent biennial rounds until completion of the 10 years. In Group 2, phase III will be completed 10 years after completion of the first examination.

5.2. Organisation and management of the project

To ensure the viability and effectiveness of this project the following is necessary: 1) Ensuring specific CRC prevention units (CRCPU) in the gastroenterology departments of each participating hospitals; 2) Effective coordination between hospital CRCPU, LSO and primary care physicians; 3) Implementation of an educational programme for the general population and primary care physicians; 4) Assurance of the development of the above-mentioned field work and an effective system for recording the results of the programme in order to determine its true impact and to correct potential malfunctions; and 5) The provision of the financial resources required for ensuring the viability of the project.

CRC prevention units (CRCPU)

These units will be located in the Gastroenterology Departments of each participant hospitals. They will have a coordinator and will work with a separate agenda in order not to interfere with the regular activity of the endoscopy units. People with a positive FIT as well as all participants in the Group 2 that accepted colonoscopy will be received in these CRCPU. These units should warrant a correct diagnosis, treatment and surveillance of participants. Finally, CRCPU will give assistance to individuals identified as having a high risk for developing CRC.

Coordination between Local Screening Offices and primary care physicians

The LSO will have a person responsible for the study. There will be also a study coordinator in each Health Care Centre participating in the study, who will be responsible for its development. Moreover, it will be a data collector in charge of the information task and recruitment; this data collector could be located at the LSO, Health Centre or CRCPU.

Educational programme and measures for improving study participation

The educational programme is aimed to improve the knowledge of the target population and primary care physicians on natural history of CRC, symptoms, treatment, prognosis, and diagnostic tests in order to improve participation in the study. This aspect is critical to achieve a high adherence with screening.

Possible actions include informative leaflets about CRC screening, campaign in the media (TV, radio and press), programme web page, organization of a "CRC prevention awareness day", among others (see Quality assurance programme).

Data recording

Demographic data, results of diagnostic tests, treatments and pathological data will be recovered in an online, centralized and protected database (www.coloncrib.org).

6. DEFINITIONS

- *Pragmatic study:* study designed to clarify whether an intervention works under real-life conditions and whether it works in terms that matter to the patient. It is simply concerned with whether the intervention works, not how or why.
- *Target population:* 50-69 year-old individuals with verified address in sanitary card.
- *Invited population:* target population excluding non-contacted individuals.
- *Eligible population:* target population excluding non-contacted and excluded individuals.
- *Participant population:* individuals who returned the FIT test (Group 1) or who completed colonoscopy (Group 2).
- *Screening inclusion data:* data of sending the invitation letter.
- *Incomplete colonoscopy:* colonoscopy in which caecal intubation is not possible. When an incomplete colonoscopy occurs, this examination must be repeated or completed with a CT-colonography.
- *Inadequate colon cleansing:* when less than 90% of colorectal mucosa can be properly evaluated due to the presence of faeces, this examination must be repeated.
- *Non-neoplastic polyp:* hyperplastic, hamartomatous or inflammatory polyps.
- *Non-advanced adenoma:* any tubular adenoma <1 cm and with low-grade dysplasia.
- *Advanced adenoma:* adenoma >1 cm in size, or with high-grade dysplasia, or with villous component (>25%).
- *High-risk adenoma*: 3 or more non-advanced adenomas, or any advanced adenoma.
- *Low-risk adenoma*: 1 or 2 non-advanced adenomas.
- *Non-invasive colorectal cancer:* colorectal carcinoma without submucose invasion (pTis). It includes intramucous carcinoma and intraepithelial carcinoma.
- *Invasive colorectal cancer*: colorectal carcinoma beyond the *muscularis mucosa* (pTNM stages I, II, III and IV).
- *Advanced neoplasia:* colorectal advanced adenoma or cancer.
- *Malignant polyp:* adenoma that harbours an area of carcinoma invading submucose (pT1).
- *Polyposis*: existence of >10 polyps. Depending on the histology, it could be adenomatous, hamartomatous or hyperplastic.
- *Non-neoplastic colorectal diseases*: any non-neoplastic disease detected in the colonoscopy (i.e. haemorrhoids, diverticulosis, angiodysplasia, etc.).

6.1. Classification of colorectal polyps

Colorectal polyps will be classified following the Paris classification (protruded, flat-elevated and flat-depressed). The size of the polyps will be established *ex vivo* after resection and before formaldehyde fixation.

When pathological study is not available because the polyp could not be recovered and pre-resection biopsy was not taken, it will be conservatively considered as adenoma.

6.2. Treatment of malignant polyps

Endoscopic polypectomy will be considered definitive treatment of a malignant polyp (pT1) if it fulfils all the following characteristics:

- Well or moderate differentiation degree,
- No vascular or lymphatic invasion, and
- Free resection margin >1 mm

In these patients, a new colonoscopy will be performed within 2-3 months with biopsies of the resection area (see Development of the study section).

6.3. Classification of colorectal cancer

CRC patients detected in the study will be classified as: 1) *Screening CRC*: CRC detected in the screening Groups 1 and 2; 2) *Interval CRC*: CRC diagnosed after a negative FIT (Group 1) or after a negative colonoscopy (Group 2), or detected after a positive FIT with a negative colonoscopy or if colonoscopy was not accepted by the patient (Group 1); 3) *Sporadic CRC*: CRC diagnosed in patients that did not accept screening in the study.

CRC stage will be established using TNM classification (*American Joint Committee on Cancer*, 6th edition):

Primary tumour (pT)

- Tx: It is not possible to evaluate primary tumour
- T0: There is not evidence of primary tumour
- Tis (in situ carcinoma): intraepithelial o intramucous tumour
- T1: Tumour invades submucose
- T2: Tumour invades *muscularis propria*
- T3: Tumour invades subserose or pericolic/perirectal tissues through *muscularis propria*
- T4: Tumour invades other organs or perforates the peritoneum

Regional lymph nodes (pN)

- Nx: It is not possible to evaluate regional lymph nodes
- N0: No metastasis in any regional lymph nodes
- N1: Metastasis in 1-3 regional lymph nodes
- N2: Metastasis in 4 or more regional lymph nodes

Distant metastasis (pM)

- Mx: It is not possible to evaluate distant metastasis
- M0: No distant metastasis
- M1: Distant metastasis

Tumour TNM stages

Stage	0	Tis	N0	M0
Stage	I	T1-2	N0	M0
Stage	IIA	T3	N0	M0
Stage	IIB	T4	N0	M0
Stage	IIIA	T1-2	N1	M0
Stage	IIIB	T3-4	N1	M0
Stage	IIIC	T1-4	N2	M0
Stage	IV	T1-4	N0-2	M1

7. STATISTICAL ANALYSIS PLAN (SAP)

Because of the study design, which allows for cross-over between both strategies, the main outcomes of the study will be analysed by intention-to-screen, as-screened and per-protocol.

Intention-to-treat

Cumulative incidence curves for the invitation arms will be estimated with the Kaplan-Meier estimator, considering the period from the day of randomization to the end of follow-up. The Kaplan-Meier estimator with daily outcome events will be used to compute the probability (risk) of the outcome during the period. For CRC incidence and mortality, non-CRC events will be considered as censoring events. We will calculate the 10-year risk differences and risk ratios between the trial arms, whereas 95% confidence intervals (95% CI) will be computed using the normal approximation.

As-screened

Cumulative incidence curves for the screening procedure actually performed will be estimated with the Kaplan-Meier estimator, considering the period from the day of randomization to the end of follow-up. The Kaplan-Meier estimator with daily outcome events will be used to compute the probability (risk) of the outcome during the period. For CRC incidence and mortality, non-CRC events will be considered as censoring events. We will calculate the 10-year risk differences and risk ratios between the trial arms, and 95% CI will be computed using the normal approximation. To provide adjusted estimates, the Kaplan-Meier estimator will be weighted with inverse probability of weighting (IPW). In this causal contrast, propensity scores for colonoscopy, FIT and no screening will be estimated with a multinomial logistic regression. The included covariates will be age, sex and centre of participants with a 3-degree of freedom natural spline.

Per-protocol

Cumulative incidence curves for the compliers (i.e. those individuals who completed the treatment originally allocated) will be estimated with the Kaplan-Meier estimator, considering the period from the day of randomization to the end of follow-up. The Kaplan-Meier estimator with daily outcome events will be used to compute the probability (risk) of the outcome during the period. For CRC incidence and mortality, non-CRC events will be considered as censoring events. We will calculate the 10-year risk differences and risk ratios between the trial arms, and 95% CI will be computed using the normal approximation. To provide adjusted estimates, the Kaplan-Meier estimator will be weighted with IPW. In this causal contrast, propensity scores for colonoscopy, FIT and no screening will be estimated with a multinomial logistic regression. The included covariates will be age, sex and centre of participants with a 3-degree of freedom natural spline.

End points of the study

Primary end point:

CRC-specific mortality at 10 years

Secondary end points:

1. Participation, detection rate, diagnostic yield and complication rate at the completion of the first round and at the end of study (10 years)

Definitions of these four key outcomes are as follows:

- Participation: number of participating individuals (i.e. individuals who completed colonoscopy in the colonoscopy group and individuals who returned the test in the FIT arm) relative to the number of eligible individuals.
- Detection rate: number of true positives relative to the number of participating individuals.
- Diagnostic yield: number of true positives relative to the number of eligible individuals.
- Complication rate: number of major complications (i.e. perforation, postpolypectomy bleeding requiring hospitalization, and cardiovascular/ pulmonary complications requiring medical management) relative to the number of participating individuals.

Differences in these four key outcomes between both strategies will be established by logistic regression analysis, adjusted by age, gender and participating centre, and reported as odds ratios (OR) with 95% CI.

2. Overall survival at the end of study (10 years)

3. CRC incidence at the end of study (10 years and 15 years)

4. Cost-effectiveness analysis

Cost-effectiveness will be studied with a Markov's model at the completion of study. Results will be reported in terms of quality-adjusted life years (QALY).

5. Analysis of factors influencing participation in the study

Factors associated with participation at the completion of first round and at the end of study (10 years) in each screening strategies will be analysed by logistic regression analysis and results reported as OR with 95% CI. Parameters analysed will include demographics, personal and familial characteristics, socio-economic status, etc.

6. *Number needed to screen to detect a colorectal cancer*

The number needed to screen to detect a CRC will be calculated using the inverse of risk (i.e. the number of participants receiving a given screening modality divided by the number of positive cases in that given modality), with 95% CI computed using the inverse of the binomial standard approximation.

8. CHRONOGRAM

The study will be developed according to the following chronogram:

- Initial meeting: October 28th, 2008
- Formative meeting for data-collectors and other auxiliary staff: December 12th, 2008
- Informative campaign launched by the Spanish Alliance for CRC Prevention and involving national and local media: from November 2008 to March 2009
- Recruitment period will be initiated in June 2009
- Quality Committee meetings will be held during the first round according to the following calendar:
  - June 12th, 2009
  - December 11th, 2009
  - June 11th, 2010
  - December 10th, 2010
- First round of screening will be finished in June 2011
- First follow-up meeting (first-round interim analysis): July 2011
- Other follow-up meetings will be held regularly during the study period, in a biennial basis (date will be announced properly)
- Other Quality Committee meetings will be held regularly during the study period, in a annual basis (date will be announced properly)
- Completion of the study: December 2021
- Analyses of main end point results (i.e. CRC mortality and incidence and any-cause mortality at 10 years): June 2024
- Follow-up conference calls among members of the Executive Committee will be held periodically, every four months, during the study period.

9. ETHICAL QUESTIONS

The study will respect the Helsinki declaration, the European Council Human Rights and Biomedicine, and the UNESCO Universal Declaration about human genome and human rights. Moreover, the study will fulfil established requisites about biomedical investigation, data protection and bioethics of the Spanish law.

People included in this study will receive appropriate information about objective, methodology and study procedures. Thereafter, they will provide written informed consent for participating in the study.

This study receives the approval of the Ethics Committee of Clinical Investigation and the Research Committee of every of the participant hospitals.

10. RESEARCH PROJECT TEAM

All the investigators will be grouped together under the name of "*Grupo Cooperativo para el Cribado del Cáncer Colorrectal en España*" or "COLONPREV study".

Every LSO, hospital and Heath Centre will designate a responsible. Among them, a **Local Coordination Committee** will be chosen and a **Coordinator** will be named.

Local Coordinators of all Autonomous Regions will constitute the **Executive Committee**. This committee will name the **National Coordinators** and will establish publication criteria for the study.

In the heading of the publications related to the main and secondary objectives of the study will appear, at least, the National Coordinators, members of the Executive Committee, responsible of every participant hospital, LSO and Health Centre, and the methodological assessors, followed by "on behalf of the *Grupo Cooperativo para el Cribado del Cáncer Colorrectal en España*" or "on behalf of COLONPREV study investigators". All other investigators will appear in a supplementary note at the end of the publication.

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