Ref. RC12_0497

**Impact of the Dissemination to general practitioners of a Nominative List of their patients not participating in organized colorectal cancer screening: A randomized study assessing the impact on patient participation in screening.**

IDLN Colorectal study

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**SYNOPSIS**

<table>
<thead>
<tr>
<th>Study title</th>
<th>Impact of the Dissemination to general practitioners of a Nominative List of their patients not participating in organized colorectal cancer screening: A randomized study assessing the impact on patient participation in screening - IDLN Colorectal study</th>
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<tr>
<td>Keywords:</td>
<td>Screening, colorectal cancer, randomized impact study, awareness of general practitioners</td>
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<td>Study Sponsor</td>
<td>NANTES UNIVERSITY HOSPITAL</td>
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<td>Coordinating Investigator (if multicenter study)</td>
<td>NGUYEN Jean-Michel, MCU-PH Service d’Épidémiologie et Biostatistiques (SEB) Hôpital St Jacques - CHU de Nantes 85, Rue Saint Jacques- 44093 Nantes cedex 1</td>
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<tr>
<td>Expected number of sites</td>
<td>2 geographic areas, 1,300 General Practitioners</td>
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<td>Study type</td>
<td>Non-interventional data-based research</td>
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<tr>
<td>Study schedule</td>
<td>2013: Data circuit and regulatory approaches  2014: Information dissemination to GPs  2015: Data collection  2016: Data analysis and feedback to GPs</td>
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<tr>
<td>Study design</td>
<td>Open-label, 3 parallel-arm, randomized, controlled study</td>
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<td>Analysis objectives</td>
<td>To demonstrate that disseminating to general practitioners (GPs) a nominative list of some of their patients who did not participate in the colorectal cancer (CRC) screening, allows increasing the participation rate in the organized screening and decreasing the number of cases of cancer diagnosed outside the organized screening.</td>
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<td>Estimated number of cases</td>
<td>GPs practicing in the French departments 44 and 85, having more than 100 patients in their patient list (regardless of the age) will be randomized into 3 groups. About 1,300 physicians.</td>
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<tr>
<td>Main selection, inclusion, non-inclusion and exclusion criteria</td>
<td>Inclusion criteria:  GP having more than 100 patients in their patient list, practicing in the Loire Atlantique or Vendée geographic areas.  Non-inclusion criteria:  GP who met the inclusion criteria but expressly refused to participate in the study.</td>
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<tr>
<td>Target indication</td>
<td>Participation rate of patients eligible for the CRC organized screening and number of cancers detected in the organized screening.</td>
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<tr>
<td>Statistical analyzes</td>
<td>A prioritized test strategy is used to test the 3 nested hypotheses:  H0: No difference in patient participation rate between the 3 arms  If this hypothesis is rejected, the second H0 will be tested: no difference in the number of detected cancers between the 3 arms  If the previous hypothesis is rejected, the third H0 will be tested: no difference in the &quot;number of detected cancers/total number of occurrences of cancer&quot; ratio between the 3 arms</td>
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**LIST OF ABBREVIATIONS**
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<tr>
<td>MA</td>
<td>Marketing Authorization</td>
</tr>
<tr>
<td>CRA</td>
<td>Clinical Research Associate</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practices</td>
</tr>
<tr>
<td>CRC</td>
<td>Colorectal Cancer</td>
</tr>
<tr>
<td>CPP</td>
<td>Comité de Protection des Personnes (Ethics Committee)</td>
</tr>
<tr>
<td>CNIL</td>
<td>Commission Nationale de l'Informatique et des Libertés / National commission Informatics and Liberties</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>OS</td>
<td>Organized Screening</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonization</td>
</tr>
<tr>
<td>RN</td>
<td>Registered Nurse</td>
</tr>
<tr>
<td>INSERM</td>
<td>Institut National de la Santé et de la Recherche Médicale</td>
</tr>
<tr>
<td>GP</td>
<td>General Practitioner</td>
</tr>
<tr>
<td>SEB</td>
<td>Service d’Épidémiologie et Biostatistiques (Epidemiology and Biostatistics Department)</td>
</tr>
<tr>
<td>CST</td>
<td>Clinical Study Technician</td>
</tr>
<tr>
<td>CMU</td>
<td>Couverture Mutuelle Universelle (universal mutual coverage)</td>
</tr>
<tr>
<td>SHIA</td>
<td>Supplemental Health Insurance Access</td>
</tr>
<tr>
<td>HI</td>
<td>Healthcare Insurance services</td>
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**DEFINITIONS**

- **Nominate list**: List of eligible unscreened patients
- **Eligible patients**: target population minus excluded patients known by the local structure in charge of CRC screening organization
- **Excluded patients**: Patients excluded from the organized screening for medical reason
- **Screened subjects**: Subjects who have performed a fecal test
- **Standard control panel**: Aggregated data containing no nominative data, currently sent to GPs.
- **Aggregated data**: Data described per variable and not per statistical unit
- **Statistical unit**: General Practitioner
- **Cluster**: medical practices (cluster randomization)
- **Participation rate**: number of screened subjects / number of eligible patients
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INTRODUCTION

In France, colorectal cancer (CRC) is the third and second most common cancer respectively in men and women. The standardized incidence rate is 37.7/100,000 in men and 24.5/100,000 in women. In France, a controlled study in the general population has shown a 16% reduction in CRC mortality after 11 years of follow-up, under certain organizational screening conditions (Faivre et al 2004). The CRC organized screening program has been generalized to the whole French territory in 2009. The participation of the population is a major prerequisite for the efficacy of the screening program. General practitioners (GPs), due to their positioning, are an essential relay for the dissemination of information on cancer screening, and in particular colon cancer. Among GPs, 72% believe that the CRC screening has a proven efficacy (IdP_Baromètre_MG2, INCa, 2010). But only 1 out of 5 GPs reports systematically verifying the completion of CRC screening and about 1 out of 3 GPs reports never verifying it. When CRC screening is discussed in consultation, physicians report being the initiators in 52% of cases [IdP_Baromètre_MG2, INCa, 2010]. Among the screenings recommended in the general population, CRC screening remains that for which the procedure is the least fitted into the physician habits [IdP_Baromètre_MG2, INCa, 2010]. Making screening a care habit is thus an objective of good practice for GPs.

The Loire Atlantique and Vendée (LAV) cancer registry is the registry with the largest population coverage, with nearly 1.93 million inhabitants. This is a general register labeled by the National Council of Registers.

CRC screening is coordinated by the "CAP Santé Plus 44" structure for organized cancer screenings for Loire Atlantique and by the "Audace" management structure (MS) for Vendée. As in the rest of the national territory, CRC screening is thus organized and coordinated with a direct invitation sent to patients by these organizations, so that CRC screening only slightly involves GPs. Several years after the implementation of this program, a strong limit of the tested screening is the high rate of patients who did not participate, and this despite numerous information campaigns targeting the general public.

In the literature, several authors have shown that the counseling provided by a GP could improve patient adherence to medical care.

Our project aims to assess the impact of the dissemination to GPs of a nominative list of their patients who did not participate in the CRC organized screening.

In their usual practice, GPs have no explicit feedback enabling them to determine whether a patient is up to date in his/her screening at a time t. We assumed that providing simple
information to GPs in the form of an edited nominative list will help them to identify, among their patients eligible for the CRC organized screening, those who have not yet participated. This list could help them to more efficiently solicit pre-identified patients.
This change in practice is expected to increase the participation rate of their patients in the organized screening and under this assumption, increase the "number of detected cancers/total number of cancers reported to the cancer registry" ratio.
1. Study rationale

   1. Research positioning

CRC is a malignant tumor of the colonic or rectal mucosa.
In 2011, the number of new cases of CRC was estimated to be 40,500 in France. This is the third cancer in terms of frequency and the second in terms of cancer mortality.
An early detection results in a decrease in mortality and improves quality of life, by avoiding aggressive treatments to patients with advanced stages.
In 2009, the CRC organized screening has been generalized to the entire French territory and involves 50-74-year old adults with no specific risk factors for CRC.
Every 2 years, this target population is invited to consult their GP for providing them with a screening kit. The participation of the population is essential for the efficacy of the screening program. Although there is no threshold effect, in practice, it should be noted that a significant 15-20% decrease in mortality is only achieved if at least half of the relevant population regularly participates in the screening and if a colonoscopy is performed in case of positive test [BEH thématique 2-3 / 13 janvier 2009]
GPs are the most likely to convince their patients to perform the test. Indeed, an experience from the pilot departments showed that 85% of tests provided by GPs were performed by patients versus 15% in case of direct mailing. Meanwhile, the first cause reported by patients who did not participate in the screening is that their physician did not discuss it with them.
That is why APs are intended to be at the center of this approach, in direct contact with the concerned population.
Currently, they are the first to provide the test, or to explain to patients that they are not concerned (depending on their history, the presence of alert symptoms and potential colonic explorations previously performed).
GPs also report to the management structure the subjects to be excluded from the screening program, to avoid inappropriate reminders.
GPs also provide advice and explanations on the practical realization modalities, which allows reducing the number of incorrect and therefore uninterpretable tests.
In case of a positive test, GPs are responsible for convincing their patients to perform colonoscopy and organizing it (10-15% of patients do not perform it).
Finally, physicians are in the front line to manage the difficult situations of false negatives and interval cancers, cancers occurring despite a negative test, between two screenings, and false positives leading to perform a colonoscopy without discovery of lesions likely to cause complications and anxiety. Passing by GPs therefore has several advantages and allows improving the quality and efficacy of the approach.

As a result of experiments in French departments and the 2008 recommendation of the High Health Authority (Role of immunological tests for investigating the presence of occult blood in the stools (FIT) in the CRC organized screening in France), the 2009-2013 Cancer Plan has planned the deployment of a new immunological test for CRC screening that could replace the Hémoccult II® test on the entire French territory (action 16.3). The new immunological test allows detecting lesser bleedings than those detected with the guaiac test. Various studies have shown that this immunological test would help to detect 2 to 2.5 times more cancers and 3 to 4 times more advanced adenomas than the current test, while performing 2 times fewer colonoscopies. The gains in sensitivity associated with the immunological test would be more relevant to precancerous lesions, which has an additional interest in the context of a preventive approach (cancers are prevented and no longer treated). The experiment conducted in two departments using the OC Sensor® test has shown a 71% detection rate of Tis stage (in situ) and stage I and II cancers versus 55% for the guaiac test. The immunological test is also easier to perform than the guaiac test: a single stool sample against six currently, a more reliable sampling technique that limits stool handling, and an enhanced test ergonomics, which is likely to improve the test acceptability by the population. In addition, the automated reading of these tests ensures both a better reliability and reproducibility of the test revelation procedures investigating the presence of blood in the stools, which enhances the quality assurance of the reading. The campaign for the provision of immunological tests in France has been several times announced but has not yet been implemented. Its potential implementation in 2014 would be a significant bias in the context of the measurement of the impact of an intervention in the field of CRC screening. The design of the IDLN study, based on the comparison of 3 groups randomized in cluster, will however enable to conclude despite a possible launch and information campaign specific to the new screening test.
Several studies have shown that the adherence to screening and prevention counseling is higher when the counseling is personalized during a face-to-face consultation with an GP (Rat, 2013) – (Levy, 2007) – (Geller AC, 2004) – (Auger Aubin, 2013).

However to our knowledge, no randomized study of the factors influencing patient adherence to the organized screening or assessing the role of the GP has been conducted.

The GP would be the most important factor in patient adherence to the screening. It is necessary to identify the factors that may modify the physician behavior to encourage their patients to adhere to the screening.

One of the approaches is purely financial, a revaluation of this specific procedure may be envisaged, but to be effective, the revaluation threshold may be prohibitive if it is based on a cost/effectiveness ratio.

Another approach is to facilitate their work. We assume that if GPs have a nominative sheet available (as a reminder) of patients eligible for screening who have not yet participated in it, this may trigger a questioning of GPs and an entry point for addressing CRC screening with their patients during consultations.

**In the current practice**, GPs receive the result of their patient tests sent by the reading center when patients think to attach an identification form when they complete the screening test. The identification form includes both patient and GP identification. The identification by GPs of patients who do not return this document and who did not participate is not currently available for the local structures in charge of CRC screening organization. The following data are transmitted by the Healthcare Insurance services services to the local structures in charge of CRC screening organization: last name, first name, sex, date of birth, social insurance number and address of subjects aged 50-74 years living in the department. The identity of patients’ GP is currently not routinely reported.
2. Research description and rationale

The primary objective is to demonstrate that disseminating to GPs a nominative list in paper form of their patients who did not participate in CRC screening, allows increasing the participation rate in the organized screening and decreasing the number of cases of cancer diagnosed outside the organized screening.

Some local structures in charge of CRC screening organization send non-nominative information control panels to GPs (in order. For measuring the effect of a nominative list, it is important to have 2 control groups, one receiving no information, the other receiving a control panel of aggregated data.

3. Benefits and risks for the subjects participating in the research

1. Benefits

The organized screening allows detecting earlier colorectal cancers. An increase in quality of life and survival rate has been shown in screened patients compared to patients whose cancer has been diagnosed.

The CRC organized screening has been extended to the whole of France due to a proven collective benefit in terms of care costs, survival and quality of life.

2. Risks

Since this study only involves the transmission of information, GPs participation in this study will have no direct impact on the management and will not involve any risk for their patients.

In addition, since the organized screening is extended to the whole of France, the cost for producing and disseminating a nominative list for GPs presents no economic risk.

National and international assessments have shown a collective benefit for the CRC organized screening. Disseminating to GPs a nominative list of their own patients does not involve any increased collective risk.
3. Benefit/risk ratio

The CRC organized screening is extended to the whole of France since 2009. The aim of this study is to assess the impact of disseminating to GPs information on the participation of the eligible population. The risks are those associated with the increase in absolute number of false positives associated with the screening test. In case of significant results, the expected benefits are an increased participation rate in the organized screening, and thus an improved "number of detected cancers/number of diagnosed cancers" ratio.
2. Objectives and endpoints

1. **Objectives of the analyzes**

The design of this study is based on a cluster randomization. Patients are blinded. GPs are semi-blinded, because they are not aware of the groups that are compared.

**Primary objective**

To demonstrate that disseminating to GPs a nominative list of their patients who did not participate in the CRC screening allows increasing the participation rate in the CRC screening and decreasing the number of cases of cancer diagnosed outside the screening.

Some local structures in charge of CRC screening organization send non-nominative information control panels to GPs in order to raise awareness to CRC screening. For measuring the effect of a nominative list, it is important to have 2 control groups, one receiving no information, the other receiving a control panel of aggregated data.

1. **Primary endpoint**

The primary endpoint is composed of 3 nested criteria. The 3 hypotheses are tested in a predetermined order. The second hypothesis is only tested if the null hypothesis of the first test has been rejected at the two-sided alpha risk threshold of 5%. The third hypothesis is only tested if the null hypothesis of the second test has been rejected at the two-sided alpha risk threshold of 5%.

There are 3 prioritized primary objectives. This strategy allows maintaining an alpha risk of 5% throughout the prioritized procedure.

- **First primary endpoint**: participation rate in the organized screening. It is calculated as the "number of patients who participated in the organized screening / number of patients eligible for the organized screening" ratio.

- **Second primary endpoint**: number of CRCs detected through the organized screening.
- Third primary endpoint: "number of CRCs detected through the organized screening/number of diagnosed cancers in patients eligible for the organized screening" ratio. All cancers not detected using the test, including interval cancers and cancers occurring in patients exempted from testing due to clinical signs suggestive of CRC will be considered as diagnosed cancers. The rationale for the presence of the second and third primary endpoints is based on the different power of statistical tests used to compare means and proportions.

2. Secondary objectives

To estimate the cost for disseminating a nominative list of patients who did not participate in the organized screening.
To identify the factors (patient characteristics) associated with the non-adherence to the organized screening.
To identify the factors (patient and GP characteristics) improving the efficacy of the nominative list in paper form.

3. Secondary endpoints

Costs for disseminating a nominative list.
Patient socio-economic and demographic characteristics.
GP practice characteristics.

2. Statistical methods

Descriptive analyzes
They will focus on all the variables collected and will be performed for the 3 randomization groups.
The quantitative data will be described as the mean, median, standard deviation, 95% CI of the mean, minimum and maximum values, number of missing values, number of non-exploitable values.
The qualitative data will be described as proportions with their 95% CI for each group. The proportion of missing values, proportion of non-exploitable values will also be described with their 95% CI.

**Explanatory analyzes**
An exploratory analysis of patient and GP socio-demographic factors and GP type of exercise will be carried out to identify the other factors that may explain a better participation rate in the organized screening in the target population.

**Comparative analyzes**
A generalized linear model (GLM) will be used to compare the 3 randomized groups stratified according to the department.
The ITT (Intent-to-treat) will be applied.

**Medico-economic study**
A comparative analysis of the direct costs in the 3 arms will be carried out:
Comparisons will be made using ratios: cost per completed organized screening, cost per detected cancer.
3. Research design

1. Overall research methodology

Open-labeled, cluster-randomized study with 3 parallel arms stratified on two departments (Loire-Atlantique and Vendée).

GPs are the statistical unit. Medical practices are the clusters to avoid a contamination bias due to the proximity of physicians and patients. Medical practices may be composed of one or more GPs practicing at an identical mailing address (group practices).

The first arm (A) receives 2 documents: a list reporting non-participating patients: patients eligible for the organized screening who did not complete it in the previous 24 months (document 1) + a control panel of aggregated data on the CRC organized screening of their canton and department (document 2).

The second arm (B) only receives document 2.

The third arm (C) receives no additional document.

2. Study schedule

1- Transmission by the Healthcare Insurance services to the structures in charge of colorectal cancer screening organization of the list of physicians who 1) are practicing in Loire-Atlantique or Vendée geographic area, and 2) have more than 100 patients in their patient list (regardless of their age, whether patients live or not in Loire-Atlantique or Vendée).

2- Transmission of the following information by each “Healthcare Insurance service” to the “local structure in charge of CRC screening organization” for insured subjects aged 50-74 years living in the relevant departments:

- last name, first name, date of birth, social security number and home address (data usually transmitted),
- and the following study-specific data related to the patient : name of their GP, whether they suffered from a chronic disease, whether they benefited from reimbursement facilities associated with a low economic status : universal mutual coverage (CMU) or Supplemental Health Insurance Access (SHIA)
3- Local structures in charge of CRC screening organization generate an inclusion code per medical practice and transmit this encoded list to the coordinator,
4- The coordinator performs the centralized and stratified randomization of GP practice addresses into 3 parallel arms for the two geographic area (Loire-Atlantique and Vendée), and transmits the result of this randomization to the local structure in charge of CRC screening organization. This procedure allows avoiding a nominative transmission to the coordinator.
5- Year n (March 2014): Sending of the documents by the structures in charge of CRC screening organization to each participating practice (depending on the arm): the standard control panel (for arms A and B) and the nominative list (for arm (A),
6- Year n (2014): Collection of invasive CRCs in Year n-2 (2012) according to the usual procedure and intramucosal CRCs by the registry (study-specific collection).
6- Month +12 (March 2015): Analysis of the first primary endpoint (participation rate) and medico-economic secondary endpoint.
7- Month +21 (December 2015): Collection of cases of invasive and intramucosal CRCs corresponding to the intervention year (2014) in subjects aged 50-74 years by the cancer registry.
8- Month +22 (January 2016): Sending by the structure in charge of CRC screening organization to the registry of nominative data of patients who participated in the screening (Years n and n-2, i.e. 2014 and 2012) according to the agreement previously validated by the National Commission “Informatics and Liberties” (CNIL) (see official documents)
9- Month +22 (January 2016): Cross-checking of the cases of invasive and intramucosal CRCs in subjects aged 50-74 years, diagnosed in Years n and n-2 (i.e. 2014 and 2012) with patients who completed a FIT test in Years n and n-2 (i.e. 2014 and 2012) by the registry. The registry will identify the cancers detected in subjects who participated in the organized screening and cancers detected outside the organized screening. It will determine the type of cancer: discovered through the organized screening or interval cancer through a joint validation of each case with the local structures in charge of CRC screening organization.
10- Month +23 (February 2016): Transmission by the registry to each local structure in charge of CRC screening organization of a nominative list of the cancers diagnosed in subjects who participated in the organized screening (MS ID number, last name, first name, maiden name, date of birth, sex, date of diagnosis, cancer topography and morphology), according to the previously validated CNIL authorization.
Transmission of a second nominative list of the cancers diagnosed in subjects who did not participate in the organized screening and aged 50-74 years at the time of diagnosis (last name, first name, maiden name, date of birth, sex, date of diagnosis, cancer topography and morphology). A CNIL-specific agreement is necessary for the transmission of cases of cancers in subjects who did not participate in the organized screening.

11- Month +23 (February 2016): Transmission by the local structure in charge of CRC screening organization to the coordinator of an anonymous file of individual data per GP.

12- Month +24 (March 2016): ITT analysis of the primary endpoints.

3. Study flow chart

Refer to Appendix 1
4. STUDIED POPULATION

1. Population description

The study is conducted in the 2 departments of Loire Atlantique and Vendée. All GPs with more than 100 patients (living or not in the departments 44 and 85) in their patient list will be included in the study. The list of eligible GPs in the 2 departments (44 and 85) will be provided by the Healthcare Insurance system services.

Eligible patients will be patients 1) belonging to the target population of the screening, 2) belonging to the patients list of one of the participating GPs, 3) minus the patients excluded from the CRC screening for medical reasons.

2. Rationale for semi-blinded general practitioners

To ensure statistical robustness to the results of the study, GPs must be partially blinded. They will therefore be semi-blinded, because they will not be aware of the groups that are compared. GPs will only be informed of the conduct of a study assessing cancer screening (through a personally sent form). The statistical unit assessed is the GP, the intervention is conducted on the physician and not on the patient. In order to prevent any change in GP practice regarding the screening of eligible patients, the randomization group will not be notified.

3. Rationale for blinded patients

Patients whose data are collected by the cancer registry are informed of the transmission of information to the registry during their medical pathway for cancer management. Patients are informed by the physician(s) who manage them. Patients are also informed of the exchange of data between the registry and the local structure in charge of CRC screening organization. The cancer registry is responsible for reminding the obligation of information to physicians in contact with patients.

In the context of the IDLN colorectal study, since the intervention of GPs on patients regarding the screening approach is the subject of the scientific assessment, and not patients themselves, no information shall be transmitted to patients about how the data will be used. Patients should
rather be considered as a measurement or an indicator in the context of this study as is the number of patients consulting in a medical practice for example. In addition, informing patients that their physicians will participate may modify their behavior, which would significantly bias the study.

4. Inclusion criteria

GPs practicing in Loire-Atlantique or Vendée who have at least 100 different patients (regardless of age) in their patients list are included in the study.

Definition of patients meeting the assessment criterion: included patients aged 50-74 years minus patients with medical exclusions from the organized screening whose GP is included.

5. Non-inclusion criteria

GPs who explicitly stated that they did not want to participate in the IDLN study.
5. Study conduct

1. Study coordination

The IDLN colorectal project has been assessed, selected and funded by the 2012 national call for tenders of the INCa "Support for studies and actions aimed to improve cancer prevention, screening and early detection".

- Throughout the study, from the collection of information from the various sources to the sending of data to the GP, the coordination will be made by Dr. Jean-Michel Nguyen from the Epidemiology and Biostatistics department (SEB) of Nantes University Hospital.
- Drs. Cédric Rat and Charlotte Choplin from the department of General Practice (Nantes University) will be responsible for verifying the consistency of the data sent to each GP.
- Drs. Marie-Laure Sauvage and Frédérique Mariani, coordinating physicians for Cap Santé Plus 44 and AUDACE, will be responsible for the organized screening who have not yet completed it in the previous 24 months, and the “standard control panel” for arms A and B (in March and September 2014).
- Dr. Florence Molinié, coordinating physician for the cancer registry will be responsible for: the management of the accelerated validation procedure for invasive cancers diagnosed in Year n (2014), and the validation of invasive cases diagnosed in Year n-2 (2012) according to the normal procedure; the specific collection and validation of intramucosal CRCs in Year n (2014, according to the accelerated procedure) and n-2 (2012, according to the normal procedure); the cross-checking to identify cancers detected during the organized screening or outside the organized screening; and the transmission of these nominative individual data per department to each local structure in charge of CRC screening organization.

The validation period for the cases of CRC in patients aged 50-74 years will be accelerated by 18 months, subject to an earlier receipt of source data from the registry (anatomopathological data, PMSI and LTI) for Year n (2014). This shortening of the validation period is called accelerated procedure.
2. Documents to be sent to GPs

Currently, apart from any research protocol, Healthcare Insurance services send every 3 months to the local structures in charge of CRC screening organization (Cap Santé Plus 44 and Audace) a nominative list of patients aged 50-74 years living in the relevant department (as part of the organized screening).

For the IDLN protocol, the Healthcare Insurance services will associate to each patient the following information: whether they suffered from a chronic disease, whether they benefited from reimbursement facilities associated with a low economic status: universal mutual coverage (CMU) or Supplemental Health Insurance Access (SHIA) (for adjusting the analyzes on these variables).

The local structures in charge of CRC screening organization will be responsible for updating the status of each patient with respect to the CRC organized screening. Only patients eligible for the organized screening who did not complete their screening test in the previous 24 months will be mentioned on the nominative list sent to each GP of arm A. This list will be sent every 6 months (twice a year) in 2014. Nothing will be required from GPs who will adapt their practice on an individualized basis for each patient based on their clinical assessment. In case of loss of this list, GPs may request to receive the latest update of their patient list from the local structure in charge of CRC screening organization.

3. Definition of anonymous and aggregated data (control panel) sent to GPs of arms A and B

The standard control panel includes aggregated data on participation and results of the organized screening in the canton and relevant department.

This standard control panel corresponds to control panels that local structures in charge of CRC screening organization might already sent to GPs outside the study protocols.

No information will be sent to GPs of arm C.

4. Rationale for the data collection procedure

- From the perspective of the GP:
Knowing the name of patients who did not participate in the organized screening would help GPs to immediately identify non-participating patients and to directly discuss with them during their subsequent consultation. It would be a useful tool for GPs who will not have to search for these patients in their records. The information transmitted to the patients is thus less impersonal. A much stronger impact than that observed with a simple reminder by mail is expected on patient behaviors with respect to the organized screening.

In the absence of this concrete information transmitted to GPs, the current development of medical software and the organization of practice functioning do not allow physicians to be alerted or reminded concerning the follow-up of patients who do not consult.

Regarding patients who consult, such an information on the follow-up is often updated, but the quality of the follow-up is impacted by the interference of multiple solicitations of the consultations over time, so that the follow-up could be improved by allowing GPs to waste less energy and time to simply retrieve the information.

- From the perspective of local structures in charge of CRC screening organization: Local structures in charge of CRC screening organization manage nominative lists of patients as part of their usual mission. In this study, the name of the GP of the patients (provided by the Healthcare Insurance medical service) will be associated in order to provide a useful information to these GPs.

This joint information stops at the end of the study.

- From the perspective of the registry:

The data transmitted from the registry to the local structures in charge of CRC screening organization are currently subject to an authorization from the National Commission “Informatics and Liberties” for patients who have participated in the organized screening. A specific authorization is requested in the context of this study for the transmission of nominative individual data of CRC cases diagnosed outside the organized screening for each department.

5. Roles of the various structures involved in this study

1. Role of the Epidemiology and Biostatistics department

- Protocol design and drafting
• Management of the randomization database
• Analysis of all the data
• Medico-economic analyzes
• Design of ancillary studies with the Department of General Practice (Nantes University), analysis of ancillary studies (telephone surveys on the experience of this study with the GPs)
• Interim and final reports

2. Role of the Healthcare Insurance services

Every 3 months, provide local structures in charge of CRC screening organization with:
• The list of patients aged 50-74 years with the following characteristics: whether they suffered from a chronic disease, whether they benefited from reimbursement facilities associated with a low economic status: universal mutual coverage (CMU) or Supplemental Health Insurance Access (SHIA),
• The list of GPs who have more than 100 patients in their patient list (regardless of their age).

3. Role of the Loire Atlantique and Vendée cancer registry

Work specifically provided in the context of this study
• Identify invasive CRCs diagnosed in Year n (2014) using the accelerated procedure in Year n+1 (2015),
• Specifically collect intramucosal CRCs diagnosed in Year n (2014) using the accelerated procedure in Year n+1 (2015), and diagnosed in Year n-2 (2012) using the normal procedure in Year n (2014), for the 2 departments, in the 50-74 age group
• Receive and cross-check the nominative data of the local structures in charge of CRC screening organization (organized screening in Years n and n-2, i.e. 2014 and 2012) to identify the cancers detected during the organized screening and outside the organized screening.
• Transmit at the end of Year n+1 (2015) to each local structure in charge of CRC screening organization the nominative data on cancers diagnosed in Years n and n-2 (2014 and 2012) with the provided information.

4. Role of the Department of General Practice (DMG)

• Protocol design and drafting with the SEB
• Establish the randomization list
• Analysis of all the data
• Design of the ancillary studies assessing the factors associated with GP behaviors with respect to the nominative list
• Co-writing of the interim and final reports, manuscript writing.

5. Role of the local structures in charge of CRC screening organization

• Establish the lists of GPs and their patients eligible for the organized screening.
• Creation of the standard control panel
• Prepare the nominative list of patients who did not complete the organized screening in the previous 24 months for each GP included in the study
• Sending of documents to each GP according to the result of the randomization.
• Sending of screening data to the cancer registry in Years n and n-2 (i.e. 2014 and 2012)

6. Study schedule

<table>
<thead>
<tr>
<th>Month</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>February 2014</td>
<td>CNIL agreement</td>
</tr>
<tr>
<td>March 2014</td>
<td>First sending</td>
</tr>
<tr>
<td>September 2014</td>
<td>Second sending</td>
</tr>
<tr>
<td>March 2015</td>
<td>Interim analysis of the first primary endpoint (participation rate) and medico-economic secondary endpoint.</td>
</tr>
<tr>
<td>Month</td>
<td>Activity</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>December 2015</td>
<td>Accelerated procedure - Registry for Year 2014</td>
</tr>
<tr>
<td>January 2016</td>
<td>Cross-checking of data - Registry and local structures in charge of CRC screening organization</td>
</tr>
<tr>
<td>February 2016</td>
<td>Processing of nominative data by the local structures in charge of CRC screening organization</td>
</tr>
<tr>
<td>March 2017</td>
<td>Final analysis on anonymized data</td>
</tr>
</tbody>
</table>
6. Data Management and Statistics

1. Collection and processing of the study data

1. Data collection

The data will be centralized by each local structures in charge of CRC screening organization. Healthcare Insurance services will provide the nominative list of insured patients aged 50-74 years living in Loire-Atlantique and Vendée, with the following patient characteristics: name of their GP, whether they suffered from a chronic disease, whether they benefited from reimbursement facilities associated with a low economic status: universal mutual coverage (CMU) or Supplemental Health Insurance Access (SHIA). From this list, the local structures in charge of CRC screening organization will compile the nominative list of patients eligible for the organized screening for each GP, by excluding patients who have already completed the organized screening within 2 years and patients excluded from the organized screening for medical reason.

The methods for data transfer between the Healthcare Insurance services, the registry and the local structures in charge of CRC screening organization will be those usually used.

2. Origin and nature of the collected nominative data. Rationale for their use

Healthcare Insurance services
They provide the nominative list of insured patients aged 50-74 years who live in Loire-Atlantique and Vendée to local structures in charge of CRC screening organization, as is done in the context of the CRC organized screening.

Study-specific data will include for each patient: the name and address of their GPs, whether they suffered from a chronic disease, whether they benefited from reimbursement facilities associated with a low economic status: universal mutual coverage (CMU) or Supplemental Health Insurance Access (SHIA).
The number of detected or diagnosed cancers for each GP included in the study will be derived from the detailed individual data processed by the registry and local structures in charge of CRC screening organization.

2. Statistics

Name and contact information of the person responsible for the analysis: NGUYEN Jean-Michel, MCU-PH. Service d’Epidémiologie et Biostatistiques (SEB)-Hôpital St Jacques-CHU de Nantes-85, Rue Saint Jacques- 44093 Nantes cedex 1

1. Description of the planned statistical methods, including the planned interim analysis schedule

A mixed linear model is used to analyze the primary endpoints. The fixed factors are the departments (stratification factor) and the randomization group (A, B, C). The random factor is the address of GP practices. A prioritized procedure is used to successively test 3 nested criteria while maintaining an alpha risk of 5%

2. Statistical rationale for the number of inclusions

All the physicians of the 2 geographic areas (44 and 85), having more than 100 patients in their patients list, are included in the randomization database. Approximately 1,300 GPs will be included. These 1,300 GPs will enable to achieve a power of 80% and a two-sided alpha risk of 5% to show a 12% difference between the experimental arm A and the 2 other control arms.

3. Expected degree of statistical significance

The two-sided alpha risk is set at 5%.
4. Statistical criteria for research termination

NA

5. Management of changes made to the initial strategy analysis plan

NA

6. Choice of the persons to be included in the analyzes

Eligible GPs in the 2 departments who will not refuse to participate in the study will be included.

7. Randomization

The randomization will be centralized, stratified on the department. Upon receipt of the nominative lists of patients with their GP, the local structures in charge of CRC screening organization will first group the GPs according to their address. The practices will be coded according to their address by the local structures in charge of CRC screening organization, and then sent to the coordinator who will perform the randomization.

8. Rules for study withdrawal

Explicit request to no longer participate in the study

9. Criteria for early study withdrawal

NA
10. Procedures for early study withdrawal

Explicit refusal of the GP

11. Criteria for study termination (apart from biostatistical considerations)

NA
7. Vigilance and management of adverse events

1. Adverse events or effects

NA

2. Independent monitoring committee

Independent monitoring committee:
- one representative of the GPs: Prof. Pierre-Louis Druais
- one gastroenterologist: Dr. Marc LE RHUN
- one epidemiologist: Dr. Bruno HUBERT
- one representative of the Healthcare Insurance services

Scientific Committee
- one gastroenterologist: Prof. Bruley de Varannes
- one GP: Dr. Olivier Saint-Lary
- one biostatistician-epidemiologist: Prof. Pierre INGRAND
8. Administrative and regulatory aspects

1. Access rights to data and source documents

In addition to the principal investigator, each GP will have access to the data about their own patients.

2. National Commission “Informatics and Liberties” (CNIL)

An authorization application file will be requested to the CNIL in two steps:
- Transmission of the CCTIRS form to request for an opinion.
- The favorable opinion of the CCTIRS will allow sending the authorization application dossier to the CNIL.

The specific circumstances of the study require the blinding of patients eligible for the CRC organized screening.

Based on a methodological justification requiring the total blinding of patients whose computerized data will be the subject of a change of purpose (from an initial epidemiological purpose to a secondary scientific purpose), Nantes University Hospital will request to the CNIL an exemption from the requirement to disclose information.

3. Study follow-up

A two-step statistical analysis is performed according to the receipt of the data. The final analysis will be performed 2 years after the beginning of GP inclusions, i.e. in 2016.

4. Inspection / Audits

The investigators will authorize and facilitate any inspection or audit requested by the National Institute for Cancer (INCa), the study sponsor or any competent authority (CNIL or Health Ministry).
5. Ethical considerations

1. Non-opposition of GPs

The GPs will be informed and notified by postal mail showing the complete contact information of the principal investigator, that an assessment of the CRC screening will be organized in the Loire-Atlantique and Vendée departments. Without explicit opposition from the physician, the latter will be included in the study.

See appendix.

2. Non-opposition of patients

Given the large number of patients in the target population and in order to ensure the blinding procedure, an exemption from the requirement to disclose information to patients regarding the use of their data will be requested.

The organized target population includes patients aged 50-74 years having their GP in one of the two departments of Loire-Atlantique or Vendée, i.e. several tens of thousands of patients.

3. Ethical opinion

Since this research protocol does not fall within the scope of the French Comité de Protection des Personnes, it will be submitted to an IRB ethics committee for ethical opinion.

6. Protocol amendments

Any substantial modification of the protocol will be the subject of an update with a new date of protocol version.
7. **Registration on clinical trial registers**

This study will be registered on the Clinical Trials website.

8. **Funding and Insurance**

This study is funded through the 2012 call for tenders of the French National Institute for Cancer (INCa).

9. **Rules for publication**

A copy of the publication will be provided to Nantes University Hospital, and the study sponsor should necessarily be cited. The authors will be determined based on their contribution to this study. The coordinating investigator establishes the author list.
List of Appendices

Appendix 1: Flow chart of the study

Appendix 2: List of participating physicians

Appendix 3: References

Appendix 4: GPs information letter
1. Appendix 1: Flow chart of the study.

IDLN: Circuit des Informations
2. Appendix 2: LIST OF PARTICIPATING PHYSICIANS

- **Dr Jean-Michel NGUYEN**  
  CHU de Nantes  
  Hôpital Saint-Jacques  
  Service d’Épidémiologie et Biostatistiques (SEB)  
  85, rue Saint Jacques  
  44 093 Nantes cedex 1

- **Dr Cédric RAT**  
  Université de Nantes  
  Département de Médecine Générale  
  1 rue Gaston Veil  
  44 035 Nantes cedex 1

- **Dr Michel Bachelet** (Président) et **Dr Marie-Laure Sauvage** (médecin coordinateur)  
  Cap Santé Plus 44  
  Structure de gestion de dépistage organisé des cancers de Loire Atlantique  
  CS 96931- 44265 NANTES CEDEX 2

- **Dr Christophe Fablet** (Président) et **Dr Frédérique Mariani** (médecin coordinateur)  
  AUDACE  
  Structure de gestion de dépistage organisé des cancers de Vendée  
  82 Boulevard Angleterre,  
  85000 Roche sur Yon

- **Dr Florence Molinié** (Directrice) et **Dr Anne Cowppli-Bony** (Médecin épidémiologiste)  
  Association EPIC-PL (Registre des Tumeurs de Loire-Atlantique et Vendée)  
  CHU de Nantes  
  Plateau des écoles-Bâtiment Chaptal  
  50 route de Saint-Sébastien  
  44 093 Nantes cedex 1

- **Cecilia QUENTEL** (Attachée de Recherche Clinique)  
  CHU de Nantes  
  1 place Alexis Ricordeau  
  44 093 Nantes Cedex 1

- **Aurélie GAULTIER** (Biostatisticienne)  
  CHU de Nantes  
  Hôpital Saint-Jacques  
  Service d’Épidémiologie et Biostatistiques (SEB)  
  85, rue Saint Jacques  
  44 093 Nantes cedex 1
3. **Appendix 3: References**


4. Appendix 4: GP INFORMATION LETTER

Note d’information pour la participation à la recherche
Impact de la Diffusion au médecin traitant d’une Liste Nominative de ses patients non participants au dépistage organisé du cancer colorectal

Titre abrégé : IDLN COLORECTAL

Nantes, le 01 Janvier 2014

Cher chère consœur, cher confrère,

L’Unité Mixte de Recherche Inserm U892 et le Centre Hospitalier et Universitaire de Nantes réalisent une étude visant à améliorer la participation au dépistage organisé du cancer colorectal.

L’objectif est de démontrer que la diffusion auprès du médecin traitant d’une liste faisant état de la non-participation de certains de ses patients au dépistage du cancer colorectal permet d’augmenter le taux de couverture du dépistage organisé et de diminuer le nombre de cas de cancers diagnostiqués hors du dépistage organisé.

Il s’agit d’une étude randomisée contrôlée dont l’impact sera mesuré au terme d’un an de suivi.

Cette recherche est réalisée grâce à un financement de l’Institut National du Cancer. Elle est menée de façon collaborative par l’équipe Inserm U892-CNRS6299 - Centre de recherche en cancérologie Nantes Angers, le Service d’Épidémiologie et Biostatistiques du CHU de Nantes, le Département de Médecine Générale de Nantes, les structures de gestion de dépistage organisé des cancers : Cap Santé Plus 44 et AUDACE (85), le Registre des Cancers de Loire-Atlantique et Vendée, et l’Assurance Maladie.

Vous êtes informé(e) de la mise en œuvre de cette étude qui inclut les médecins généralistes des 2 départements (44 et 85).

Vous êtes libre d’accepter ou de refuser de participer à cette étude.

. Le protocole ne comprendra aucun impératif de changement de pratique.
. Vous adapterez LIBREMENT votre pratique (ou non) à partir des informations supplémentaires que vous pourriez avoir à disposition dans le cadre de l’étude.
. VOUS NE SEREZ PAS SOLLICITE POUR LE RECUEIL DE DONNEES SUPPLEMENTAIRES DANS LE CADRE DE CETTE ETUDE
. Cette recherche est réalisée à partir de données déjà collectées habituellement par les structures Cap Santé plus 44, AUDACE, et le Registre des Cancers.
Par mesure de confidentialité, vos données seront systématiquement codées. Seuls les professionnels de Cap Santé Plus 44 et AUDACE (85) centralisant les données de l’étude auront connaissance de vos données nominatives.

Conformément à la loi, vous disposez d’un droit d’accès, d’opposition et de rectification des données enregistrées sur informatique, à tout moment, par l’intermédiaire des contacts ci-dessous. Vous pouvez exercer vos droits d’accès et de rectification auprès de l’investigateur coordonnateur dont le nom figure ci-dessous :

**Investigateur coordonnateur**

Dr Jean-Michel NGUYEN  
Pôle d’épidémiologie et santé publique  
CHU de Nantes  
Hôpital Saint Jacques  
Service d’Epidémiologie et Biostatistiques (SEB)  
85, rue Saint-Jacques  
44093 Nantes cedex 1  
Tel: 02 40 84 69 35  
jmnguyen@chu-nantes.fr

Vous serez informé(e) des résultats globaux de cette étude lors de l’écriture du rapport final à destination de l’Institut National du Cancer