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Trying to improve the compliance to colorectal cancer screening: A complex study design for a complex planning question

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Abstract

The efficacy of faecal occult blood test as primary screening for colorectal cancer has been demonstrated. Screening programs, to be effective, should guarantee high compliance in the target population. The aim of this paper is to describe the design of three connected studies aimed at obtaining precise indications for planning a colorectal cancer screening program with high compliance. We designed a survey, with a randomised controlled trial nested within it, and a case–control study nested within that and defined by the results of the trial. The complex interconnection of studies reflects the aim to produce indications for an evidence-based planning of a public health program, which is itself, a complex phenomenon. The trial was designed to evaluate two different types of tests, Immunochemical and Guaiac, and two different providers, general practitioner and hospital, with a 2×2 factorial design. The randomization was performed at two different levels to minimize the loss of power: at the practice level for test type (cluster randomisation) and individual level for provider type.

Keywords: Faecal occult blood test; Colorectal cancer; Screening; Compliance; Cluster randomisation; Factorial design

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1. Introduction

The efficacy of colorectal cancer screening (CRCS) using faecal occult blood test (FOBT) in reducing colorectal cancer (CRC) mortality in a population at generic risk, has been shown in several large randomized trials [1].

The screening programs need to contact the whole target population and involve as many people as possible in order to be actually effective. The scientific literature about the reasons for noncompliance have generated few definitive operational recommendations [2–5].

Two types of FOBT are now available: the Guaiaco and the Immunochemical test. The sensitivity and specificity of the two tests are similar and do not clearly indicate which one is better for screening, Table 1 summarizes the evidence available in 2002 [6–9]. The price of the immunochemical test is actually about 1.5 times higher than the Guaiaco, but there are no data about the costs per person screened [10]. The Guaiaco test recommends three different evacuations, and requires the patient to store the samples, and follow dietary restrictions. The immunochemical test is recommended on a single evacuation and does not require dietary restrictions. The discomfort and embarrassment of faecal sampling and the dietary restrictions have been hypothesized to be determinants of noncompliance [11]. These background may determine lower compliance to the Guaiaco test.

Several guidelines for screening programme implementation recommend the involvement of general practitioners (GP) and family practitioners (FP); nevertheless the role of the GPs and FPs varies between countries and health service organizations, making this recommendation hard to implement [5,12,13].

The Agency for Public Health of Lazio, Italy, decided to design a trial phase in order to plan an evidence-based implementation of the CRCS program. The aim of this approach is to guarantee that the efficacy of CRCS can be translated to effectiveness in a public health intervention. The screening strategy adopted was: yearly FOB testing for 50–74 year olds and, for positives, colonoscopy. A special focus was how to obtain a high compliance to screening; the topics studied were: GPs' attitudes and practices, type of FOBT, test provider, and the individual reasons.

The objective of this paper is to describe the design of a complex series of studies: a survey, a randomized factorial trial nested in the survey, and a case–control study nested in the trial. We also describe the results of the randomization and the power of the study.

Table 1
Review of the sensitivity and specificity data for FOBT available in 2002

Test	Study design	Setting	Sensitivity	Specificity
Guaiaco	prospective study (7)	symptomatic patients	37%	94%
	randomized trial (8)	screening	46%	99%
	prospective study (9)	screening	37%	97%
Immunochemical	prospective study (7)	symptomatic patients	49%	90%
	systematic review (10)	symptomatic patients	50–90%	95–97%
	prospective study (9)	screening	69%	94%

2. Study design and methods

2.1. Objective of the studies

The objectives of the studies were:

- To determine which type of FOBT, Guaiac or Immunochemical, guarantees higher compliance.
- To determine which provider, GPs or Hospitals, guarantees higher compliance.
- To understand the determinants of noncompliance to CRCS.
- To evaluate the attitudes of GPs to CRCS.

A survey about endoscopy and gastroenterologic surgery facilities was recently performed to study the problems relative to the implementation of screening programs [14].

2.2. Setting

Lazio has 5.3 million inhabitants and includes the metropolitan area of Rome (2.9 million). The CRCS target population (50–74 year olds) is 1.5 million. The local government has administrative and legislative control on health service. The health service is organised into 12 Local Health Units, which include 50 districts.

We selected 13 hospitals, out of 20 to participate in the screening programme, in order to represent all types of gastroenterology units (5 university hospitals, 2 large research hospitals, 6 local hospitals) and all geographic areas (7 in the metropolitan area of Rome, 2 in the outskirts of Rome, 4 in towns and small cities of the province). We included in the survey all the GPs with an office in the 13 selected hospital districts.

2.3. The survey

The survey was translated and contextually changed from a questionnaire proposed and validated by the National Cancer Institute [15]. It was designed to be self administered in 15 min. It included: demographic characteristics, items aimed to measure the knowledge about oncological screenings and the degree of agreement with international guidelines on CRCS, and items regarding the prescription or recommendation of CRCS tests (FOBT, sigmoidoscopy, colonscopy) to the practice population. In June 2002 we mailed the survey to 1192 GPs. After 1 month we offered the nonrespondents the opportunity to complete the questionnaire in a telephone interview; this re-collection lasted from July to October 2002; a second re-collection phase was performed in the spring 2003.

During the survey, all the GPs were asked to participate in a trial to evaluate the best strategies to enhance the compliance to CRCS. The conditions for eligibility of the GPs were: more than 100 people aged 50–74 in the practice population; a personal computer in the office; and consent (Fig. 1).

2.4. The trial

For each of the 13 districts we sampled 10 eligible GPs. The sampled GPs, primary sampling units, were randomised as follows: for each district, five to the immunochemical test and five to the Guaiaco

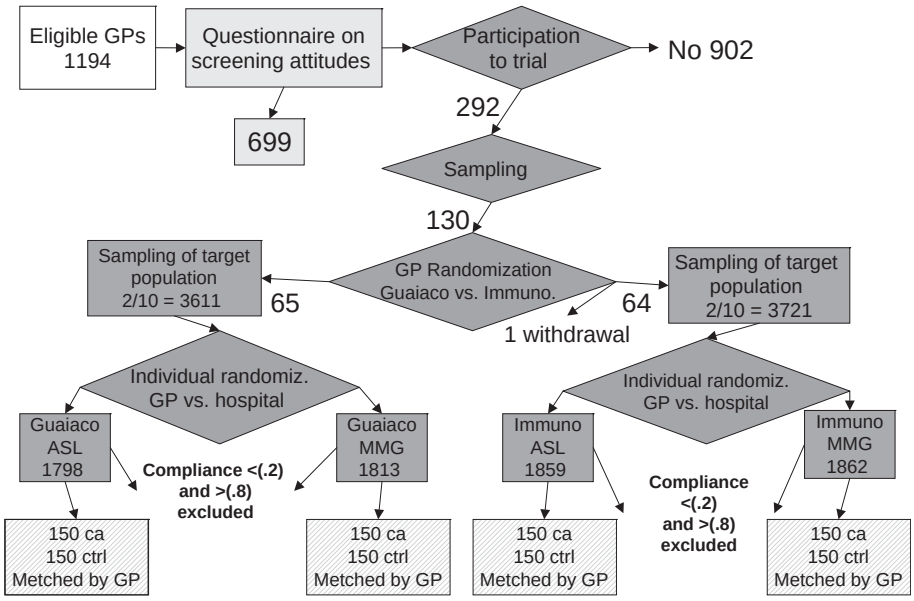

Fig. 1. Study designs. The figure illustrates the design of the three linked studies. The white box represents the reference population; the survey is summarised in the light grey boxes; the trial in the dark grey boxes; and the case–control study in the shadowed boxes.

test. We sampled 2/10 of the target practice population for each GP; 1/10 of the population was randomised to the GP arm and 1/10 to the hospital arm (Fig. 1). We decided to assign 1/10 of the target population to each arm to be invited in 1 month in order to simulate a routine work load for yearly screening, considering 10 working months per year. We analysed the lists of randomised patients: the second member of a pair with the same telephone number was rejected and substituted, if assigned to a different arm. The coordinating centre performed the two randomisations using random number generator of Stata 7.0 [16]. The statistical tests used to compare the population randomised to the two tests take into account the cluster randomisation.

The coordinating centre organised a 1-day course about CRCS counselling and the objectives of the study for the participating GPs. The centre mailed a letter to the sampled population: for the half randomised to the GP arm, the letter was signed by the GP and invited the patients to pick up and return the FOBT at the GP's office; for the population randomised to the hospital arm the letter was signed by the GP and invited the patient to pick up and return the FOBT at the hospital. Fig. 2 represents the time schedule for the trial conduction.

During the collection the patient received all test instructions: the Guaiac test (Hemo-Fec Roche Diagnostic, Mannhaim Germany), was prescribed on three different evacuations, the abstention from meat was necessary and generic abstention from anticoagulant drugs in the previous 3 days was recommended. The immunochemical test (OC-Hemodia, Eiken, Tokyo Japan, distributed by Alpha Wasserman, Milan Italy) was prescribed on a single evacuation with no dietary restrictions but with the same generic recommendation of abstention from anticoagulants. The interpretation of the Guaiaco test was visual colorimetric, the interpretation of the immunochemical test was automatic optical (OC-Sensor). All the tests were analysed in the hospital gastroenterology centre of the district.

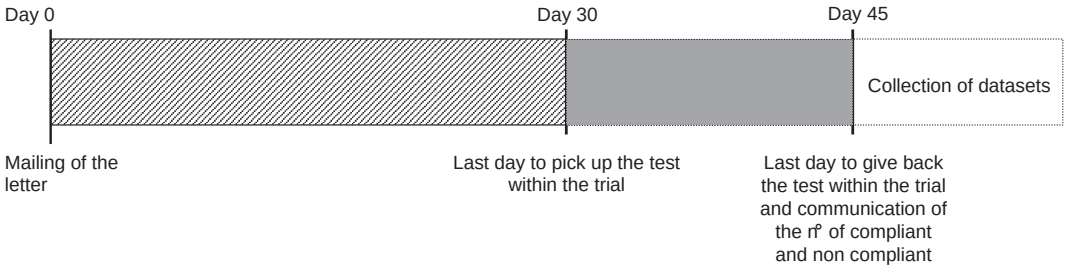

Fig. 2. Time schedule for the trial conduction. For each GP day 0 was the starting date. The test pick-up period lasted 1 month, and 45 days after that was the last time it could be returned. The time schedule was the same for the two arms. Patients could participate in the screening anytime after the deadlines, but were not considered as compliant for the trial outcome.

Patients with positive FOBTs were referred by the GP or the hospital personnel for a colonoscopy, with an appointment with absolute priority at the gastroenterology centre.

All the providers were equipped with the software EpiData 2.1 [17] for data entry.

2.5. The case–control

To understand the major determinants of non-compliance we designed a Case–Control study nested within and defined by the trial results. We defined the noncompliant population as cases, and the compliant population as controls. We will sample 600 cases from the GPs with a compliance between 20% and 80% and 600 controls matched by GP and arm of randomisation (Fig. 1). For these 1200 people we will look for an updated telephone number and submit a brief telephone questionnaire about the reasons for noncompliance to the cases or for compliance to the controls, we will enquire about: distance from the provider, logistical problems, perception of the CRC risk, confidence in the screening efficacy, fear of the results, presence of CRC cases in the family [18].

3. Results

3.1. Compliance and randomization

We reached a 58.6% (699) response rate among the GPs in three rounds: 21.1% by mail, 23.2% after a first phone reminder and 13.3% after a second phone reminder. Only 24% (292) consented to participate in the trial, and varied from 12.3% to 39.0% among the districts, but in all we had more than 10 GPs to be randomized. After the randomisation, one GP fell ill and we decided to not replace him, resulting in a small imbalance between the two types of test arms. Table 1 summarizes the characteristics of the GPs and of their beneficiaries in the two arms (Fig. 1). The individual randomization of the GPs' beneficiaries resulted absolutely balanced in the two arms, 1807 to the GP and 1797 to the hospital for Guaiac and 1858 to the GP and 1858 to the hospital for Immuno (Table 2 compares the characteristics of beneficiaries in the two arms).

Table 2
Randomised target population by gender, age, residence, provider and type of test

		Target population		Test	*p*	Target population		Test	*p*
		Hospital	GPs			Guaiaco	Immuno		
N	7320	3655	3655			3604	3716		
Gender	% male	45.7	46.3	χ^2 (1) 0.29	0.59	46.9	45.8	χ^2 (1) 0.90	0.34
Age	50–59	42.7	42.9			43.8	42.7		
	60–69	40.3	40.8			39.0	41.3	χ^2 (2) 4.51	0.1
	70+	16.9	16.3	χ^2 (2) 0.52	0.77	17.2	16.0	χ^2 (linear trend) 0.003	0.96
Residence	Rome	51.0	50.7			53.3	48.5		
	other	49.0	49.3	χ^2 (1) 0.08	0.78	46.7	51.5	*t* 0.28	0.78
Type of test	Guaiaco	49.2	49.3						
	Immuno	50.8	50.7	χ^2 (1) 0.02	0.89				
Provider	hospital					49.9	50.0		
	GPs					50.1	50.0	χ^2 (1) 0.01	0.92

3.2. Sample size and power of the studies

3.2.1. Survey

The statistical power of our survey (699 GPs) is 80% to detect a relative risk of 1.5 for an exposure prevalence of 30%, a mean outcome prevalence of 50%, and 95% confidence.

3.2.2. Trial

The study size was calculated, in the hypothesis of absence of interaction, to obtain a power of 90%, with alpha 0.05, to detect a relative risk of 1.44 for the type of test, with an expected response rate of 18% in the lowest group (data from pilot a study), an intra cluster correlation of 0.1 and an average cluster size of 55. As a consequence the minimum detectable relative risk for the provider factor was 1.17. The resulting study size was 130 cluster and 7150 subjects [19]. The power reduction due to interaction, and to the consequent stratified analysis, allows us to detect a relative risk of 1.5 for the type of test factor and of 1.25 for the provider effect.

3.2.3. CaCo

The sample size was calculated to obtain a power of 80%, with alpha 0.05, to detect a difference in exposure prevalence of 1/3 and a lowest prevalence of exposure of 30%. The expected response rate was 60%. The resulting sample size was 600 cases and 600 controls.

4. Discussion

Thanks to the linkage of a survey, a nested trial and a nested–nested case–control study, we will be able to evaluate the internal and external validity of the trial, to individuate determinants of the compliance not considered in the trial and, finally, to understand which characteristics of the GP are relevant for enhancing compliance.

In this trial we tried to minimize the loss of power due to cluster randomization [20,21] keeping the dimension of a community-based intervention: in fact the natural environment of a GP-based public

health intervention is the practice and we kept this dimension clustering the randomised beneficiaries by practice [22]. This was possible because the cluster randomisation for the provider was not necessary, given that the GP did not know the list of patients assigned to the hospital and vice versa, avoiding contamination. On the other hand, we decided for a cluster randomisation for type of test to help GPs in the screening counselling. Cluster randomisation produces a strong loss of statistical power if the intra-cluster correlation (ICC) is high [23]. The hypothesis was that the GP is a strong determinant of compliance and consequently the ICC was high. Using the strategy of two randomization levels, we loose statistical power only for one of the factors.

In order to simulate a routine workload [13], keeping the cost of the trial low, we adopted a strategy in which the number of patients to be invited is proportional to the time given to screen them : 1/10 of the practice population to be tested in 1 month (i.e. 1/10 of the work time in a year) for a screening requiring a test every year.

The nested case–control study presented some critical points: we decided to match cases (non compliant) with controls (compliant patients) by GP, given the hypothesis that the GP's characteristics are strong determinants, but they are already studied with the trial. The difference in the compliance among GPs was actually very high, in fact there are GPs with a percentage close to 0 and others with a percentage close to 100 (preliminary results from the trial). Given that, patients of GPs with a very low compliance have a high probability to be sampled among the cases, but there are very few controls for matching in the same practice. Consequently, we decided to drop the GPs with compliance lower than 20% or higher than 80%. We are not concerned about this exclusion, because in these extreme cases, by definition, the most important determinant was the GP.

5. Conclusions

Some elements and strategies adopted in our study design, in our opinion, may be useful for other researchers:

- The survey, trial and case–control studies were linked to make a study that produces precise indications for an evidence-based planning of a public health program.
- The two levels of randomisation for the two factors, one at the primary sample unit and one at the individual level, in a factorial controlled trial, optimise the power of the study, keeping the dimension of a practice-based intervention.
- The simulation of a routine workload using a sample proportional to the study time permits a rapid and affordable study.

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