1. Statistical Analysis Plan

1.1 Study type

This study is a community-based clustered randomized controlled trial. The study design (**Figure 4- 1**) is shown as follows:

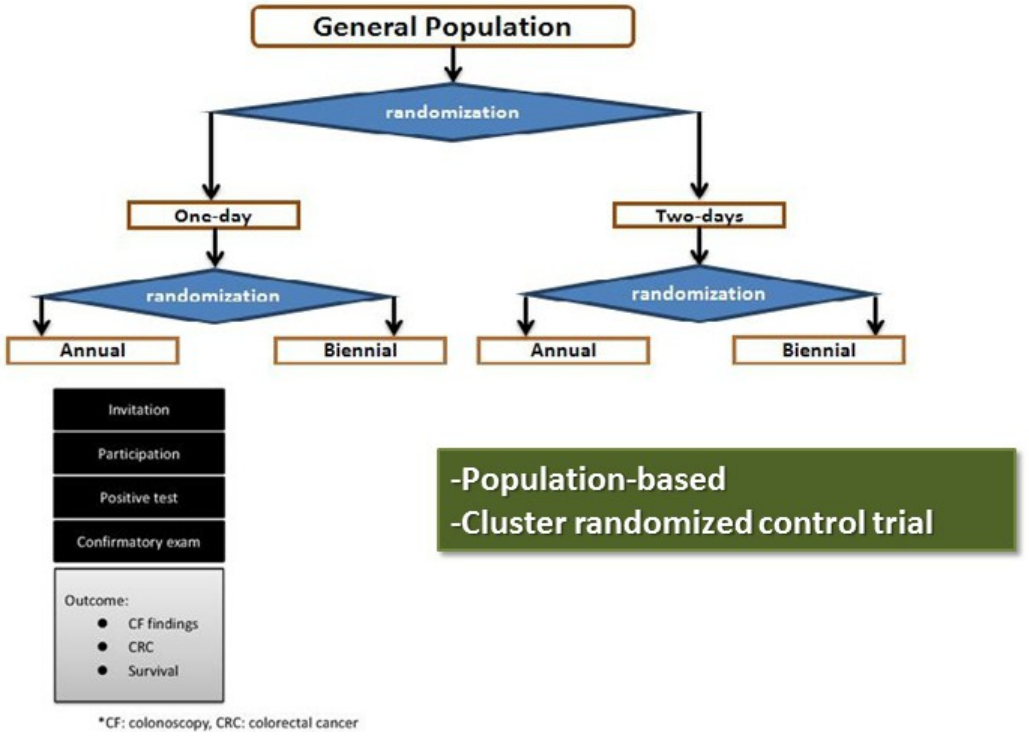

Figure 4- 1 Schematic diagram of the study design

1.2 Scope

The study will be conducted in three different regions of Taiwan: Changhua, Tainan, and Kaohsiung.

1.3 Target population

The study is a population-based cluster-randomized trial. Participants aged between 50 and 69 will be invited to take the screening test and will be randomly allocated each study arms.

1.4 Study groups, randomisation, and stratification

Subjects who meet inclusion/exclusion criteria will be randomized to 4 groups in

this stratified, clustered randomized trial:

1. FIT one-day sampling with one-year interval
2. FIT one-day sampling with two-year interval
3. FIT two-day sampling with one-year interval
4. FIT two-day sampling with two-year interval

1.5 Sample size calculation

Sample size estimation will be conducted based on literature review and empirical data from our national program. We are assuming colorectal cancer detection rate of 2.4/1000 by one-sample FIT and 4.8/1000 by two-sample FIT with a FIT screening uptake rate of 60% in both arms, 80% power and one-tail significant level at 0.05, also taking into account cluster size of 65 (The total number of townships in Changhua, Tainan and Kaohsiung) with inter-cluster correlation coefficient of 0.01, the estimated sample size is 14,625 subjects for each arm.

1.6 Selecting and inviting the population to be screened

Initially, men and women between the ages of 50 and 69 will be identified and screened for eligibility and interest. Those who fulfill the eligibility criteria and are interested will be recruited into the trial and must provide a signed informed consent form. Participants will be randomly assigned into one of two study arms: the one-day sampling group and the two-day sampling group. Baseline data collection for participants in both arms of the trial includes completion of a questionnaire which collects basic demographic data and risk factor information. Invitation list will be generated by each site, based on the household registry in the individual region.

1.7 Determination of fecal occult blood

Quantitative FIT (OC-SENSOR by Eiken Chemical Co., Ltd., Tokyo, Japan,) with fecal hemoglobin cutoff of 100 ng/ml (equivalent to 20 μg hemoglobin/g feces) will be used in this trial. The mass of feces collected and volume of the device buffer were claimed as 10 mg and 2 mL by the manufacturer. Reading of the FIT

tests will be done in a centralized manner in each region. Individuals will be advised to collect the fecal sample at home using the collecting stick and return the completed kit within a week, and maintaining it in their refrigerator until such a moment. A positive test for one-sample group will be defined as a result that is above the defined cutoff and a positive test for two-sample group will be defined as positive of any one of the two samples. Those who come up positive FIT will then be referred for verification colonoscopy.

1.8 Technical characteristics of colonoscopies

All colonoscopies being performed in a screening program must be of the highest quality to avoid false negative results and to minimize potential complications. 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.

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, immediate complications, etc.).

Proper cleansing should be another pillar of colonoscopy in the screening program. 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 to provide the last dose for cleansing as close to the time of the colonoscopy as possible.

All colonoscopies will be performed under sedation.

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.

1.9 Quality assurance program

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

- Data will be registered in a centralized, safe database.
- 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 Society of Colon and Rectal Surgeons, Taiwan. Quality Indicators include:
  1. A 6-minute colonoscopy withdrawal time policy;
  2. Bowel preparation for endoscopy involves the emptying of the bowels of all fecal matter. We are interested in recording the outcome of the final bowel preparation for each endoscopy visit using Aronchick scales:
     5- Inadequate (repeat preparation needed);
     4- Poor (semisolid stool could not be suctioned and <90% of mucosa seen);
     3- Fair (semisolid stool could not be suctioned, but >90% of mucosa seen);
     2- Good (clear liquid covering up to 25% of mucosa, but >90% of mucosa seen);
     1- Excellent (>95% of mucosa seen);
  3. Photo-documentation will be used to confirm the cecum intubation. In the medical record, the gastroenterologist who performs the colonoscopy will have noted whether or not the cecum is visualized. If the colonoscopy report states that the colonoscope is advanced to the terminal ileum, it can be assumed that the cecum is visualized, even if the report does not specifically mention cecum visualization.

A specific Quality Committee will be created to oversee the quality assurance program 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).