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Keywords:	Colorectal cancer, Early detection, Risk score, Advanced adenoma

Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Introduction: Screening for colorectal cancer (CRC) has been demonstrated to be effective in reducing the burden of this disease. However, high-level evidence from randomized controlled trials on the effectiveness of CRC screening modalities is still lacking. We conducted a large-scale multi-center randomized controlled trial for CRC screening in China to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies in Chinese population.

Methods and analysis: 200,000 eligible participants aged 50-74 years are enrolled in five provinces in China. After getting signed informed consent, the participants will be randomized into one of the three screening groups: 1) one-time colonoscopy (N=4,000); 2) annual FIT (N=8,000); 3) annual risk-adapted screening strategy (N=8,000). For the risk adapted screening strategy, participants will be conducted risk assessment using Asia-Pacific Colorectal Cancer Score. Participants of high-risk for CRC will be referred to colonoscopy and participants of low-risk for CRC will be referred to take FIT. Information on clinical reports, epidemiological risk factors and health economic factors will be collected and stored in a web-based data management system. We further request the participants to donate blood, fecal and saliva samples before conducting colonoscopy. The primary outcome is the detection rate of advanced colorectal neoplasia, and the secondary outcomes include the CRC-related mortality rate, incidence rate of CRC, participation rate and complication rate. The study will last for at least four years and the cohort will be followed for ten years to

adequately answer the scientific questions.

Ethics and dissemination: This study was approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (18-013/1615). The results of the study will be submitted for publication to peer-reviewed journals and will be discussed by policy and decision makers.

Trial registration: Chinese Clinical Trial Registry (ChiCTR1800015506, prospectively registered on 3 April 2018).

Keywords

Colorectal cancer, Early detection, Risk score, Advanced adenoma

Strengths and limitations of this study

- This is the first large-scale population-based colorectal cancer screening trial to compare the effectiveness of three different screening strategies targeting population aged 50 to 74 years old in China.
- Comprehensive health-economic evaluation will be performed to evaluate the cost-effectiveness of different screening arms and policy advices will therefore be provided based on the study findings.
- Prospective biospecimens collected before screening colonoscopy will be valuable resources to explore novel biomarkers for early detection of colorectal cancer in further research.
- The sample sizes of the study population may not be adequate to compare the mortality reduction among the three screening arms after long-term follow-ups.

Introduction

Colorectal Cancer (CRC) is the third most commonly diagnosed cancer and fourth most common cause of cancer worldwide [1]. In China, with an estimate of 376,300 newly diagnosed CRC cases and 191,000 CRC-related deaths in 2015, the incidence ranked the fourth and the mortality ranked the fifth of all cancer types. Notably, the incidence and mortality of CRC has been steadily increasing for the past decades in China [2]. Therefore, establishment of strategies on curbing the rising momentum of CRC in China is strongly required.

Evidences from randomized controlled trials and observational studies have demonstrated that screening could reduce the burden of CRC [3-5]. The established screening modalities include colonoscopy, flexible sigmoidoscopy, and stool-based test (such as fecal occult blood test (FOBT), fecal DNA test), which have been widely used in many screening programs worldwide [6-8]. Colonoscopy is the gold standard for colorectal cancer. However, in population-based screening programs, colonoscopy is limited by low compliance rate, potential complication, high cost and limited resources [9, 10]. Guaiac-based FOBT (gFOBT) was introduced in 1980s. Although the sensitivity of gFOBT for detecting CRC is not optimal, randomized controlled trials demonstrated that screening by gFOBT yielded a reduction of CRC mortality [5]. To date, the newly developed fecal immunochemical test (FIT) for hemoglobin showed superior diagnostic performance than traditional gFOBT [11]. However, evidence from randomized controlled trials to evaluate the screening efficacy of FIT

is still not lacking, especially in Chinese population [11].

Current guidelines recommend CRC screening for average-risk population at a start age of 50 years old [12-15]. However, in countries having unbalanced and limited healthcare resources, identification of high-risk populations and development of risk-adapted screening strategies would be potentially more cost-efficient than traditional screening strategies. In previous studies, CRC risk scores based on environmental and/or generic factors were developed, which typically presented moderate diagnostic efficacy [16]. Further combing risk scores with established screening modalities such as colonoscopy and FIT was proposed and showed promising diagnostic performance [13, 17, 18]. However, further validation of such risk-adapted screening strategies in large prospective cohorts and randomized controlled trial are still sparse.

Searching for biomarkers in early detection of CRC is a promising research area. Different types of biomarkers, including blood proteins, blood DNA methylation, fecal DNA, fecal microbiota and oral microbiota, were reported to be associated with CRC and could be potential targets for early detection of CRC [19]. To date, resources of biobank using prospectively collected biospecimens from large screening cohorts is still lacking. Using the ongoing screening trials to construct the biobank will be both time- and economic- saving, which will also be an important platform for biomarker identification and validation for further researches.

For China, screening for CRC has been implemented in several regions for the past

decades [20, 21]. However, high-quality evidence of evidence-based medicine for recommendation of CRC screening for Chinese population is still lacking and highly demanding [20]. Therefore, we planned to conduct a population-based, multicenter, randomized controlled trial comparing colonoscopy, FIT and a novel risk-adapted screening strategy for CRC screening in Chinese population, with the following aims: 1) to establish a large-scale CRC screening cohort with long-term follow-ups in China; 2) to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies in Chinese population; 3) to construct a large epidemiological and clinical database and a biobank for further studies.

Methods/Design

Study setting and design

This is a prospective, multicenter, randomized controlled trial comparing multiple screening strategies on colorectal cancer screening in China. Participants who meet the study inclusion and exclusion criteria are recruited in five provinces in China. We aim to recruit at least 20,000 eligible participants at baseline. After obtaining signed informed consent, eligible participants are randomly allocated into one of the following three colorectal cancer screening groups in a 1:2:2 ratio (Figure 1). The study will be conducted for at least four years (including one year for baseline screening and at least three-year follow-ups) and the follow-up will be conducted at least ten years until the scientific questions are answered adequately.

1) ***Colonoscopy group (N=4,000):*** participants are recommended to undertake one-time screening colonoscopy at baseline. Participants with abnormal findings during colonoscopy are conducted further pathology examination. For the following years, all the participants will be interviewed by the follow-up questionnaire annually.
2) ***FIT group (N=8,000):*** FITs are offered to the participants annually. Participants who have positive FIT results are recommended to take screening colonoscopy. Participants with abnormal findings during colonoscopy are conducted further pathology examination.
3) ***Risk assessment group (N=8,000):*** Colorectal cancer risk are assessed using an

established colorectal cancer risk stratification score system at baseline. For participants with high risk of colorectal cancer, screening colonoscopy are offered. For participants with low risk of colorectal cancer, FITs are offered and those with positive FIT results are recommended to take further colonoscopy. During the annual follow-ups, participants who have negative FIT results and participants who have not taken screening colonoscopy will conducted another round of risk assessment and the same screening procedures as baseline intervention will be conducted. For participants who have already undertaken screening colonoscopy, no further screening intervention will be provided but will be interviewed by questionnaire annually during the study period.

Randomization and allocation procedure

The randomization is conducted in a centralized controlled manner. The leading institute (Cancer Hospital, Chinese Academy of Medical Sciences) is responsible for the generation of randomization scheme using a predefined seed by the statistical software R. Before recruitment, the staffs who are responsible for the recruitment at each site and the participants are blinded to the allocation results. The allocation results are revealed after successful registration of the subject in a web-based data system. At the time of randomization, a unique Study Identification Number (SIN) is allocated to the participant and will be the used for the participants during the entire study period.

Study population and recruitment

Participants aged 50 to 74 years who are habitant of the study region and are able to sign informed consent are eligible for this study. Exclusion criteria are: 1) prior history of colorectal cancer; 2) prior history of colonic resection; 3) undertaking any kind of cancer related therapy (except for non-melanoma skin cancer); 4) prior colonic examination, including colonoscopy, flexible sigmoidoscopy, CT colonograpy and Barium enema within five years; 5) prior history of fecal occult blood test and fecal DNA test within 1 year; 6) symptoms of lower gastrointestinal tract disease warranting colonoscopic evaluation, including: a) more than one episode of rectal bleeding within the past 6 months; b) documented iron deficiency anemia; c) significant documented unintentional weight loss (>10% of baseline weight) over 6 months; 7) significant comorbidity that would preclude benefit from screening or pose significant risk for the performance of colonoscopy (e.g. severe lung disease, end-stage renal disease, end-stage liver disease, severe heart failure, recent diagnosis of cancer (with the exception of non-melanoma skin cancer).

Recruitment procedures will involve the following steps:

(1) Recruitment of potential participants aged 50 to 75 years in selected communities and check for eligibility by trained study staff;

(2) Signed written informed consent obtained from the eligible participants by trained study staffs;

(3) Subjects registration in the web-based data management system, SIN allocated, and randomization results revealed;

(4) Conducting respective intervention strategies per protocol;

Interventions

Colonoscopy

Standard clinical procedures of the screening colonoscopy will be followed, including appointment, obtaining informed consent, routine blood test for infectious diseases including hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections, distribution of bowel preparation drugs, diet control, anesthesia (if required by the participants) and colonoscopy examination. Colonoscopy will be performed by experienced endoscopists who are attending physician or above and have more than five-year working experiences for colonoscopy. Abnormal findings during colonoscopy are carefully checked under standard clinical procedures and tissue specimens are collected for further pathology diagnosis. Any findings during colonoscopy are required to be photo documented. Clinical information such as time of examination duration, sedation status, completeness, bowel preparation status, complication, polyp feature (such as number, position, size, color and shape), description of other abnormal findings than polyp, as well as pathology diagnosis will be collected and documented in the web-based data management system.

For quality control, expert panel including experienced endoscopists and pathologist will be formed. Each year, a selection of colonoscopy and pathology documentation will be assessed by the expert panel, and review reports will be transferred to the respective physicians about their performance.

Fecal immunochemical test (FIT)

Fecal immunochemical tests for human hemoglobin are provided by the study staff to participants for after the successful registration of this study. The FIT used in this study is a self-administered qualitative test, providing an endpoint that is read as positive or negative by eye if the fecal hemoglobin concentration exceeds the manufacturer-specific threshold. The participants can submit the results to the study website along with the pictures of test window or will be interviewed by the study staff for the test results within three days of distributing the FIT. For participants having invalid test results, new test devices are provided until getting valid test results. Participants are contacted and arranged for following colonoscopy if they are confirmed to have positive FIT results.

Colorectal cancer risk assessment

In this study, an established colorectal cancer risk score system, Asia-Pacific Colorectal Cancer (APCS) score [22, 23], will be used. The APCS score is derived based on five common risk factors of colorectal cancer, including age, gender, family history of colorectal cancer in a first-degree relative and smoking. Detailed information of the APCS score is shown in Table 1. Generally, for the risk-adapted screening group (risk assessment group), participants are asked to filled in a questionnaire including the above mentioned risk factors, participants with a score ≥ 4 are defined as high-risk of colorectal cancer with the others being defined as low-risk of colorectal cancer. Participants will be informed about their evaluation results and receive respective screening intervention per study protocol.

Biospecimen collection and handling

Participants who need to undertake colonoscopy are invited to donate stool, saliva and blood samples prior to colonoscopy. Standard Operating Procedures (SOPs) regarding biospecimen collection, handling and storage have been formulated and will be followed.

For stool samples, collection devices (including sample collection vials, ice bags, isothermal bags and operation brochures) are distributed. At the day before colonoscopy, participants are suggested to collect raw stool samples before taking bowel cleaning drugs for colonoscopy. The participants are recommended to store the samples in the freezer or in the isothermal bags with ice bags until transported to the hospital. The samples are stored in the freezer (-80℃) immediately for future use when received.

For saliva samples, participants are provided with samples collection tubes (with oral DNA stabilization buffer) during their visit of hospital before colonoscopy. Study staffs will guide the participants for the saliva sample collection procedure. Collected samples will be aliquoted immediately and stored in the freezer (-80℃) for future use.

For blood samples, around 10ml vein blood samples (including 5ml EDTA anticoagulated blood and 5ml non-anticoagulation blood) are withdrawn from the participants during their visit of the hospital before colonoscopy. Under the SOPs, blood samples are centrifuged, aliquoted and then stored in the freezer (-80℃) for future use.

Follow up

Both active follow-up and passive follow-up will be conducted in this study. For the active follow-up, all the participants will be interviewed by trained study staff by telephone call, home visit or other contact methods for collection information such as diagnostic examination, health status and outcome. For the passive follow-up, linkage data from cancer registry system, death surveillance system, medical insurance and claim databased will be used to track the outcome of the participants as supplement.

Contamination evaluation

During the study period, study team will contact the participants to evaluate the status of colorectal cancer beyond the study protocol. The extra screening examinations conducted by the participant during the study period are not allocated by the randomization, and therefore may introduce contamination to the study results. To evaluate the contamination status of this study, all the participant who are screened to have negative findings will be conducted one round of questionnaire interview in the fourth year of the study. Information regarding the history of diagnostic or screening colonic examination will be collected and assessed. We anticipate controlling the contamination rate to be below 10%. For the final analysis report, the contamination will be taken into consideration to estimate the screening effects.

Outcome measures

The primary outcome is the detection rate of advanced colorectal neoplasia (i.e., colorectal cancer and advanced adenoma). The secondary outcomes include mortality rate of colorectal cancer, incidence rate of colorectal cancer, participation rate,

complication rate.

Data collection

Epidemiological risk factor investigation

A standardized epidemiological questionnaire will be administered by trained interviewers for all participants to investigate the risk factors of colorectal cancer. Information including sociodemographic factors, history of bowel disease and clinical treatment, living habits, disease history and family history of cancer are collected and stored in the web-based data management system.

Health economic information

Comprehensive health economic evaluation will be conducted. Questionnaires including EuroQol five dimensions questionnaire (EQ-5D) and EQ-5D-3L will be used to measure health state of the participants. The direct costs on materials, equipment, personnel, drug and other resources will be collected from all participating sites to estimate the cost-effectiveness of different screening strategies in this clinical trial.

Statistical Considerations

Sample size

Sample sizes were calculated based on the evaluation of primary outcomes, i.e., advanced neoplasia detection rate (ADR). The hypothesis was that the ADR of risk-adapted screening group was superior to the FIT group and non-inferior to the colonoscopy group. According to the previous studies, the ADR of colonoscopy, FIT

and risk-adapted screening groups were 6.5%, 1.8% and 5.0% [13, 24]. We assumed the compliance rate was 50% to 70% for colonoscopy, 60%-90% for FIT and 60%-90% for the risk-adapted screening strategy and an overall loss-to-follow-up of 10%. For the comparison between the risk-adapted screening strategy and FIT group at different scenarios of the compliance rates, the largest sample size needed was 6550 when we set the significance level of α=0.05, the power of 0.8 and superiority margin (δ) of -0.005. For the comparison between the risk-adapted screening group and colonoscopy group, when assuming the respective compliance rates were 85% and 60%, the required sample sizes were 6032 and 3016, respectively, when we set the significance level of α=0.05, the power of 0.8, non-inferiority margin (δ) of -0.001. Therefore, the sample sizes of this study design (4000 for the colonoscopy group, 8000 for the FIT group and 8000 for the risk-adapted screening group) will accomplish the study hypotheses.

Statistical analyses

The primary outcome analysis will be a comparison of histologically confirmed colorectal cancer and advanced adenoma between the three intervention arms taking into consideration of compliance rate. Intention-to-treat and per-protocol analyses will be conducted. For secondary outcomes, mortality rate will be calculated as the ratio of the number of death due to colorectal cancer to the person-year at risk for each group. Person-years will be estimated from the time of randomization to the diagnosis date of colorectal cancer, death or censoring at the end of the study. Incidence rate will be estimated in a similar way. Chi-square tests and t-tests are used to compare categorical

and continuous variables between the two groups, respectively. The Cox proportional hazards regression model is adopted to examine the difference of incidence and mortality between different screening groups. For health economic evaluation, Markov model will be developed to evaluate the cost-effectiveness of different screening strategies for colorectal cancer in China. Statistical software, such as SAS software (version 9.2; SAS Institute, Cary, NC, USA), R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria) and TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA), will be used in the data analyses.

Ethics and dissemination

This study was approved by Ethics Committee of National Cancer Center/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College (approved number:18-013/1615) and the protocol was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1800015506).

The results of the study will be submitted for publication to peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. The results will be discussed by policy and decision makers. Access to the detailed research plan, participant-level dataset and statistical analysis code will be granted based on reasonable requests after the publication of the study.

Trial status

This screening trial is currently in the participant enrolment phase. 1600 eligible

participants have been randomised and are under respective colorectal cancer screening at August 2018. We anticipate the full analysis will be finalised in December 2021.

Discussion

Our study aims at evaluation the effectiveness and cost-effectiveness of three strategies for CRC screening in China. To our knowledge, this is the first large-scale randomized controlled trial on CRC screening based on community population in China. Colonoscopy is the gold standard for CRC screening, and FIT is the most widely used non-invasive CRC screening test. However, the magnitude of the effect of colonoscopy and FIT in population-based CRC screening is uncertain due to lack of evidence from randomized controlled trial. To date, there are four large-scale randomized controlled trials (NordICC, SCREESCO, CONFIRM and COLONPREV) comparing colonoscopy or FIT screening with regard to CRC incidence and mortality [25-28]. All the four trials are currently ongoing and conducted in Europe and North America. Our study will be the first large-scale CRC screening trial in Asia. In addition, we also include a novel risk-adapted screening strategy in our trial, which incorporates risk assessment with established screening methods. Our study will provide strong evidence on the effectiveness and feasibility of different strategies for CRC screening in China.

In recent years, the burden of CRC has been increasing in East-Asia which has been explained by changes in diet and a westernized lifestyle [29]. Countries including China, Japan and South Korea have implemented organized screening programs. For instance, in Japan, the CRC screening program was initiated since 1992 which uses FIT as the main screening method and the cost is covered by the national health

insurance [30]. In China, individuals aged 40-74 years are screened with FOBT or colonoscopy based on clinical risk indexes in some regions but not the entire country [20]. Furthermore, the most appropriate techniques for different populations in China are still under debate. The results of our study will therefore provide high-level evidence to aid for high demanding on the prevention and screening strategy for China and provides essential references for other countries.

In this study, we plan to finish the baseline recruitment and screening at the end of 2018 and continue long-term follow-up to evaluate the long-term effect of screening. There are several strengths for our study. Firstly, we use a prospective randomized design which would minimize the selection bias and provide high-level evidence compared to other study designs such as cross-sectional studies. In addition, except for active follow-up, we will use multiple resources such as cancer registry, death surveillance system, medical insurance and claim databases to track the outcomes of all the study participants. We will also construct a large biobank using prospectively collected specimens. Such biobank will serve as an essential platform for biomarker identification and validation for further researches.

The major challenges of this study are the control of loss to follow-up and the quality control of multi-center project. To address such concern, we will employ experienced study staff to contact and visit the participants regularly. Moreover, health education campaign will be conducted to improve the health literacy by means of lectures, videos, advertisement and social media. For the quality control, we will build an

expert panel including experts of epidemiologist, endoscopiest, pathologist and surgeons. Capacity training workshop will be held annually, and selection of study reports will be reviewed to ensure the study quality.

To sum up, this is a large-scale multi-center randomized controlled trials on comparing three strategies for CRC screening. Successful implementation of this study will provide strong evidence on the effectiveness and cost-effectiveness of CRC screening and provide essential references for policy-makers to design national screening programs in the future.

Authors' contributions

HC, NL and MD designed the study protocol, HC and NL drafted the manuscript, JR, CL, YZ, ZJ, ZZ and MD critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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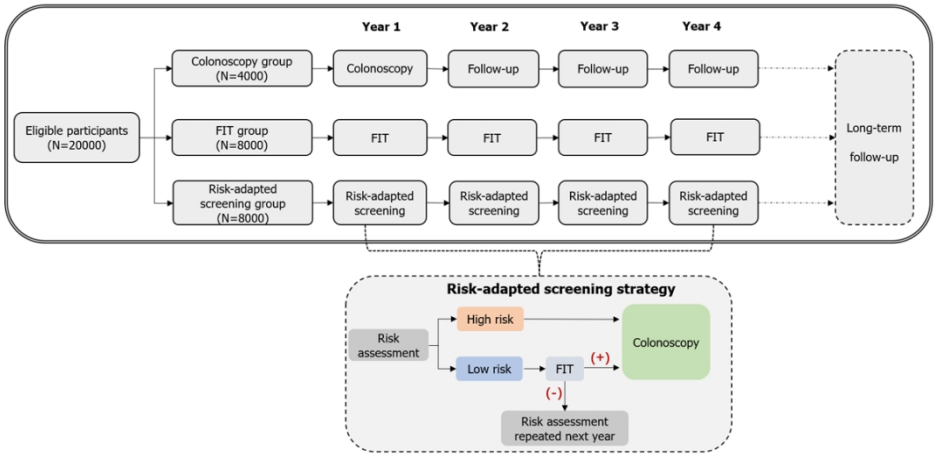
Table 1. Risk factors included in the colorectal cancer risk assessment score

Risk factor	**Criteria**	**Points**
Age (years)	<50	0
	50-69	1
	≥70	2
Gender	Female	0
	Male	1
Family history of colorectal cancer in a first-degree relative	Absent	0
	Present	1
Smoking	No	0
	Current or past	1
BMI	<23	0
	≥23	1

Figure Legend

Figure 1. SPIRIT flow diagram of the study design



SPIRIT flow diagram of the study design

338x190mm (96 x 96 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5 and 6
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 and 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): Study Protocol for a Multicenter Randomized Controlled Trial

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Keywords:	Colorectal cancer, Early detection, Risk score, Advanced adenoma, Randomized controlled trial

Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Introduction: Screening for colorectal cancer (CRC) has been demonstrated to be effective in reducing the burden of the disease. However, high-level evidence from randomized controlled trials on the effectiveness of CRC screening modalities is still lacking. We will conduct a large-scale multi-center randomized controlled trial for CRC screening in China to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies.

Methods and analysis: 20,000 eligible participants aged 50-74 years are enrolled in five provinces in China. After providing signed informed consent, the participants will be randomized into one of the three screening groups: 1) one-time colonoscopy (N=4,000); 2) annual fecal immunochemical test (FIT) (N=8,000); 3) annual risk-adapted screening strategy (N=8,000). For the risk adapted screening strategy, an established colorectal cancer risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score, will be used. Participants at high-risk of CRC will be referred to colonoscopy and participants at low-risk of CRC will be referred to take a FIT. Information on clinical reports, epidemiological risk factors and health economic factors will be collected and stored in a web-based data management system. We further request the participants to donate blood, fecal and saliva samples before conducting colonoscopy. The primary outcome is the detection rate of advanced colorectal neoplasia, and the secondary outcomes include the CRC-related mortality rate, incidence rate of CRC, participation rate and complication rate. The study will last for at least four years and the cohort will

be followed for ten years to adequately answer the scientific questions.

Ethics and dissemination: This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and the Peking Union Medical College (18-013/1615). The results of the study will be submitted for publication in peer-reviewed journals and will be discussed by policy and decision makers.

Trial registration: Chinese Clinical Trial Registry (ChiCTR1800015506, prospectively registered on 3 April 2018).

Keywords: Colorectal cancer, Early detection, Risk score, Advanced adenoma; Randomized controlled trial

Strengths and limitations of this study

- This is the first large-scale population-based colorectal cancer screening trial to compare the effectiveness and cost-effectiveness of three different screening strategies targeting adults aged 50 to 74 years old in China.
- A comprehensive health-economic evaluation will be performed to evaluate the cost-effectiveness of different screening arms and policy advice will therefore be provided based on the study findings.
- Prospective biospecimens collected before screening colonoscopy will be a valuable resource to explore novel biomarkers for early detection of colorectal cancer in further research.
- The sample sizes of the study population may not be adequate to compare the mortality reduction among the three screening arms after long-term follow-up.

Introduction

Colorectal Cancer (CRC) is the third most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide [1]. In China, with an estimate of 376,300 newly diagnosed CRC cases and 191,000 CRC-related deaths in 2015, the incidence ranked fourth and mortality ranked fifth of all cancer types. Notably, the incidence and mortality of CRC has been steadily increasing over the past decades in China [2]. Therefore, establishment of strategies on curbing the rising momentum of CRC in China is strongly required.

Evidence from randomized controlled trials and observational studies have demonstrated that screening could reduce the burden of CRC [3-5]. The established screening modalities include colonoscopy, flexible sigmoidoscopy, and stool-based tests (such as the fecal occult blood test (FOBT)), which have been widely used in many screening programs worldwide [6-8]. Colonoscopy is the gold standard for CRC. However, in population-based screening programs, colonoscopy is limited by low compliance rate, potential complication, high cost and limited resources [9, 10]. Guaiac-based FOBT (gFOBT) was introduced in the 1980s. Although the sensitivity of gFOBT for detecting CRC is not optimal, randomized controlled trials demonstrated that screening by gFOBT yielded a reduction in CRC mortality [5]. To date, the newly developed fecal immunochemical test (FIT) for hemoglobin showed superior diagnostic performance than traditional gFOBT [11]. However, evidence from randomized controlled trials to evaluate the screening efficacy of FIT is still lacking,

especially in the Chinese population [11].

Current guidelines recommend CRC screening for average-risk adults at a starting age of 50 years old [12-15]. However, in countries with unbalanced and limited healthcare resources, identification of high-risk populations and the development of risk-adapted screening strategies would be potentially more cost-efficient than traditional screening strategies. In previous studies, CRC risk scores based on environmental and/or generic factors were developed, which typically presented moderate diagnostic efficacy [16]. Further combing risk scores with established screening modalities such as colonoscopy and FIT was proposed and has shown promising diagnostic performance [13, 17, 18]. However, further validation of such risk-adapted screening strategies in large prospective cohorts and randomized controlled trial are still sparse.

Searching for biomarkers in early detection of CRC is a promising research area. Different types of biomarkers, including blood proteins, blood DNA methylation, fecal DNA, fecal microbiota and oral microbiota, were reported to be associated with CRC and could be potential targets for early detection of CRC [19]. Using the ongoing screening trials to construct the biobank will be both time- and economic- saving, which will also be an important platform for biomarker identification and validation for further investigations.

In China, screening for CRC has been implemented in several regions over the past decades [20, 21]. However, high-quality evidence ofor recommendation of CRC screening in the Chinese population is still lacking and in high demand [20]. Therefore,

we planned to conduct a population-based, multicenter, randomized controlled trial comparing colonoscopy, FIT and a novel risk-adapted screening strategy for CRC screening in the Chinese population, with the following aims: 1) to establish a large-scale CRC screening cohort with long-term follow-ups in China; 2) to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies in the Chinese population; 3) to construct a large epidemiological and clinical database and a biobank for further studies.

Methods/Design

Study setting and design

This is a prospective, multicenter, randomized controlled trial comparing multiple screening strategies on CRC screening in China. Participants who meet the study inclusion and exclusion criteria are recruited in five provinces in China. We aim to recruit at least 20,000 eligible participants at baseline. After obtaining signed informed consent, eligible participants are randomly allocated into one of the following three CRC screening groups in a 1:2:2 ratio (Figure 1). A four-year screening phase (with one-year baseline screening and three years follow-up screening) will be conducted for all participants, and a subsequent passive follow-up phase will also be implemented until the scientific questions are answered adequately. Detailed information about follow-up is shown in the following section.

1) ***Colonoscopy group (N=4,000):*** participants are recommended to undertake one-time screening colonoscopy at baseline. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis. . For the following years, all the participants will be interviewed to complete the follow-up questionnaire annually.
2) ***FIT group (N=8,000):*** FITs are offered to the participants annually. Participants who have positive FIT results are recommended to have a diagnostic colonoscopy. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis.

3) ***Risk assessment group (N=8,000):*** Colorectal cancer risk will be assessed using an established CRC risk stratification scoring system at baseline. For participants with high risk of CRC, screening colonoscopy will be offered. For participants with low risk of CRC, FITs are offered and those with positive FIT results are recommended to take further colonoscopy. During the annual follow-ups, participants who have negative FIT results and participants who have not had a screening colonoscopy will complete another round of risk assessment and the same screening procedures as at baseline will be offered. For participants who have already undertaken screening colonoscopy, no further screening intervention will be provided but will complete a questionnaire annually during the study period.

Randomization and allocation procedure

The randomization is conducted in a centralized controlled manner. The leading institute (Cancer Hospital, Chinese Academy of Medical Sciences) is responsible for the generation of the randomization scheme using a predefined seed by the statistical software R. Before recruitment, the staff who are responsible for the recruitment at each site and the participants are blinded to the allocation results. The allocation results are revealed after successful registration of the subject in a web-based data system. At the time of randomization, a unique Study Identification Number (SIN) is allocated to the participant and will be used for the participants during the entire study period.

Study population and recruitment

Participants aged 50 to 74 years who live in the study region and are able to sign

informed consent are eligible for this study. Exclusion criteria are: 1) prior history of colorectal cancer; 2) prior history of colonic resection; 3) undertaking any kind of cancer related therapy (except for non-melanoma skin cancer); 4) prior colonic examination, including colonoscopy, flexible sigmoidoscopy, CT colonography and Barium enema within five years; 5) prior history of fecal occult blood test and fecal DNA test within 1 year; 6) symptoms of lower gastrointestinal tract disease warranting colonoscopic evaluation, including: a) more than one episode of rectal bleeding within the past 6 months; b) documented iron deficiency anemia; c) significant documented unintentional weight loss (>10% of baseline weight) over 6 months; 7) significant comorbidity that would preclude benefit from screening or pose significant risk for the performance of colonoscopy (e.g. severe lung disease, end-stage renal disease, end-stage liver disease, severe heart failure, recent diagnosis of cancer (with the exception of non-melanoma skin cancer).

Recruitment procedures will involve the following steps:

(1) Recruitment of potential participants aged 50 to 74 years in the selected communities and check for eligibility by trained study staff;

(2) Signed written informed consent obtained from the eligible participants by trained study staff;

(3) Registration of the participant in the web-based data management system, SIN allocated, and randomization results revealed;

(4) Conducting respective intervention strategies per protocol;

Interventions

Colonoscopy

Standard clinical procedures of the screening colonoscopy will be followed, including appointment, obtaining informed consent, routine blood test for infectious diseases including hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections (if required by the hospitals, otherwise not implemented), distribution of bowel preparation drugs, diet control, anesthesia (if required by the participants) and colonoscopy examination. Colonoscopy will be performed by experienced endoscopists who have more than five-year experience performing colonoscopy. Abnormal findings during colonoscopy are carefully checked under standard clinical procedures and tissue specimens are collected for further pathology diagnosis. Any findings during colonoscopy are required to be photo documented. Clinical information such as the examination duration, sedation status, completeness, bowel preparation status, complication, polyp features (such as number, position, size, color and shape), description of other abnormal findings, as well as pathology diagnosis will be collected and documented in the web-based data management system.

For quality control, an expert panel including experienced endoscopists and pathologists will be formed. Each year, a selection of colonoscopy and pathology documentation will be assessed by the expert panel, and review reports will be transferred to the respective physicians about their performance.

Fecal immunochemical test (FIT)

Fecal immunochemical tests for human hemoglobin are provided by the study staff to participants after successful registration in this study. The FIT used in this study is a self-administered qualitative test, providing an endpoint that is read as positive or negative by eye if the fecal hemoglobin concentration exceeds the manufacturer-specific threshold. The participants can submit the results to the study website along with the picture of the test window or will be interviewed by the study staff for the test results within three days of distributing the FIT. For participants having invalid test results, new test devices will be provided until a valid test result is available. Participants are contacted and a follow up colonoscopy will be arranged if they are confirmed to have positive FIT results.

Colorectal cancer risk assessment

In this study, an established colorectal cancer risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score [22, 23], will be used. The APCS score is derived based on five common risk factors of CRC, including age, sex, family history of CRC in a first-degree relative, smoking and BMI (Body Mass Index). In a previous study conducted in Hong Kong, the subjects of high-risk defined by the APCS score had 2.48-fold increased prevalence of advanced neoplasm than the low-risk subjects, with the c-statistics of 0.65. Detailed information of the APCS score used in our study is shown in Table 1. Generally, for the risk-adapted screening group, participants are asked to filled in a questionnaire including the above mentioned risk factors. Participants with a score ≥ 4 are defined to be at high-risk of CRC, and participants with a score <4are

defined to have a low-risk of CRC. Participants will be informed about their evaluation results and receive the respective screening intervention as per the study protocol.

Patient and Public Involvement

During the process of recruitment, the participants will be informed about the research question, study design and screening intervention by study staff. The participants can quit the study and withdrawn the informed consent at any time based on their priorities, experiences or preferences. The participant and public had no role in the study design, recruitment and conduct of the study. All the screening intervention will be provided to the participants at no cost (compensated by this study), except for the subsequent therapeutic costs which must be paid by the participants themselves. The burden of the intervention and potential subsequent therapeutic procedure will be informed by the study staff at the recruitment phase. A report summarizing the screening results will be disseminated to the participants by study staff.

Biospecimen collection and handling

Participants who need to undertake colonoscopy are invited to donate stool, saliva and blood samples prior to colonoscopy. Standard Operating Procedures (SOPs) regarding biospecimen collection, handling and storage have been formulated and will be followed.

For stool samples, collection devices (including sample collection vials, ice bags, isothermal bags and operation brochures) are distributed. At the day before

colonoscopy, participants are suggested to collect raw stool samples before taking bowel cleaning drugs for colonoscopy. The participants are recommended to store the samples in the freezer or in the isothermal bags with ice bags until transported to the hospital. The samples are stored in the freezer (-80℃) immediately for future use when received.

For saliva samples, participants are provided with sample collection tubes (with oral DNA stabilization buffer) during their visit to the hospital before colonoscopy. Study staff will guide the participants for the saliva sample collection procedure. Collected samples will be aliquoted immediately and stored in the freezer (-80℃) for future use.

For blood samples, around 10ml vein blood samples (including 5ml EDTA anticoagulated blood and 5ml non-anticoagulation blood) will be drawn from the participants during their visit to the hospital before colonoscopy. Under the SOPs, blood samples are centrifuged, aliquoted and then stored in the freezer (-80℃) for future use.

Follow up

Both active follow-up and passive follow-up will be conducted in this study. For the active follow-up, all the participants will be interviewed by trained study staff by telephone call, home visit or other contact methods for collection of information such as physical examination, health status and outcome. For the passive follow-up, linkage data from cancer registry system, death surveillance system, medical insurance and claim database will be used to track the outcome of the participants.

Contamination evaluation

During the study period, the study team will contact the participants to evaluate the status of CRC beyond the study protocol. The extra screening examinations conducted by the participant during the study period are not allocated by the randomization, and therefore may introduce contamination to the study results. To evaluate the contamination status of this study, all participants who are screened to have negative findings will complete one round of questionnaire interview in the fourth year of the study. Information regarding the history of diagnostic or screening colonic examination will be collected and assessed. We anticipate controlling the contamination rate to be below 10%. For the final analysis report, the contamination will be taken into consideration to estimate the screening effects.

Outcome measures

The primary outcome is the colorectal cancer mortality rate . The secondary outcomes include detection rate of CRC, detection rate of precancerous lesions of CRC, compliance rate, complication rate.

Data collection

Epidemiological risk factor investigation

A standardized epidemiological questionnaire will be administered by trained interviewers to all participants to investigate the risk factors of colorectal cancer. Information including sociodemographic factors, history of bowel disease and clinical treatment, living habits, disease history and family history of cancer are collected and stored in the web-based data management system.

Health economic information

Comprehensive health economic evaluation will be conducted. Questionnaires including the EuroQol five dimensions questionnaire (EQ-5D) and EQ-5D-5L will be used to measure the health state of the participants. The direct costs on materials, equipment, personnel, drug and other resources will be collected from all participating sites to estimate the cost-effectiveness of different screening strategies in this clinical trial.

Data monitoring committee

A data monitoring committee composed of epidemiologists, endoscopists, pathologists and colorectal surgeons will monitor the data collection process and analyses. All data will be transmitted to the Central Data Management Team in the National Cancer Center of China/Cancer Hospital Chinese Academy of Medical Sciences, where the databases are constructed, and analyses are performed. In addition, any adverse events (e.g., perforation, bleeding) will be recorded in standardized forms by the study sites and will also be reported to the Ethics Committee for record.

Statistical Considerations

Sample size

Sample sizes were calculated based on the evaluation of primary outcomes, i.e., advanced neoplasia detection rate. The hypothesis was that the advanced neoplasia detection rate of the risk-adapted screening group was superior to the FIT group and non-inferior to the colonoscopy group. According to previous studies, the advanced neoplasia detection rate of colonoscopy, FIT and risk-adapted screening groups were

6.5%, 1.8% and 5.0% respectively [13, 24]. We assumed the compliance rate was 50% to 70% for colonoscopy, 60%-90% for FIT and 60%-90% for the risk-adapted screening strategy and an overall loss-to-follow-up of 10%. For the comparison between the risk-adapted screening strategy group and the FIT group at different scenarios of the compliance rates, the largest sample size needed was 6550 when we set the significance level of α=0.05, the power of 0.8 and superiority margin (δ) of -0.005. For the comparison between the risk-adapted screening group and the colonoscopy group, when assuming the respective compliance rates were 85% and 60%, the required sample sizes were 6032 and 3016, respectively, when we set the significance level of α=0.05, the power of 0.8, non-inferiority margin (δ) of -0.001. Therefore, the sample sizes of this study design (4000 for the colonoscopy group, 8000 for the FIT group and 8000 for the risk-adapted screening group) will accomplish the study hypotheses.

Statistical analyses

The primary outcome analysis will be a comparison of histologically confirmed CRC and advanced adenoma between the three intervention arms taking into consideration the compliance rate. Intention-to-treat and per-protocol analyses will be conducted. For secondary outcomes, mortality rate will be calculated as the ratio of the number of deaths due to CRC to the person-years at risk for each group. Person-years will be estimated from the time of randomization to the diagnosis date of CRC, death or censoring at the end of the study. The incidence rate will be estimated in a similar way. Chi-square tests and t-tests are used to compare categorical and continuous variables between the two groups, respectively. The Cox proportional hazards regression model

is adopted to examine the difference of incidence and mortality between different screening groups. For health economic evaluation, Markov models will be developed to evaluate the cost-effectiveness of different screening strategies for CRC in China. Statistical software, such as SAS software (version 9.2; SAS Institute, Cary, NC, USA), R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria) and TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA), will be used in the data analyses.

Ethics and dissemination

This study was approved by Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and the Peking Union Medical College (approved number:18-013/1615) and the protocol was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1800015506).

The results of the study will be submitted for publication to peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. The results will be discussed by policy and decision makers. Access to the detailed research plan, participant-level dataset and statistical analysis code will be granted based on reasonable requests after the publication of the study.

Trial status

This screening trial is currently in the participant enrolment phase. 1600 eligible participants have been randomized and are under respective colorectal cancer screening as of August 2018. We anticipate the full analysis to be finalized in December 2021.

Discussion

Our study aims to evaluate the effectiveness and cost-effectiveness of three strategies for CRC screening in China. To our knowledge, this is the first large-scale randomized controlled trial on CRC screening based on a community population in China. Colonoscopy is the gold standard for CRC screening, and FIT is the most widely used non-invasive CRC screening test. However, the magnitude of the effect of colonoscopy and FIT in population-based CRC screening is uncertain due to lack of evidence from randomized controlled trials. To date, there are three large-scale randomized controlled trials (SCREESCO, CONFIRM and COLONPREV) comparing colonoscopy or FIT screening with regard to CRC incidence and mortality [25-28]. All the three trials are currently ongoing and conducted in Europe and North America. Our study will be the first large-scale CRC screening trial in Asia. In addition, we also include a novel risk-adapted screening strategy in our trial, which incorporates risk assessment with established screening methods. Our study will provide strong evidence on the effectiveness and feasibility of different strategies for CRC screening in China.

In recent years, the burden of CRC has been increasing in East-Asia which has been explained by changes in diet and a westernized lifestyle [29]. Countries including China, Japan and South Korea have implemented organized screening programs. For instance, in Japan, the CRC screening program initiated in 1992, uses FIT as the main screening method and the cost is covered by the national health insurance [30]. In China, individuals aged 40-74 years are screened with FOBT or colonoscopy based on clinical

risk indexes in some regions but not the entire country [20]. Furthermore, the most appropriate techniques for different populations in China are still under debate. The results of our study will therefore provide high-level evidence to design CRC screening strategy for China and provides essential references for other countries.

In this study, we plan to finish the baseline recruitment and baseline screening before June of 2019 and will continue to have a total of three rounds of the screening intervention FIT group and the risk-adapted screening group. Long term passive follow-up will also be conducted to obtain the health outcomes of the participants and will be used for evaluation of the long-term effect of CRC screening. There are several strengths of our study. Firstly, we use a prospective randomized design which would minimize the selection bias and provide high-level evidence compared to other study designs such as cross-sectional studies. In addition, except for active follow-ups, we will also implement passive follow-ups using multiple resources such as cancer registry, death surveillance system, medical insurance and claim databases to track the outcomes of all the study participants. We will also construct a large biobank using prospectively collected specimens. Such a biobank will serve as an essential platform for biomarker identification and validation for further investigations.

The major challenges of this study are the control of loss to follow-up and the quality control of a multi-center project. To address such concern, we will employ experienced study staff to contact and visit the participants regularly. Moreover, a health education campaign will be conducted to improve the health literacy by means of lectures, videos,

advertisement and social media. For the quality control, we will build an expert panel including experts of epidemiologists, endoscopists, pathologists and surgeons. A capacity training workshop will be held annually, and a selection of study reports will be reviewed to ensure the study quality.

To sum up, this is a large-scale multi-center randomized controlled trial, comparing three strategies for CRC screening. Successful implementation of this study will provide strong evidence on the effectiveness and cost-effectiveness of CRC screening and provide essential references for policy-makers to design national screening programs in the future.

Authors' contributions

HC, NL and MD designed the study protocol, HC and NL drafted the manuscript, JS, JR, CL, YZ, ZJ, ZZ and MD critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

Acknowledgements

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Table 1. Risk factors and respective advocated points of the Asia-Pacific Colorectal Screening (APCS) score used in this trial

Risk factor	**Criteria**	**Points**
Age (years)	<50	0
	50-69	1
	≥70	2
Sex	Female	0
	Male	1
Family history of colorectal cancer in a first-degree relative	Absent	0
	Present	1
Smoking	No	0
	Current or past	1
BMI	<23	0
	≥23	1

Abbreviations: BMI, Body Mass Index, calculated as Weight (kg)/height^2(meter^2)

Figure Legend

Figure 1. SPIRIT flow diagram of the study design

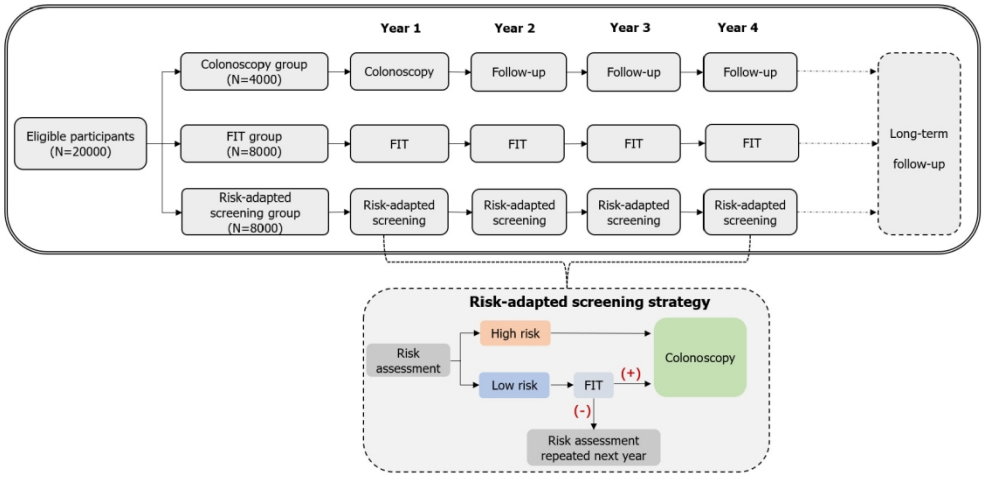

Figure 1. SPIRIT flow diagram of the study design

338x190mm (133 x 120 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5 and 6
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 and 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): Study Protocol for a Multicenter Randomized Controlled Trial

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Secondary Subject Heading:	Epidemiology, Gastroenterology and hepatology, Health economics, Public health
Keywords:	Colorectal cancer, Early detection, Risk score, Advanced adenoma, Randomized controlled trial

Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): Study Protocol for a Multicenter Randomized Controlled Trial

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Word account:3820

Abstract

Introduction: Screening for colorectal cancer (CRC) has been demonstrated to be effective in reducing the burden of the disease. However, high-level evidence from randomized controlled trials on the effectiveness of CRC screening modalities is still lacking. We will conduct a large-scale multi-center randomized controlled trial for CRC screening in China to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies.

Methods and analysis: 20,000 eligible participants aged 50-74 years are enrolled in five provinces in China. After providing signed informed consent, the participants will be randomized into one of the three screening groups: 1) one-time colonoscopy (N=4,000); 2) annual fecal immunochemical test (FIT) (N=8,000); 3) annual risk-adapted screening strategy (N=8,000). For the risk adapted screening strategy, an established colorectal cancer risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score, will be used. Participants at high-risk of CRC will be referred to colonoscopy and participants at low-risk of CRC will be referred to take a FIT. Information on clinical reports, epidemiological risk factors and health economic factors will be collected and stored in a web-based data management system. We further request the participants to donate blood, fecal and saliva samples before conducting colonoscopy. The primary outcome is the detection rate of advanced colorectal neoplasia, and the secondary outcomes include the CRC-related mortality rate, incidence rate of CRC, participation rate and complication rate. The study will last for at least four years and the cohort will

be followed for ten years to adequately answer the scientific questions.

Ethics and dissemination: This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and the Peking Union Medical College (18-013/1615). The results of the study will be submitted for publication in peer-reviewed journals and will be discussed by policy and decision makers.

Trial registration: Chinese Clinical Trial Registry (ChiCTR1800015506, prospectively registered on 3 April 2018).

Keywords: Colorectal cancer, Early detection, Risk score, Advanced adenoma; Randomized controlled trial

Strengths and limitations of this study

- This is the first large-scale population-based colorectal cancer screening trial to compare the effectiveness and cost-effectiveness of three different screening strategies targeting adults aged 50 to 74 years old in China.
- A comprehensive health-economic evaluation will be performed to evaluate the cost-effectiveness of different screening arms and policy advice will therefore be provided based on the study findings.
- Prospective biospecimens collected before screening colonoscopy will be a valuable resource to explore novel biomarkers for early detection of colorectal cancer in further research.
- The sample sizes of the study population may not be adequate to compare the mortality reduction among the three screening arms after long-term follow-up.

Introduction

Colorectal Cancer (CRC) is the third most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide [1]. In China, with an estimate of 376,300 newly diagnosed CRC cases and 191,000 CRC-related deaths in 2015, the incidence ranked fourth and mortality ranked fifth of all cancer types. Notably, the incidence and mortality of CRC has been steadily increasing over the past decades in China [2]. Therefore, establishment of strategies on curbing the rising momentum of CRC in China is strongly required.

Evidence from randomized controlled trials and observational studies have demonstrated that screening could reduce the burden of CRC [3-5]. The established screening modalities include colonoscopy, flexible sigmoidoscopy, and stool-based tests (such as the fecal occult blood test (FOBT)), which have been widely used in many screening programs worldwide [6-8]. Colonoscopy is the gold standard for CRC. However, in population-based screening programs, colonoscopy is limited by low compliance rate, potential complication, high cost and limited resources [9, 10]. Guaiac-based FOBT (gFOBT) was introduced in the 1980s. Although the sensitivity of gFOBT for detecting CRC is not optimal, randomized controlled trials demonstrated that screening by gFOBT yielded a reduction in CRC mortality [5]. To date, the newly developed fecal immunochemical test (FIT) for hemoglobin showed superior diagnostic performance than traditional gFOBT [11]. However, evidence from randomized controlled trials to evaluate the screening efficacy of FIT is still lacking,

especially in the Chinese population [11].

Current guidelines recommend CRC screening for average-risk adults at a starting age of 50 years old [12-15]. However, in countries with unbalanced and limited healthcare resources, identification of high-risk populations and the development of risk-adapted screening strategies would be potentially more cost-efficient than traditional screening strategies. In previous studies, CRC risk scores based on environmental and/or generic factors were developed, which typically presented moderate diagnostic efficacy [16]. Further combing risk scores with established screening modalities such as colonoscopy and FIT was proposed and has shown promising diagnostic performance [13, 17, 18]. However, further validation of such risk-adapted screening strategies in large prospective cohorts and randomized controlled trial are still sparse.

Searching for biomarkers in early detection of CRC is a promising research area. Different types of biomarkers, including blood proteins, blood DNA methylation, fecal DNA, fecal microbiota and oral microbiota, were reported to be associated with CRC and could be potential targets for early detection of CRC [19]. Using the ongoing screening trials to construct the biobank will be both time- and economic- saving, which will also be an important platform for biomarker identification and validation for further investigations.

In China, screening for CRC has been implemented in several regions over the past decades [20, 21]. However, high-quality evidence ofor recommendation of CRC screening in the Chinese population is still lacking and in high demand [20]. Therefore,

we planned to conduct a population-based, multicenter, randomized controlled trial comparing colonoscopy, FIT and a novel risk-adapted screening strategy for CRC screening in the Chinese population, with the following aims: 1) to establish a large-scale CRC screening cohort with long-term follow-ups in China; 2) to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies in the Chinese population; 3) to construct a large epidemiological and clinical database and a biobank for further studies.

Methods/Design

Study setting and design

This is a prospective, multicenter, randomized controlled trial comparing multiple screening strategies on CRC screening in China. Participants who meet the study inclusion and exclusion criteria are recruited in five provinces in China. We aim to recruit at least 20,000 eligible participants at baseline. After obtaining signed informed consent, eligible participants are randomly allocated into one of the following three CRC screening groups in a 1:2:2 ratio (Figure 1). A four-year screening phase (with one-year baseline screening and three years follow-up screening) will be conducted for all participants, and a subsequent passive follow-up phase will also be implemented until the scientific questions are answered adequately. Detailed information about follow-up is shown in the following section.

1) ***Colonoscopy group (N=4,000):*** participants are recommended to undertake one-time screening colonoscopy at baseline. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis. . For the following years, all the participants will be interviewed to complete the follow-up questionnaire annually.
2) ***FIT group (N=8,000):*** FITs are offered to the participants annually. Participants who have positive FIT results are recommended to have a diagnostic colonoscopy. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis.

3) ***Risk assessment group (N=8,000):*** Colorectal cancer risk will be assessed using an established CRC risk stratification scoring system at baseline. For participants with high risk of CRC, screening colonoscopy will be offered. For participants with low risk of CRC, FITs are offered and those with positive FIT results are recommended to take further colonoscopy. During the annual follow-ups, participants who have negative FIT results and participants who have not had a screening colonoscopy will complete another round of risk assessment and the same screening procedures as at baseline will be offered. For participants who have already undertaken screening colonoscopy, no further screening intervention will be provided but will complete a questionnaire annually during the study period.

Randomization and allocation procedure

The randomization is conducted in a centralized controlled manner. The leading institute (Cancer Hospital, Chinese Academy of Medical Sciences) is responsible for the generation of the randomization scheme using a predefined seed by the statistical software R. Before recruitment, the staff who are responsible for the recruitment at each site and the participants are blinded to the allocation results. The allocation results are revealed after successful registration of the subject in a web-based data system. At the time of randomization, a unique Study Identification Number (SIN) is allocated to the participant and will be used for the participants during the entire study period.

Study population and recruitment

Participants aged 50 to 74 years who live in the study region and are able to sign

informed consent are eligible for this study. Exclusion criteria are: 1) prior history of colorectal cancer; 2) prior history of colonic resection; 3) undertaking any kind of cancer related therapy (except for non-melanoma skin cancer); 4) prior colonic examination, including colonoscopy, flexible sigmoidoscopy, CT colonography and Barium enema within five years; 5) prior history of fecal occult blood test and fecal DNA test within 1 year; 6) symptoms of lower gastrointestinal tract disease warranting colonoscopic evaluation, including: a) more than one episode of rectal bleeding within the past 6 months; b) documented iron deficiency anemia; c) significant documented unintentional weight loss (>10% of baseline weight) over 6 months; 7) significant comorbidity that would preclude benefit from screening or pose significant risk for the performance of colonoscopy (e.g. severe lung disease, end-stage renal disease, end-stage liver disease, severe heart failure, recent diagnosis of cancer (with the exception of non-melanoma skin cancer).

Recruitment procedures will involve the following steps:

(1) Recruitment of potential participants aged 50 to 74 years in the selected communities and check for eligibility by trained study staff;

(2) Signed written informed consent obtained from the eligible participants by trained study staff;

(3) Registration of the participant in the web-based data management system, SIN allocated, and randomization results revealed;

(4) Conducting respective intervention strategies per protocol;

Interventions

Colonoscopy

Standard clinical procedures of the screening colonoscopy will be followed, including appointment, obtaining informed consent, routine blood test for infectious diseases including hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infections (if required by the hospitals, otherwise not implemented), distribution of bowel preparation drugs, diet control, anesthesia (if required by the participants) and colonoscopy examination. Colonoscopy will be performed by experienced endoscopists who have more than five-year experience performing colonoscopy. Abnormal findings during colonoscopy are carefully checked under standard clinical procedures and tissue specimens are collected for further pathology diagnosis. Any findings during colonoscopy are required to be photo documented. Clinical information such as the examination duration, sedation status, completeness, bowel preparation status, complication, polyp features (such as number, position, size, color and shape), description of other abnormal findings, as well as pathology diagnosis will be collected and documented in the web-based data management system.

For quality control, an expert panel including experienced endoscopists and pathologists will be formed. Each year, a selection of colonoscopy and pathology documentation will be assessed by the expert panel, and review reports will be transferred to the respective physicians about their performance.

Fecal immunochemical test (FIT)

Fecal immunochemical tests for human hemoglobin are provided by the study staff to participants after successful registration in this study. The FIT used in this study is a self-administered qualitative test, providing an endpoint that is read as positive or negative by eye if the fecal hemoglobin concentration exceeds the manufacturer-specific threshold (100 ng Hb/mL buffer, corresponds to 10 μg Hb/g feces). A previous pilot analysis demonstrated that the sensitivities for detecting CRC and advanced adenomas were 76% and 37%, respectively, at a specificity of 92% (data not publicly available). The participants can submit the results to the study website along with the picture of the test window or will be interviewed by the study staff for the test results within three days of distributing the FIT. For participants having invalid test results, new test devices will be provided until a valid test result is available. Participants are contacted and a follow up colonoscopy will be arranged if they are confirmed to have positive FIT results.

Colorectal cancer risk assessment

In this study, an established colorectal cancer risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score [22, 23], will be used. The APCS score is derived based on five common risk factors of CRC, including age, sex, family history of CRC in a first-degree relative, smoking and BMI (Body Mass Index). In a previous study conducted in Hong Kong, the sensitivity, specificity, positive predictive value and negative predictive value of the risk score for detecting advanced neoplasms were 33.3%, 81.0%, 5.17% and 97.5%, respectively, defining score ≥4 as high risk for CRC

[23]. Based on previous evidences, we designed the risk score system and detailed information is shown in Table 1. Generally, for the risk-adapted screening group, participants are asked to fill in a questionnaire including the above mentioned risk factors. Participants with a score ≥ 4 are defined to be at high-risk of CRC, and participants with a score <4 are defined to have a low-risk of CRC. Participants will be informed about their evaluation results and receive the respective screening intervention as per the study protocol.

Patient and Public Involvement

During the process of recruitment, the participants will be informed about the research question, study design and screening intervention by study staff. The participants can quit the study and withdrawn the informed consent at any time based on their priorities, experiences or preferences. The participant and public had no role in the study design, recruitment and conduct of the study. All the screening intervention will be provided to the participants at no cost (compensated by this study), except for the subsequent therapeutic costs which must be paid by the participants themselves. The burden of the intervention and potential subsequent therapeutic procedure will be informed by the study staff at the recruitment phase. A report summarizing the screening results will be disseminated to the participants by study staff.

Biospecimen collection and handling

Participants who need to undertake colonoscopy are invited to donate stool, saliva and blood samples prior to colonoscopy. Standard Operating Procedures (SOPs) regarding

biospecimen collection, handling and storage have been formulated and will be followed.

For stool samples, collection devices (including sample collection vials, ice bags, isothermal bags and operation brochures) are distributed. At the day before colonoscopy, participants are suggested to collect raw stool samples before taking bowel cleaning drugs for colonoscopy. The participants are recommended to store the samples in the freezer or in the isothermal bags with ice bags until transported to the hospital. The samples are stored in the freezer (-80℃) immediately for future use when received.

For saliva samples, participants are provided with sample collection tubes (with oral DNA stabilization buffer) during their visit to the hospital before colonoscopy. Study staff will guide the participants for the saliva sample collection procedure. Collected samples will be aliquoted immediately and stored in the freezer (-80℃) for future use.

For blood samples, around 10ml vein blood samples (including 5ml EDTA anticoagulated blood and 5ml non-anticoagulation blood) will be drawn from the participants during their visit to the hospital before colonoscopy. Under the SOPs, blood samples are centrifuged, aliquoted and then stored in the freezer (-80℃) for future use.

Follow up

Both active follow-up and passive follow-up will be conducted in this study. For the active follow-up, all the participants will be interviewed by trained study staff by

telephone call, home visit or other contact methods for collection of information such as physical examination, health status and outcome. For the passive follow-up, linkage data from cancer registry system, death surveillance system, medical insurance and claim database will be used to track the outcome of the participants.

Contamination evaluation

During the study period, the study team will contact the participants to evaluate the status of CRC beyond the study protocol. The extra screening examinations conducted by the participant during the study period are not allocated by the randomization, and therefore may introduce contamination to the study results. To evaluate the contamination status of this study, all participants who are screened to have negative findings will complete one round of questionnaire interview in the fourth year of the study. Information regarding the history of diagnostic or screening colonic examination will be collected and assessed. We anticipate controlling the contamination rate to be below 10%. For the final analysis report, the contamination will be taken into consideration to estimate the screening effects.

Outcome measures

The primary outcome is the detection rate of advanced colorectal neoplasia (CRC and advanced adenoma). The secondary outcomes include mortality rate of CRC, detection rate of any neoplasm, compliance rate and complication rate.

Data collection

Epidemiological risk factor investigation

A standardized epidemiological questionnaire will be administered by trained interviewers to all participants to investigate the risk factors of colorectal cancer. Information including sociodemographic factors, history of bowel disease and clinical treatment, living habits, disease history and family history of cancer are collected and stored in the web-based data management system.

Health economic information

Comprehensive health economic evaluation will be conducted. Questionnaires including the EuroQol five dimensions questionnaire (EQ-5D) and EQ-5D-5L will be used to measure the health state of the participants. The direct costs on materials, equipment, personnel, drug and other resources will be collected from all participating sites to estimate the cost-effectiveness of different screening strategies in this clinical trial.

Data monitoring committee

A data monitoring committee composed of epidemiologists, endoscopists, pathologists and colorectal surgeons will monitor the data collection process and analyses. All data will be transmitted to the Central Data Management Team in the National Cancer Center of China/Cancer Hospital Chinese Academy of Medical Sciences, where the databases are constructed, and analyses are performed. In addition, any adverse events (e.g., perforation, bleeding) will be recorded in standardized forms by the study sites and will also be reported to the Ethics Committee fo r record.

Statistical Considerations

Sample size

Sample sizes were calculated based on the evaluation of primary outcomes, i.e., advanced colorectal neoplasia detection rate. The hypothesis was that the advanced neoplasia detection rate of the risk-adapted screening group was superior to the FIT group and non-inferior to the colonoscopy group. According to previous studies, the reference advanced neoplasia detection rate of colonoscopy, FIT and risk-adapted screening groups were 6.5%, 1.8% and 5.0%, respectively [13, 24]. We assumed the compliance rate was 50% to 70% for colonoscopy, 60%-90% for FIT and 60%-90% for the risk-adapted screening strategy and an overall loss-to-follow-up of 10%. For the comparison between the risk-adapted screening strategy group and the FIT group at different scenarios of the compliance rates, the largest sample size needed was 6550 when we set the significance level of α=0.05, the power of 0.8 and superiority margin (δ) of -0.005. For the comparison between the risk-adapted screening group and the colonoscopy group, when assuming the respective compliance rates were 85% and 60%, the required sample sizes were 6032 and 3016, respectively, when we set the significance level of α=0.05, the power of 0.8, non-inferiority margin (δ) of -0.001. Therefore, the sample sizes of this study design (4000 for the colonoscopy group, 8000 for the FIT group and 8000 for the risk-adapted screening group) will accomplish the study hypotheses.

Statistical analyses

The primary outcome analysis will be a comparison of histologically confirmed CRC and advanced adenoma between the three intervention arms taking into consideration the compliance rate. Intention-to-treat and per-protocol analyses will be conducted. For

secondary outcomes, mortality rate will be calculated as the ratio of the number of deaths due to CRC to the person-years at risk for each group. Person-years will be estimated from the time of randomization to the diagnosis date of CRC, death or censoring at the end of the study. The incidence rate will be estimated in a similar way. Chi-square tests and t-tests are used to compare categorical and continuous variables between the two groups, respectively. The Cox proportional hazards regression model is adopted to examine the difference of incidence and mortality between different screening groups. For health economic evaluation, Markov models will be developed to evaluate the cost-effectiveness of different screening strategies for CRC in China. Statistical software, such as SAS software (version 9.2; SAS Institute, Cary, NC, USA), R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria) and TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA), will be used in the data analyses.

Ethics and dissemination

This study was approved by Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences and the Peking Union Medical College (approved number:18-013/1615) and the protocol was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1800015506).

The results of the study will be submitted for publication to peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. The results will be discussed by policy and decision makers. Access to the detailed research

plan, participant-level dataset and statistical analysis code will be granted based on reasonable requests after the publication of the study.

Trial status

This screening trial is currently in the participant enrolment phase. 1600 eligible participants have been randomized and are under respective colorectal cancer screening as of August 2018. We anticipate the full analysis to be finalized in December 2021.

Discussion

Our study aims to evaluate the effectiveness and cost-effectiveness of three strategies for CRC screening in China. To our knowledge, this is the first large-scale randomized controlled trial on CRC screening based on a community population in China. Colonoscopy is the gold standard for CRC screening, and FIT is the most widely used non-invasive CRC screening test. However, the magnitude of the effect of colonoscopy and FIT in population-based CRC screening is uncertain due to lack of evidence from randomized controlled trials. To date, there are three large-scale randomized controlled trials (SCREESCO, CONFIRM and COLONPREV) comparing colonoscopy or FIT screening with regard to CRC incidence and mortality [25-28]. All the three trials are currently ongoing and conducted in Europe and North America. Our study will be the first large-scale CRC screening trial in Asia. In addition, we also include a novel risk-adapted screening strategy in our trial, which incorporates risk assessment with established screening methods. Our study will provide strong evidence on the effectiveness and feasibility of different strategies for CRC screening in China.

In recent years, the burden of CRC has been increasing in East-Asia which has been explained by changes in diet and a westernized lifestyle [29]. Countries including China, Japan and South Korea have implemented organized screening programs. For instance, in Japan, the CRC screening program initiated in 1992, uses FIT as the main screening method and the cost is covered by the national health insurance [30]. In China, individuals aged 40-74 years are screened with FOBT or colonoscopy based on clinical

risk indexes in some regions but not the entire country [20]. Furthermore, the most appropriate techniques for different populations in China are still under debate. The results of our study will therefore provide high-level evidence to design CRC screening strategy for China and provides essential references for other countries.

In this study, we plan to finish the baseline recruitment and baseline screening before June of 2019 and will continue to have a total of three rounds of the screening intervention FIT group and the risk-adapted screening group. Long term passive follow-up will also be conducted to obtain the health outcomes of the participants and will be used for evaluation of the long-term effect of CRC screening. There are several strengths of our study. Firstly, we use a prospective randomized design which would minimize the selection bias and provide high-level evidence compared to other study designs such as cross-sectional studies. In addition, except for active follow-ups, we will also implement passive follow-ups using multiple resources such as cancer registry, death surveillance system, medical insurance and claim databases to track the outcomes of all the study participants. We will also construct a large biobank using prospectively collected specimens. Such a biobank will serve as an essential platform for biomarker identification and validation for further investigations.

The major challenges of this study are the control of loss to follow-up and the quality control of a multi-center project. To address such concern, we will employ experienced study staff to contact and visit the participants regularly. Moreover, a health education campaign will be conducted to improve the health literacy by means of lectures, videos,

advertisement and social media. For the quality control, we will build an expert panel including experts of epidemiologists, endoscopists, pathologists and surgeons. A capacity training workshop will be held annually, and a selection of study reports will be reviewed to ensure the study quality.

To sum up, this is a large-scale multi-center randomized controlled trial, comparing three strategies for CRC screening. Successful implementation of this study will provide strong evidence on the effectiveness and cost-effectiveness of CRC screening and provide essential references for policy-makers to design national screening programs in the future.

Authors' contributions

HC, NL and MD designed the study protocol, HC and NL drafted the manuscript, JS，JR, CL, YZ, ZJ, ZZ and MD critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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Table 1. Risk factors and respective advocated points of the Asia-Pacific Colorectal Screening (APCS) score used in this trial

Risk factor	**Criteria**	**Points**
Age (years)	<50	0
	50-69	1
	≥70	2
Sex	Female	0
	Male	1
Family history of colorectal cancer in a first-degree relative	Absent	0
	Present	1
Smoking	No	0
	Current or past	1
BMI	<23	0
	≥23	1

Abbreviations: BMI, Body Mass Index, calculated as Weight (kg)/height^2(meter^2)

Figure Legend

Figure 1. SPIRIT flow diagram of the study design

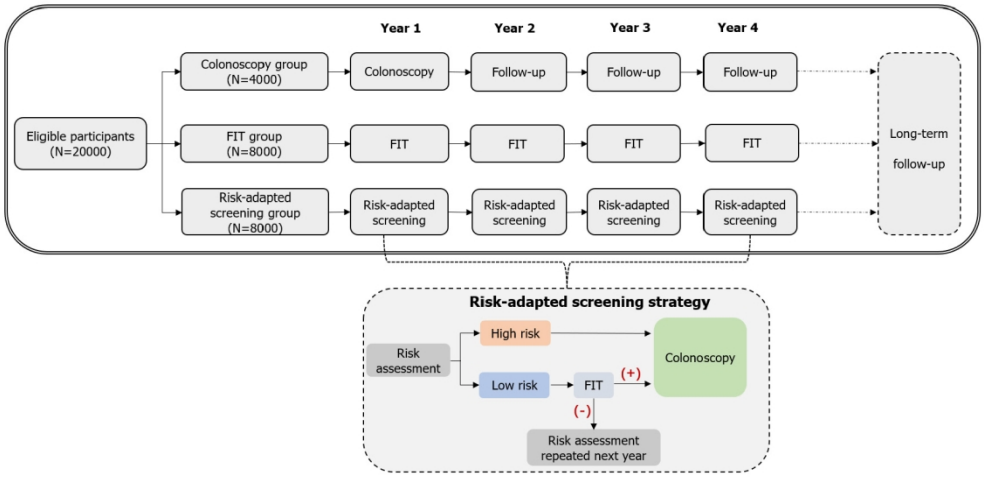

Figure 1. SPIRIT flow diagram of the study design

338x190mm (133 x 120 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5 and 6
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 and 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): A Study Protocol for a Multicenter Randomized Controlled Trial

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Comparative Evaluation of Novel Screening Strategies for Colorectal Cancer Screening in China (TARGET-C): A Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Introduction: Screening for colorectal cancer (CRC) is effective in reducing the disease burden. However, high-level evidence from randomized controlled trials on the effectiveness of CRC screening modalities is still lacking. We will conduct a large-scale multi-center randomized controlled trial in China to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies.

Methods and analysis: 20,000 eligible participants aged 50-74 years are enrolled in five provinces in China. After providing signed informed consent, the participants will be randomized into one of the three screening groups: 1) one-time colonoscopy (N=4,000); 2) annual fecal immunochemical test (FIT) (N=8,000); and 3) annual risk-adapted screening strategy (N=8,000). The risk-adapted screening strategy will use an established CRC risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score. Participants at high-risk of CRC will be referred for colonoscopy, while participants at low risk will be referred for an FIT. Information on clinical reports, epidemiological risk factors, and health economic factors will be collected and stored in a web-based data management system. We will further request the participants to donate blood, fecal, and saliva samples before conducting the colonoscopy. The primary outcome will be the detection rate of advanced colorectal neoplasia and the secondary outcomes will include the rates of CRC-related mortality, incidence of CRC, participation, and complications. The study will last for at least 4 years and the cohort will be followed for 10 years to adequately answer the scientific questions.

Ethics and dissemination: This study was approved by the Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College (18-013/1615). The results of the study will be submitted for publication in peer-reviewed journals and will be discussed by policy and decision makers.

Trial registration: Chinese Clinical Trial Registry (ChiCTR1800015506, prospectively registered on 3 April 2018).

Keywords: Colorectal cancer, Early detection, Risk score, Advanced adenoma, Randomized controlled trial

Strengths and limitations of this study

- This is the first large-scale population-based trial in China to compare the effectiveness and cost-effectiveness of three different colorectal cancer screening strategies targeting adults aged 50–74 years.
- A comprehensive health-economic evaluation will be performed to evaluate the cost-effectiveness of the different screening arms and policy advice will, therefore, be provided based on the study findings.
- Prospective biospecimens collected before screening colonoscopy will be a valuable resource to explore novel biomarkers for the early detection of colorectal cancer in further research.
- The sample sizes of the study population may not be adequate to compare mortality reduction among the three screening arms after long-term follow-up.

INTRODUCTION

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and the second most common cause of cancer-related death worldwide.[1] In China, with estimated 376,300 newly diagnosed CRC cases and 191,000 CRC-related deaths in 2015, the incidence and mortality ranked fourth and fifth of all cancer types, respectively. The incidence and mortality of CRC in China have been steadily increasing in recent decades.[2] Therefore, the establishment of strategies to curb the rising momentum of CRC in China is strongly required.

Evidence from randomized controlled trials and observational studies has demonstrated that screening could reduce the burden of CRC.[3-5] The established screening modalities include colonoscopy, flexible sigmoidoscopy, and stool-based tests such as the fecal occult blood test (FOBT), which have been widely used in many screening programs worldwide.[6-8] Colonoscopy is the gold standard for CRC. However, in population-based screening programs, colonoscopy is limited by low compliance rates, potential complications, high costs, and limited resources.[9, 10] Guaiac-based FOBT (gFOBT) was introduced in the 1980s. Although the sensitivity of gFOBT for detecting CRC is not optimal, randomized controlled trials demonstrated that screening by gFOBT yielded a reduction in CRC mortality.[5] The newly developed fecal immunochemical test (FIT) for hemoglobin showed superior diagnostic performance compared to that of traditional gFOBT.[11] However, evidence from randomized controlled trials evaluating the screening efficacy of FIT is still lacking, especially in

the Chinese population.[11]

Current guidelines recommend CRC screening for average-risk adults starting at 50 years of age.[12-15] However, in countries with unbalanced and limited healthcare resources, identification of high-risk populations and the development of risk-adapted screening strategies may be more cost-efficient than traditional screening strategies. Previous studies developed CRC risk scores based on environmental and/or genetic factors, which typically presented moderate diagnostic efficacy.[16] The combination of risk scores and established screening modalities such as colonoscopy and FIT had been proposed and has shown promising diagnostic performance.[13, 17, 18] However, further validation of such risk-adapted screening strategies in large prospective cohorts and randomized controlled trial are sparse.

Identification of biomarkers for the early detection of CRC is a promising area of research. Different types of biomarkers, including blood proteins, blood DNA methylation, fecal DNA, fecal microbiota, and oral microbiota, have been associated with CRC and could be targets for the early detection of CRC.[19] The use of ongoing screening trials to construct a biobank will be both time-saving and economical and will also be an important platform for future biomarker identification and validation.

CRC screening in China has been implemented in several regions over the past decades.[20, 21] However, high-quality evidence for the recommendation of CRC screening in the Chinese population is still lacking and in high demand.[20] Therefore, we plan to conduct a population-based, multicenter, randomized controlled trial

comparing colonoscopy, FIT, and a novel risk-adapted CRC screening strategy in the Chinese population, with the following aims: 1) to establish a large-scale CRC screening cohort with long-term follow-ups in China; 2) to evaluate the effectiveness and cost-effectiveness of different CRC screening strategies in the Chinese population; and 3) to construct a large epidemiological and clinical database and a biobank for further studies.

METHODS AND ANALYSIS

Study setting and design

This prospective, multicenter, randomized controlled trial will compare multiple CRC screening strategies in China. Participants who meet the study inclusion and exclusion criteria will be recruited in five provinces in China. We aim to recruit at least 20,000 eligible participants at baseline. After obtaining signed informed consent, eligible participants will be randomly allocated into one of the three CRC screening groups in a 1:2:2 ratio (Figure 1). A 4-year screening phase (with 1-year baseline screening and 3 years of follow-up screening) will be conducted for all participants and a subsequent passive follow-up phase will also be implemented until the scientific questions are answered adequately. Detailed information about the follow-up is described in the following section.

1) Colonoscopy group (N=4,000): participants are recommended to undergo a one-time screening colonoscopy at baseline. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis. In the following years, all participants will be interviewed to complete the follow-up questionnaire annually.
2) FIT group (N=8,000): FITs are offered to the participants annually. Participants with positive FIT findings are recommended to undergo a diagnostic colonoscopy. Abnormal findings removed during colonoscopy will be sent to pathology for further analysis.

3) Risk assessment group (N=8,000): Colorectal cancer risk will be assessed using an established CRC risk stratification scoring system at baseline. For participants at high risk of CRC, screening colonoscopy will be offered. For participants at low risk of CRC, FITs will be offered and those with positive FIT results will be recommended to undergo further colonoscopy. During the annual follow-ups, participants with negative FIT results and those who have not had a screening colonoscopy will complete another round of risk assessment and the same screening procedures as at baseline will be offered. Participants who have already undergone screening colonoscopy will be provided no further screening intervention but the participants will complete a questionnaire annually during the study period.

Randomization and allocation procedure

The randomization will be conducted in a centralized, controlled manner. The leading institute (Cancer Hospital, Chinese Academy of Medical Sciences) is responsible for the generation of the randomization scheme using a predefined seed from the statistical software R. Before recruitment, both the staff responsible for recruitment at each site and the participants will be blinded to the allocation results. The allocation results will be revealed after successful registration of the subject in a web-based data system. At the time of randomization, each patient will be assigned a unique Study Identification Number (SIN), which will be used during the entire study period.

Study population and recruitment

Participants aged 50–74 years who live in the study region and are able to sign informed

consent are eligible for this study. The exclusion criteria are: 1) prior history of CRC; 2) prior history of colonic resection; 3) receipt of any kind of cancer-related therapy (except for non-melanoma skin cancer); 4) prior colonic examination, including colonoscopy, flexible sigmoidoscopy, computed tomography (CT) colonography, and barium enema within 5 years; 5) prior history of fecal occult blood test and fecal DNA test within 1 year; 6) symptoms of lower gastrointestinal tract disease warranting colonoscopic evaluation, including a) more than one episode of rectal bleeding within the past 6 months, b) documented iron deficiency anemia, and c) significant documented unintentional weight loss (>10% of baseline weight) over 6 months; and 7) significant comorbidity that would preclude benefit from screening or pose a significant risk to the performance of colonoscopy (e.g., severe lung disease, end-stage renal disease, end-stage liver disease, severe heart failure, or recent diagnosis of cancer, with the exception of non-melanoma skin cancer).

The recruitment procedures will include the following steps:

(1) Recruitment of potential participants aged 50–74 years in the selected communities and checking for eligibility by trained study staff;

(2) Signed written informed consent obtained from the eligible participants by trained study staff;

(3) Registration of the participant in the web-based data management system, SIN assignment, and randomization results revealed; and

(4) Conducting respective intervention strategies per protocol;

Interventions

Colonoscopy

Standard clinical procedures for the screening colonoscopy will be followed, including appointment; obtaining informed consent; routine blood testing for infectious diseases including hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency virus (HIV) infections (if required by the hospitals, otherwise not implemented); distribution of bowel preparation drugs; diet control; anesthesia (if required by the participants); and colonoscopy examination. The colonoscopies will be performed by experienced endoscopists with more than 5 years of experience in performing colonoscopy. Abnormal findings during colonoscopy will be carefully checked under standard clinical procedures and tissue specimens will be collected for further pathology diagnosis. Any findings during colonoscopy are required to be documented photographically. Clinical information such as the examination duration, sedation status, completeness of colonoscopy, bowel preparation status, complications, polyp features (number, position, size, color, and shape), description of other abnormal findings, as well as pathology diagnosis will be collected and documented in the web-based data management system.

For quality control, an expert panel will be formed, including experienced endoscopists and pathologists. Each year, a selection of colonoscopy and pathology documentation will be assessed by the expert panel and review reports will be transferred to the respective physicians regarding their performance.

Fecal immunochemical test (FIT)

FITs for human hemoglobin will be provided by the study staff to participants after successful registration in this study. The FIT used in this study is a self-administered qualitative test, providing an endpoint that is visually interpreted as positive or negative by eye if the fecal hemoglobin concentration exceeds the manufacturer-specific threshold (100 ng Hb/mL buffer, corresponding to 10 μg Hb/g feces). A previous pilot analysis demonstrated that the sensitivities of 76% and 37%, respectively, for the detection of CRC and advanced adenomas, at a specificity of 92% (data not publicly available). The participants can submit the results to the study website along with the picture of the test window or will be interviewed by the study staff regarding the test results within 3 days of distributing the FIT. For participants with invalid test results, new test devices will be provided until a result is available. Participants with confirmed positive FIT results will be contacted and a follow-up colonoscopy will be arranged.

CRC risk assessment

This study will use an established CRC risk scoring system, the Asia-Pacific Colorectal Screening (APCS) score.[22, 23] The APCS score is derived from five common risk factors of CRC, including age, sex, family history of CRC in a first-degree relative, smoking, and body mass index (BMI). In a previous study conducted in Hong Kong, the sensitivity, specificity, positive predictive value, and negative predictive value of the risk score for detecting advanced neoplasms were 33.3%, 81.0%, 5.17%, and 97.5%, respectively, defining a score ≥4 as high risk for CRC.[23] Based on previous evidence, we designed the risk score system and detailed information shown in Table 1. Generally,

the participants of the risk-adapted screening group will be asked to complete a questionnaire including the above-mentioned risk factors. Participants with a score ≥4 are defined to be at high risk of CRC, while those with a score <4 are defined to be at low risk of CRC. Participants will be informed about their evaluation results and receive the respective screening intervention as per the study protocol.

Patient and public involvement

During the process of recruitment, study staff will inform the participants about the research question, study design, and screening intervention. The participants can quit the study and withdraw their informed consent at any time based on their priorities, experiences, or preferences. The participants and the public had no role in the study design, recruitment, and conduct. All screening interventions will be provided to the participants at no cost (compensated by this study), except for the subsequent therapeutic costs which must be paid by the participants themselves. At the recruitment phase, the study staff will inform the participants of the burden of the intervention and potential subsequent therapeutic procedure. The study staff will also disseminate to the participants a report summarizing the screening results.

Biospecimen collection and handling

Participants who require colonoscopy will be invited to donate stool, saliva, and blood samples prior to colonoscopy. Standard Operating Procedures (SOPs) regarding biospecimen collection, handling, and storage have been formulated and will be followed.

For stool samples, collection devices (sample collection vials, ice bags, isothermal bags, and operation brochures) will be distributed. On the day before the colonoscopy, the participants will be suggested to collect raw stool samples before taking bowel cleaning drugs for colonoscopy. The participants will be recommended to store the samples in the freezer or in the isothermal bags with ice bags until transported to the hospital. The samples will be stored at -80°C immediately upon receipt for future use.

For saliva samples, participants will be provided with sample collection tubes containing oral DNA stabilization buffer during their visit to the hospital before the colonoscopy. Study staff will guide the participants on the saliva sample collection procedure. The collected samples will be aliquoted immediately and stored at -80°C for future use.

Approximately 10 mL venous blood samples (including 5 mL ethylenediaminetetraacetic acid anticoagulated blood and 5 mL non-anticoagulated blood) will be drawn from the participants during their visit to the hospital before colonoscopy. Under the SOPs, the blood samples are to be centrifuged, aliquoted, and stored at -80°C for future use.

Follow-up

The study will conduct both active and passive follow-up. For the active follow-up, all the participants will be interviewed by trained study staff by telephone call, home visit, or other contact methods for the collection of information such as physical examination, health status, and outcome. For the passive follow-up, linkage data from the cancer

registry system, death surveillance system, and medical insurance and claim databases will be used to track the outcome of the participants.

Contamination evaluation

During the study period, the study team will contact the participants to evaluate the status of CRC beyond the study protocol. The extra screening examinations attended by the participants during the study period are not allocated by randomization and, therefore, may introduce bias to the study results. To evaluate the contamination status of this study, all participants whose screening findings are negative will complete one round of questionnaire interview in the fourth year of the study. Information regarding the history of diagnostic or colonic examination screening will be collected and assessed. We anticipate controlling the contamination rate to be below 10%. The final analysis report will consider the contamination when estimating the effects of screening.

Outcome measures

The primary outcome is the detection rate of advanced colorectal neoplasia (CRC and advanced adenoma). The secondary outcomes include the rates of CRC mortality, detection of any neoplasm, compliance, and complications.

Data collection

Epidemiological risk factor investigation

A standardized epidemiological questionnaire will be administered by trained interviewers to all participants to investigate the risk factors of CRC. Information including sociodemographic factors, history of bowel disease and clinical treatment,

living habits, disease history, and family history of cancer will be collected and stored in a web-based data management system.

Health economic information

A comprehensive health economic evaluation will be conducted. Questionnaires including the EuroQol five dimensions questionnaire (EQ-5D) and EQ-5D-5L will be used to measure the health state of the participants. The direct costs of materials, equipment, personnel, drug, and other resources will be collected from all participating sites to estimate the cost-effectiveness of different screening strategies in this clinical trial.

Data monitoring committee

A data monitoring committee comprising epidemiologists, endoscopists, pathologists, and colorectal surgeons will monitor data collection and analyses. All data will be transmitted to the Central Data Management Team at the National Cancer Center of China/Cancer Hospital Chinese Academy of Medical Sciences, where the databases are constructed and analyses are performed. In addition, any adverse events, such as perforation, and bleeding, will be recorded in standardized forms by the study sites and will also be reported to the Ethics Committee for their records.

Statistical Considerations

Sample sizes

Sample sizes were calculated based on the evaluation of primary outcomes; i.e., the detection rate of advanced colorectal neoplasia. The hypothesis was that this rate in the risk-adapted screening group was superior to that of the FIT group and non-inferior to

that of the colonoscopy group. According to previous studies, the reference advanced neoplasia detection rates of colonoscopy, FIT, and risk-adapted screening groups were 6.5%, 1.8%, and 5.0%, respectively.[13, 24] We assumed compliance rates of 50–70% for colonoscopy, 60–90% for FIT, and 60–90% for the risk-adapted screening strategy and an overall loss-to-follow-up rate of 10%. For the comparison between the risk-adapted screening strategy and the FIT groups for different scenarios of compliance rates, the largest sample size needed was 6,550 at a significance level of $\alpha = 0.05$, power of 0.8, and superiority margin (δ) of -0.005. For comparison between the risk-adapted screening and colonoscopy groups, assuming respective compliance rates of 85% and 60%, the required sample sizes were 6,032 and 3,016, respectively, for a significance level of $\alpha = 0.05$, power of 0.8, and non-inferiority margin (δ) of -0.001. Therefore, the sample sizes in this study design (4,000 for the colonoscopy group, 8,000 for the FIT group, and 8,000 for the risk-adapted screening group) will accomplish the study hypotheses.

Statistical analyses

The primary outcome analysis will be comparisons of histologically-confirmed CRC and advanced adenoma between the three intervention arms, taking the compliance rate into consideration. Intention-to-treat and per-protocol analyses will be conducted. For secondary outcomes, the mortality rate will be calculated as the ratio of the number of deaths due to CRC to the person-years at risk for each group. Person-years will be estimated from the time of randomization to the diagnosis date of CRC, death, or censoring at the end of the study. The incidence rate will be estimated similarly. Chi-

square and t-tests will be used to compare categorical and continuous variables between the two groups, respectively. The Cox proportional hazards regression model will be adopted to examine the differences in incidence and mortality between different screening groups. For health economic evaluations, Markov models will be developed to evaluate the cost-effectiveness of different CRC screening strategies in China. Statistical software such as SAS (version 9.2; SAS Institute, Cary, NC, USA), R (version 3.4.1, R Foundation for Statistical Computing, Vienna, Austria), and TreeAge Pro 2016 (TreeAge Software, Inc., MA, USA), will be used for the data analyses.

Ethics and dissemination

This study was approved by Ethics Committee of the National Cancer Center/Cancer Hospital, the Chinese Academy of Medical Sciences, and Peking Union Medical College (approved number: 18-013/1615) and the protocol was registered in the Chinese Clinical Trial Registry (registration number: ChiCTR1800015506).

The results of the study will be submitted for publication to peer-reviewed journals and conferences following the Consolidated Standards of Reporting Trials guidelines. The results will be discussed by policy and decision makers. Access to the detailed research plan, participant-level dataset, and code for statistical analysis will be granted based on reasonable requests after the publication of the study.

Trial status

This screening trial is currently in the participant enrolment phase. A total of 1,600 eligible participants have been randomized and are under respective CRC screening as

of August 2018. We anticipate the full analysis to be finalized in December 2021.

DISCUSSION

Our study aims to evaluate the effectiveness and cost-effectiveness of three CRC screening strategies in China. To our knowledge, this is the first large-scale randomized controlled trial on CRC screening based on a community population in China. Colonoscopy is the gold standard for CRC screening and FIT is the most widely used non-invasive CRC screening test. However, the magnitude of the effect of colonoscopy and FIT in population-based CRC screening is uncertain due to a lack of evidence from randomized controlled trials. To date, three large-scale randomized controlled trials (SCREESCO, CONFIRM, and COLONPREV) have compared colonoscopy or FIT screening regarding CRC incidence and mortality.[25-28] All three trials are ongoing and being conducted in Europe and North America. Our study will be the first large-scale CRC screening trial in Asia. In addition, we also include a novel risk-adapted screening strategy that incorporates risk assessment with established screening methods. Our study will provide strong evidence on the effectiveness and feasibility of different strategies for CRC screening in China.

In recent years, the burden of CRC has been increasing in East-Asia due to changes in diet and Westernized lifestyles.[29] Countries including China, Japan, and South Korea have implemented organized screening programs. For instance, in Japan, the CRC screening program initiated in 1992 uses FIT as the main screening method, the cost of which is covered by the national health insurance.[30] In China, individuals aged 40–74 years are screened with FOBT or colonoscopy based on clinical risk indexes in some

regions but not the entire country.[20] Furthermore, the most appropriate techniques for different populations in China are still under debate. The results of our study will, therefore, provide high-level evidence to design CRC screening strategies for China and will also provide an essential reference for other countries.

We plan to finish the baseline recruitment and baseline screening for this study before June 2019 and will have a total of three rounds of screening intervention FIT and risk-adapted screening groups. Long-term passive follow-up will also be conducted to determine the health outcomes of the participants for the evaluation of the long-term effect of CRC screening. Our study has several strengths. First, the prospective randomized design will minimize selection bias and provide high-level evidence compared to those of other designs such as cross-sectional studies. In addition, except for active follow-up, we will also implement passive follow-up using multiple resources such as cancer registry, death surveillance system, and medical insurance and claim databases to track the outcomes of the study participants. We will also construct a large biobank using prospectively collected specimens. This biobank will serve as an essential platform for biomarker identification and validation for further investigations.

The major challenges of this study are control of loss to follow-up and quality control of a multi-center project. To address such concerns, we will employ experienced study staff to regularly contact and visit the participants. Moreover, a health education campaign will be conducted to improve health literacy by means of lectures, videos, advertisements, and social media. For quality control, we will build an expert panel

including experts in epidemiology, endoscopy, pathology, and surgery. A capacity training workshop will be held annually and a selection of study reports will be reviewed to ensure study quality.

In summary, this large-scale multi-center randomized controlled trial will compare three CRC screening strategies. Successful implementation of this study will provide strong evidence on the effectiveness and cost-effectiveness of CRC screening and provide an essential reference for policy-makers to design national screening programs.

AUTHORS' CONTRIBUTIONS

HC, NL, and MD designed the study protocol; HC and NL drafted the manuscript; and JS, JR, CL, YZ, ZJ, ZZ, and MD critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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Table 1. Risk factors and respective proposed points for Asia-Pacific Colorectal Screening (APCS) scores to be used in this trial

Risk factor	**Criteria**	**Points**
Age (years)	<50	0
	50-69	1
	≥70	2
Sex	Female	0
	Male	1
Family history of colorectal cancer in a first-degree relative	Absent	0
	Present	1
Smoking	No	0
	Current or past	1
BMI	<23	0
	≥23	1

Abbreviations: BMI, Body mass index, calculated as weight (kg)/height^2(meters^2)

Figure Legend

Figure 1. Standard Protocol Items for Randomized Trials (SPIRIT) flow diagram of the study design

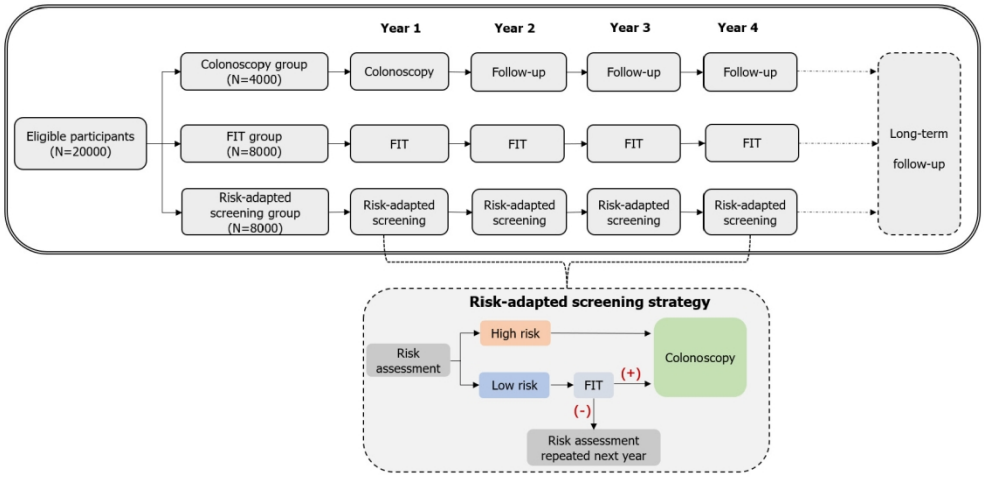

Figure 1. SPIRIT flow diagram of the study design

338x190mm (133 x 120 DPI)

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	4
	2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	22
	5b	Name and contact information for the trial sponsor	NA
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	11
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5
	6b	Explanation for choice of comparators	5 and 6
Objectives	7	Specific objectives or hypotheses	5 and 6
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	7

Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8 and 9
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	10
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	11
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	8
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	15
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	9

Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	9
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	9
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	9
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	16
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	16
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	16
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11

	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	17
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	17
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	10
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	9
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	NA
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	NA
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA

Appendices

Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	13

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.