Author's response to reviews

Title: Screening for colorectal cancer with FOBT, Virtual colonoscopy and optical colonoscopy: protocol of a randomized clinical trial in the Florence district (SAVE study).

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Author's response to reviews: see over
Dear Editor,

Please find enclosed the revised version of the paper entitled “Screening for colorectal cancer with FOBT, Virtual colonoscopy and optical colonoscopy: protocol of a randomized clinical trial in the Florence district (SAVE study).” (MS: 7252467157729706) which my co-workers and I modified according to the suggestions and requests from You and the Reviewers. As requested the changes in the manuscript are in outlined in red.

In particular:

Editor:

Randomization process was detailed in the Methods and Design section as follows (page 9, last line):

“Simple randomization will be performed by personnel of epidemiology unit of ISP O in a single procedure using STATA software version 12. Randomization of married people will be forced, i.e. individuals will be assigned to the same arm of their husband/wife, to prevent subjects’ requests to be allocated to another group. Invitees and investigators will not be masked from the allocation.”

Reviewer #1:

Minor essential revisions

1. Please clarify “...procedural or biological risks” as not completely clear as to the meaning.

   Re: In the Background section, the sentence containing “...procedural and biological risks” (page 5, line 22) was clarified as follows:

   “…procedural risks (i.e. complications, such as colonic perforation) or biological risks (i.e. ionizing radiation exposure).”

2. “...this reason is affected by false negative and false positive results”. Can the authors give examples to illustrate this point?

   Re: In the Background section, the sentence containing “…this reason is affected by false negative and false positive results” (page 5, line 18) was modified including examples, as follows:

   “…this reason is affected by false negative results due to, for example, incorrect storage of sample or drug assumption, and false positive results due to haemorrhoids or diet and medications in case of guaiac test.”
3. “Differently from FS...”. Please rephrase eg “unlike FS...”

Re: In the Background section “Differently from FS,...” (page 6, line 14) was rephrased as “Unlike FS...”, as requested.

4. Please clarify “randomized per household and street”. Are they randomised per house or per street? Bit unclear how it can be both.

Re: Reconsideration of the randomization procedure yielded as the sole forcing to allocate married people to the same arm while it was irrespective of household and street. Randomization process was clarified in Methods and Design section, as follows (page 9, line 22):

“Simple randomization will be performed by personnel of epidemiology unit of ISPO in a single procedure using STATA software version 12. Randomization of married people will be forced, i.e. individuals will be assigned to the same arm of their husband/wife, to prevent subjects’ requests to be allocated to another group. Invitees and investigators will not be masked from the allocation.”

5. The internal validation of the information sheets is interesting. Can a bit more detail be provided?

Re: Internal validation of information leaflets was detailed as follows (page 10, line 12):

“…underwent an internal validation procedure using the “focus group technique”, which involved 10 ISPO employees aged 55-64 years.”

6. Please briefly explain the ISPO, how it works and what information it collects

Re: In the Background section the role of ISPO was explained (page 6, line 6):

“ISPO is an institution of the Tuscany Health Service, which is aimed to organize, realize and monitor clinical and research activities in population-based screening programmes for breast, cervical and colorectal cancer in the Tuscany region of Italy [18].”

The ISPO web site was included in references [18]. Subsequent references were renumbered.
7. Please define “experienced” radiologist in terms of what they must achieve in the pre-read test dataset.

Re: In the CTC section (page 13, line 5) the word “experienced” was deleted and the required threshold the radiologist should achieve was specified as follows (page 13, line 10):

“…and to have completed a qualified test based on a series of 30 endoscopically verified CTCs achieving per-patient sensitivity and specificity of at least 90% for lesions ≥ 6mm.”

8-9. How will less important extra-colonic findings be handled eg gallstones? Will patients need to be seen in the screening centre by the radiologist? If not, will the patient’s family practitioner be informed? Will extra tests generated by CTC be actively recorded?

Re: In the CTC section, the management of extra-colonic findings was clarified as requested: (page 13, line 20):

“Relevant extracolonic findings (C-RADS E3, E4) seen by the radiologist during quick axial images scrolling will be annotated and communicated to the subject in the screening centre [37]. Less important extracolonic findings (e.g. gallstones) will not be reported. Diagnostic examinations generated by relevant extracolonic findings will not be recorded.”

Patient’s family practitioner will not be informed.

10. It would be useful to give the definitions of the various polyp morphologies on CTC and colonoscopy, particularly for flat polyps which is important for subsequent comparison of detection rates.

Re: In CTC and OC sections, the definition of flat lesions was inserted: (page 13, line 14)

“Flat lesions will be defined as polyp with height less than 3 mm above the mucosal surface [36].” and “Definition of flat lesions will be the same used for CTC.” (page 14, line 12).

11. If patients request follow up CTC for polyps instead of colonoscopy-will this be allowed?

Re: In case of positive CTC and refusal of colonoscopy, the option of follow up CTC will be not offered, as now stated in the Methods and Design section:

“In these cases the option of follow up CTC will not be offered.” (page 16, line 6)

12. Cost effectiveness of the pathways is a stated aim. Can a little detail be added as to how this will be done eg handling of extra-colonic findings, cost model assumptions etc?
Re: A cost-effective analysis is not planned at the moment. We will perform an evaluation of costs of the three screening strategies using activity-based costing model, as now stated in “Primary Objectives” section:

“To compare costs of the three screening strategies using an activity-based costing model.” (page 9, line 1).

Discretionary revisions

1. Can details be provided of the randomisation block and who will do this?
   Re: See above (point 4).

2. The information leaflets given to people will be key as they cover performance, risks etc. Can the journal print these as an appendix or online supplement?
   Re: We provide in attachment the four information leaflets (in Italian) for publication as appendices if allowed by Editor.

3. Perhaps list the contraindications to scopolamine as they can be controversial!
   Re: The following contraindications to scopolamine butylbromide were inserted in the CTC section:
   “(e.g. hypersensitivity to scopolamine butylbromide or to any of the product inactive ingredients; untreated narrow angle glaucoma; prostatic hypertrophy with urinary retention)” (page 12, line 16)

4. Is it possible or planned to offer the reduced bowel prep option to those refusing CTC with full bowel prep? This will help decipher if it is the bowel prep which is the problem or CTC screening itself.
   Re: It is not planned to offer reduced bowel prep to subjects who refuse CTC with standard prep. Study is designed to compare adherence to CTC with limited bowel prep vs CTC with standard prep. This aim of the study was inserted separately in “Primary Objectives” (page 8, line 20):
   “To compare the participation rate to CTC with reduced cathartic preparation versus CTC with standard bowel preparation.”

5. Will CTC colonic insufflation be done by a radiologist or technician?
   Re: In the CTC section we inserted (page 12, line 12):
   “performed by radiologist”.

6. It seems CTC reading will be 2D based. Are there any stipulations as to the use of 3D endoluminal review? Will a 3D flythrough be permitted? Will 3D problem solving be available?
   Re: 3D endoluminal view will be available but only for problem solving. In the CTC section
the reading approach was clarified as follows (page 13, line 7):

“Firstly the radiologist will examine the polyp candidates proposed by CAD using 2D images with 3D view for problem solving. Then he/she will perform a quick unassisted 2D reading, again supplemented by 3D for problem solving, to look for missed lesions by CAD.”

7. A first CAD read paradigm is very interesting and arguably how CTC would be read in a large volume screening setting given the lack of trained readers and need for efficiency. Is there any plan to compare this with the conventional second read CAD paradigm?

Re: Not. A comparison between CAD as first reader and CAD as second reader is not an aim of the present study.

8. Presumably CTC read times will be measured

Re: Yes, they will be. In the CTC section, this sentence was inserted:

“CTC reading times will be annotated.” (page 13, line 15)

9. Which teleradiology system will be used? Will CTC data be anonymized for transfer?

Re: In the CTC section, this sentence was inserted:

“...be transferred to a centralized reading centre for interpretation, through RIS/PACS metropolitan area network using uncompressed DICOM format.” (page 12, line 21).

CTC data will not be anonymized.

10. How many CTC readers will take part in the study?

Re: In the CTC section, this sentence was inserted:

“Two to 5 CTC readers will take part in the study” (page 13, line 8)

11. Will a proforma be provided for each recruited patient with regard to complications or will data collection rely on self reporting from recruitment sites?

Re: In the Complications section, collection of information about complications was explicated as follows:

“Complications arisen during CTC and OC, or immediately after, will be annotated in the study database. Information about subsequent complications will be collected through self-reporting,
telephonic questionnaire administered one month after the examination and hospital discharge database.” (page 15, line 1)

12. Given the intention to treat analysis, patients with positive CTC refusing to undergo colonoscopy will presumably be classified as CTC pathway “negative” for advanced adenomas? Probably worth stating.

Re: In the Statistical analysis section, this sentence was inserted:
“Notably, in the intention to treat analysis, subjects with positive CTC refusing to undergo colonoscopy will be classified as CTC pathway “negative” for advanced adenomas.” (page 18, line 3)

13. The assumption of 30% compliance with colonoscopy is arguably quite high. Have the trialists any local data to support this assumption?

Re: The assumption of an adherence to OC of 30% is based on data from a previous multicentric trial (SCORE3), which showed an adherence to colonoscopy of 27.9% in the district of Florence. This phrase was inserted in the Sample size section (page 18, line 15):
“This assumption is based on data from SCORE3 trial, where adherence to colonoscopy in the Florence district was 27.9% [22].”

14. Also a stated aim is to test a teleradiology solution for CTC. Can the authors expand what aspects will actually be tested?

Re: We discussed again about this aim and shared the conclusion that within the frame of the SAVE protocol we simply shall use the RIS/PACS metropolitan area network for transmission of CTC datasets from acquisition hospitals to the unified reading centre. Accordingly this aim was dropped from the list of “Secondary objectives”.

Hoping that the present version of the paper will satisfy requirements to be accepted for publication on Trials my co-workers and I would like to thank You and the Reviewers for the help in improving the quality of our protocol.

Best regards,

Lapo Sali MD, Ph.D.