Continuous development of colorectal cancer screening programmes

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Colorectal cancer (CRC) screening programmes are far from perfect. Many crucial questions remain, yet expensive CRC screening services are implemented throughout the world without a plan on how to evaluate and improve the service. The time is ripe for improving the design of CRC screening programmes.

A prerequisite for introducing new health services should be that efficacy has been shown in randomized clinical trials (RCT). CRC screening services, however, have often been introduced on political grounds prior to favorable results on CRC mortality in RCTs which additionally have not been designed for separate sex and age-group analyses [1-6].

There is concern that CRC screening may not be suitable for a 'one-size fits all' approach. Recent studies have shown that women, in contrast to men, have little or no benefit from either sigmoidoscopy or fecal occult blood testing (FOBT) [7-9], and screening efficacy may be lower for colonoscopy and FOBT with advancing age [10, 11].

Under such circumstances, it is important that screening programmes are designed to generate knowledge about efficacy and safety valid for the target population because:

a. Continuous comparative effectiveness research (CER) can yield essential information at key decision points in the screening programme during roll-out and full coverage.

   I. In a roll-out phase of a programme stretching over several years, randomization should provide a no-screening control group until roll-out is complete (*randomized implementation*)

   II. After complete roll-out, the screening programme should incorporate randomized arms for testing of new methods and strategies (*randomized testing*).

b. Trials may be outdated when results are ready because new tests emerge. A frequent excuse for not funding new trials has been to await results from ongoing studies. Parallel and time-saving rather than successive, serial trials may be conducted within screening programmes.

c. Problems with funding sufficiently large, stand-alone trials will be minimized when performed within the framework of a screening programme. Funding for screening trials has proved difficult. These are large, expensive trials with a time horizon of more than 10 years. Political patience has proved to be much shorter, and screening programmes have been introduced prematurely [1].

As an example of *randomized implementation*, the Finnish FOBT screening programme used guaiac-FOBT (gFOBT) in a randomized roll-out in 2004 [12]. Randomized implementation during a roll-out phase stretching over years was accepted since it takes time to build up a screening organization and sufficient capacity for histopathology and colonoscopy services required whichever primary screening modality is chosen. In 2016, the Finnish programme was halted because evaluation of the randomized introduction showed no reduction in CRC mortality [13]. The Polish colonoscopy screening programme similarly introduced randomized roll-out in 2012 [14]. An example of *randomized testing* is the Norwegian screening pilot programme launched in 2012 with

randomization between immunochemical FOBT (iFOBT) and sigmoidoscopy. The national CRC screening programme itself, planned to start in 2019, is aiming for randomization between iFOBT and colonoscopy screening. Those who do not accept randomization, will be screened with iFOBT. Randomized comparison of newer methods and strategies should be encouraged in the full-coverage phase of a programme.

These examples show that randomized implementation and randomized testing integrated as part of a screening programme, is both feasible and scientifically justified. We suggest that any programme should be designed in a way that enables assessment of efficacy and safety of different methods, screening strategies (how to invite, when to invite, whom to invite) and organization (e.g. travelling distance to screening facilities).

Only two of the currently used screening methods have been through RCTs with sufficient follow-up time to provide results on CRC mortality: gFOBT and sigmoidoscopy.[15]. Studies on test performance suggest that iFOBT is better than gFOBT [16] and intuitively, colonoscopy should be better than sigmoidoscopy which only covers the distal colon. Still, we do not know the ultimate additional gain on CRC mortality and incidence, how to secure equal service for women and men (although different cut-off values for iFOBT positivity have been suggested [17]) and possible improvements by targeting specific age groups. FOBT screening must be repeated biennially and causes a number of false positive tests with subsequent exposure to colonoscopy. Colonoscopy screening, the “gold standard” examination for patients with colon symptoms, leads to overtreatment of polyps in a screening setting with increased complication rates as techniques and technologies improve detection and encourage more aggressive polypectomy in the thin-walled proximal colon [18, 19]. Accepting imperfection of current CRC screening should make it easier to embrace the concept that the road towards a continuously improving screening programme should be paved with randomized trials within the existing programme to improve the programme itself. With most of the western world soon to be covered by CRC screening programmes, there will not be

a valid population for RCTs on screening outside the programme target population. There is a long list of important issues to address when planning and running a screening programme [20]. Integration of RCTs when appropriate should be added to this list.

In summary, screening programmes should address the limited knowledge traditionally supporting implementation of screening. They should be designed to fill general knowledge gaps in CRC screening in general, and for the local programme in particular. Knowledge may reveal that programmes do not deliver according to expectations and underpin a need for further integrated studies for continuous improvement – or closing down.

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