Ongoing RCT in CRC screening

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Disclosure statement

• Consultancy:
  • Alpha-Sigma
  • Norgine
  • MSD
BACKGROUND

• CRC screening reduces CRC incidence and mortality
• FOBT and sigmoidoscopy have demonstrated its efficacy as screening method in RCT
• No RCT demonstrating efficacy of colonoscopy
• There is not direct comparison between screening methods
• Several ongoing RCT are comparing the most used screening methods: FIT vs colonoscopy
Colorectal Cancer Screening in Average-Risk Population: a Pragmatic, Multicenter, Randomized Controlled Trial Comparing Colonoscopy and Immunochemical Fecal Occult Blood Testing

Enrique Quintero & Antoni Castells on behalf of the COLONPREV Study investigators
Aims

Primary end-point

- To compare the efficacy of one-time colonoscopy vs. biennial FIT for the reduction of CRC-related mortality at 10 years in average-risk population.

Secondary end-points

1) **At baseline screening (1st round):** participation rate, diagnostic yield, major complications and consume of resources

2) **At completion of the trial (2021):** accumulative participation and compliance rates, diagnostic yield, major complications, consume of resources and cost-effectiveness
Study design

- Conducted in 8 Spanish regions

- Without population-based program
- With population-based program

Assymptomatic 50-69 years
Quality audits

- **Observational nested studies:**
  1. *Modifiable endoscopic factors that influence the ADR in CRC screening colonoscopies*
     
     *Jover et al. Gastrointest Endosc 2013*

  2. *Factors related to the endoscopist*

     *Jover et al. Endoscopy 2016*

  3. *Correlation between ADR in primary colonoscopy & FIT*

     *Cubiella et al. UEG Journal 2017*
Colonoscopy arm: quality indicators

Jover, Endoscopy 2016
Randomization 1:1 (Zelen’s design)

Target population (CHR)
(grouped by address, stratified by age & gender)

Information + invitation ± reminding letters

Appointment: Local Screening Office
(questionnaire, post-randomization consent)

Group I: Biennial FIT
(n= 27,749)

Group II: Colonoscopy
(n= 27,749)
Chronogram

Inclusion period (1st round)
Group I: FIT
Group II: colonoscopy

Analysis at Baseline Screening

June 2009

June 2011

FIT
FIT
FIT
FIT

Screening (continued)

Analysis of mortality

Analysis of CRC incidence

Cost-efficacy

2019

2021
Participation & Crossover rates

Intention-to-Screen analysis (interim report)

**Participation rate**

- **Colonoscopy:** 24.6%
- **FIT:** 34.2%

*P* = 0.0001

**Crossover rate**

- **Colonoscopy > FIT:** 6.2%
- **FIT > colonoscopy:** 0.40%

*P* = 0.0001

OR, 0.63 (95% CI, 0.60-0.65)

OR, 16.8 (95% CI, 13.9-20.2)

Quintero & Castells et al. NEJM 2012
Diagnostic yield (intention-to-screen analysis)

FIT Colonoscopy

Cancer
30 (0.1%)
33 (0.1%)

Advanced adenoma
514 (1.9%)
231 (0.9%)

Non-advanced adenoma
1109 (4.2%)
119 (0.4%)

Odds ratio (adjusted by age, gender and participating center)

Quintero & Castells, NEJM 2016
Summary

- Subjects in the FIT group were more likely to participate in CRC screening than subjects in the colonoscopy group.

- On the baseline screening examination, the number of subjects in whom CRC was detected was similar in the two study groups, but more adenomas were detected in the colonoscopy group.

- The comparative effectiveness of FIT and colonoscopy for preventing death from CRC will be assessed at the completion of this 10-year trial.

Quintero & Castells et al. NEJM 2012
NordICC

The Nordic-European Initiative on Colorectal Cancer trial

NordICC study design

94,959 individuals randomised

Screening group 31,589 individuals
15 years follow-up (Interim analysis 10 years)

Control group (care as usual) 63,370 individuals
15 years follow-up (Interim analysis 10 years)

Poland
Netherlands
Norway
Sweden
Iceland

NordICC - The Nordic-European Initiative on Colorectal Cancer
NordICC - The Nordic-European Initiative on Colorectal Cancer
Results so far

• Screening 2009 to 2014
  • Poland      54,927
  • Norway      26,588
  • Netherlands 9,780
  • Sweden      3,664

• Participation rate 40% (12,574 c’scopies)
  • Norway      60.7%
  • Poland      33.9%
  • Sweden      39.8%
  • Netherlands 22.9%

Results

- Coecum intubation rate 97.2% (77.3% non-sedated)
- CRC 0.5%
- Adenomas: 30.7% (30% advanced)
- Similar prox. vs. distal

- Complications
  - 1 perforation (0.01%)
  - 18 bleedings (0.15%)
  - 51 vasovagal reactions (0.41%)

NordICC - The Nordic-European Initiative on Colorectal Cancer
NordICC future

• Now about 7 year mean follow-up

• First analyses on main endpoints (CRC incidence and mortality) after 10 years follow-up
Colonoscopy versus FIT in Reducing Mortality from CRC (CONFIRM)

Update 2018
Primary Aim

To determine if a strategy of screening colonoscopy decreases CRC mortality over 10 years in average risk adults as compared to annual FIT screening.
Recruit 50,000 ‘screen eligible’ Veterans (Age 50-75)

Randomize

Screening Colonoscopy  
Annual FIT Test

FIT Test Positive?  
Yes  
Evaluation by Site PI for further Follow-up

No  

10th Year of Follow-Up?  
No

Follow-up for outcomes over 10 years  
- CRC Mortality (Primary Outcome)  
- CRC Incidence (Secondary Outcome)
Current Status of Trial

• Recruitment milestones
  • First randomization May 22, 2012
  • 5,000\textsuperscript{th} recruitment in June 2013
  • 15,000\textsuperscript{th} recruitment in April 2014
  • 25,000\textsuperscript{th} recruitment in March 2015
  • 35,000\textsuperscript{th} recruitment in February 2016
  • 45,000\textsuperscript{th} recruitment in February 2017
  • 50,000\textsuperscript{th} recruitment in November 2017
Study Participants- Gender Through December 1, 2017 (N=50128)

- Male: 93.1%
- Female: 6.9%
Colonoscopy Measures
N=16794

• High Definition Colonoscopes: 97.1%

• Cecal Intubation Rate: 97.0%
  • Terminal Ileum Intubation Rate: 23.4%

• Average Withdrawal Time: 11.2 minutes
Bowel Prep Quality
N=16794

92.4%

52.4%

5.1%

Missing

Not Adequate

Adequate
Summary

- Recruitment is finished!
- Study participants are very diverse
- We are meeting colonoscopy quality benchmarks
- FIT to colonoscopy—reasonable study wide
  - Further work to understand regional variation being considered
- Trial design favors pragmatism (large simple trial)
Experiences from the SCREEESCO project (SCREEENing of Swedish Colons)

Rolf Hultcrantz
Screening- Background

• Sweden outside Stockholm (20%), does not have colorectal cancer screening.

• 20 countries in EU have population based screening.

• In 2011 the dept of Health and Welfare did still not want to recommend screening in Sweden. I was asked to design and run a study.
SCREESCO: Study design
Clinicaltrials.gov NCT02078804

Initial randomization
1. Arm A - Colonoscopy 20 000
2. Arm B - FIT 60 000
3. Arm C - Control 120 000

Updated randomization due to lower than expected participation in the colonoscopy arm.
1. Arm A - Colonoscopy 30 500
2. Arm B - FIT 60 000
3. Arm C - Control 183 000

Inclusion criteria: Swedish identification number
Living in one of the 18 Swedish counties, representing 7.5 million of a total of 10 million in Sweden
Age 60 years old

Exclusion criteria: Previous colorectal cancer
Progress
Colonoscopy arm

1954
1955
1956
1957
1958

1 – 2014
2 – 2015
3- 2016
4 - 2017
5 – 2018

April
April
August
August
August

6700
6700
6700
5250
5250
Progress
FIT arm

1954 1
1955 1
1956 1
1954 2
1955 2
1956 2

1 – 2014
April

2 - 2015
April

3 - 2016
August

4 - 2017
August

5 – 2018
August
Quality measures

Ceacal intubation rate

Adequate bowel preparation

N: 377

96%

97%

Ceacum intubated

Not intubated

Adequate bowel prep

Not adequate bowel prep
Ongoing RCT in CRC screening

Table 3. Description of ongoing controlled trials of colonoscopy vs FIT or no screening

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Size</th>
<th>Age at recruitment</th>
<th>Assignment of screening intervention</th>
<th>Comparison (ratio)</th>
<th>Follow-up years</th>
<th>CRC outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONFIRM (United States)</td>
<td>50,000</td>
<td>50–75</td>
<td>Consent prior to randomization</td>
<td>Colonoscopy- Program vs. annual FIT (1:1)</td>
<td>10</td>
<td>1° Mortality 2° Incidence</td>
</tr>
<tr>
<td>COLONPREV (29) (Spain)</td>
<td>57,000</td>
<td>50–69</td>
<td>Post-randomization invitation</td>
<td>Colonoscopy-one time vs. biennial FIT (1:1)</td>
<td>10</td>
<td>1° Mortality and Incidence</td>
</tr>
<tr>
<td>NordiCC (30) (Netherlands, Norway, Poland, Sweden)</td>
<td>95,000</td>
<td>55–64</td>
<td>Post-randomization invitation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Colonoscopy one time vs. no screening (1:2)</td>
<td>15</td>
<td>1° Incidence and Mortality</td>
</tr>
<tr>
<td>SCREESCO (31) (Sweden)</td>
<td>200,000</td>
<td>59–62</td>
<td>Post-randomization invitation&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Colonoscopy one time vs. FIT at year 1 and 3 vs. no screening (1:2:3)</td>
<td>15</td>
<td>1° Mortality 2° Incidence</td>
</tr>
</tbody>
</table>
Summary

• 4 ongoing RCTs comparing colonoscopy vs FIT or usual care

• Preliminary results colonoscopy vs 1st round FIT published in COLONPREV (Quintero, NEJM 2016)
  • FIT as good as colonoscopy for detecting CRC
  • Colonoscopy finds double advanced adenomas that only 1 round FIT

• Other studies only published quality audits

• First final results expected in 2-3 years
Thanks

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