



National Institute for Public Health
and the Environment
Ministry of Health, Welfare and Sport

**Adjustment to the implementation of the colorectal cancer
screening programme in 2014 and 2015**

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and the supply of data for ColonIS and to decision-making on
adjustments to the programme*

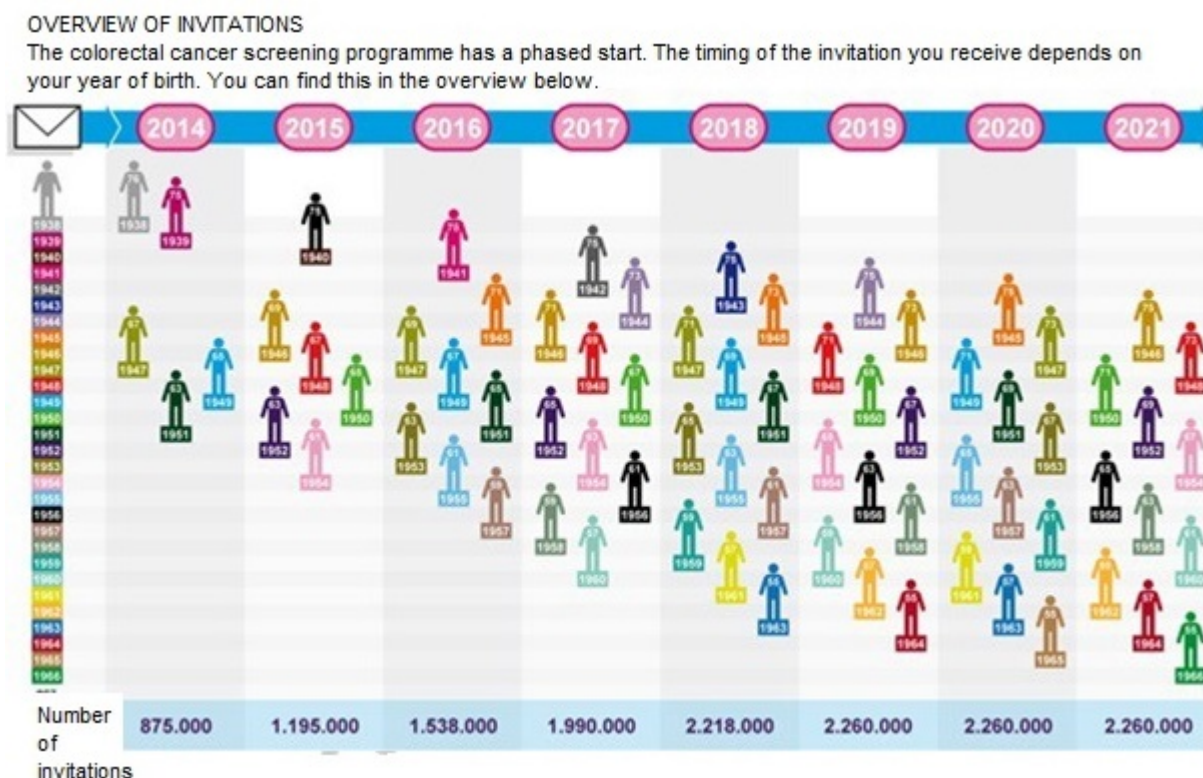
Screening organisations, labs, colonoscopy centres, PA labs, IT
suppliers, National Committee on the Introduction of the Colorectal
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1. Introduction

The colorectal cancer screening programme (SP) began in January 2014. It was agreed that in the first year of the screening programme men and women born in 1938 (aged 76), 1939 (aged 75), 1947 (aged 67), 1949 (aged 65) and 1951 (aged 63) would be invited. There will then be a scheduled, gradual rollout of the screening programme, so that from 2018 all men and women aged between 55 and 75 will be invited every two years (see Figure 1).

Figure 1: Phased rollout of colorectal cancer screening programme



The calculations and expected numbers of participants to be invited in 2014 and subsequent years are based on a number of assumptions. These were made on the basis of the trial screening conducted in the Amsterdam, Rotterdam and Nijmegen regions in the period 2006–2008.

This provided the following parameters which were used in the scenario calculations:

Expected participation: 60% recommendation of the Health Council of the Netherlands (HCN) based on trial screenings) Referral rate: 6.4% (HCN recommendation based on trial screening for 50-75-year-olds)

Referral cut-off value: 88 ng/ml (HCN recommendation; converted to FOB Gold)¹

Participation in colonoscopy after referral: 85% (average of trial screenings)

The parameters used were the best estimates before the start of the screening programme.

¹ In order to compare the cut-off values of iFOBTs from various suppliers, it is necessary to convert from ng Hb/ml of buffer to µg Hb/g of faeces, because the self-sampling tubes of the various suppliers contain different quantities of buffer. For example, 15 µg Hb/g of faeces in the case of FOB Gold corresponds arithmetically to 88 ng Hb/ml of buffer, and in the case of OC Sensor to 75 ng Hb/ml of buffer.

It was decided to set up a national appointments centre at the time of the introduction, with central referral from the screening organisations. Because of the great uncertainties involved, and the fact that a shortage of colonoscopy capacity was expected over the years if capacity in the healthcare system is developed too slowly. An advantage of this national appointments centre is that invitations can be sent on the basis of the available capacity, so waiting times in the healthcare system do not become too long when too little capacity is available in the colonoscopy centres. In addition, any regional dispersion of capacity can be absorbed more effectively by referring people in areas with little capacity to colonoscopy centres at a slightly greater travel distance where capacity is available. The basic principle is that the maximum travel distance is 40 km as the crow flies and that the national appointments centre will first seek availability in a nearby colonoscopy centre.

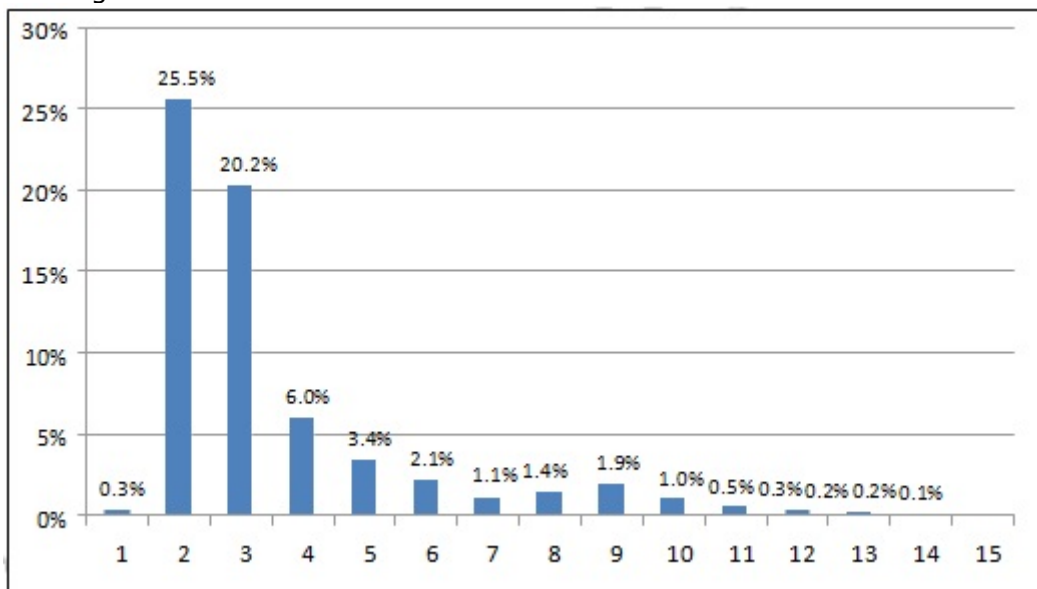
2. Participation rate, referral rate and participation in colonoscopy

The first results of the national screening programme are now available. The national screening programme began with invitations sent to the oldest age groups. Approximately 70% of those invited up to 1 June were aged 75 or 76.

The first provisional results show:

- A participation rate of approximately 68% (data up to 1 June 2014; see figure 2)
- An average referral rate of 13.1% (data up to 1 June 2014; see table 2)
- Estimated participation in the colonoscopy after referral of 89%

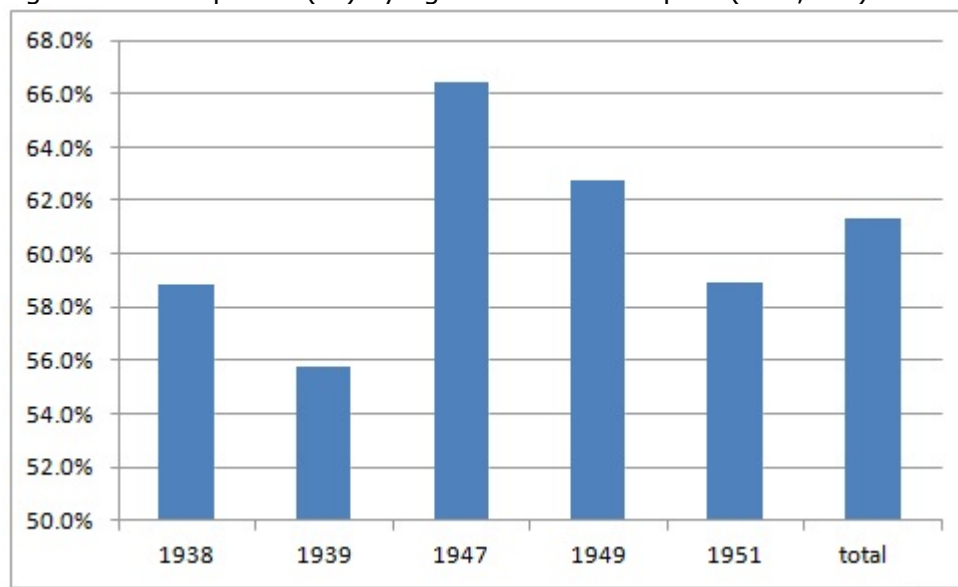
Figure 2: Average participation (%) in the screening programme per week after sending the invitation in week 1



In the pilot in the South-West region of the Netherlands (Sep-Dec 2013, 3,219 invited) we found a lower participation of 61% in the five invited age groups which are also being invited this year for the national screening programme. The referral rate of 9.2% was also lower in the pilot than the referral rate that is now found in the national screening programme.

Figure 3 shows the results of the South-West pilot, in which as well as a lower participation rate than in the national screening programme the participants in the oldest age category had a 4% lower participation rate than the younger participants in the South-West pilot.

Figure 3: Participation (%) by age in South-West pilot (n=3,219)



As table 1 shows, the referral rate increases with age. The referral rate in the five age groups to be invited in 2014 is estimated on the basis of the trial screening in the Amsterdam and Rotterdam regions at 6.7% (OC sensor cut-off value 75 ng/ml). In the oldest age group (n=167 74-75-year-olds) this referral rate was 8.0%. These trial screenings took place in 2006/2008. Thereafter both iFOBTs, the OC Sensor from Eiken and the FOB Gold from Sentinel, were improved. The manufacturers of both tests changed the buffer to stabilise the haemoglobin in the test tube. The haemoglobin consequently breaks down more slowly and smaller quantities of blood in the stool material can also produce a positive result. That may make these tests more sensitive at the chosen cut-off value, but also less specific.

More recent results from countries implementing a screening programme with the iFOBT are known from Scotland and Flanders (part of Belgium)¹. In Scotland we see a referral rate in the 70-74 age group of 13.8% for men and 10.4% for women (OC Sensor, cut-off point 75 ng/ml)². The average referral rates across the 50-75 age group were 9.3% for men and 6.7% for women. Flanders began the screening programme at the end of 2013. It finds a referral rate of 9.3% in the 66, 68, 70, 72 and 74 age groups (OC Sensor, cut-off value 75 ng/ml; oral communication²). In terms of age, this group is comparable to the group invited in the South-West pilot; here we found a referral rate of 9.2%.

Table 1: Referral rates in national screening programme up to 1 June 2014 by age

| year of birth | positive | negative | total | positive (%) | 95% conf. interval |
|---------------|----------|----------|--------|--------------|--------------------|
| 1938 | 7,151 | 43,319 | 50,470 | 14.17% | 13.86-14.47% |
| 1939 | 2,631 | 17,056 | 19,687 | 13.36% | 12.89-13.84% |
| 1947 | 1,156 | 9,541 | 10,697 | 10.81% | 10.22-11.40% |
| 1949 | 836 | 7,871 | 8,707 | 9.60% | 8.98-10.22% |
| 1951 | 45 | 672 | 717 | 6.28% | 4.50-8.05% |
| total | 11,819 | 78,459 | 90,278 | 13.09% | 12.87-13.31% |

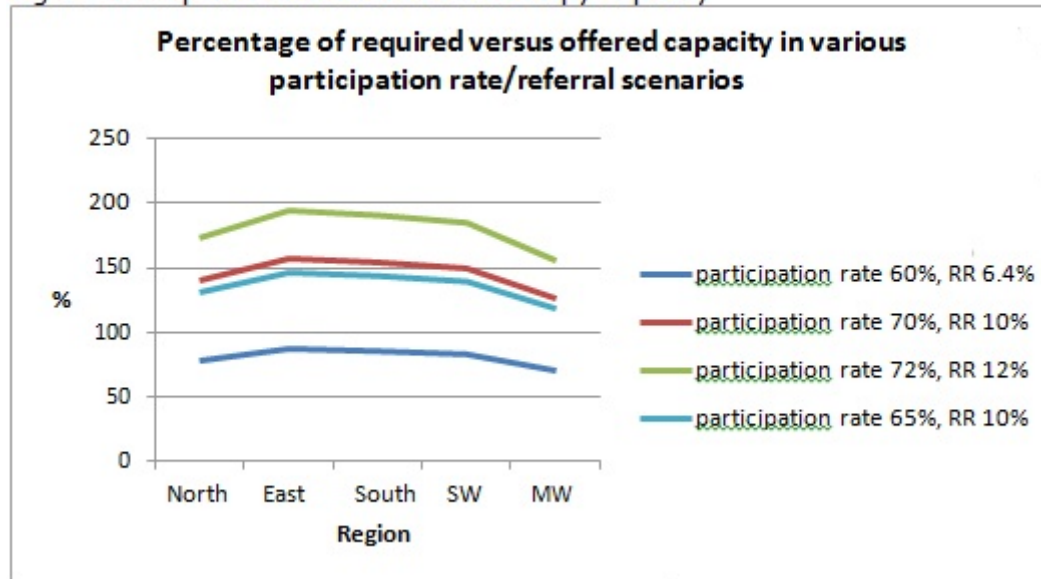
¹ <https://www.bevolkingsonderzoek.be/dikkedarmkanker/professionelen-motivatatie-keuze-van-de-iFOB-test>

² Mc Donald PJ, Strachan JA, Digby J, Steele RJC and Fraser CG. Faecal haemoglobin concentrations by gender and age: implications for population screening for colorectal cancer. Clin Chem Lab Med 2012; 50(5) 935-940.

3. Estimate of required capacity based on participation and referral figures

Figure 4 shows what effect participation and the referral rate have on the required capacity. It had previously been expected that with a participation rate of 60% and a referral rate of 6.4%, an average of 79% of the capacity offered by the colonoscopy centres to the screening organisations at the end of 2013 would actually be required in 2014. With the first estimates of participation and the referral figure in the current screening programme, an average of 173% of the colonoscopy capacity offered at the end of 2013 is required with 70% participation and 12% referral (green line in chart where participation rate is stated erroneously to be 72% instead of 70%). This means that if the invitation policy remains unchanged, long waiting times may/will arise for intakes and colonoscopy.

Figure 4: Required and offered colonoscopy capacity



In order to absorb unforeseen capacity problems in the screening programme, it was decided when setting up the screening programme to establish a national appointments centre. This has been built and is part of the ColonIS national IT system which supports the implementation of the screening programme as well as its monitoring and evaluation. In the national appointments centre the colonoscopy centres indicate their available timeslots for intakes and when clients are referred with unfavourable results, the screening organisations schedule the intake interviews on the basis of the available time slots. In the implementation of the screening programme, the number of persons invited can be slowed down by the ColonIS national appointments centre if waiting times become too long. In March and at the beginning of April the waiting times rose above the agreed standard of conducting an intake within 15 working days (21 calendar days) (see figure 5). The number of invitations sent out each day was therefore adjusted downwards. In view of the lead time from prior notification and invitation to intake, it is some weeks before an adjustment has the intended effect of lowering waiting times.

Figure 5: Waiting times for intake in calendar days (y axis) by date (x axis, data up to 1 June 2014). The blue line shows the average waiting time at a given moment, the red line the minimum and the green line the maximum.

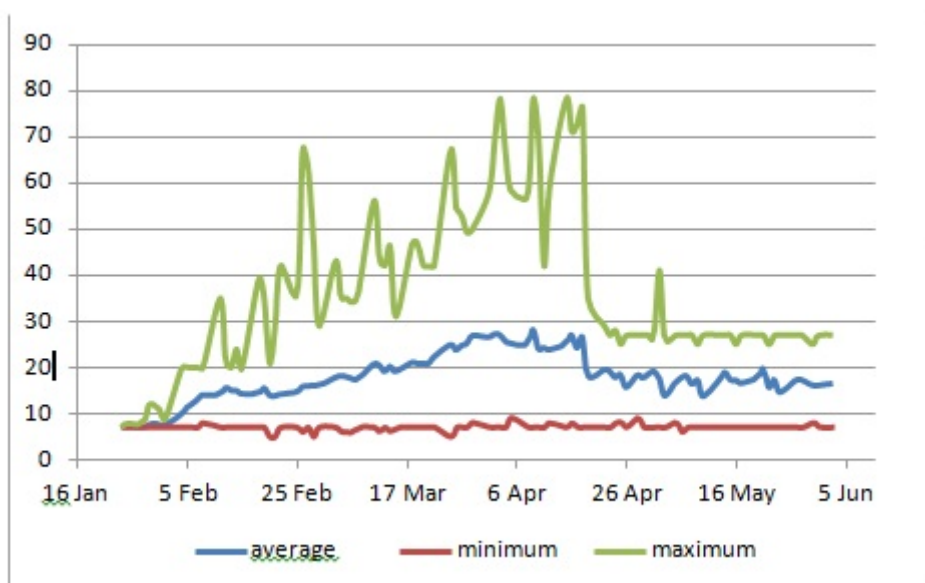


Table 2 presents a picture of the actions taken to regulate the number of invitations. The average waiting time between the sending of the results letter and the intake is now an average of 17-18 calendar days again (data up to 1 June 2014). The waiting times from intake to colonoscopy have always remained within the agreed standard.

As a result of these changes made to the number of invitations to be sent, approximately 158,000 invitations were sent out up to 1 June. The reduction in the number of invitations per day means that without a change in the implementation of the screening programme, the specified target of inviting 890,000 citizens from the above five age groups will not be achieved this year. This clearly shows the need for rapid decision-making on adjustments to parameters and/or additional capacity. A number of scenarios to this end are outlined in section 5.

Table 2: Number of invitations sent per week up to 1 June 2014

| Week | Start | End | Invited |
|--|--------------|------------|----------------|
| 4 | 20-01-2014 | 26-01-2014 | 6,768 |
| 5 | 27-01-2014 | 02-02-2014 | 6,510 |
| 6 | 03-02-2014 | 09-02-2014 | 7,046 |
| <i>referral rate 6.4%, participation 60%</i> | | | |
| 7 | 10-02-2014 | 16-02-2014 | 15,260 |
| 8 | 17-02-2014 | 23-02-2014 | 15,332 |
| 9 | 24-02-2014 | 02-03-2014 | 16,758 |
| <i>referral rate 6.4% → 10%</i> | | | |
| 10 | 03-03-2014 | 09-03-2014 | 10,527 |
| 11 | 10-03-2014 | 16-03-2014 | 10,970 |
| 12 | 17-03-2014 | 23-03-2014 | 10,613 |
| <i>referral rate 10% → 20%</i> | | | |
| 13 | 24-03-2014 | 30-03-2014 | 8,166 |
| <i>participation rate 60% → 70%</i> | | | |
| 14 | 31-03-2014 | 06-04-2014 | 3,928 |
| 15 | 07-04-2014 | 13-04-2014 | 4,631 |
| 16 | 14-04-2014 | 20-04-2014 | 3,330 |
| 17 | 21-04-2014 | 27-04-2014 | 2,367 |
| 18 | 28-04-2014 | 04-05-2014 | 3,018 |
| <i>participation rate 70% → 68%, referral rate 20% → 13%</i> | | | |
| 19 | 05-05-2014 | 11-05-2014 | 4,985 |
| <i>1949, participation rate 70%, referral rate 9%</i> | | | |
| 20 | 12-05-2014 | 18-05-2014 | 9,477 |
| 21 | 19-05-2014 | 25-05-2014 | 9,340 |
| 22 | 26-05-2014 | 01-06-2014 | 9,160 |

4. First provisional results for the yields of the screening programme

If the iFOBT produces an unfavourable result, a referral is made to a colonoscopy centre for a follow-up diagnosis. An intake is scheduled, after which a colonoscopy takes place. Colonoscopy centres are requested to submit the data of the results and the follow-up policy for the colonoscopy to ColonIS; this can be done by electronic messaging or manually. This is not yet happening fully in this start-up phase of the screening programme. Table 3 presents a picture of the submitted and expected colonoscopy data per week in ColonIS; good progress is clearly being made, but at the same time 50% of the colonoscopy data is currently being received. In addition, no system is yet in place for the submission of colonoscopy data for a follow-up colonoscopy if a colonoscopy is not completed and a referral is made for an additional colonoscopy, and no reporting takes place on this in ColonIS.

Table 3: Colonoscopy data available in ColonIS per week, data up to mid-April 2014

| Week number | Number of planned colonoscopies | Colo reports received | Colo reports electronic | Colo reports manual |
|---------------|---------------------------------|-----------------------|-------------------------|---------------------|
| 6 | 3 | | | |
| 7 | 40 | 3 | 0 | 3 |
| 8 | 138 | 15 | 3 | 12 |
| 9 | 206 | 32 | 6 | 26 |
| 10 | 255 | 61 | 24 | 37 |
| 11 | 453 | 96 | 40 | 56 |
| 12 | 461 | 125 | 75 | 50 |
| 13 | 539 | 323 | 232 | 91 |
| 14 | 565 | 354 | 224 | 130 |
| 15 | 607 | 349 | 245 | 104 |
| 16 | 600 | 427 | 330 | 97 |
| Totaal | 3867 | 1785 | 1179 | 606 |

The first analyses of the colonoscopy yields and follow-up actions carried out show a different picture from that offered by the trial screenings. The first round of the trial screening in the Amsterdam and Rotterdam regions found 8% colorectal cancer, 43% advanced adenomas and 25% non-advanced adenomas. These first provisional results of the national screening programme show lower yields in the case of advanced adenomas and higher yields in the case of non-advanced adenomas. The proportion of the yield accounted for by all adenomas combined is comparable to that in the trial screenings. At the same time it is clear that further data validation is required. For example, the yields of a complex follow-up colonoscopy are not yet included. An analysis of the data also shows inconsistencies, for example in the follow-up policy with regard to the colonoscopy findings. The method used to record the conclusion and make a judgement about advanced and non-advanced adenomas in the trial screenings (scientific research) may also differ from regular practice in the screening programme. Table 4 shows the provisional yields available at present.

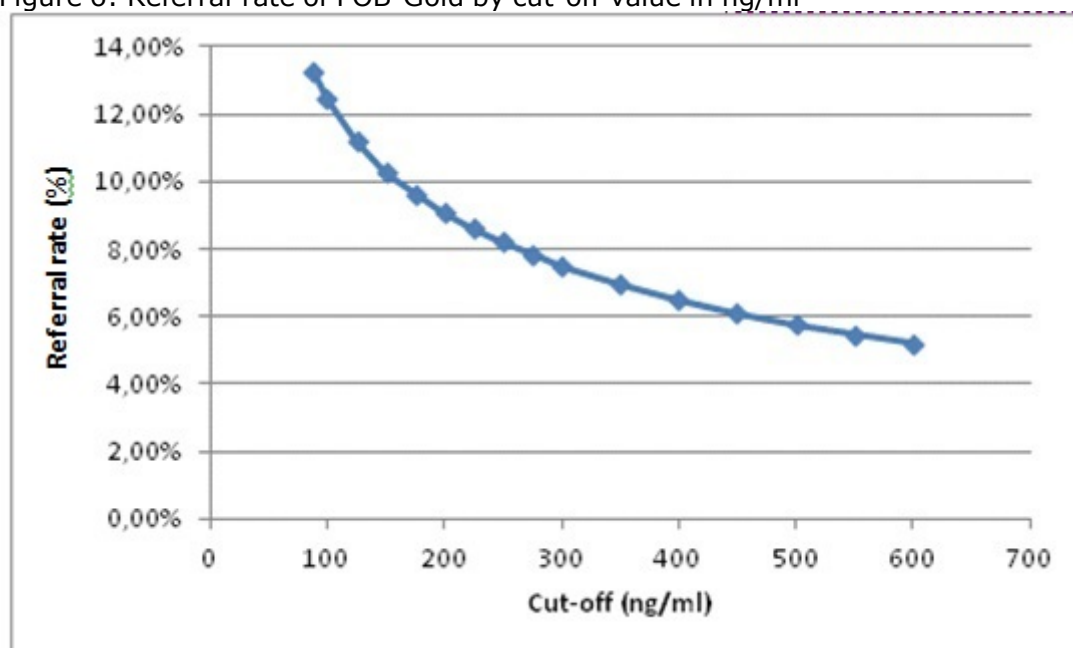
Table 4: Colonoscopy yield (data up to 25 June 2014)

| Conclusion | Number | Percentage |
|--|---------------|-------------------|
| Advanced adenoma | 1,306 | 22.5% |
| Colorectal cancer | 433 | 7.5% |
| No colorectal cancer or precursor | 1,381 | 23.8% |
| Serrated polyps | 322 | 5.6% |
| Neuroendocrine tumour (disorder) | 1 | 0.0% |
| Non-advanced adenoma | 2,360 | 40.6% |
| Final total | 5,803 | 100.00% |

The evaluator of the programme (Erasmus MC in cooperation with the Antoni van Leeuwenhoek hospital) has further investigated the referral rate and the associated colonoscopy yield and compared it with the results of the trial screening in the Rotterdam region. As stated above, these are provisional figures due to the incomplete recording of colonoscopies; in addition, there are a number of recording issues which need to be further investigated. Data from ColonIS up to 23 April 2014 have been used. They first looked at the pattern of the referral rate of FOB-Gold for different cut-off values (figure 6). As expected, the referral rate of the FOB-Gold declines sharply with the cut-off value:

from a little over 13% with the current cut-off value of 88 ng/ml to a little over 5% with a cut-off value of 600 ng/ml.

Figure 6: Referral rate of FOB-Gold by cut-off value in ng/ml



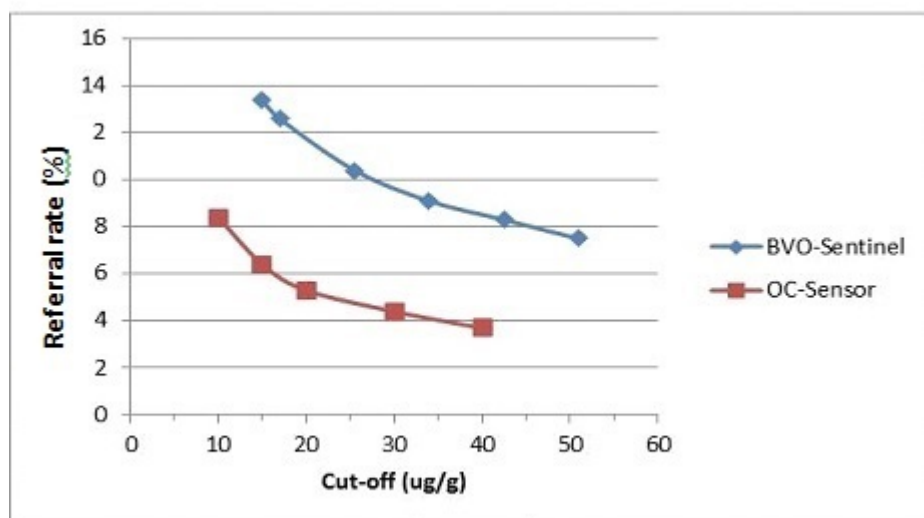
In order to allow a comparison with the OC-Sensor from the trial screenings, the concentration of haemoglobin per ml of buffer for both tests was converted to the concentration of haemoglobin per gram of faeces (figure 7). This clearly shows that the referral rate with the same cut-off value is markedly higher for a positive test in the case of the current FOB-Gold (BVO-Sentinel) than for the OC-Sensor at the time of the trial screening in the Rotterdam region. For example, with a cut-off value of 15 µg/g (corresponding to 75 ng/ml for the OC sensor and 88 ng/ml for the FOB-Gold) the referral rate was just above 6% in the trial screening compared to 13% in the screening programme now. This difference is explained in part by the higher age of the participants in the screening programme (particularly 75 and 76-year-olds at present) compared to the trial screening (50 to 75-year-olds); see table 1, which shows that the referral rate becomes higher as the age of the participants rises.

As well as the higher referral rate with the FOB-Gold, there is also a higher rate of detection³ of advanced adenomas and cancer (figure 8) with the current provisional figures. With the same cut-off of 15 µg Hb/g of faeces, the rate of detection of advanced adenomas and cancers in the trial screening with the OC-Sensor at that time was around 2.7% of the screened participants, compared to almost 4% with the current FOB-Gold. In other words, the positive predictive value⁴ (PPV) of a positive iFOBT is currently lower in the national screening programme than in the trial screening programmes, and given a positive iFOBT the likelihood of advanced adenomas and cancer is also lower for the time being (see table 4). Per 1,000 screened persons, however, the rate of detection of advanced adenomas and cancer is higher. After all, more people are referred.

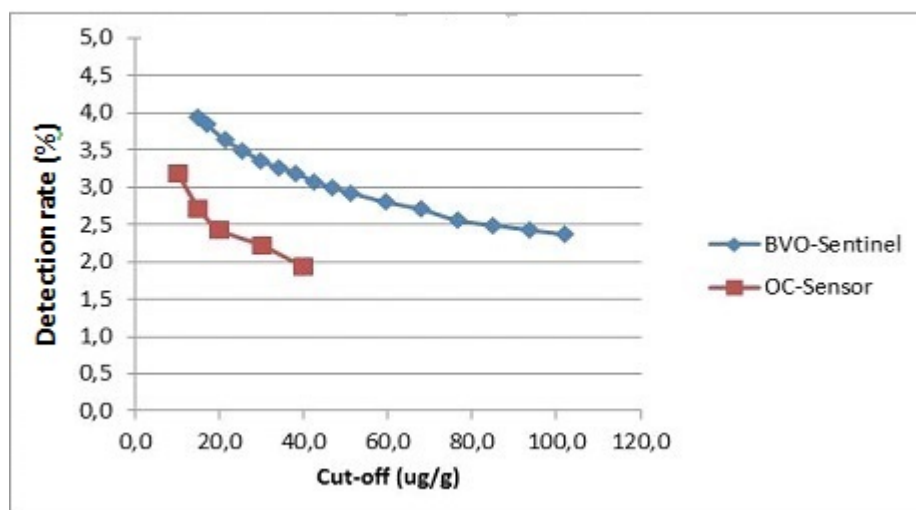
³ The detection rate is the percentage of screened persons (participants in the screening) in whom an advanced adenoma or cancer is found, in other words the percentage of screened persons with a true positive iFOBT result. The detection rate is the product of the referral rate and the positive predictive value.

⁴ The positive predictive value is the proportion of participants in the screening with a positive iFOBT in whom an advanced adenoma or cancer is found in the colonoscopy, i.e. number of true positives divided by true and false positives.

Figure 7: Referral rate of the current FOB-Gold and the OC-Sensor at the time of the trial screenings, by cut-off values in $\mu\text{g/g}$



ent FOB-Gold and
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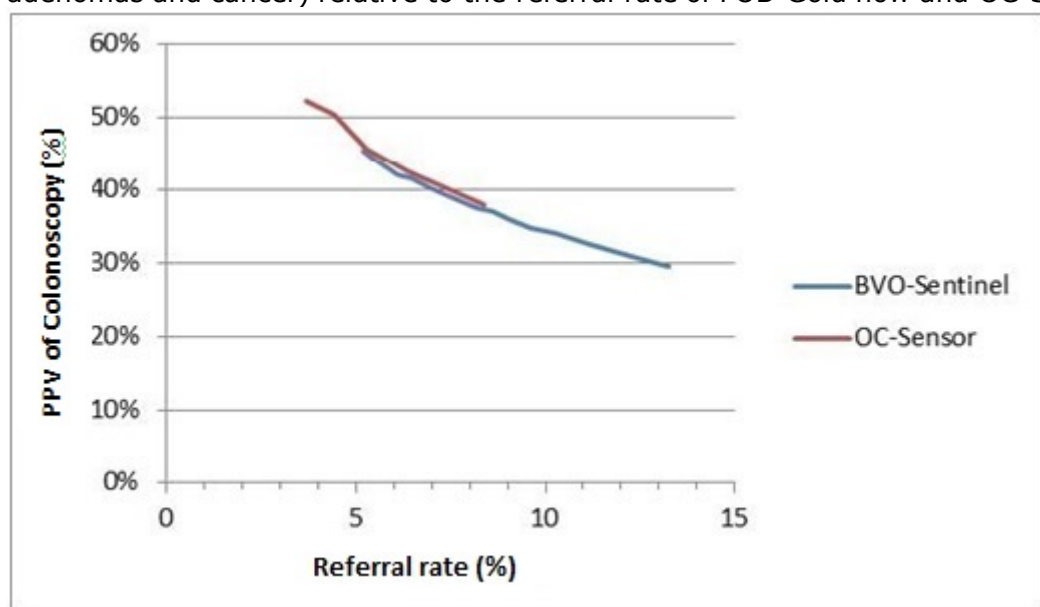


The FOB-Gold in the national screening programme has simultaneously a higher referral rate and a higher detection rate for both advanced adenomas and cancer. The evaluator therefore made a comparison of colonoscopy yields according to the referral rate (figure 9). The results of this were very striking. With an equivalent referral rate (for example 5%), the colonoscopy yield (i.e. the positive predictive value (PPV) of a positive iFOBT for advanced adenomas and cancer) was exactly the same for both tests, i.e. 45%. Figure 9 also shows this clearly for other referral rates: the lines for OC-Sensor from the trial screenings and for FOB-Gold (Sentinel) from the screening programme are almost superimposed.

These results indicate that the then OC-Sensor and the current FOB-Gold are comparable tests, but that the cut-off value chosen in the national screening programme does not deliver the previously required referral rate and detection rate. In other words, the characteristics of the FOB Gold test at 88 ng/ml do not correspond to those of the OC-Sensor from the trial screening at 75 ng/ml.

However, by adjusting the cut-off value, the FOB-Gold can indeed result in the referral and detection rates observed in the trial screenings. An important caveat in these conclusions is that the comparison between the then OC-Sensor and the current FOB-Gold is based on different age groups (i.e. 50 to 75-year-olds for the then OC-Sensor and 75 to 76-year-olds for FOB-Gold now). The relationship between the referral rate and the colonoscopy yield could be different for other ages. It is also important to note that this is a comparison with the OC-Sensor at the time of the trial screenings (6-8 years ago). In view of the high referral rates which are now being observed in other European countries, a comparison with the OC-Sensor could now yield comparable referral figures and detection rates to those of the FOB-Gold.

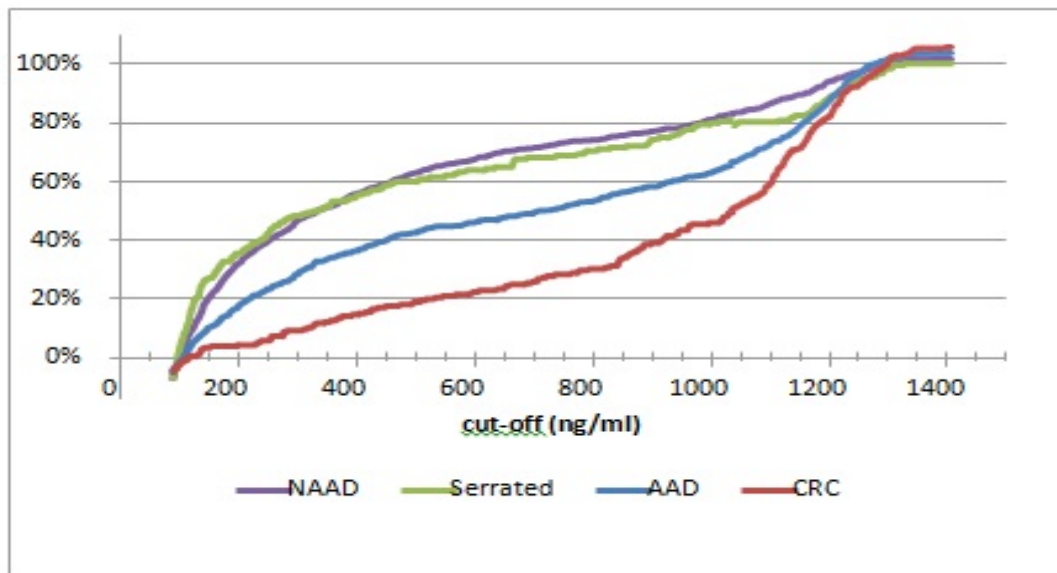
Figure 9: Colonoscopy yield (i.e. positive predictive value of a positive iFOBT for advanced adenomas and cancer) relative to the referral rate of FOB-Gold now and OC-Sensor then.



With the current referral rate, screening takes place for a different ratio between positive and negative effects from what the Health Council of the Netherlands had in mind in its 2009 recommendation with a cut-off value of 75 ng/ml for the OC-Sensor. If the cut-off value is raised, the referral rate falls. This has consequences for the detection of advanced adenomas and cancer, but many more for the false positives. After all, when the cut-off value is increased, the PPV of a positive iFOBT rises and the percentage of false positives declines more than the percentage of true positives.

Figure 10 shows the percentage of the yield which is lost when raising the cut-off value. It shows – as expected – that the sensitivity to all types of adenoma, polyps and cancer decreases, but that this is mainly the case with serrated polyps and non-advanced adenomas.

Figure 10: Percentage of lost yield of non-advanced adenomas, advanced adenomas, serrated polyps and carcinoma of the large intestine with increased cut-off value.



NAAD = non-advanced adenomas, serrated = serrated polyps, AAD = advanced adenomas and CRC = colorectal carcinoma

The evaluator has also used the MISCAN model to estimate what the long-term effects of the screening programme would be with these data if the programme could be continued in this way. Figure 11 shows that this would lead to an extra health gain of 300 deaths, which is due particularly to the much larger numbers of small and medium-sized adenomas detected in the national screening programme. Figure 12 shows the amount of additional colonoscopy capacity required for that, including in the longer term.

In figures 11 and 12, the red bar shows the results of the MISCAN model as used for the Implementation Test³ in the spring of 2011, based on the originally intended rollout with the screening programme due to start in 2013 with 65 and 75-year-olds, with the following adjustments:

- the 2002 surveillance guideline has been incorporated (the most recent surveillance guideline from 2013 has yet to be incorporated)
- account has been taken of the fact that adenomas take longer to develop into cancer than in previous model parameters
- new test characteristics for the iFOBT. On the basis of the results of the COCOS study, the evaluator has concluded that the size distribution of adenomas in the MISCAN model does not correspond to that of the Dutch population. The size distribution was originally based on autopsy studies, but that proved not to correspond to the findings of the COCOS study⁴. Because there were now fewer large adenomas in the model, the evaluator also had to adjust the test characteristics for the iFOBT accordingly: in order to achieve the same detection rate for large

⁴ Lancet Oncol. 2012 Jan;13(1):55-64. doi: 10.1016/S1470-2045(11)70283-2. Epub 2011 Nov 15. Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial.

adenomas while fewer large adenomas are present, the sensitivity of the iFOBT to large adenomas has to be increased.

The stated adjustments have not resulted in substantially different estimates for the values calculated at the time of the Feasibility Study.

The black bar in figure 12 shows the results of the model calculations expected with the current rollout (i.e. starting in 2014 with 63, 65, 67, 75 and 76-year-olds).

The grey bar in figure 12 represents the results of the model calculations as in the black bar also incorporating the higher participation in the national screening programme (results up to the beginning of May).

The blue bar in figures 11 and 12 shows the results of the model calculations as in the grey bar also incorporating the provisional higher referral rate and the lower PPV (based on the provisional yield of the colonoscopies in the national screening programme (results up to the beginning of May)).

Figure 11: Deaths prevented by national screening programme

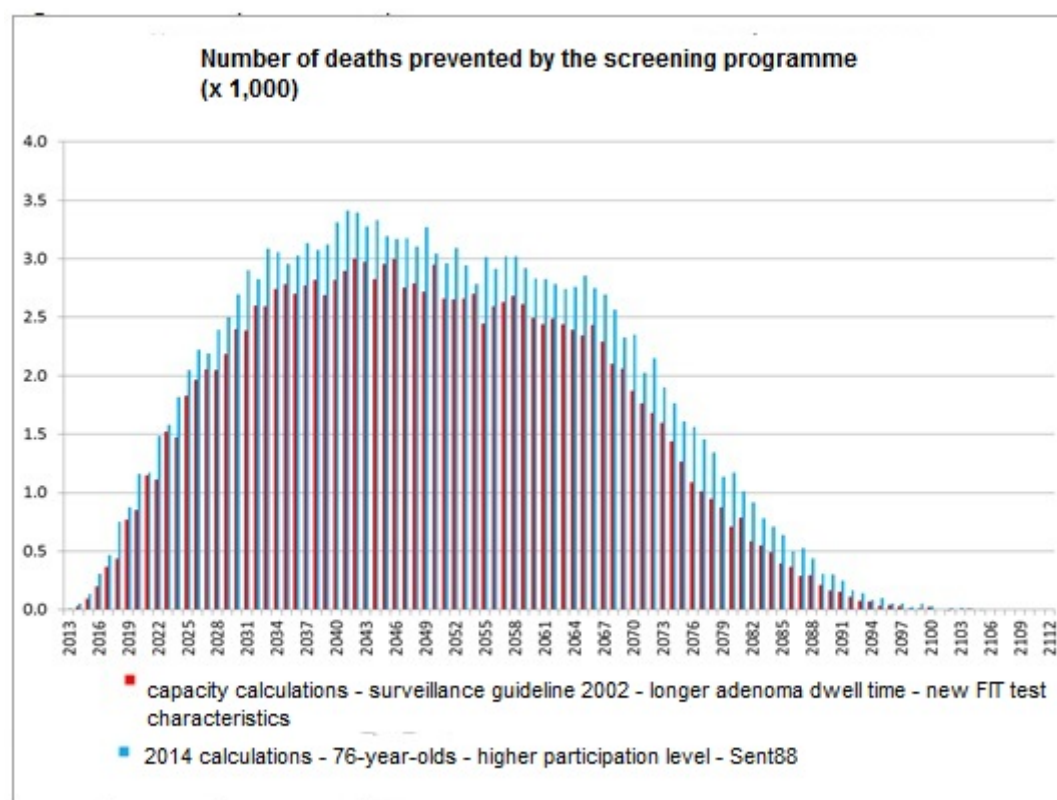
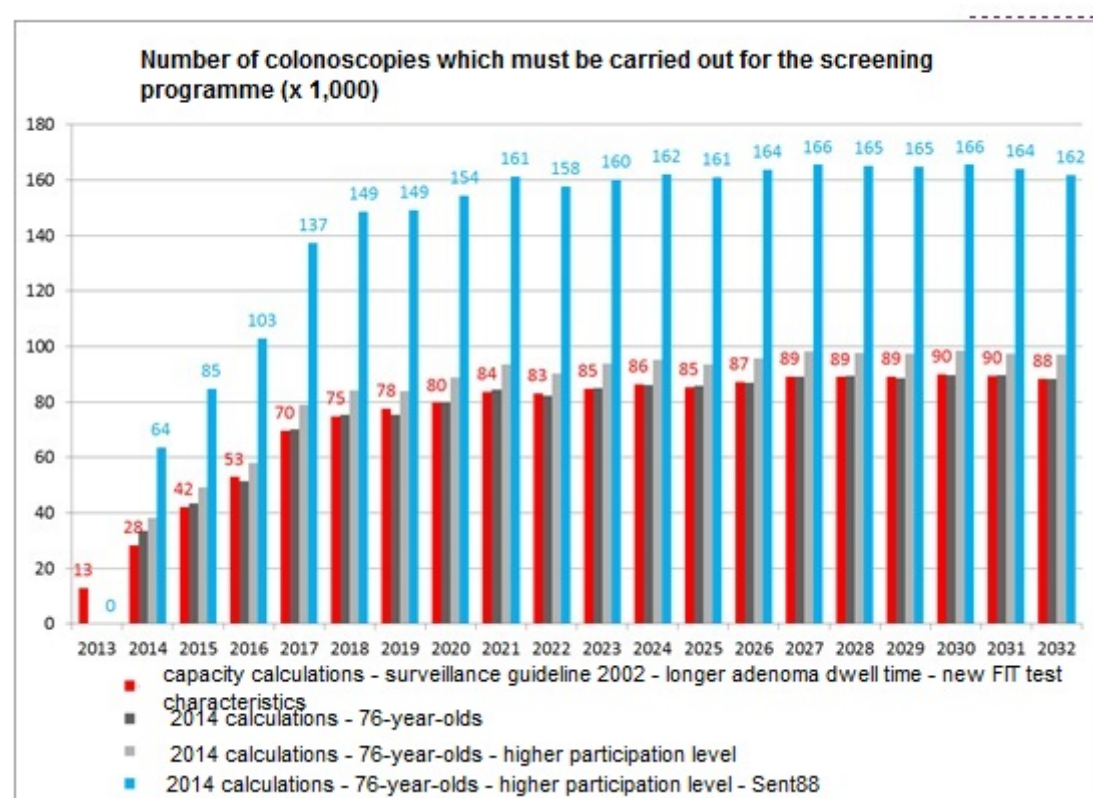


Figure 12: Required colonoscopy capacity for national screening programme



As figure 12 shows, the estimated number of colonoscopies required with an unchanged implementation of the screening programme is substantially higher than the original number of colonoscopies expected to be required. Because the required colonoscopy capacity is currently unavailable, the programme needs to be adjusted. Section 5 outlines the possible adjustment scenarios and are based on the current available data that the evaluator used in the analyses. These scenarios can contribute to a proposal for adjustment to the programme.

5. Phased introduction scenarios

This section outlines a number of scenarios which could be used given that the first provisional results of the screening programme point in a different direction from the figures on which the Health Council of the Netherlands recommendation and the Feasibility Study were based. The presented scenarios were build on those which were already provided for in the Feasibility Study in the spring of 2011. In the choice of scenarios it is important to take into account various aspects, such as the effectiveness of the programme, communication with citizens and professionals and the feasibility of building up colonoscopy capacity in the ongoing phased introduction.

An exploration of the scenarios was first carried out and described, and the most promising of them were then analysed by Erasmus MC using the MISCAN mode

Scenario 1: Adjusting the age groups to be invited in 2014 and possibly 2015

1a: Not inviting the 1951 age group in 2014, adding this to the age group to be invited in 2016. Inviting five age groups in 2015 instead of the proposed six.

Figures for the new scenario

In this scenario, four age groups are invited in 2014 instead of five; 1951 is postponed to 2016. Five age groups are invited in 2015 (1940, 1946, 1948, 1950 and 1952; the 1954 age group is postponed to 2017). In the decision not to invite an age group, the scenario of the Health Council of the Netherlands in which 65 and 75-year-olds would be invited in the first year would be adhered to as far as possible.

This means that 671,500 invitations would be sent out in 2014. On the basis of the above participation rate and referral figure, this means that 131% of the available capacity would still be required; this would involve 56,041 colonoscopies.

967,000 invitations would be sent out in 2015. The available capacity for 2015 is currently unknown.

Advantage

- Numbers to be invited are more in line with available capacity in 2014
- Oldest age groups (75 and 76) are invited in full this year
- When the four age groups have been completed, we can start on the 1949 age group in 2014

Disadvantage

- Still insufficient capacity available for the four age groups (131%)
- Phased rollout may take longer than 2018; short-term solution for 2014; the problem is shifted to later years
- Communication on postponing people from 1951, and the following year people from 1954, may raise questions among the population
- Not the most efficient adjustment to the screening programme (i.e. increasing the cut-off value leads to less loss of health gain with the same reduction in colonoscopy capacity, see table 5 below)

1b: Not inviting the 1951 and 1947 age groups in 2014, inviting them for the first time in 2016. Inviting four age groups in 2015 instead of the proposed six.

Figures for the new scenario

In this scenario, three age groups are invited in 2014 instead of five; 1947 and 1951 are postponed to 2016. Four age groups (1940, 1948, 1950 and 1952) are invited in 2015; the 1946 and 1954 age groups are postponed to 2017.

Advantage

- Numbers to be invited are in line with the available capacity (still needs to be analysed)
- Oldest age groups (75 and 76) are invited in full this year
- When the three age groups have been completed, we can start on the 1949 age group in 2014

Disadvantage

- Phased rollout may take longer than 2018; short-term solution for 2014; the problem is shifted to later years
- Communication on postponing people from 1951 and 1947, and the following year people from 1946 and 1954, may raise questions among the population
- Not the most efficient adjustment to the screening programme (i.e. increasing the cut-off value leads to less loss of health gain with the same reduction in colonoscopy capacity, see table 5 below)

The following applies to both scenarios 1a and 1b:

Unknown

- It is not yet known what the participation and the referral figure will be among the four age groups to be invited (1938, 1939, 1949 and 1947)

Scenario 2: Raising the cut-off value

The cut-off value of the screening test is raised in order to reduce the number of referrals from the screening programme. In the Feasibility Study, this was shown to be most cost-effective scenario with the results of the trial screening. Figure 6 shows that the increase in the cut-off value will result in a lower referral rate.

Advantage

- No major impact expected on the effectiveness and the risk-benefit ratio of the programme
- Lowers the referral rate, fewer false positives
- Adjustment can be implemented in communication with population because the test appears to measure more sensitively than intended
- Solution for short and long term
- Efficient
- Scenario also applied in Ireland due to unexpected capacity problem

Disadvantage

- Impact on positive predictive value and false positives and negatives: possibly more false negative results and interval cancers than when maintaining the cut-off value
- Communication to limited part of target group and professionals requires attention
- People in same year cohort to be invited are screened with a different cut-off value

Scenario 3: Additional colonoscopy capacity

The colonoscopy centres could have even more capacity available in 2014 than has been purchased by the healthcare insurers and passed on to the screening organisations. In any case, there are some centres which are not contracted by the healthcare insurer(s). A key point for 2015 is that the healthcare insurers' care purchasing process starts no later than June; they must then have an idea of the quantity of care to be purchased for 2015. Other solutions which have been identified to deliver additional colonoscopy capacity in the medium term are training additional hepatogastroenterologists, transferring tasks and adjusting the surveillance guideline. However, this is not a solution for this year (and probably next year).

Advantage

- Additional capacity means the programme can be implemented without change so that the planned cohorts can be invited each year
- Greater health gain

Disadvantage

- Depending on the care purchasing procedure, healthcare insurers must be willing/able to purchase this additional care
- Additional care purchasing by healthcare insurers is probably only a short-term solution; with a higher participation and referral rate than expected during the phased introduction as a whole, a much higher and faster build-up of colonoscopy capacity is necessary than was originally thought. Additional capacity may be available through training, transfers of duties and adjustment to the surveillance guideline.
- Risk-benefit ratio of the screening test differs from that intended in the Health Council recommendation and the Population Screening Act permit.

Unknown

- It is not currently known how much extra capacity would be available and whether it would be sufficient; purchasing in some regions has been selective; additional capacity may be available.

Scenario 4: Adjust target group of screening programme

The age group to be invited for the screening programme is 55 to 75. In view of the capacity problems, consideration could be given to adjusting this age group.

Advantage

- Implementation of screening programme is adapted to the available colonoscopy capacity and thus made feasible again

Disadvantage

- Intended health gain is not achieved
- Target group to be invited may take action to oppose it
- Risk-benefit ratio of the screening test differs from that intended in the Health Council recommendation and the Population Screening Act permit

Scenario 5: Vary the cut-off value on basis of age and gender-specific referral figures

With a particular cut-off value, the referral figure varies depending on age and gender (see footnote 2); this may be used to optimise the programme. It is then important to incorporate the test characteristics for each age and gender in order to calculate the optimum scenario.

Advantage

- Optimisation of health gain of programme within the available capacity

Disadvantage

- Communication with citizens on effect of programme is more difficult

Unknown

- Good data required; currently unknown what the effect is

Scenario 6: Increasing the screening interval

As was also indicated in the Feasibility Study , using a screening interval of four years, for example, means that all age groups have their first screening rapidly. When sufficient capacity is available, increasing numbers of age groups can be invited every two years.

Advantage

- The total target group is called for the first time before certain people are due to have their second screening
- The decision to adjust the screening interval can be deferred to May 2015 (start of care purchasing)
- Capacity can be built up slowly while the whole target group is invited over a number of years

Disadvantage

- Increased likelihood of interval carcinomas
- Impact on the cost-effectiveness of the programme
- Change in communication with citizens about different screening interval
- Scenario that can only be implemented in the first two years; thereafter citizens will have been invited at two-year intervals;
- As a solo solution, provides no consolation for the planned target group to be invited in 2014 and 2015.

Unknown

- Not known what effects will be with a four-year interval in this screening test

Scenario 7: Combinations of above scenarios

Combinations of the above scenarios could be applied.

Using the data available up to the beginning of May, which had not yet been sufficiently validated, the evaluator analysed a number of short-term scenarios. Table 5 shows the results, in each case per thousand persons. For various options involving postponing the different age groups and increasing the cut-off value to different levels (column 1), a calculation was made of how many colonoscopies would be required per thousand persons (column 2) and what reduction in colonoscopies that would mean compared to continuing with the current rollout (column 3). Column 5 then shows the reduction in the number of required colonoscopies (column 3) divided by the number of prevented deaths (column 4). Column 6 shows the number of deaths not prevented per thousand saved colonoscopies. It follows from this that raising the cut-off value is the most efficient measure, with the least loss of health gain occurring per saved colonoscopy.

Table 5: Comparison of efficiency of various measures

Efficiency of measures to reduce the required colonoscopy capacity in 2014 (numbers per thousand persons aged 63, 65, 67, 75 and 76 in 2014)

| Measure | Number of required colonoscopies in 2014 | Reduction | Number of prevented deaths | Reduction | Number of non-prevented deaths per thousand saved colonoscopies | Rank* |
|------------------------------|--|-----------|----------------------------|-----------|---|-------|
| none | 79.3 | - | 9.61 | - | - | - |
| postpone 63 age group | 61.5 | 17.9 | 9.28 | 0.33 | 18 | 3 |
| postpone 65 age group | 60.9 | 18.4 | 9.30 | 0.31 | 17 | 2 |
| postpone 67 age group | 59.4 | 19.9 | 9.24 | 0.38 | 19 | 4 |
| no screening of 75 age group | 67.5 | 11.8 | 9.05 | 0.56 | 48 | 6 |
| no screening of 76 age group | 68.1 | 11.3 | 9.10 | 0.51 | 45 | 5 |
| raise cut-off to 150 ng/mL | 60.4 | 18.9 | 9.38 | 0.24 | 12 | |
| raise cut-off to 200 ng/mL | 52.9 | 26.4 | 9.26 | 0.35 | 13 | 1 |
| raise cut-off to 275 ng/mL | 45.0 | 34.3 | 9.11 | 0.50 | 15 | |

* Rank based on number of deaths not prevented per thousand saved colonoscopies.

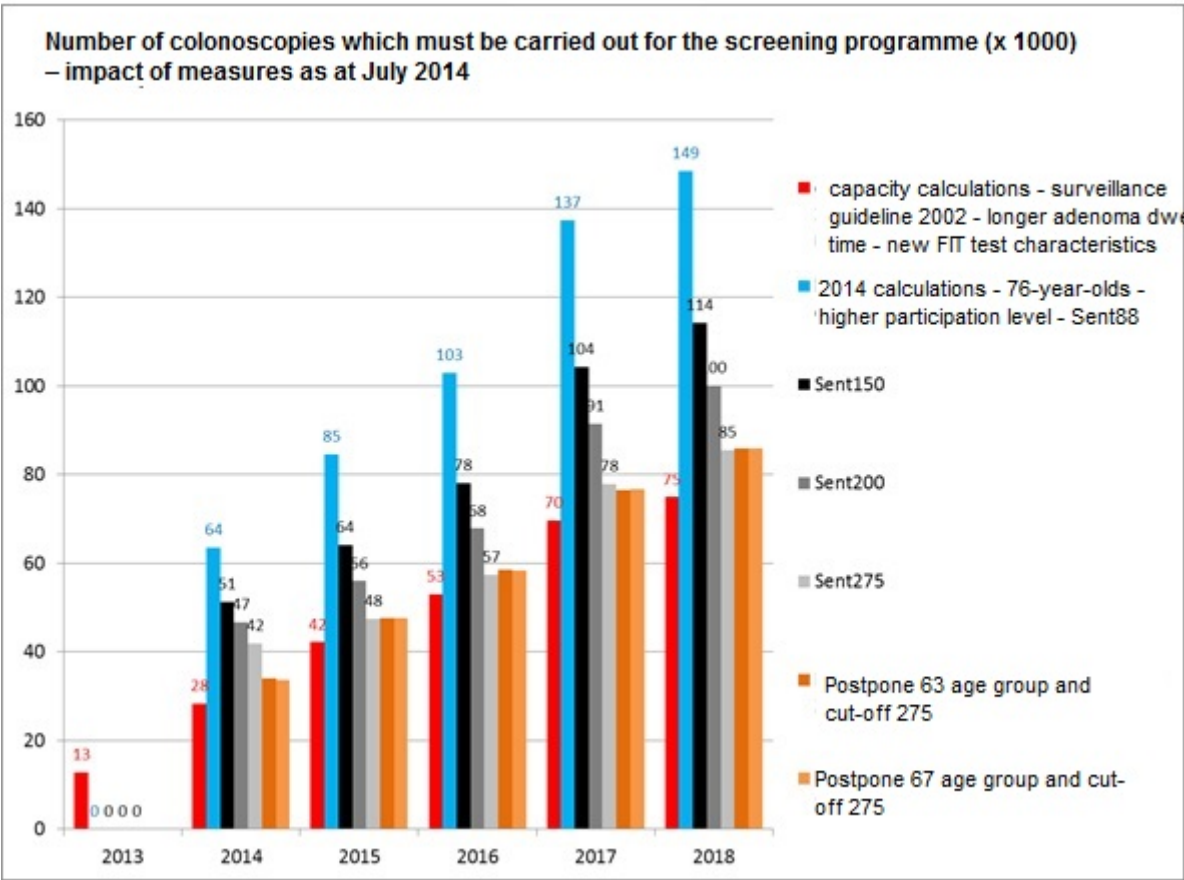
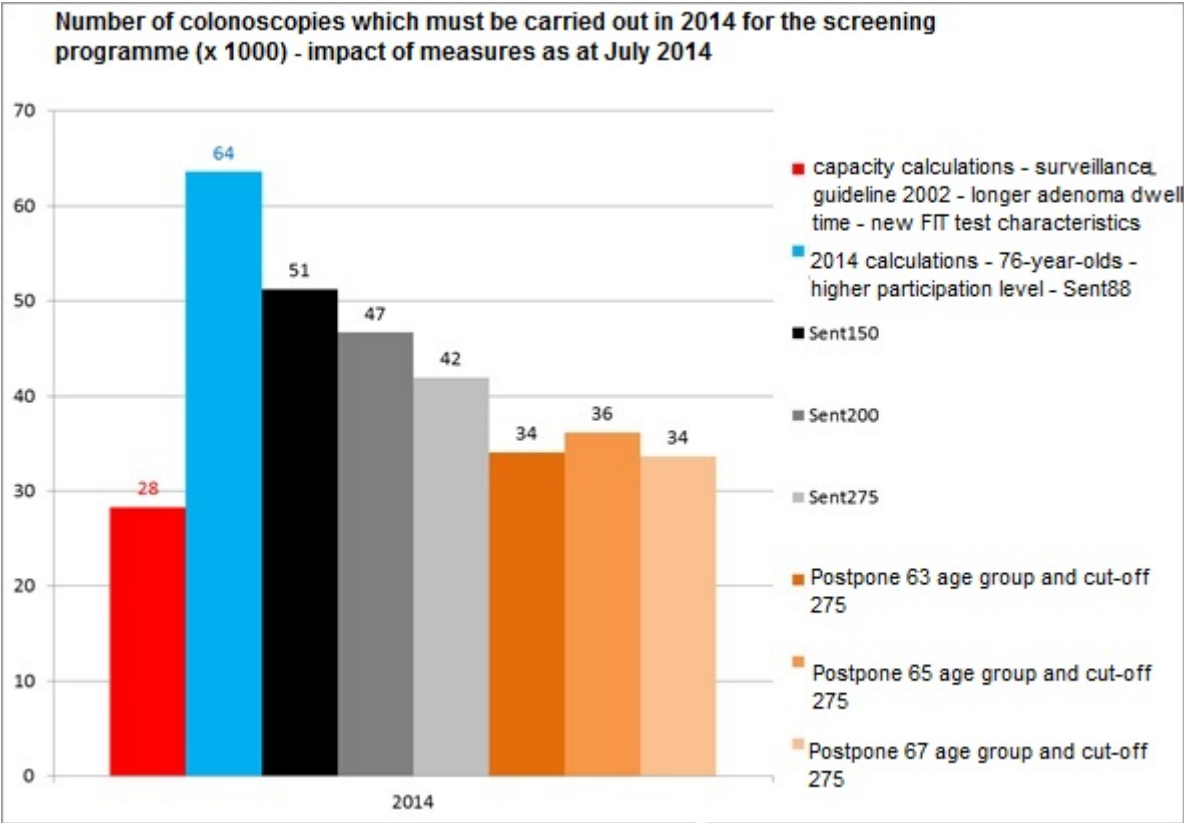
The effects of these measures have also been calculated for the required colonoscopy capacity if the measure were introduced with effect from 1 July 2014. This is shown in figures 13 (for 2014) and 14 (for 2014 to 2018).

The red bar shows the expected number of colonoscopies as calculated for the Feasibility Study with the original rollout and a number of adjustments (see notes to figures 11 and 12).

The blue bar shows the effect on the number of required colonoscopies if the programme continues to be implemented in the current manner. Accordingly, with a start in 2014, the current rollout, participation, referral rate and PPV, 64,000 colonoscopies are required in 2014, instead of 28,000 as calculated at the time of the Feasibility Study Test. Such colonoscopy capacity is not currently available.

The black and grey bars indicate that raising the cut-off value to 150, 200 or 275 ng/ml produces a considerable reduction in the number of required colonoscopies. If in addition to raising the cut-off value to 275 ng/ml a (young) age group were to be postponed, the required number of colonoscopies could fall to a maximum of 34,000 in 2014 (orange bar).

Figures 13 and 14: Effects of the different measures on the required colonoscopy capacity



6. Adjusting the implementation of the colorectal cancer screening programme

The current colonoscopy capacity problem demands a rapid adjustment in the short term.

Adjustment for 2014: raise cut-off value to 275 ng/ml and deploy as much additional colonoscopy capacity for the screening programme as possible

On the basis of the health gain and the intended risk-benefit ratio resulting from the Health Councils' recommendation and the Population Screening Act permit, the best scenario for the short term is where possible to gain additional colonoscopy capacity for the screening programme and adjust the cut-off value from 88 to 275 ng/ml.

A higher referral rate leads to an appropriate positive predictive value (PPV), i.e. lower than in the Health Council of the Netherlands recommendation of 2009. In order to bring the PPV, an important proxy for the risk-benefit ratio for the participant, more into line with the starting values in this recommendation, the referral rate would have to be reduced. As the Health Council already indicated in 2009, that is indeed one of the important benefits of a quantitative stool material test, which the FOB-gold also is. The referral rate can be lowered by raising the cut-off value of the test. By raising this cut-off value to 275 ng/ml, the PPV (and hence the risk-benefit ratio) of the stool material test is, or is expected to be, more in line with the original recommendation of the Health Council.

Table 6 shows the expected effects of raising the cut-off value compared to the current situation in the national screening programme and compared to the three trial screenings. This shows that with the adjustment to the cut-off value the expected yields are more in line with those of the trial screenings, on the basis of which the Health Council of the Netherlands published its recommendation. The true positives reflect the positive predictive value. That is the percentage of colonoscopies with an advanced adenoma and/or a colorectal cancer (see page 8 for more information on this). With an increase in the cut-off value this percentage increases compared to the current situation. This shows that the colonoscopies can be used more efficiently.

Table 6: Effects of the trial screenings and the national screening programme with a cut-off value of 88 ng/ml and a cut-off value of 275 ng/ml.

| Screening | Participation | Positive tests | True positives ⁵ | True positives per 1,000 screened | True positives per 1,000 invited |
|--|------------------|-------------------------------|-----------------------------|-----------------------------------|----------------------------------|
| Trial ⁶ | 60% | 6.4% | 51.6% | 28.4 | 17.0 |
| National, cut-off value 88 ng/ml ⁷ | 68% | 13.3% | 29.7% | 35.0 | 26.1 |
| National, cut-off value 275 ng/ml ⁸ | 68% ⁹ | 7.9% ¹⁰ (6.0%)* | 38.2% | 26.7 | 18.2 |

* The expected referral rate from 1 July 2014 is 6%. For a more detailed explanation, see the paragraph below.

The expected percentage of positive tests if the cut-off value is raised to 275 ng/ml in the national screening programme (7.9% in the table) is the observed referral figure up to 23 April (based largely on 75 and 76-year-olds). The expected referral rate from 1 July 2014 is 6% if a mix of ages is invited and the cut-off value from 1 July is 275 ng/ml. This percentage arose with the estimated referral figures by age based on data from ColonIS up to mid-June 2014, and the proportion of the number of persons still to be invited in each age cohort. The proportion of 75 and 76-year-olds in the second half of 2014 will be relatively lower than in the other age cohorts to be invited.

The percentage of true positives (the positive predictive value) is then expected to increase somewhat. The detection rate is expected to remain unchanged. As a result, with a cut-off value of 275 ng/ml, the values are expected to come out around those of the trial screenings.

The screening programme is this found to be too sharply tuned relative to the Health Council of the Netherlands' intention with its 2009 recommendation. A cut-off value of 275 ng/ml is more in line with the effects intended by the Health Council. If the cut-off value had been 275 ng/ml from the start of the screening programme, 117 carcinomas would have been found up to 23 April rather than the 133 detected (433 carcinomas found up to 25 June, see table 4) and 290 advanced adenomas instead of 404 up to 23 April (1,306 advanced adenomas found up to 25 June, see table 4). This appears to be deterioration, but at group level it is not, because the low cut-off value is also at the expense of the too many unnecessarily referred persons who undergo a demanding colonoscopy.

The increase in the cut-off value to 275 ng/ml is the adjustment that delivers most health gain, because as many people as possible from the 2014 target group are offered a first round screening, with as few people as possible being referred unnecessarily and the aim being to achieve a maximum possible yield in the colonoscopy for the entire group (riskbenefit ratio). Due account must be taken of limited colonoscopy capacity, as it reduces the expected number of colonoscopies required from 64,000 to 42,000

⁵ Percentage of people with a positive test in which cancer or an advanced adenoma is detected in the colonoscopy (positive predictive value).

⁶ Data based on the three trial screenings and used in the recommendation of the Health Council of the Netherlands. Cut-off value 75 ng/ml with the OC Sensor (trial screening) corresponds arithmetically to a cut-off value of 88 ng/ml with the FOB Gold (national Screening Programme).

⁷ Results up to 23 April 2014, not fully validated, mainly 75 and 76-year-olds invited.

⁸ The numbers are based on the insufficiently validated results of the screening up to 23 April 2014, mainly 75 and 76-year-olds invited.

⁹ Forecast, with no reason at this stage to assume that raising the cut-off value will lead to lower participation.

¹⁰ Observed referral figure in national SP up to 23 April, based mainly on 75 and 76-year-olds.

compared to the originally expected 28,000. Together with healthcare insurers, hospitals, endoscopists, colonoscopy centres and the Netherlands Association of Hepatogastroenterologists, an assessment will be made of the possibility of an expansion with additional colonoscopy capacity in the second half of 2014, on the basis of no increase in waiting times for regular colonoscopies. With these measures it is currently still unclear whether it is feasible in 2014 to invite everyone from all the age groups intended for 2014; if not, some of the people will be postponed to 2015.

Intention for 2015: aim of purchasing 48,000 colonoscopies; cut-off value maintained at 275 ng/ml

For 2015, the ambition with regard to colonoscopy capacity to be purchased and delivered is 48,000 colonoscopies. If that proves successful, the age groups proposed for 2015 can be invited with a cut-off value of 275 ng/ml. This means that 6,000 more colonoscopies will be required than was previously proposed for 2015. This is without any colonoscopies required for people who had to be postponed in 2014 and who will have to be invited at the beginning of 2015 if despite the raising of the cut-off value there proves to be insufficient colonoscopy capacity in 2014.

If this proves not to be feasible, a decision will have to be taken in 2015 on an adjustment to the rollout schedule (postponement of one or more age groups).

More information needed for longer-term scenarios

The monitoring and provision of data in a national IT system is systematically well established. In this phase just after the start, however, a number of improvements in the recording and delivery of data from the healthcare system are still required; this applies both to the submission of colonoscopy data and validation of these data. We see that a transition from recording by a number of dedicated academic research centres to recording in the day-to-day practice of colonoscopy centres leads to problems in uniform recording across the country, which require further investigation. We conclude that further validation of the data will be necessary in the period ahead before conclusions can be drawn concerning, for example, colonoscopy yields, the follow-up policy, etc. These adjustments and improvements require time; a number of steps have now been taken to make progress on this point.

At the same time, the above data are necessary in order to provide a good recommendation on the deployment of some of the proposed scenarios in the longer term, such as the adaptation of the screening interval, and where possible to analyse consequences for the efficiency and cost-effectiveness of the programme.

Long-term proposal from 2016

For the long-term, in view of the necessary capacity growth, other scenarios must be considered, such as an adjustment to the rollout schedule and/or amending the screening interval of invitations. In this regard it is important that, in addition to the effectiveness of the screening and communication with the citizen, an assessment is made of the speed with which the build-up of the additional colonoscopy capacity can take place in the healthcare system. Further discussions will take place on this with the Netherlands Association of Hepatogastroenterologists. Together with the evaluator (ErasmusMC and the Antoni van Leeuwenhoek hospital) an assessment will be made to determine which analyses will be necessary in the forthcoming period and years to arrive at a good proposal for possible other invitation scenarios. A proposal on this is expected in the first half of 2015.