FIT for Screening

Summary of the third Expert Working Group meeting

17 May 2013, Orlando, Florida, USA

Meeting chaired by Professor Stephen Halloran (minutes Dr Helen Seaman)

Introduction

Guaiac-based faecal occult blood (FOB) tests (gFOBT) have been available for many years and their use in colorectal cancer (CRC) population screening programmes is supported by evidence from randomised controlled trials (RCTs).[1] gFOBT provide little opportunity for provider-initiated optimisation but also little opportunity for significant misuse. They are, however, biochemically crude and limited in their clinical effectiveness. The development of immunochemical-based FOB tests has provided greater opportunities for enhanced clinical effectiveness but also opportunities for making mistakes and thereby causing clinical problems and damaging the reputation of CRC screening.

The Expert Working Group (EWG) 'FIT for Screening' was formalised during the UEGW 2011 in Stockholm, Sweden and is guided by Professors Callum Fraser, Stephen Halloran, Jim Allison and Graeme Young. The EWG met in San Diego (May 2012) and again in Amsterdam (October 2012).

The EWG's remit is to optimise the effectiveness of faecal immunochemical tests for haemoglobin (FIT) in CRC population screening programmes (Table 1).

Table 1: FIT for Screening - the Expert Working Group's remit

To promote the optimal use of faecal immunochemical tests for haemoglobin (FIT) in population screening for colorectal cancer and to enhance the comparability of results over time, geography and method through establishment of:

- agreed international standards on FIT performance characteristics,
- consistent units for reporting test results and for assessing the haemoglobin cut-off concentrations used to designate positive test results,
- agreed methods of determining the haemoglobin concentrations used to calibrate FIT measurement systems: these methods will relate to internationally agreed haemoglobin standards, materials and methods,
- consistent methods of determining and reporting FIT device analytical performance characteristics (e.g. stability, sample mass, etc),
- guidelines on the criteria that should be considered when selecting FIT devices for population screening,
- guidance on specific issues and general areas for improvement of FIT test technology.

Since the inauguration of the FIT for Screening EWG the Group's leaders have published five editorials and commentaries[2-7] in high impact journals that highlight the benefits of FIT in screening and stress the importance of standardising elements of FIT manufacture and use, which will be critical if this relatively new screening modality is to achieve its potential as a population screening tool. Since the last meeting of the EWG in Amsterdam (October 2012),

the EWG's published articles have been cited elsewhere in the literature, demonstrating that the group's efforts are beginning to be recognised.[4, 6, 8-15]

The Group's leaders have prepared six discussion documents (Table 2) that describe the critical issues to be considered by the EWG. These papers are based on the EWG's remit but expand upon it and make practice recommendations for consideration by the larger group; they provide the framework for current and future EWG agendas and targets. The remit of these meetings is to reach agreement on as many items as possible and, when appropriate, to initiate further work that will facilitate agreement of standardised procedures at the later EWG meetings.

Table 2: FIT for Screening Expert Working Group Discussion Documents (as at 17 May 2013)

No. 1	FIT Standardisation
No. 2	FIT Reporting units
No. 3	Stability of haemoglobin
No. 4	Internal quality control & external quality assessment
No. 5	A Standard for Faecal Immunochemical TesTs for Haemoglobin Evaluation Reporting (FITTER)
No. 6	Quantitative FIT procurement

Summary of conclusions from previous EWG meetings (San Diego, May 2012 and Amsterdam, October 2012)

- Nomenclature
  - Faecal immunochemical test for haemoglobin (abbreviated as 'FIT').
- The analytical technique is 'immunochemical' and not 'immunological'.
- Use of the term 'immunoturbidimetry' is more appropriate than 'latex agglutination'.
- Avoid using FIT^{50}, FIT^{100} and similar descriptions when detailing faecal haemoglobin cut-off concentrations
  - Reporting units should be µg haemoglobin/g faeces (full adoption can be achieved once we have identified and adopted standardised methods for determining sample mass and buffer volume)
- All manufacturers should use a WHO traceable standard and the recommended spectrophotometric cyanmethaemoglobin method to assign the haemoglobin concentration of calibrators used in all FIT assays.
- FIT Publications: as a guide for reviewers, authors and journal editors, EWG will progress the development of a WEO-endorsed document which describes the essential analytical content of FIT-related medical and scientific papers.
- FDA approval of quantitative FIT: The EWG will continue in its efforts to engage with the FDA.
- IQC/EQA: EWG to provide guidance on quality management of FIT laboratory testing to encourage acceptable analytical performance in colorectal cancer screening programmes. EWG to advise what IQC/EQA information should be included in tender documents.

- Procurement: The EWG will prepare a document to provide guidance on procurement of FIT systems (now Discussion Document no. 6).
- The WEO will prepare a website where documents relevant to the activities of the FIT for Screening EWG will be made available.

Objectives of the meeting in Orlando, May 2013

The third full meeting of the EWG in Orlando, ahead of DDW 2013, had the opportunity of addressing and agreeing actions on a further series of critical issues that will progress standardisation of FIT technology and its use. Several issues were tabled for discussion:

- WEO-endorsed website.
- FIT manufacturer questionnaire survey.
- FDA & quantitative FIT – update and discussion.
- Development of FIT evaluation guidelines.
- Procurement of quantitative FIT systems (Discussion Document no. 6).
- Standards for FIT publications (Discussion Document no. 5).
- Updates on the use of FIT in national screening programmes .

WEO endorsed web pages – *Helen Seaman*

The EWG's activities will be summarised and promulgated via dedicated web pages hosted by the World Endoscopy Organization. (It is unclear at this time whether or not the other WEO CRC Screening Committee EWGs will launch web pages.) Dr Helen Seaman presented a few slides to illustrate the proposed design for the web pages. Links will be provided to:

- EWG Discussion Documents.
- EWG publications.
- Reference documents:
  - Country-specific information on FIT screening programmes.
  - FIT publications.
- EWG meeting reports and contributors' presentations (with permission).
- Other EWG activity (*e.g.* FIT manufacturer questionnaire survey).
- An 'Ask the Expert' facility will be provided.

It is anticipated that the web pages will 'go live' within a few weeks; all will be notified.

EWG Publications – *Helen Seaman*

The EWG has now published six Discussion Documents (Table 2 above) and six editorials/commentaries:

No.	Citation
1	Fraser C, Halloran S, Allison J, Young G. Making colorectal cancer screening fitter for purpose with quantitative faecal immunochemical tests for haemoglobin (FIT). Clinical Chemistry and Laboratory Medicine 2013. doi: 10.1515/cclm-2013-0408. Epub ahead of print 20 June 2013.
2	Fraser CG, Allison JE, Young GP, Halloran SP. Quantitation of hemoglobin improves fecal immunochemical tests for noninvasive screening. Clinical Gastroenterology and Hepatology 2013:11;839-40. doi: 10.1016/j.cgh.2013.02.031.
3	Fraser CG, Allison JE, Halloran SP, Young GP. A proposal to standardize reporting units for fecal immunochemical tests for hemoglobin. Journal of the National Cancer Institute 2012; 104(11):810-4.
4	Fraser C, Allison JE, Young GP, Halloran S. Newer fecal tests: opportunities for professionals in laboratory medicine. Clinical Chemistry 2012;58(6):963-5. Epub 27 March 2012.
5	Young GP, Fraser CG, Halloran SP, Cole S. Guaiac based faecal occult blood testing for colorectal cancer screening: an obsolete strategy? Gut 2012;61(7):959-60.
6	Allison JE, Fraser CG, Halloran SP, Young GP. Comparing fecal immunochemical tests: improved standardization is needed. Gastroenterology 2012;142(3):422-4. Epub 28 Jan 2012.

There is evidence too that the EWG's recommendations are being recognised elsewhere in the published literature.[4, 6, 8-17]

FIT manufacturer questionnaire survey – *Helen Seaman*

The FIT manufacturer questionnaire survey was initiated in November 2011. All FIT manufacturers identified were asked to provide details about individual FIT products. The information gathered was used to direct the current evaluation of quantitative FIT devices for the NHS in England. Up-dated information from manufacturers will be formally requested in time for the next EWG meeting in Berlin, October 2013 (manufacturers will be given two weeks to reply). The information will be shared on the web site and kept up-to-date with regard to new FIT products and/or changes to currently marketed FIT characteristics.

It is anticipated that countries moving towards FIT procurement will look to the web site to see what products are on the market. A good working relationship between manufacturers and the EWG is needed. Please contact Helen Seaman (helenseaman@nhs.net) with new information and updates.

FDA & quantitative FIT – *contributors Professor Jim Allison, Max Robinowitz and Ron Schoengold*

To date, the Food and Drug Administration (FDA) in the USA has approved only the qualitative use of FIT. Colonoscopy remains the test of choice for CRC screening in the

USA. In 2005 opinion leaders were of the opinion that faecal occult blood is a non-specific and insensitive marker for "screen-relevant" neoplasia [18]; since then, however, published literature from other countries has supported the use of FIT in the detection of CRC[19, 20].

Since the last EWG meeting in Amsterdam (October 2012), the EWG has established a relationship with Max Robinowitz at the FDA.

Max Robinowitz, Senior Medical Officer & Pathologist, FDA Division of Immunology and Hematology Devices, White Oak Campus, Silver Spring, Maryland, USA.

The FDA has 12,000 employees at the White Oak campus, 1200 of whom are employed by the Centre for Devices and Radiological Health, a department with a strong science base. Since 1976, the US has regulated the **manufacturers** of *in vitro* diagnostic tests (*i.e.* the FDA does not regulate research activities or laboratory performance). To commercialise a product in the US, manufacturers must approach the FDA.

The FDA now has the authority to support a pre-submission process whereby any manufacturer in the planning phase of developing/commercialising a new product can contact the FDA. The pre-submission process is organised and comprehensive and allows for provision of comments on proposals, there is a clear timeline, the process is free and offers a level playing field without favouritism. Ultimately the FDA receives better submissions and manufacturers do not waste time on inadequate submissions.

The FDA's powers are similar to ISO in Europe, although the FDA has power to enforce good practice on manufacturers, for example if a manufacturer is not reporting recalls.

FOB tests were classified by the FDA in 1980 as tests to detect occult blood in urine or faeces – no mention was made in the *Class II* classification of the use of FOB in screening for CRC (although more recently CRC screening has been mentioned, screening is not listed as an intended use). The FDA classifies cancer screening tests as *Class III* (for which a Premarket Application [PMA] must be submitted). Manufacturers wishing to gain approval of Class III devices must submit a PMA.

Ron Schoengold, RAC, Quality, Regulatory & Product Development Consulting, Saratoga, CA, USA

Pathway towards approval of quantitative FIT in the US market through the FDA

Before approaching the FDA: (a) establish a consortium of experts with appropriate scientific knowledge from the EWG*; (b) nominate a manufacturer and an FDA-cleared qualitative FIT (candidate predicate device); (c) review existing FIT validation work (use 'FITTER' criteria: clinical trials/studies, laboratory/analytical studies, risk analysis [gap analysis is key and should use existing tools - FMEA; Failure Mode Effects Analysis] and product efficacy). (*Including representatives from R&D, clinical chemistry, clinical research trials, biostatistics, product development & engineering (commercial manufacturer).)

The FDA offers manufacturers an opportunity to attend a free pre-submission meeting (pre-IDE review) to discuss and review an application, provided that the raw data from laboratory analyses are available (performance data [analytical* & clinical]), the intended use and indications for use are clear, expected values (cut-off), instrumentation and software documentation is complete, minimum requirements for safety and effectiveness are clear (limitations [false negatives, false positives]) and any gaps in the knowledge (to establish labelling claims) have been identified. (*Precision, interference, assay range, linearity, recovery, calibrators and controls.)

Manufacturers wishing to petition the FDA for what might be classified as a 'Class II Special Controls Guidance Document* for Quantitative FIT for Screening' should determine the cost and feasibility of meeting FDA requirements and must be prepared to underwrite the cost of submitting an application. (*Formerly a Class II Special Controls Document.)

Discussion

Max Robinowitz is part of the FDA team that would review applications from quantitative FIT manufacturers (although applications should not be directed to Max by name). The cost of submitting a PMA for Class III approval is substantial; it is still possible that efforts to have quantitative FIT recognised as Class II devices could be fruitful. The FDA will recognise data supporting the clinical effectiveness of FIT from outside the USA, according to international CLSI (Clinical and Laboratory Standards Institute) recommendations.

It was noted that the FDA may have a role in controlling the inappropriate use of FOB, *e.g*. for symptomatic patients.

Efforts should be made to try and get the FDA to recognise quantitative FIT as a class II device (510K) (or to develop a new class II classification) and it should be possible to prove that the clinical work on FIT is valid and suitable for 510K classification. There was agreement that a quantitative FIT for Hb does not have to have cancer screening claim as detection of Hb is not intrinsic to cancer.

The FDA will accept supporting technical data from outside the US provided that the study or studies providing those data met the standards expected from US studies (*i.e.* informed consent, ethical consideration, pre-market inspections *etc*).

Professor Jim Allison, Max Robinowitz, Ron Schoengold and Stephen Halloran will progress this activity and share the plan on the new web pages. The importance of involving the commercial sector in these efforts was stressed.

Scientific and technical evaluation

Development of a FIT evaluation protocol, evaluation guidelines and a funding mechanism

Dr Magdalen Carroll

The FIT evaluation work currently underway in Guildford, UK, was described, although data remain confidential.

Devices for evaluation were selected as suitable for population-based CRC screening if:

- The device provides a *quantitative* measure of haemoglobin concentration
- The analysis can be automated
- The sample collection device is suitable for home-use

Four automated, quantitative FIT devices/analysers are being evaluated (selected according to information provided by manufacturers on FIT questionnaires [see above]):

- FOB Gold NG, Sentinel CH. SpA, Italy/Biomajesty, Sysmex, UK
- HM-JACKarc, Kyowa Medex Co Ltd, Japan
- NS-Plus Hb, Alfresa Parma Corp, Italy
- OC-Sensor DIANA, Eiken Chemical Co. Ltd, Japan.

For the evaluation each manufacturer has been asked to supply:

- The analyser
- Consumables
- Training for Dr Carroll and two laboratory scientist colleagues
- Ongoing technical support

For each device/analyser, the evaluation will:

- Address the question - is the product fit for purpose (in this case population-based cancer screening)?
  - Assessing and comparing design of instrumentation and collection devices
  - suitability of collection device for sending through a postal system
- Examine analytical performance:
  - analytical sensitivity (smallest amount of analyte that can be measured accurately)
  - carryover (between samples)
  - precision profile (7-10 concentrations measured, mean and S.D.)
  - imprecision (intra- and inter-day, intra- and inter-batch on same day and different days)
  - linearity/measurement range
  - specificity (cross-reaction between human and other species Hb/Hb variants?)
  - reporting units (ng/mL or ug/g)
  - stability (of the matrix/faeces, at different ambient temperatures and periods of time)
  - collection devices (mass of sample collected, volume of buffer)
- Inform the procurement process
- Confirm (or refute) manufacturers' claims
- Compare features and performance across the market.

Selection of the cut-off threshold used in screening must be done carefully with knowledge of the precision profile of the FIT device used. One of the parts of the evaluation will be to look at materials that can be used for QA purposes and also for quantification of the mass of faecal sample.

The evaluation in Guildford is scheduled for completion in the autumn of 2013. It is anticipated that the results will be available at the next EWG meeting in Berlin, October 2013, ahead of UEG Week. A Discussion Document will be prepared and circulated for that meeting.

Future evaluations/re-evaluations

In the UK, the NHS requested the evaluation of FIT devices for use in the national screening programme. Once complete, there will not be a source of money to continue with new evaluations and re-evaluations. It may be possible for the WEO to act as an independent organisation that could talk with manufacturers re new products/product enhancements. If appropriate, the WEO could then approach one of several potential evaluators for high-quality impartial evaluation. WEO would take a cut for providing that service.

Background to screening programme in the Netherlands and evaluation work
Dr Ernst Kuipers

Dr Kuipers outlined three different pilot trials in screening-naïve populations in the Rotterdam area of the Netherlands with organised invited screening to illustrate the importance of considering issues around FIT as used for population-based cancer screening, not on an individual basis.[10, 21-23] It has been demonstrated by Hol et al[23] that the update of the first screening round invitations was 13-15% higher with FIT (OC-Sensor, Eiken Chemical Co. Ltd.) than with gFOBT and that FIT detected more than three times as many advanced neoplasias (gFOBT 6/1,000 vs FIT 21/1,000 at a cut-off of 10 µg Hb/g faeces (50 ng Hb/mL buffer)). The number of positive screenees needed to scope to detect one advanced lesion was similar for gFOBT and FIT. Another paper from the Netherlands[22] reported on a study that randomly recruited individuals for two screening rounds using 1-sample FIT (OC-Sensor, Eiken Chemical Co. Ltd.; cut-off 10 µg Hb/g faeces [50 ng Hb/mL buffer]) at intervals of one, two or three years. The number of advanced neoplasia found at repeat screening was not influenced by interval length (1-3 years) and participation in the first and second rounds was stable and acceptably high (between 61% and 64.7%). Thus, screening intervals can be tailored to local resources.

The use of FIT in the screening programme in the Netherlands was approved by the Dutch Minister of Health in July 2011 (http://www.rivm.nl/en/Topics/Topics/B/Bowel_cancer_screening_programme). Biennial FIT will be offered to a population of 3.5 million, with roll out over 5 years from September 2013. The European tender identified FOB Gold as the FIT that will be used in the national programme (*i.e.* a different FIT from that used in the pilots (OC-Sensor)). It is anticipated that there will be a 45% increase in demand for colonoscopy. There will be a dedicated QA programme with licensed screening endoscopists and endoscopy units. Initially, invitations will be sent to 65 and 75-year-olds (ultimately to 55-75-year-olds) (although a starting age of 50 years was recommended from the pilot study). A comparative analysis will compare FOB Gold and OC-Sensor 4th round pilot screening programme.

The selection of the new screening modality in the NL was based partly on the scientific evidence (25%) and partly on cost (75%). After economic evaluation it has been decided that the cut-off will be 75 ng/mL (with FOB Gold equivalent to 12.75 µg Hb/g faeces); the pilot suggested a cut-off of 50 ng/mL [10 µg Hb/g faeces] with OC-Sensor). FIT-positive individuals who have a negative colonoscopy will return to the screening programme but will not be invited to participate again for the subsequent two FIT rounds.

The Dutch do not have plans to incorporate a risk algorithm into their screening programme at present. Research in the Netherlands has not found a difference in PPVs for men and women, although consideration might be given to how often to offer repeat testing to FIT-negative individuals and the interval between testing, which would amount to personalised screening of a kind.

MUSTANG, the Bavaria Health Centre study group (**MU**nich **STAN**dardisation **G**roup) – an update (with further information from Dr Friedrich-Wilhelm Tiller, Bavaria Health Centre provided on slides).

MUSTANG is a group of scientists looking at improving understanding of FIT measurements and also at ways of measuring low Hb concentrations accurately. Stephen Halloran has met with the group and highlighted to them the difficulty of measuring Hb in faeces given the nature and variety of products currently used to collect samples, inconsistencies in stool,

diet, biochemical elements, biological variations and additional bowel disease. The Group accepted that standardisation is not going to be easy.

Procurement

As agreed at the last EWG meeting in Amsterdam, the Discussion Document on quantitative FIT procurement has been circulated (Discussion Document no. 6). Comments are requested from the commercial sector. Colleagues involved in procurement will be asked for their input to refine the document. Delegates in Orlando were asked to comment provide comments as soon as possible with a view to having a finalised document ready Berlin (October 2013).

A guideline for Faecal Immunochemical TesTs for haemoglobin Evaluation Reporting (FITTER)

A Discussion Document (prepared by Professor Callum Fraser) has been circulated to the group with recommendations for authors, referees and editors as to what information should accompany papers on FIT (Discussion Document no. 5). The document, which includes a checklist, is in almost final form so delegates are asked to comment as soon as possible.

It was confirmed that some of the information recommended for inclusion by the FITTER guidelines would be suitable for inclusion in the supplementary online material facility offered by many journals.

There was suggestion that the recommendations could be circulated initially to editors of high impact factor journals.

The use of FIT across the world

Country-specific information will be available on the web pages. The following paragraphs summarise contributions received from delegates during the meeting.

FIT in Asia – Dr Yi-Chia Lee

Dr Lee presented slides on screening activity in Korea, Japan, Singapore and Taiwan.

It was evident that uptake in Asian countries is poor. This was attributed to restricted budgets and insufficient endoscopic resource (limits age-range too). Whilst improvements to uptake might be realised by considering that one FIT is enough, the uptake figures could be misleading if they represent the proportion of the eligible population screened rather than the proportion of people invited who take up the offer.

Australia – Professor Graeme Young

Funding for CRC screening in Australia is intended to be nationwide; it is managed centrally by the Federal Government and is separate from funds for medical care. The screening programme sends a free FIT and individuals with a positive FIT have a follow-up colonoscopy (either through the programme or privately). The pilots ran 2003-2006 and a decision to roll-out nationwide was taken in 2006. Implementation dates are staged. The Programme now invites people aged 50, 55, 60 (from July 2013) and 65 and the plan is that by 2035 all 50-75-year-olds will be offered biennial FIT (it was noted that by 2035 a new technology may well have replaced FIT). A faster roll-out is hampered by costs. Consideration needs to be given on how to integrate new technologies into the programme.

As a result of the tendering process, the Programme uses MagStream. The cut-off currently used gives a positivity of 6.5%; the cut-off may be adjusted as resources allow. The Programme is working hard at ways to improve the current uptake figure of 39%, although it was noted that because 65% of colonoscopies are performed privately in Australia and about 35% of the population could be considered up-to-date with screening, the ideal uptake may be only about 65%.

As yet, there has not been a major publicity programme because roll-out has been gradual and the Government does not want to raise expectations in people who do not yet have access to screening. It is likely, however, that promotion of the programme will develop. At present, the Australian government is reluctant to consider an age-adjusted cut-off algorithm.

A cost-effective analysis is on-going, which may speed-up roll-out. The Australian government usually considers only up-front costs; although the Australian economy is strong, this in part reflects how the Australian government is very careful and cautious over how it allocates spending.

Crossing Borders Trial – covering Austria/Germany/Czech Republic – Thomas Seufferlein, Medical Director of the Clinic for Internal Medicine, University of Ulm, Germany

The Crossing Borders Trial is funded by Austria, Germany and Czech Republic. In Germany there has been opportunistic screening with colonoscopy since 2002. There are areas of high incidence of CRC and, although offered free, uptake of colonoscopy is low (1-1.5% annual) in areas characterised by high unemployment, suggesting that social deprivation has a role. The trial will target two regions of Bavaria, Upper Franconia and Western Bohemia, both of which are very poor areas with high CRC incidence. Parts of Austria have for 25 years now had an outstanding CRC screening programme that offers a choice of FIT or colonoscopy, thereby increasing uptake. The Crossing Borders Trial will be designed to reach non-responders to screening invitations and to improve uptake by offering FIT. The target population will be aged 55-75 years, and screening will be offered by invitation. A fee will be given to GPs for providing counselling services (€30) and another fee for forwarding completed tests to the laboratory (the fee paid to GPs will be the same for FIT and colonoscopy). The hope is to increase uptake of screening by at least 10% and for >90% of FIT-positive individuals to have a colonoscopy. The trial will accumulate interesting data on patient preference (by questionnaire) and celebrities will contribute to promotion. The plan is to commence the trial in 2014.

The validation and quantitative FIT for use in a province-wide colorectal cancer screening programme in Newfoundland and Labrador, Canada

Scott Antle, Manager, Newfoundland and Labrador Colon Cancer Screening Program

A validation study conducted in Newfoundland and Labrador was conducted, ahead of the launch of a provincial population-based cancer screening programme. The Province has a population of ½ million people spread over a large area. Temperature fluctuations and geographical distances are challenges, and the Province has the highest age-standardised incidence of CRC in Canada.

A screening programme was launched in one region of the province in July 2012 and is now expanding into a second region (expansion is limited by colonoscopy capacity). It is hoped that the programme will be implemented fully in three years.

The validation study evaluated the NS-plus analyser and collecting device. The northern climate and the possibility of freezing temperatures were challenges to the efficacy of the test for the population. The evaluation had two components – **analytical** investigating FIT

performance (*e.g.* stability, including freeze/thaw cycles) and **clinical** (*i.e.* sensitivity and comparison of FIT with gFOBT and colonoscopy).

521 participants were identified from colonoscopy lists and those who agreed were asked to complete two FIT and two gFOBT. 70% of those *who agreed to participate* (check) returned tests on the day of their colonoscopy. FIT showed acceptable performance characteristics. The investigators noted a decrease in stability of 10% after 4 days and 20% after 12 days. With freeze/thaw cycles saw <10% decrease in stability. The results of the evaluation provided confidence that the FIT device could be used in their area.

The investigators also looked at 1- versus 2–sample testing and found a 25% decrease in sensitivity using 1-day compared with a 2-day FIT strategy. A 2-day FIT sample strategy will therefore be employed.

It was found that FIT detected all cancers and high-grade adenoma with a slight advantage with 2-day FIT.

The investigators concluded that FIT was acceptable under variable temperatures and are now planning to compare FIT with transferrin and colonoscopy results.

Relevant publication: Randell et al, Clinical Biochemistry, 2012 [24]

Information provided by Canadian Partnership against Cancer for other regions in Canada is available on the slide. All 10 provinces are either planning or implementing province-wide programmes. Seven provinces use FIT.

Observations

The NS-Plus cut-off 100 ng/mL (19 µg Hb/g faeces) is almost equivalent to OC-Sensor 100 ng/mL (20 µg Hb/g faeces).

The detection rate was 25% higher with 2-sample versus 1-sample FIT, although the collection strategies differed only for low-grade disease, not for advanced disease. Using 1-sample FIT at a lower cut-off would detect a similar proportion of disease whilst possibly improving uptake.

Denmark

Denmark is not using FIT and there are no plans to change from gFOBT.

England

In England, there is a commitment to move from gFOBT to FIT. Implementation has been delayed by the introduction of flexible sigmoidoscopy. The FIT pilot will start in March 2014 – 1 in 28 invitees will asked to complete a FIT test (OC-Sensor, Eiken Chemical Co. Ltd.) over six months. The purpose is not to prove already known benefits of FIT but to establish a process that ensures development of appropriate software, the mailing process and also to ascertain what the uptake and positivity of FIT is in a population that has been invited for screening before. Uptake of FIT screening must be affordable – using OC-Sensor cut-off 20 µg Hb/g faeces (100 ng/mL), positivity would be expected to be about 6% in a screening-naïve population or 4% in a population already screened, thus manageable.

The pilot is expected to be completed at the end of 2014. Then the British government has to agree to roll-out FIT (FIT is recognised in its cancer plan). A facility for developing a risk algorithm is being incorporated into the software for FIT roll-out in the England.

Finland – FIT not yet being considered

France – gFOBT will be replaced with a FIT (timescale?). Uptake is currently poor and an issue for concern.

Hungary – OC-Sensor – there is limited knowledge on coverage; uptake is reported to be satisfactory.

Ireland (Republic) – The programme is still in its early stages using biennial OC sensor (20 µg/g cut-off). It is progressing well; as yet no reliable uptake data.

Israel – there has been interest in FIT in the past but, as yet, no plan for a national programme.

Italy, Carlo Senore

All regions in Italy have adopted a quantitative FIT for CRC screening for various age groups and using different invitation methods. There are marked differences in screening uptake between regions with a north (high uptake) / south (poor uptake) divide. Until recently, all regions used the same test (OC-Sensor) with cut-off 100 ng/mL (20 µg/g) but now new tests are being used. One region (Milan) decided to move to NS-Plus (cost-saving) but used the same cut-off which resulted in an increased positivity (100 ng/mL cut-off is 20 µg/g with OC-Sensor, 19 µg/g with NS-Plus). It was proposed that a pilot study is needed to look at this as the impact at the population level might be significant.

Kits are returned for analysis via pharmacists, couriers or cool boxes.

Latvia

Marcis Leja spoke about CRC screening in Latvia where uptake is poor. There is a possibility that Latvia will move towards organised screening using FIT. In their pilot OC-Sensor performed better (than gFOBT) with regard to uptake but the final decision as to which FIT to use has not yet been made. The pilot study assessed gFOBT, FOB Gold and OC-Sensor. A total of 15,000 invitees were divided equally between the groups. More than 2,000 FIT kits were returned, a few more in the OC-Sensor group.

Same detection rate for advanced neoplasias for FOB Gold and OC-sensor but uptake of colonoscopy was poor – more colonoscopies were indicated with FOB Gold compared with OC-Sensor. Positivity with OC-Sensor similar as for the Dutch pilot. The study conclusion is that there are big differences with 'identifical' cut-offs between positivity but no difference in detection rates.

It was noted that the volume of the buffer in FOB Gold (1.9 mL) is slightly less than for OC-Sensor (2.0 mL) so using 'identical' cut-offs in terms of ng/mL does not provide directly comparable data.

Malta - very recently commenced screening using OC-Sensor – it is too early to comment on uptake.

New Zealand

Dr Susan Parry summarised the latest results from the New Zealand bowel screening pilot:

http://www.health.govt.nz/our-work/diseases-and-conditions/cancer-programme/bowel-cancer-programme/bowel-screening-pilot/bowel-screening-pilot-results/bowel-screening-pilot-january-december-2012-results

A pilot study is underway in New Zealand – 130,000 people will be tested using a single sample OC-Sensor (cut-off 75 ng/mL [15 µg/g faeces]) over 4 years. Results from Round 1 (Jan to Dec 2012) indicate that uptake is 54% and positivity is 7.2%. Data have been

consistent through summer/winter and are 'good' for males and females. Uptake by Pacific people is poor as a test performed in the home and not validated by a medical practitioner is generally unacceptable. The NZ team is working to try and improve screening amongst Pacific people. Monitoring indicators are posted every three months on the website (see above). So far, 60 cancers have been diagnosed, the positive predictive value for cancer with FIT is 3.9%, 31.6% for advanced adenoma and 57.9% for adenoma.

There are pressures in New Zealand to roll-out the programme more quickly than the 4-year plan proposed by Minister of Health. Efforts are on-going to ensure that there are the systems in place to support national roll-out, including a nationwide quality assurance programme for colonoscopy (similar to the GRS (Global Rating Scale) in England). A national bowel cancer working group is seeking to standardise the outcomes for CRC (surgery, management, access to chem- and radiotherapy) and also looking at the workforce. Consideration is being given to training nurse endoscopists, although the long lead time could be an issue.

Dr Parry stressed how important it is to get a consensus about which is the best screening test to use. There is someone in NZ who is advocating that FS is the *only* screening test that should be used and every time there is publicity, the same argument is put forward – *e.g.* 3x as may colonoscopies using a FIT. Ideally, NZ would provide international comparative data on their web site.

Norway – RCT planned – await data

Scotland – currently use a qualitative FIT as second part of a two-tier screening algorithm and aspire to move to quantitative FIT.

Slovenia – uptake is good

Spain – a mixture of programmes – some guaiac, some FIT. Biennial FIT is used in some parts of country and, although uptake is poor, it is expected to improve with time.

Sweden, Rolf Hultcranz

There has been a pilot screening programme in Stockholm (using guaiac-based FOBT) amongst 60-65 yrs where uptake was about 60%. In 2011, 70,000 tests were completed and 600 colonoscopies; 26 cancers were diagnosed. RH is designing a study that will use FIT versus colonoscopy; approval for the study was given on 17 May 2013. The study will probably turn into the programme.

Uruguay - Dr Eduardo Fenocchi – by law all the population has to be screened. The programme uses OC-Sensor biennial one-day sample. Positivity is 9.5% using a cut-off of 100 ng/mL (20 µg/g faeces) amongst 50-70 yrs.

European School of Screening Management

The ESSM is a programme designed to equip people planning any screening programme for their population. So far, there have been two weeks of intensive training with very good uptake.

MSc in Cancer Screening at the University of Surrey

An MSc in Cancer Screening at the University of Surrey is planned for 2014 (subject to validation). A 'taster' masters-level CPD course ('The principles and practice of population-based cancer screening') will run 9-13 September 2013 in Guildford, UK.

Final comments from the floor

Jim Allison suggested that a systematic review of comparative FIT trials would be useful, but because they are all so different it would be difficult.

Ernst Kuipers noted that direct comparative studies like Marcis Leja's (see above) looking at all aspects, including uptake, are very important – small differences in device characteristics can affect uptake.

The FIT evaluation will provide useful data. Some of the products are very different in their design and appeal to potential participants. Jill Tinmouth reported that in Ontario, Canada, they are comparing five available quantitative and qualitative FIT.

Tom Imperiale remarked that the best way to get conclusive FIT data is head-to-head clinical trials. Ernst Kuipers noted that some FIT have already been assessed in populations of 100,000+ subjects from which fair comparisons can be made.

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