World Endoscopy Organization
Colorectal Cancer Screening Committee

DDW, San Diego 2012

1st Meeting of the Expert Working Group (EWG) – 'FIT for Screening'

Friday, 18 May 2012

MEETING REPORT

Introduction
Prof Jim Allison
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Population screening for CRC is quickly becoming a reality for many countries – this presents major health benefits but also challenges for those providing the services. Quality has to be at the centre of any screening programme and the implications of not achieving and maintaining adequate quality are substantial for the sponsors and providers and primarily for the population served.

Guaiac-based FOB tests have been available for many years and provided the RCT evidence for the efficacy of CRC population-based screening. These tests 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 both 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 following discussion between Prof. Graeme Young, Jim Allison, Callum Fraser and Stephen Halloran. Its remit is described in an associated document but in essence it is to optimise the effectiveness of screening using immunochemical FOBT and that includes taking whatever measures are necessary to enhance the reliability of FIT, to promote its use in screening programmes and to facilitate its maximum clinical effectiveness.

Since the inauguration of the 'FIT for Screening' EWG the Group's leaders have published four editorials 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.

This first full meeting of the EWG at DDW 2012 has the opportunity of addressing and agreeing actions on a series of critical issues that will progress standardisation of FIT technology and its use. The Group's leaders have prepared four discussion documents 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. These discussion documents provide the framework for current and future EWG agendas and targets. The remit of this meeting 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.

Prof Stephen Halloran described the FIT manufacturer questionnaires that Helen Seaman had circulated to 41 companies to elicit details about individual products. He thanked Helen for her diligent work in managing the questionnaire activity and helping to assemble the data. He also thanked those members of the audience who had responded to the many detailed questions posed. Whilst some of the details are still being checked, we have data that will form the basis for much of the work of this and future EWG meetings.

Key discussion points and conclusions

1. **Questionnaires** - 14 of the 41 FIT manufacturers completed and returned a questionnaire. Stephen Halloran's UK group will continue to validate the data extracted from the questionnaires, will attempt to engage with those companies who have hitherto not responded to the questionnaire and will have as a remit maintenance of a detailed international registry of FIT products, both quantitative and qualitative.

2. **FDA Approval of quantitative FIT** - The use of quantitative FIT has not been accredited by the FDA for clinical use in the US. This places the US at a significant disadvantage when addressing comprehensive CRC screening, particularly in attempts to reach the population that, for financial or social reasons, is resistant to using colonoscopy as the primary screening modality.
    a. It was agreed that the EWG should see as a priority the adoption of FIT by the FDA.
    b. Jim Allison would act as the EWG's US focus for progressing FDA approval of FIT. Ron Schoengold will provide a supporting role.
    c. It was thought that the EWG could improve the likelihood of FDA approval if:
        i. Standardisation of some critical aspects of the analytical performance could be addressed
        ii. An expert-endorsed portfolio of clear clinical evidence of the effectiveness of FIT were assembled
    d. Progress with this agenda would be reviewed at the UEGW meeting in Amsterdam, October 2012.

3. **Nomenclature** - The nomenclature used for FIT was diverse and potentially misleading and the EWG agreed the following:
    a. The full description of the test would be:
        i. Faecal (Fecal) Immunochemical Test for Haemoglobin (Hemoglobin)
    b. The abbreviation for the test would be:
        i. FIT
    c. The test comes in two forms:
        i. The first form produces quantitative numeric concentrations of haemoglobin in the matrix upon which the analysis is performed. This device will be described as **quantitative** FIT and will not be abbreviated and the term semi-quantitative FIT will not be used.
        ii. The second form, usually a once-only use point-of-care testing device that uses lateral flow immunochromatography technology, indicates either a positive or negative test result, the cut-off concentration being integral to the design of the test device. This device will be described as **qualitative** FIT and will not be abbreviated.
    d. The practice of adding the study/programme cut-off concentration as a superscript to the FIT abbreviation was not endorsed by the EWG because current units of reporting are not transferable across devices or studies/programmes.

4. **FIT Reporting units** – Manufacturers currently use two different reporting systems, haemoglobin concentration in faeces and haemoglobin in collection buffer. The EWG agreed that the common practice of expressing FIT concentrations as faecal haemoglobin in the collection buffer made comparisons of FIT device performance and clinical studies difficult and potentially misleading.
    a. It was agreed that:
        i. Manufacturers would progress to having all products report haemoglobin in faeces concentrations using µg Hb/mg faeces.

ii. That whilst manufacturers could use their currently quoted sampling mass to derive the µg Hb/mg faeces, the mass measurement did not follow a standardised procedure and therefore the transition should await a standardised procedure agreed by the EWG.
iii. That the use of haemoglobin in buffer concentration was valid for an individual product but was unsuitable for simple product or study comparisons and that manufactures' literature should highlight this fact.
iv. The new µg Hb/mg faeces concentrations would be included in company literature with the conversion factors from ng Hb/mL buffer.
v. Whilst it was desirable for instruments to use the new units, the cost of software modification would have an impact upon the period of transition.
vi. The UEGW meeting in Amsterdam, October 2012, will provide an opportunity to review progress.

5. **Standardised procedure for sample mass measurement** – The questionnaires demonstrated that manufacturers have developed a range of procedures for estimating the mean sample collection mass for FIT devices. No single procedure could reflect the range of stool samples that a population-based programme could encounter and no single manufacturer had developed a procedure that could be considered superior to others.
    a. It was agreed that:
        i. Whilst it was likely that 'very hard' or 'very loose' stools would challenge the efficacy of current device sampling techniques, no published evidence provided guidance on the unsuitability of particular stool consistencies. The group could not provide any recommendation to manufacturers on what should be stated in product literature designed to help device users.
        ii. Manufacturers need to be provided with an EWG-agreed standardised procedure for determining sample mass that is not dependent upon biological or physiological variability.
        iii. Stephen Halloran agreed to explore suitable standardised procedures.

6. **Traceability of haemoglobin standard** – The questionnaires showed that most manufacturers were utilising a standardisation procedure that was traceable to a World Health Organisation (WHO) standard. Most manufacturers were using a spectrophotometric cyanmethaemoglobin reference method to calibrate their reference material from the WHO standard.
    a. It was agreed that:
        i. All manufactures should conform to the good practice adopted by the majority of companies and use the current WHO traceable standard and use the spectrophotometric cyanmethaemoglobin reference method for preparing a reference standard.
        ii. All companies should state the characteristics of the haemoglobin used for calibration.

7. **Haemoglobin stability in the collection device** – The questionnaire data demonstrated a diverse range of procedures adopted by manufacturers when determining the stability characteristics of faecal haemoglobin in their collection devices. These procedures have been derived because no standardised procedure is recommended.
    a. It was agreed that:
        i. Haemoglobin is not stable and degrades from the time it is released into the gastrointestinal tract. The rate of degradation will depend on the chemical and microbiological composition of the faeces, the temperature, possibly exposure to light, the effectiveness of stabilising and bactericidal preservatives and critically the period of time from the GI bleed to analysis.

   ii. The statement that a sample is stable for a set period of time is inaccurate and should not be reported in product literature without being suitably qualified.
   iii. Product procurement documents should request stability characteristics, not 'period of stability'.
   iv. The group would consider endorsement of a stability assessment procedure that might utilise both an aqueous or artificial matrix and a faecal matrix.
   v. Stephen Halloran agreed to explore suitable standardised procedures.

8. **Procurement of FIT devices** – Although the EWG did not have sufficient time to discuss the details of what FIT product information should be considered important for those procuring these devices, on several occasions, the critical importance of expert procurement guidance was highlighted.
   a. Agreed action;
      i. The EWG would prepare draft procurement guidance to assist those looking to purchase FIT devices.

9. **Internal quality control and external quality assessment:** The EWG meeting was not able to commence work on this and discussion will be deferred to the next meeting at UEGW in Amsterdam, October 2012.

10. **Clinical experience and lessons learnt** – practical tips from screening programmes (pooled experience from companies and from organisers in The Netherlands, New Zealand, UK, Latvia, Scotland, US, Italy):
    a. FIT uptake consistently increased.
    b. Sensitivity increased, particularly to advanced adenomas.
    c. Need more endoscopy resource to realise clinical benefits.
    d. Stability can be a problem, even in a country with a cool climate and swift return of test kits
    e. Potential changes in positivity and colonoscopy referral rates as new and better buffer preservatives are introduced.
    f. Misuse of test kits can be a substantial problem – instructions need to be clear and the kit well-designed.
    g. Barcodes used to identify participant can be damaged by contamination by faeces or buffer.
    h. Participants need to record when the sample was collected and the kit design needs to facilitate this.
    i. Some products lose buffer if not opened correctly.
    j. The space available to record the collection date on some sample collection tubes is often small and this lowers the proportion of test kits returned with details recorded adequately.
    k. The functionality of IT systems to support the programmes are critical.
    l. Participants attaching barcodes to test devices increases failure rates.
    m. Stable low Hb standard solutions not commercially available.
    n. Different FIT analysers can exhibit different bias.
    o. Very high cut-off concentrations for FIT may not improve clinical outcomes over guaiac-based FOBT but they have better uptake and a single device can be used.