## *Expert Working Group – 'FIT for Screening'*

### *Short Discussion Document No. 5*

# A Standard for Faecal Immunochemical TesTs for Haemoglobin Evaluation Reporting (FITTER)

*A standard and check-list endorsed by the Colorectal Cancer Screening Committee, World Endoscopy Organization, for those preparing, reviewing and editing manuscripts on studies using Faecal Immunochemical Tests for haemoglobin (FIT).*

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## Introduction

There are many publications of different types concerning faecal immunochemical tests for haemoglobin (FIT). These have appeared in a variety of journals and other media. Although most document the major clinical findings and outcomes in detail, adequate descriptions of the pre-analytical aspects, which include specimen collection, handling and storage prior to analysis, and the analytical performance attained, are very often deficient or missing. Such a situation can also be found in publications on many other biomarkers.[1] However, in order to evaluate published data, to compare and contrast the results of published studies, and to translate published results into practice, these analytically related aspects should be adequately described and documented.

The Expert Working Group (EWG) on FIT for Screening, Colorectal Cancer Screening Committee, World Endoscopy Organization, recognised the importance of improving published papers on FIT and was given a mandate by those attending meetings in Stockholm (October 2011), San Diego (May 2012), and Amsterdam (October 2012) to produce a standard for adequate reporting. This would involve, as is the case for other such standards, a check-list of items to be documented in any publication describing the use of FIT. This paper provides the recommended reporting standard in the form of a check-list for Faecal Immunochemical TesTs for Haemoglobin Evaluation Reporting (FITTER); it follows the format used for randomised controlled trials (CONSORT), systematic reviews or meta-analyses of randomised trials and other evaluation studies (PRISMA), meta-analyses of observational studies (PRISMA) and observational studies (STROBE).

## Development of the standard and check-list

The Standards for Reporting of Diagnostic Accuracy (STARD) statement provides consensus designed to improve the quality of publications and makes available a check-list of 15 important items that authors and editors should document.[2] Item 8 (see www.stard-statement.org/) refers to the importance of describing, in full, the laboratory methods used and the analytical performance characteristics. Adherence to STARD guidelines is required by many journals for studies on diagnostic accuracy and this is supported by the EWG.

More recently, the Consortium of Laboratory Medicine Journal Editors acknowledged the significant impact of the STARD guidelines on reporting of crucial laboratory data and emphasised that authors should report analytical performance characteristics if the reader is to gain maximum insight from the research. Such analytical characteristics include imprecision of the assay in the

investigators' laboratories, the assay's reportable range and any reference (normal) range (or, in the context of FIT: cut-off concentration[s]) used.[1] Although these three items might be considered as a minimum requirement, the EWG considers them not demanding enough, because data vital to the full understanding of published works are not documented.

**Application of the standards and check-list**

Taking these two standards[1,2] into account, we have further incorporated the need to document other important pre-analytical and analytical aspects of special relevance to the use of FIT in screening studies. Investigators are encouraged to include both laboratory and clinical elements of the check-list and to report on adherence to the standard. The check-list should be included with the submitted manuscript to demonstrate that the FITTER standard has been followed and to document where the necessary data are presented in the submitted manuscript or elsewhere. Reports on clinical studies that use already well described commercially available analytical systems without local modification should document the "essential" items and consider inclusion of the "desirable" items. Laboratory evaluations of analytical performance characteristics require more detailed information as shown in the check-list. The EWG recognises that assembling some of the "essential" items might prove to be difficult, but much of this information should be available from the manufacturer of the FIT. Involvement of professionals in laboratory medicine at the beginning of, and throughout, the study, including the preparation of the report, might prove advantageous, as has been suggested elsewhere.[3]

As a practical demonstration, the EWG has created two examples as models, showing how the standard can be applied using the check-list: these are documented in the Appendix. The examples are restricted to the FITTER check-list; other vital information, such as population characteristics and statistical analyses, should be documented elsewhere in the manuscript using other relevant standards such as STARD.

The WEO FIT for Screening EWG recognises that journal space is limited. Electronic supplements or appendices that are available for easy review and reference and not integral to the published work can provide a mechanism to include the information necessary for objective interpretation of the study. Moreover, if such supplemental file systems were unavailable, authors should consider inserting a "data-sharing" statement in their manuscript informing readers that the FITTER check-list, with concise data, is available on request.

The EWG strongly recommends that investigators adhere to the FITTER standards detailed here and use the check-list provided, and that reviewers of submitted works on FIT request full adherence to the standards and look for inclusion of a completed check-list. The EWG hopes that the editors of medical journals and editorial staff will appreciate the need for good documentation of studies on FIT and insist on having the information in the check-list available to all readers.

**References**

1. Rifai N, Annesley TM, Berg JP, et al. An appeal to medical journal editors: the need for a full description of laboratory methods and specimen handling in clinical study reports. Statement by the Consortium of Laboratory Medicine Journal Editors. Ann Clin Biochem 2012;49:105-7.

2. Bossuyt PM, Reitsma JB, Bruns DE,, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. Standards for Reporting of Diagnostic Accuracy. Clin Chem 2003;49:1-6.

3. Fraser CG, Allison JE, Young GP, Halloran SP. Newer fecal tests: opportunities for professionals in laboratory medicine. Clin Chem 2012;58:963-5.

# The FITTER check-list for the reporting of studies using Faecal Immunochemical Tests for haemoglobin (FIT)

| Topic | Item | Priority | Documentation |
|---|---|---|---|
| **Specimen collection and handling** | | | |
| | Name of specimen collection device and supplier (address). | Essential | |
| | Description of specimen collection device (vial with probe/stick, card, other). | Essential | |
| | Description of specimens used if an *in vivo* study (single or pooled faeces, artificial matrix with added blood, etc). | Essential for laboratory evaluations | |
| | Details of faecal collection method (sampling technique and number of samples). | Essential | |
| | Who collected the specimens from the samples (patient, technician, etc). | Essential | |
| | Number of faecal specimens used in the study (single, pooled, individual patient faeces). | Essential for laboratory evaluations | |
| | Mean mass of faeces collected.* | Essential | |
| | Volume of buffer into which specimen is taken by probe, applicator stick or card.* | Essential | |
| | Time and storage conditions of faecal specimen from "passing" to sampling, including time and temperature (median and range). | Essential for laboratory evaluations | |
| | Time and storage of collection devices from specimen collection to analysis, including time and temperature (median and range). A concise description of process from collection to analysis is recommended. | Essential | |
| **Analysis** | | | |
| | Name of analyser, model, supplier (address), number of systems if more than one used. | Essential | |
| | Number of times each sample was analysed. | Essential | |
| | Analytical working range* and whether samples outside this range were diluted (factor) and re-assayed. | Essential for laboratory evaluations | |
| | Source of calibrator(s) (supplier with address), number of calibrator(s), how concentrations were assigned* and details of calibration process including frequency. | Essential for laboratory evaluations | |
| | Analytical imprecision*, ideally with number of samples analysed, concentrations, and mean, SD and CV. | Essential for all studies | |
| **Quality management** | | | |
| | Source (address) or description of internal quality control materials, number of controls, assigned target concentrations and ranges, how target concentrations were assigned, rules used for acceptance and rejection of analytical runs. | Desirable for laboratory evaluations | |
| | Participation in external quality assessment schemes: (name and address of scheme), frequency of challenges, performance attained. | Desirable for laboratory evaluations | |
| | Accreditation held by the analytical facility (address). | Desirable for laboratory evaluations | |
| | The number, training and expertise of the persons performing the analyses and recording the results. | Essential | |
| **Result handling** | | | |
| | Mode of collection of data – manual recording or via automatic download to IT system, single or double reading. | Desirable | |
| | Units used, with conversion to µg Hb/g faeces if ng Hb/mL used. | Essential | |
| | Cut-off concentration(s) if used and explanation of how assigned locally or by manufacturer.* | Essential | |
| | Were the analysts blinded (masked) to the results of the reference investigation and other clinical information? | Essential | |
| *** information available from manufacturer or supplier** | | | |

# Appendix

## Examples of compliance with FITTER guidelines

### 1. Example of FITTER requirements fulfilled for a simple study

*Specimen collection and handling*

Potential participants (78000) were sent one specimen collection device (Omega FIT Co, Dundee, Scotland) from a single manufacturing lot. The device collects 20 mg faeces with a serrated probe attached to the cap into 2.0 mL buffer. Participants stabbed the probe six times at random into one freshly passed whole faeces and then re-inserted the probe into the device. 48000 participants completed the collection and wrote the date of sample collection on the device label before returning by first class freepost to Scot-FIT Reference Laboratory (Dundee, Scotland). Specimens (1000) that were received >10 days from date of collection were termed expired and not tested further.

*Analysis*

Specimens (45000) were assayed once on the day of receipt in the Laboratory on a single Omega FIT Co. FITTEST analytical system (Omega FIT Co., Dundee, Scotland), 2000 specimens were stored at 4°C (median: 3 days, range:1-7 days) and then allowed to warm to room temperature for analysis. The analytical working range was 10 – 200 µg Hb/g faeces: specimens with f-Hb above the upper limit were not diluted and re-analysed.

*Quality management*

All analyses were carried out by three clinical scientist staff whose sole function is to perform FIT analyses: the Laboratory has a total quality management system and is unconditionally accredited to ISO15189 standards by Lab Med Accreditation (Scot) Ltd (Tayport, Scotland). The analyser was calibrated once per month with the calibrators provided (Omega). Each analytical run was preceded by analysis of two quality control materials (Omega) and analyses of these were then done every 120 samples. The target values for the four lots of materials used were set *a priori* by 20 replicate analyses and a $1_{2s}$ rule used for acceptance or rejection of analytical runs. The combined weighted CV obtained were 3.5% at ca. 20 µg Hb/g faeces (n = 400) and 3.8% at ca. 100 µg Hb/g faeces
(n = 420).

*Data handling*

The f-Hb concentrations were recorded electronically, along with the kit number, by the analyser and these data electronically captured through propriety middle-ware by the Scot-FIT Reference Laboratory IT system. Participants with f-Hb concentration > 20 µg Hb/g faeces were referred for colonoscopy as recommended by the Laboratory.[1]

*Reference*

1. Kilt JA, Clan FR, Scotch, YP. The ideal single faecal haemoglobin cut-off concentration in native Gaelic speakers. Scot J Screen 2013;13:65-8.

## 2. Example of FITTER requirements fulfilled for a more complex study with two analysers

*Specimen collection and handling*

Potential participants (380000) were sent two specimen collection devices from each of two manufacturers (Omega FIT Co, Dundee, Scotland, and Alpha Occult Blood Ltd, Kobe, Japan) both from three manufacturing lots. The Omega device collects 20 mg faeces with a serrated probe attached to the cap into 2.0 mL buffer. The Alpha device collects 15 mg faces with a spoon-shaped probe attached to the cap into 1.5 mL buffer. Participants stroked the two probes, in either order, along the surfaces of two sequential freshly passed specimens of faeces and then re-inserted the probes into the respective devices. Participants were asked to keep the samples collected in a cool place or refrigerator and then post as soon as possible after collection of all four samples. 18000 participants completed the collection and wrote the dates of sample collection on the device labels before returning at ambient temperature by first class freepost to Scot-FIT Reference Laboratory (Dundee, Scotland). All specimens (800) that were received >8 days from date of collection were termed expired and not tested further; all specimens from that participant were excluded from further analysis.

*Analysis*

Specimens (32800) were assayed in duplicate on the day of receipt in the Laboratory on one Omega FIT Co. FITTEST analytical system (Omega FIT Co., Dundee, Scotland) and on one Alpha Occult Blood Ltd Supra analytical system (Alpha Occult Blood Ltd, Kobe, Japan), 1600 specimens collected into the Omega devices were stored at 4°C (median: 3 days, range:1-7 days) and then allowed to warm to room temperature for analysis and 1600 specimens collected with the Alpha device were stored at 4°C (median: 2 days, range:1-5 days) and then allowed to warm to room temperature for analysis . The analytical working ranges for the Omega and Alpha systems were 10 – 200 µg Hb/g faeces and 15 – 150 µg Hb/g faeces respectively: specimens with f-Hb above the upper analytical working limits were not diluted and re-analysed.

*Quality management*

All analyses were carried out in a four-month period by two biomedical scientist staff who perform FIT and a wide range of other analyses: the Laboratory has a total quality management system and is unconditionally accredited to ISO15189 standards by Lab Med Accreditation (Scot) Ltd (Tayport, Scotland). The Omega analyser was calibrated once per month with the two calibrators provided (Omega). Each analytical run was preceded by analysis of two quality control materials (Omega) and analyses of these were then done every 120 samples. The target values for the four lots of materials used were set *a priori* by 20 replicate analyses and a $1_{2s}$ rule used for acceptance or rejection of analytical runs. The combined weighted CV obtained were 3.5% at ca. 20 µg Hb/g faeces (n = 360) and 3.8% at ca. 100 µg Hb/g faeces (n = 410). The Alpha analyser was calibrated each day that analyses were performed with the set of six calibrators provided (Alpha). Each analytical run was preceded by analysis of two quality control materials (Alpha) and analyses of these were then done every 60 samples. The target values for the two lots of materials used were set *a priori* by 20 replicate analyses and a $1_{2s}$ rule used for acceptance or rejection of analytical runs. The combined weighted CV obtained were 4.5% at ca. 30 µg Hb/g faeces (n = 750) and 5.0% at ca. 100 µg Hb/g faeces (n = 820).

*Data handling*

The f-Hb concentrations were recorded electronically, along with the kit number, by both analysers and the mean f-Hb concentrations from the duplicate analyses were calculated automatically by both analysers. The mean f-Hb concentration of the two specimens from each participant were calculated manually and the data entered into the Scot-FIT Reference Laboratory IT system. The results were double entered, that is, one person entered the result and another checked the entry before result validation. To facilitate comparison, for both FIT, participants with mean f-Hb concentration > 20 µg Hb/g faeces were referred for colonoscopy as recommended. [1]

*Reference*

1. Kilt JA, Clan FR, Scotch, YP. The ideal single faecal haemoglobin cut-off concentration in native Gaelic speakers. Scot J Screen 2013;13:65-8.