

Expert Working Group (EWG) – ‘FIT for Screening’
Short Discussion Document No. 4 – Internal Quality Control
& External Quality Assessment

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1. Reasons for change

- To ensure acceptable international analytical performance in CRC screening.
- To enable screening programmes to provide evidence that analysis is of adequate quality.
- To enable and encourage publications that describe the use of FIT to include standardised information about analytical performance and quality.

2. Proposed solution

(a) Standardised units of reporting. Subject to a separate discussion document.

(b) Internal Quality Control (IQC). This is used to monitor analytical performance continuously and includes consideration of the imprecision of each assay and the random changes in relative bias that are typically introduced by recalibration or changes in reagent lots. One of many respected sources of information about IQC is www.westgard.com.

- Every FIT result should have associated results of IQC analyses demonstrating that the measurements were of acceptable quality.
- IQC should be done for all qualitative and quantitative FIT analyses using replicate analyses of a stable control material that is as similar as is possible to clinical samples.
- The material used must be stable so that analytical changes can be monitored (currently this precludes use of real faeces since haemoglobin is unstable in faeces without preservation).
- Quantitative FIT assays should include IQC material that has a haemoglobin concentration at or near the concentration used to assign positive or negative results (‘cut-off concentration’).
- Qualitative FIT performance is more difficult to monitor but analyses of IQC material are essential and IQC materials should be used at concentrations that give negative and positive results either side of the cut-off concentration.
- Criteria for acceptance and rejection of analyses must be set before analysis is performed.
- All results of analyses of IQC materials must be documented.
- IQC performance should be discussed regularly with staff to encourage quality improvement.
- The limits quoted by manufacturers for acceptable IQC performance should be replaced by limits derived from objective assessment of the system used and quality required (see below).

(c) External Quality Assessment (EQA). EQA monitors the performance of the analytical method compared with a ‘true value’ which, for practical reasons, is usually obtained from other analytical data. EQA provides a measure of the relative bias of a method compared with the ‘true value’ but can also be used to compare the assay imprecision of different systems and laboratories.

- EQA should be carried out for all qualitative and quantitative analyses of haemoglobin through analyses of stable materials at regular intervals.
- Every test result reported should have associated results of EQA material analyses showing that the measurements were of acceptable quality.
- Although the ideal FIT EQA material is faecal haemoglobin, its lack of stability currently precludes its use and as similar as possible substitutes need to be used.
- EQA materials should be available at a range of haemoglobin concentrations that are close to the cut-off concentrations used by participating analytical sites.
- EQA materials should mimic faeces as closely as possible and should preferably be taken through the entire procedure including sample collection, analysis and reporting of results.

- Criteria for acceptable performance in EQA should be agreed, documented and monitored by an EQA oversight body that is independent of the individual participating laboratories.
- EQA results should be made available to all involved in analysis and discussed regularly.
- There is an urgent need for EQA schemes that are independent and fulfil all internationally agreed guidelines.

(d) Setting desirable standards of performance. ISO 15189 5.6.1 states that “The laboratory shall design IQC systems that verify the attainment of the intended quality of results”.¹ The analytical quality needed for qualitative and quantitative FIT has received little attention. A hierarchy of methods for setting desirable quality specifications for performance characteristics is as follows:

- Level 1. Assessment based on performance for specific clinical decisions and clinical situations.
- Level 2. Assessment based on performance for general clinical decision-making.
- Level 3. Professional recommendations.
- Level 4. Quality specifications laid down by regulation or by EQA Scheme organisers.
- Level 5. Published state-of-the-art data.

A WEO EWG recommendation could provide interim Level 3 criteria for the analytical acceptability of all FIT analyses.

3. Issues for consideration

- While IQC must be instituted in all settings in which FIT analyses are performed, EQA requires urgent development since CRC screening programmes are in place or being introduced in many countries.
- Quality control and assessment cannot be done unless the desired quality is defined. The setting of standards for the quality required needs considerable theoretical (and possibly practical) work.
- A sub-group tasked with developing these standards and led by a full Member of the EWG should be considered.

4. Standards in publication and clinical analysis

(a) Peer-reviewed journals – standards for reporting laboratory tests results. The Standards for the Reporting of Diagnostic Accuracy (STARD) statement provides consensus guidelines designed to improve the quality of publications and a checklist of 15 important items that authors and editors should adopt.² Item 8 refers to the importance of describing in full the laboratory methods used and their **performance characteristics**. The Consortium of Laboratory Medicine Journal Editors has advised that: *Authors must report performance characteristics, such as the imprecision of the assay in the investigators’ laboratories, the assay’s reportable range and any reference (normal) range used in the study.*³

Analytical **performance characteristics** are of two types:

- Practicability includes throughput, turnaround time of results, sample types, sample volume, stability of samples, stability of reagents and calibrators, skills required.
- Reliability is important for the correct interpretation of numerical results and includes imprecision (a measure of the random variation of the analytical method), bias (a measure of how close the result is to a true value), working range (the range in which a valid result is obtained without any manipulation of sample or reagents) and detection limit (the least amount of haemoglobin that can be detected).

(b) Clinical laboratory analytical quality – accreditation standards. The requirements for analytical quality control and assessment have mature international guidelines:

- IQC is detailed in ISO 15189:2007 Medical laboratories – Particular requirements for quality and competence.¹
- EQA schemes organisation and execution are described in:
 - ISO/IEC 17043:2010 – Conformity assessment – General requirements for proficiency testing,⁴
 - ILAC G13 - Guidelines for the requirements for the competence of providers of proficiency testing schemes.⁵
- Medical laboratories are accredited to ISO 15189 standards.¹
- The relevant standard for wards, clinics and other point-of-care testing settings where faecal tests are performed is:
 - ISO 22870:2006 – Point-of-care testing (POCT) – Requirements for quality and competence.⁶

Publications cited

1. ISO 15189:2007. Medical laboratories - Particular requirements for quality and competence. Geneva: ISO Publications; 2007.
2. Bossuyt PM, Reitsma JB, Bruns DE, Gatsonis CA, Glasziou PP, Irwig LM, et al. Towards complete and accurate reporting of studies of diagnostic accuracy: the STARD initiative. *Standards for Reporting of Diagnostic Accuracy. Clinical Chemistry* 2003;49:1-6.
3. Rifai N, Annesley TM, Berg JP, Brugnara C, Delvin E, Lamb EJ, 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. Annals of Clinical Biochemistry* 2012;49:105-7.
4. ISO/IEC 17043:2010 – Conformity assessment – General requirements for proficiency testing. Geneva: ISO Publications; 2010.
5. ILAC-G13:08/2007: ILAC Guidelines for the requirements for the competence of providers of proficiency testing schemes. Australia: The ILAC Secretariat; 2007.
6. ISO 22870:2006 – Point-of-care Testing (POCT) – Requirements for quality and competence. Geneva: ISO Publications; 2006.

Other relevant publications

IQC and EQA for FAECAL TESTS - Halloran SP, Launoy G, Zappa M. Faecal occult blood testing. In *European Guidelines for Quality Assurance in Colorectal Cancer Screening and Diagnosis. First Edition.* Segnan N, Patnick J. von Karsa L, eds. International Agency for Research on Cancer. Luxembourg: Publications Office of the European Union, 2010, pp103-14.

ANALYTICAL QUALITY SPECIFICATIONS - Petersen PH, Sandberg S, Fraser CG. Do new concepts for deriving permissible limits for analytical imprecision and bias have any advantages over existing consensus? *Clin Chem Lab Med* 2011;49:637-40.