

# Protocol for quality assurance of FIT-analyses

## 1 Purpose and area of application

This protocol describes the method of quality assurance for the implementation of FIT analyses by the three screening laboratories in the context of the Netherlands' bowel cancer screening programme. The purpose of the protocol is to ensure uniformity in working methods and results across the three laboratories. The three laboratories should function as a single laboratory.

This protocol is applicable for the three screening laboratories which carry out the FIT analyses in the context of the bowel cancer screening programme and for the organisation (SKML) and officers (LFMI, clinical chemists) who are responsible for the quality assurance of the analyses.

## 2 Abbreviations and definitions

BioMajesty	=	analyser or detecting haemoglobin in faeces
NSP	=	National bowel cancer screening programme
ColonIS	=	IT-system supporting the implementation, quality assurance, and monitoring and evaluation of the bowel cancer screening programme.
FSB	=	umbrella organisation of the five regional screening organisations in the Netherlands
CC	=	Clinical Chemist
LFMI	=	National coordinator in charge of monitoring FIT
NEMO	=	the software guiding the analysis track to which the analyser, the input/output module, the automatic decapper and the automatic sealer are linked. NEMO is linked to ColonIS
Q-BASE	=	the software with which the results of control samples can be evaluated and interpreted
QC sample	=	Quality Control sample
SKML	=	Dutch Foundation for Quality Assessment in Medical Laboratories
SO	=	Screening organisation (there are five screening organisations in the Netherlands, one in each region)

## 3 Methods

Quality assurance in the context of the bowel cancer screening programme within the three laboratories consists of the following components:

1. Entry checks (advance quality control of tubes, calibrators and reagents)
2. Internal QC samples (by Sentinel and SKML)
3. External QC samples (by SKML)
4. Evaluation of results (by LFMI)
5. Internal audits
6. External quality reviews
7. External audits
8. Protocols
9. Structural consultations

The QC samples from SKML are commutable material, i.e. the same matrix as patient samples: mixed feces samples suspended as patient samples in buffer,

spiked with known amounts of haemoglobin, lyophilized and reconstitution in water.

The clinical chemist at each laboratory holds final responsibility for releasing results from his or her laboratory to SKML and to ColonIS. The LFMI provides the clinical chemist with information about the way in which the results from his or her laboratory relate to the results from the other two laboratories.

### **3.1 Entry checks**

The quality checks carried out prior to the analysis consist of inspections of the following three components:

- (i) Batch check of calibrators
- (ii) Batch check of internal Sentinel QC samples

Checks i. and ii. are carried out by measuring with both the new and the old batch of calibrator and QC samples for five days at the start and end of the measurements of the client samples.

- (iii) Batch check of tubes

A proposal for this is being worked out by SKML.

### **3.2 Internal QC samples**

The internal quality assurance check consists of four components per measurement day. The goal of this is to determine the analytical stability of the system.

#### Component 1

In the morning, prior to analysing the samples from NSP participants, it is determined whether the samples can be analysed by looking at the following internal Sentinel QC samples:

- 1 QC sample at around 50 ng/ml
- 1 QC sample at around 70-80 ng/ml
- 1 QC sample at around 300 ng/ml

The test results of these checks must fall within the 2.5 SD limits on the basis of all accumulated QC results from the validation protocols from the three laboratories.

The following procedure is implemented in case of deviation: If the test results from two or three QC samples do not fall within the margins, internal action is taken in conformity with the protocols available and under the responsibility of the clinical chemist.

The LFMI determines, in consultation with the clinical chemists, what action the laboratories should take in the case of consistent deviations and advises them in this regard. The LFMI is responsible for ensuring that the three laboratories take action that is consistent with one another in case of deviations.

The method for dealing with deviating samples is described in flowchart 1.

#### Component 2

Approximately midway through the series of the samples from NSP participants: One SKML QC sample, alternating between a low SKML QC sample [65 ng/ml] and a high SKML QC sample [120 ng/ml]. SKML is responsible for performing the checks. The laboratory itself is responsible for entering the SKML QC samples k on a daily basis midway through the series.

In case of deviation (the starting point is the 3 SD Westgard rule) this QC sample is carried out again. The LFMI determines, in consultation with the clinical chemists, what action the laboratories should take in the case of consistent deviations and advises them in this regard. The LFMI is responsible for ensuring that the three laboratories take action that is consistent with one another in case of deviations.

### Component 3

After the end of the series of samples from NSP participants, a check is carried out into whether the results obtained are reliable based on the following Sentinel QC sample :

- 1 QC sample at around 50 ng/ml
- 1 QC sample at around 70-80 ng/ml
- 1 QC sample at around 300 ng/ml

The test results for these QC samples must be within the same margins described under Component

1. If the results do not fall within this range, the procedure is the same as described for component 1 (see flowchart 1).

### Component 4

The clinical chemist and/or delegated clinical chemical analyst evaluates the results of the samples of NSP participants together with the results of the QC samples. Upon the authorisation of the clinical chemist or delegated clinical chemical analyst, the results are electronically presented to the LFMI via ColonIS.

After the results have been sent from one of the laboratories, the following results are visible to the LFMI and the clinical chemist sending the results.

1. Percentage results  $\geq 88$  ng/ml (cut-off value)
2. Percentage results  $< 20$  ng/ml (20 ng/ml is the detection limit).
3. Percentage results between the detection limit and the cut-off value, i.e.  $\geq 20$  ng/ml and  $< 88$  ng/ml
4. A daily average calculated on the basis of binomial statistics
5. A SD calculated on the basis of binomial statistics

The LFMI can see the results from all three laboratories, while the clinical chemists can only see the results of their own laboratories.

For follow-up actions, see 3.4 Evaluation of results.

The proposal is to build up one report per laboratory in ColonIS in future. The purpose is to gain insight into possible factors influencing possible variation between laboratories, such as:

- Gender of participants
- Age of participants
- Place of residence of participants
- Length of time between taking sample and evaluation in laboratory
- Country of birth/nationality of participants
- From which batch did the participant receive a self-testing tube?

### **3.3 External QC samples**

The external quality check is a check of the functioning of the system carried out after completion of the analyses; it consists of SKML QC samples and possibly

participation in an additional external quality assessment scheme (as soon as a suitable scheme has been identified).

The external SKML QC samples are measured twice per week by the three laboratories during the first year of the population sampling programme. There are fifteen different samples. These two external QC samples are applied each week with an established end date for the report of the test result:

Application	Established end date
Tuesday	Wednesday
Thursday	Friday

The results of both the internal and the QC checks are sent, after the approval of the clinical chemist and/or the delegated clinical chemical analyst, to the LFMI before 3:00 PM each day of analysis.

### 3.4 Evaluation of results

The joint screening organisations (FSB) hire the national officer in charge of monitoring FIT (LFMI) from SKML. The national officer is in charge of ensuring, maintaining and, where necessary, improving the high quality of the FIT analysis in the context of the bowel cancer screening programme. A description of the LFMI's duties is included in Appendix 1.

In this context, the LFMI is expected to perform the daily evaluation of the test results of the Sentinel and SKML QC samples. The LFMI is also expected to evaluate the parameters below with regard to the faeces samples from the three laboratories, with the assistance of:

1. Percentage results  $\geq 88$  ng/ml
2. Percentage results  $< 20$  ng/ml
3. Percentage results between the detection limit and the cut-off value, i.e.  $\geq 20$  ng/ml and  $< 88$  ng/ml
4. A daily average calculated on the basis of binomial statistics
5. A SD calculated on the basis of binomial statistics

The LFMI examines the test results from the Sentinel and SKML QC samples and the above parameters from the faeces samples from the three laboratories and:

- if necessary, directly responds to deviations (in conformity with contract Agreements/description of duties).
- discusses the results in the structural consultation with the clinical chemists and a representative of the screening organisations.
- ensures that the overviews of the results are sent to the laboratories and the FSB.

The LFMI or the person acting on the LFMI's behalf communicates by e-mail with the laboratory contact persons as follows:

Day	Production	Time	Route
<b>Tuesday to Friday</b>	Weekday production	Before 3:00 PM	Lab sends to LFMI
	Weekday production	Before 5:00 PM	LFMI sends to lab
<b>Monday</b>	Saturday production	Before 10:00 AM	Lab sends to LFMI
	Saturday production	Before 12:00 noon	LFMI sends to lab

Once the results have been confirmed by an analyst and authorised by a staff member/CC or authorised employee, the results are sent via NEMO to ColonIS. Once the LFMI has received the results from all three laboratories, downloaded them into QBASE and thoroughly reviewed the daily report, he or she will offer advice to the CCs or the authorised employees of the three laboratories. This occurs within the time agreed in advance. If the LFMI advises positively, the CC or authorised employee can release the client data by sending it from NEMO to ColonIS. If the LFMI advises negatively, the LFMI will offer a suggestion and consult with the CC or authorised employee to arrive at steps which can be taken to achieve a result which is satisfactory to both parties. The LFMI provides individual advice to each laboratory.

If no positive advice can be given on the day itself, it may be possible to release part of the results of the daily production. It may also be the case on some days that no results are released in the laboratory.

Once the LFMI has advised positively and the data has been sent to ColonIS and ColonIS has confirmed that the data has been received, the laboratory will destroy that day's faeces samples that have been analysed in conformity with the protocol for disposal and destruction of materials. In practice, this is the day after analysis.

### 3.5 Internal audits

Internal audits take place within the laboratories themselves. The specific work activities carried out within the laboratory for the bowel cancer screening programme are noted in the laboratory's own audit cycle. In consultation with FSB, the LFMI reaches agreements with the laboratories about the frequency with which internal audits are carried out in the context of the bowel cancer screening programme.

During the internal audit, the following aspects are tested for compliance:

- ISO 15189/ CCKL
- relevant protocols for the activities of the national screening programme (see Appendix 2)
- the standards set in the national screening indicator set

The results of the audits are communicated to FSB and the LFMI.

### **3.6 External quality reviews**

External reviews are carried out by the LFMI under contract from SKML as accredited in conformity with the standard for reviewing bodies. The LFMI carries out the reviews as ordered by the screening organisations /FSB, possibly together with an employee of the screening organisations/FSB specifically assigned to the bowel cancer screening programme for the duration of the work activities. The purpose of the external reviews, which take the form of an audit, is to guarantee the quality and uniformity of the work performed by the laboratories, so that they can function as a single laboratory. The starting point for this is the established quality standards and indicators.

### **3.7 External audits**

Each laboratory must be ISO 15189 and/or CCKL certified (the contract party will receive a copy of the certificate and a new copy upon renewal of the certification). Certified laboratories are accredited and re-accredited by the Dutch Accreditation Council (RVA) and participate in the RVA inspections, which are part of the accreditation and fulfil the requirements, which are part of ISO 15189.

Flowchart Method for dealing with deviating QC samples



### **3.8 Protocols**

The work activities within the three laboratories focused on the national bowel cancer-screening programme are described in protocols. QC samples and internal audits provide insight into whether the laboratories are working in conformity with the protocols.

### **3.9 Structural consultations**

Once a month for the first six months of the national screening programme, a consultative meeting will be held during which at least the following points will be discussed:

- the results of checks (including rejected, non-released results)
- the results of the faeces samples of participants of the NSP
- the use of protocols/uniformity
- the evaluation of protocols
- incidents

After the first six months, the frequency of these consultative meetings will be re-established.

Participants in the consultative meetings: the clinical chemists from the three laboratories, one operational manager per laboratory, the LFMI and the contact person for the screening organisations/FSB. Advisors may be invited to these meetings.

Next to these meetings, there are monthly meetings on a more operational level.

### **4 Problems and deviations**

The LFMI discusses deviations with the laboratory in order to gain insight into the possible causes. The LFMI is to be informed of possible relevant changes and calamities or incidents. In consultation with the clinical chemist, the LFMI offers immediate advice regarding adjustments to be made.

The LFMI is also responsible for advising FSB and the clinical chemists about structural improvements.

The registration of problems and deviations will serve as input for FSB's supplier assessment of the parties.

In addition, both the LFMI and the laboratories keep a register of the progress of the work agreements reached. Which components are to be registered will be decided at a future point in time. Possibilities include the timeliness of deliveries and the speed of reaction by the laboratories and the LFMI. This register will also serve as input for FSB's supplier assessment of the parties.

FSB is to be informed about problems with producing the FIT results timely and processes. SKML and the LFMI are to be informed of problems which affect or which could affect quality of the FIT analyses.



## 5 Responsibilities

Subject	SKML (organiser)	LFMI (quality officer)	Clinical chemist
Entry checks			
Buffer	■		
Reagens			■
Calibrators			■
Preparation of internal and external QC samples	■		
Implementation of internal and external QC samples		■	■
Evaluation of internal and external QC samples		■	■
Client data parameter evaluation		■	
Internal audits			■
External reviews		■ with FSB	
Implementation of external audits			■
<b>Other responsibilities</b>	<b>Laboratory</b>	<b>FSB</b>	
Protocol use	■		
Protocol management		■ with LFMI	
<b>Organisation and chairing of the structural consultations</b>		■	

## **6 Appendices**

Appendix 1 Description of duties for the national officer in charge of monitoring FIT

Appendix 2 Overview of protocols for FIT laboratories (specifically for the Netherlands' bowel cancer screening programme)

## **7 Remarks**

This document is to be evaluated by the participants to the structural consultation (see point 3.8) after it has been in use for six months.

On the basis of the results of the QC samples and the internal audits, the participants to the structural consultation are to evaluate whether this protocol needs any changes.

## **Appendix 1 Description of duties for the national officer in charge of monitoring FIT**

Version 1.1: 8 February 2013

### **1. Description of position**

Population screening offered to people who have no symptoms or physical complaints demands high-quality implementation. The Netherlands' bowel cancer screening programme is an example of this. Participants have a right to expect consistently high quality and responsible implementation throughout the country. It should make no difference to the results of participants in the screening programme in which laboratory their samples are tested. In order to achieve and maintain this high quality, the professionals and organisations carrying out the population screening programme and the concomitant post-referral diagnostics are subject to nationwide standards.

The national officer in charge of monitoring FIT is primarily concerned with the aspect of screening in the chain. This takes place in the three screening laboratories which have been contracted to work on the bowel cancer screening programme.

The national officer is in charge of ensuring, maintaining and, where necessary, improving the uniformly high quality of the FIT analysis in the context of the national bowel cancer screening programme.

### **2. Position within the organisation**

Within the bowel cancer screening programme, there are several parties with a role in ensuring the quality of the primary process and the associated care and/or monitoring and evaluation. These parties are the national officer in charge of monitoring FIT; the Regional coordinating gastroenterology officer (RCMDL); the Regional coordinating pathologist (RCP); in future possibly a Regional coordinating radiologist (RCR); the Dutch Ministry of Health, Welfare and Sport; the Dutch National Institute for Public Health and the Environment (RIVM) and its Centre for Population Screening; the Health Council of the Netherlands; the Netherlands Organisation for Health Research and Development; and the Dutch Health Care Inspectorate.

The national officer in charge of monitoring FIT is contracted by the screening organisations.

The national officer in charge of monitoring FIT is responsible for the independent quality assurance of the FIT.

### **3. Work activities**

The national officer in charge of monitoring FIT:

1. Gives shape to the quality assurance model in the first months of 2013, together with the screening organisations), the Clinical Chemists at the three laboratories contracted for the bowel cancer screening programme and the RIVM (lead manager), and in coordination with the RIVM's quality working group and Bowel Cancer Screening Programme Advisory Committee (LCIBD). This entails:
  - a. Daily evaluation of the results obtained by the three laboratories. This takes place at the end of the day on weekdays; Saturday results are evaluated on Monday morning. The national officer in charge of monitoring FIT includes the number of positive results (negative results for the participant) in these considerations as additional information. The necessary frequency of this activity will be evaluated later in the procedure. Initially, in connection with the start-up

phase of the national screening programme, evaluation will be carried out on a daily basis (at the end of every weekday and on Monday mornings; no evaluations on Saturday or Sunday).

- b. Taking responsibility for organising the sending of QC samples.
  - c. Regular evaluation of the results of the three laboratories on the basis of the indicators established in advance (still to be developed).
  - d. Carrying out audits within the context of the national screening programme.
  - e. Regular consultation with the three laboratories with the purpose of establishing uniform quality and learning from each other.
  - f. Deciding what information and reports are necessary to guarantee quality, how often they need to be supplied and how they should be supplied (via ColonIS or another method).
2. Takes responsibility for the correct implementation of the quality assurance of the FIT analysis as developed in the first half of 2013 (as mentioned under point 1 above).
  3. Informs and advises the SOs about the quality of the FIT implementation by the three contracted laboratories and the quality of these laboratories.
  4. On a weekly basis, checks the contracted lead times as agreed with the laboratories and informs the screening organisations about this.
  5. Participates in national consultations regarding the bowel cancer screening programme.
  6. Keeps abreast of national and international developments relating to the test method used, the quality standards to be set and improvements to the bowel cancer screening programme; and provides solicited and unsolicited advice on this to the screening organisations, the three laboratories and the RIVM.
  7. Contributes to quality optimisation, by ensuring the promotion of expertise in the laboratories, among other methods.

#### **4. Scope for discretion**

- The national officer in charge of monitoring FIT is responsible to the screening organisations.
- The framework is formed by the current legislation and regulations, the CCKL and/or ISO 15189 guidelines and the protocols.
- The national officer in charge of monitoring FIT must have access to all information which is necessary in order to fulfil the position well.
- The national officer in charge of monitoring FIT must not be employed or have recently been employed by one of the laboratories carrying out the FIT analysis in the context of the bowel cancer screening programme.

#### **5. Knowledge and skills**

- Demonstrable knowledge and experience in the area of quality management, including professional quality assurance of clinical-chemical results.
- Demonstrable experience with CCKL and/or ISO 15189 or comparable standards.
- Completed education at the level of higher vocational education or university of applied sciences (HBO) in the field of Biology and Medical Laboratory Research or a comparable field.
- An affinity with population screening and public health is preferred.

6. Competencies
- Outstanding communicative skills
  - Focus on quality
  - Good ability to form judgements
  - Critical attitude
  - Analytical ability
  - Reliability
  - Independence

## Appendix 2 Overview of protocols for the FIT laboratories

Specifically for the Netherlands' bowel cancer screening programme

Protocol	Contents
Apparatus SOP	A description of how human haemoglobin in faeces is detected with the help of the BioMajesty 6010/C in the context of the bowel cancer screening programme and concomitant maintenance.
SOP for the Inpeco track	A description of how the tubes are put onto the track and offered to the BioMajesty and concomitant maintenance of the track.
Protocol for return envelopes and treatment of samples	A description of how return envelopes in the context of the bowel cancer screening programme enter the laboratory and are processed and how to deal with deviations from standard procedure.
Protocol for disposal/destruction of materials	A description of how materials obtained in the context of the bowel cancer screening programme are to be disposed of/destroyed in the laboratories in order to protect the privacy of the participants and comply with agreements regarding storage periods.
Calamity protocol	A description of the way in which calamities in the FIT laboratory are to be dealt with in order to guarantee quality and respond to the calamity quickly.
Batch check protocol	In development