Chapter 3 - Laboratory Quality Assurance

Maria Alejandra Picconi[1], Nazlı Songur[2], María Dolores Fellner[1],

Rita Mariel Correa[1], Murat Gultekin[2], Kate Cuschieri[3]

[1] Oncogenic Viruses Service, HPV National and Regional Reference Laboratory, National Institute of Infectious Diseases-ANLIS "Dr. Malbrán", C1282AFF Buenos Aires, Argentina.

[2] Hacettepe University Faculty of Medicine, Department of Obstetrics and Gynecology, Division of Gynaecological Oncology, Ankara, Turkey.

[3] Scottish HPV Reference Laboratory, Department of Laboratory Medicine, Royal Infirmary of Edinburgh, EH16 4SA & HPV Research Group, Centre for Reproductive Health, University of Edinburgh.

*Correspondence: Kate Cuschieri, kate.cuschieri@nhslothian.scot.nhs.uk

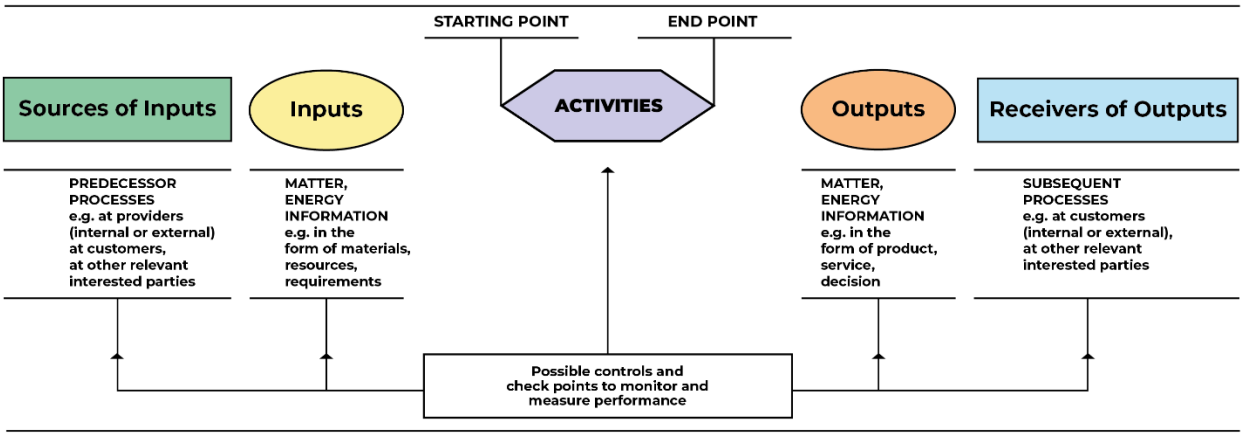
Contents

3.1 QUALITY MANAGEMENT SYSTEMS

A Quality Management System (QMS) is a set of policies, processes, procedures and resources designed to ensure high quality within an organization. A QMS helps coordinate and direct laboratory activities to meet the needs and requirements of the users and regulators. In medical laboratories QMS can establish and sustain high levels of accuracy, ensure the laboratory's competence and create an environment conducive to continual improvement. To implement a QMS, it is important to identify and manage various key processes, which include preanalytical, analytical and post-analytical phases, covering the activities from the sample receipt to release of results. The schematic representation of a process is given below **(Figure 3-1)**.

ISO 15189 is a well-recognized international standard used by medical laboratories (https://www.iso.org/obp/ui/en/#iso:std:iso:15189:ed-4:v1:en, last accessed June 2, 2024). Laboratories endeavor to work to the standards and are then assessed by external independent accreditation agencies who review the QMS overall as well as any individual test the laboratories have in their "scope" that they wish to be accredited. Laboratories that are accredited to perform a particular test(s) have been shown to meet the standards by the external agency although assessment is a rolling process which can often involve yearly inspection. Other quality standards and accreditation systems exist such as those offered by the College of American Pathologists (CAP) and while the specifics of the standards differ, the general principles of working to (and maintaining) standards that are scrutinized independently are the same.

Figure 3-1 Schematic representation of the elements of a single process



Adapted from https://www.iso-9001-2015.org, last accessed March 10, 2024.

The laboratory director may appoint a quality manager to establish and sustain a QMS; while it is usually the responsibility of the head of the laboratory to ensure compliance with it, it the responsibility of *all* laboratory and affiliate personnel to understand and work to the policies that support it. While external accreditation is clearly valuable and helps inform the expectations of service-users it does, takes time and significant material and human resources to set up and

maintain. Importantly, external accreditation (e.g. to CAP) is relevant for medical laboratories i.e. those that provide a diagnostic service. For laboratories that exclusively provide results for epidemiology and/or research, it is not mandatory although many of the principles reconcile with good laboratory practice in general terms. Furthermore, requirements for standardization of test processes and associated reporting of research results may be required for peer review and publication. A good example of this relates to the "Minimum Information for publication of quantitative real-time PCR experiments" (MiQE), this document details the minimum information necessary for evaluating qPCR experiments.[1] By providing detail on experimental conditions and assay characteristics, reviewers can assess the validity of the protocols used and enable other investigators to reproduce results. For surveillance, assay standardization and incorporation of QMS principles support reliability of results and longitudinal and between-study assessment(s).

3.2 BASIS OF QUALITY MANAGEMENT SYSTEMS

Implementing a QMS helps to minimize errors, while identifying areas for continuous improvement. It should reflect the end-to-end process of a sample: preanalytical, analytical and post-analytical. The pre-analytical stage covers (sample) capture, transfer/delivery, reception and initial processing; basically, all activities before the sample is applied to the test platform(s). Analytical processes relate the test itself and its outputs. Post-analytical processes include reviewing, reporting and monitoring results. An organization may also use risk-based thinking approach to identify the factors that could cause its processes and quality management system to deviate from the intended results, implement preventative controls to reduce negative effects, and identify opportunities for early intervention.

Core components of a QMS include:

- Creating a quality policy
- Creating a quality manual
- Setting quality objectives
- Setting key performance indicators
- Creating standard operating procedures
- Setting an audit schedule
- Creating a prospective log of issues and incidents and in line with this to log Corrective and Preventive Action (CAPA)

When creating the QMS, it is fundamental to consider all the objectives, requirements, and services that the particular laboratory provides. The "process approach" is key to achieving the intended results; it includes a Plan-Do-Check-Act (PDCA) cycle and risk-based thinking.

Plan-Do-Check-Act Cycle:

The organization may use the PDCA cycle to assure its processes are managed and resourced appropriately and opportunities for continuous improvement are identified and followed effectively (https://asq.org/quality-resources/pdca-cycle, last accessed February 1, 2024)

1. **Plan:** The cycle begins with the “Plan” stage. This step is the most important step of the cycle. At this stage, the risks and opportunities are considered and decisions on whom, why, how, where, when and for how long the work, project or process will take, are made
2. **Do:** The second stage of PDCA is the “Do” stage – i.e. execution of the plan
3. **Check:** The “Check” stage, involves a review to determine whether the project achieved the intended results and what the issues were.
4. **Act:** The strengths and weaknesses observed in the check phase are used to inform and enhance the subsequent activity/project

When implementing a quality management system, first, the laboratory needs to design and build its structure, devise the processes, and create an implementation plan. Personnel should be aware of and adhere to the quality policy of the laboratory and the quality manual and be trained on the aspects relevant to their activities. The laboratory needs to review the effectiveness of their internal systems on a regular basis and internal audits (section 3.11) are an effective way to achieve this as is participating in external quality control programs and proficiency testing (section 3.5.4). Findings from audits can feed into documented CAPA. Custom quality management software can help house, curate, and manage quality information including that on documentation, equipment and audit. Such software can be very helpful, particularly if the laboratory provides diagnostic services, but there is a license/cost implication.

3.3 ELEMENTS OF SOPS

An organization's routine or repetitive actions are documented in a set of written instructions called a Standard Operating Procedure (SOP). SOPs represent a key component of creating and maintaining an effective quality system because they describe tasks carried out and help ensure that processes are followed consistently. They can range in scope and are not confined to lab processes; for example, they can be used to describe how to perform a specific analytical test or how to organize and document department meetings. SOPs should be easy to read, informative, and provide step-by-step information. The present tense and active voice should be used. If any prior training, qualification, or experience is required to follow the SOP, this should be stated.
Every SOP should contain a title which identifies the activity. Additionally, each page should contain

- An identifier for the organization/laboratory
- A unique SOP identifier
- The current version number and date
- Page number/total number of pages
- Author
- Authority for issue
- Duration of validity
- Revision history

A table of contents can also help orientate the reader and a glossary of terms and acronyms should be provided. A revision history with dates and details of associated changes is advised and this can be physically added to the end of an SOP or it can be part of an electronic record if the laboratory has an electronic QMS. While it is accepted that SOP templates will vary across laboratory setting (depending on and accreditation status) the template headings below are provided as a guide. Some headings may not apply to all SOPs.

1. Purpose

It should be explained what the purpose of the SOP is, why it is needed and/or what is planned to be achieved with that SOP.

2. Scope

It should be defined to whom or what the particular set of procedures applies. It may be helpful to include here aspects that are explicitly out of scope.

3. Responsibilities

The grade roles and responsibilities of the staff required to execute activities in the SOP should be defined here. It may be that certain grades/roles of staff can perform certain parts (only) of the SOP. If so, this should be clearly defined.

4. Terms

Acronyms, or abbreviations which may not be familiar to the users should be explained.

5. References

Related documents that support understanding and execution of the SOP should be listed here.

6. Safety

Information to ensure the safe delivery of the procedure should be described here. This should cover biological, chemical or physical hazards and associated mitigations. References to relevant material data safety sheets and risk assessments should be made.

7. Materials & Equipment

Any specific materials or equipment required to perform the SOP should be listed; including those not supplied by a manufacturer if SOP relies on commercial packages.

8. Procedure

The main activities should be explained step by step in this section. If the procedure involves a computer interface for running the test, diagrams or screen shots of the software can be helpful when explaining the steps.

9. Performance Characteristics

For assays, describe the anticipated performance in terms of analytical and clinical performance. For other processes, expected results may be described.

10. Quality Control Procedures

Describe what quality controls are required to ensure validity of the procedure, and the anticipated results of the controls.

11. Interferences

Describe any known agents that could interfere with the process and influence the result.

12. Principle of Result Calculation

Describe how results are analyzed and determined, describe if this is a function of the assay software and if any manual checks/interpretation is required.

13. Laboratory Clinical interpretation

Describe how results generated by the assay are then interpreted/described for clinical purposes and users.

14. Reporting Results

Describe the process for approving results for reporting, process and time frame for reporting, and data storage.

15. Sources of Variation

Describe the areas (pre, during and post examination) that could influence the validity of the result; include the potential effect (e.g. wrong result generated) and steps taken to minimize.

Figure 3-2 SOP Template

<LOGO>	<SOP NAME>	SOP ID:	XXXXXX
		Release Date:	XX.XX.XXXX
		Revision Date:	XX.XX.XXXX
		Revision No.	0X
		Page No:	Page No/ Total Page

1. PURPOSE

This SOP aims to……

2. SCOPE

This SOP applies to ……

3. RESPONSIBILITIES

FUNCTION / DEPARTMENT	RESPONSITIBILITY
……. Department	Implementing……
Head of the Laboratory	Ensuring ……
Laboratory Personnel	Performing……

4. TERMS

TERM	DEFINITION
XXX	XXXX

5. REFERENCES

XXX

XXX

6. SAFETY

7. MATERIALS & EQUIPMENT

8. PROCEDURE

Revision History:

Revision No	Revised By	Description

<PREPARED BY>	<CONTROLLED BY>	APPROVED BY
<TITLE>	<TITLE>	<TITLE>

3.4 RISK MANAGEMENT

Laboratories are advised to have an inventory of risks that could affect the effective running of a service. Depending on the responsibilities of a laboratory, a risk register may be project-specific or relate to a whole service. It should be clear as to what the risk register relates to, who maintains it and which individual or group is responsible for its management. Risk registers should include a description of the risk and (1) its likelihood and (2) its potential severity. In this way a weighting can be applied to help prioritization. Mitigation, steps taken to reduce or manage risk should be included along with reassessment of likelihood and severity post-mitigation. Risk registers should be reviewed and updated frequently to support closure and trigger escalation of mitigation where required.

3.4.1 Pre-analytical considerations (quality control, QC) for robust clinical samples management.[2,3]

Proper “upstream” management of laboratory samples (i.e. from point of collection to receipt and storage) is essential for the quality and reliability of results. The quality of work a laboratory produces depends on the quality of the samples received and their associated information. The laboratory must be proactive in ensuring that the samples it receives meet all the requirements for producing accurate test results.

With adequate identification and labeling procedures, serious problems generated by sample losses or confusion in their identification, which represent a threat, are avoided, especially for laboratories that receive a large number of specimens. Likewise, correct storage supports long-term viability. It is important to highlight that the difficulties generated by clinical sample management failures, beyond having a serious ethical weight due to the potential harm they can cause to the patient, generate economic losses to laboratory, both due to the waste of resources and time.

Although the Sampling Chapter focuses on these aspects in more detail, it is worth mentioning some key good laboratory sample management practices:

1. Implement a robust and comprehensive sample management protocol, which describes each step from sample collection to disposal. Written policies should detail the components, including:

- Clear information for users and expectations placed on users to support adequate sample collection.
- Collection, labeling, conservation and transportation.
- Evaluation, processing and monitoring of samples.
- Storage, retention and disposal
- Relevant forms and information requirements
- Security practices

2. Standardized sample handling and storage procedures should be created to ensure that all laboratory personnel handle and store samples in the same way, minimizing the risk of errors. Each step of the sample handling process should be described should be reviewed and updated periodically. User and staff feedback should be encouraged and documented to inform and evolve the systems.

3. Use of high-quality labels that remain legible and intact over time can minimize errors in sample identification. This can be strengthened if a routine schedule is established to audit labeled samples, including readability, adhesion, and overall condition.

4. For greater security, laboratories can implement a chain of custody system for strict care and monitoring of sample movement.

5. Train staff: Proper training is essential for laboratory personnel to understand and follow sample management protocols. Without training, protocols and standards can be quickly forgotten or unintentionally ignored. Consider implementing:

- Initial training
- Regular and ongoing training sessions to ensure all team members are aligned with best practices.
- Visual reminders of best practices in the form of signs and graphics.
- Training on essential tools such as barcode readers and applicable software.

3.5 QUALITY MONITORING AND ASSAY VALIDATION

3.5.1 Quality Assurance Specific for Human Papillomavirus (HPV) DNA Testing

Quality assurance of the specific performance of HPV tests is supported by a combination of internal quality control (IQC), and external quality assessment (EQA), among other aspects [2,4] **(Figure 3-3)**.

Internal quality control supports the day-to-day monitoring of assay performance and helps detect errors associated with the process/test.[2,4] This is achieved by using control materials of known composition, which should generate the correct, anticipated result if the procedure is performing robustly. [2,5,6]

The composition of the quality control will reflect the activities and responsibilities of the laboratory. For laboratories that perform HPV testing for cervical screening, the results are often reported at the qualitative level (ie high-risk HPV positive or negative). Consequently, the IQCs need to involve both negative and positive HPV control materials, the latter ideally close to the test's cut-off. For laboratories that provide type specific results the IQC should ideally allow assessment of type specific performance.

Figure 3-3 Quality assurance universe for HPV testing in cervical cancer screening

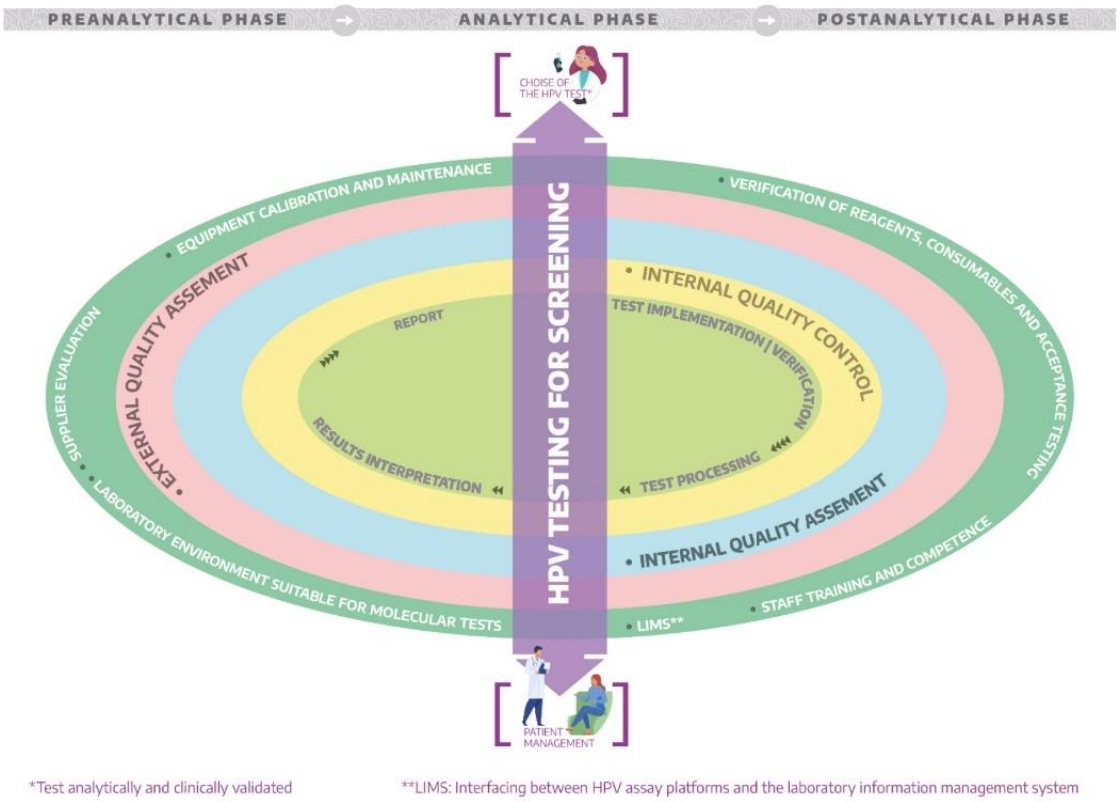


Illustration used with permission from Cuschieri et al, IJGC, 2023.16

3.5.2 Internal Quality Control

Acceptability criteria for IQC should be clearly documented and IQC performance should be monitored relative to these. For HPV assays that provide a numerical read out, recording these values allows the creation of charts[5] which can help assess the between-run consistency of the IQC and identify issues such as assay drift or lot to lot variation in a timely way. Control charts can be created in-house or are available from some commercial providers.

A positive and negative IQC should be included in each run (or minimum daily in the case of continuous loading machines). Also, IQC should be included in addition to any controls provided by the manufacturer of a particular commercial kit.

The results of the IQC must be formally recorded and if acceptability criteria are not met, an investigation into IQC failure should occur with corrective actions documented.[4-6] The detection of random errors (deviation from an expected result) inform whether a particular run is acceptable. Comparatively, systematic errors (significant deviation from the expected range of the IQC) may trigger equipment calibration, and assessment of reagent performance.

Some HPV assays are self-contained, integrating sample extraction and testing. For laboratories processing specimens prior to HPV testing (i.e. extraction, lysis or concentration), processing controls are important to monitor cross-contamination. These may consist of water “blanks” taken through the process. These processing controls should be negative for HPV (and human cellular targets). Positive results trigger cleaning and review of processing steps.

3.5.3 Internal Quality Assessment

Internal quality assessment is the repeat testing of a percentage (typically 0.5–1 % of the workload) of samples. IQA can provide insight into the laboratory’s ability to obtain consistent results. One challenge of IQA of individual samples, is that storage can affect test consistency, particularly if a sample has a viral load at or around assay cut-off. Additionally, for HPV tests used for cervical screening repeatability can be challenged in samples where there is no underlying disease and where the viral load is around cut-off. To obviate some of these issues, pooling samples can be helpful.[5]

3.5.4 External Quality Assurance

External Quality Assurance (EQA) is a system that permits comparison of a laboratory’s test performance to a source outside the laboratory, allowing an assessment of test proficiency/accuracy[5,6] (https://asq.org/quality-resources/pdca-cycle, last accessed February 1, 2024). It should, as far as possible, cover the entire examination process (sample reception, preparation, analysis, interpretation, and reporting). The panels should ideally reflect the biomatrix of the specimens routinely analysed. Different types of schemes exist:

- Interlaboratory schemes (ILS) (reciprocal exchange of material)
- Interlaboratory exchange schemes (creation of a material/s by a central laboratory which are then then disseminated to participating laboratories)
- External Quality Assessment schemes (provided by a third party, often accredited by an external agency to provide EQA services). EQA is generally provide through defined and specific cycles

The ILS and EQA may be available internationally, regionally or nationally **(Table 3-1)**.

Analysis of the results and corrective actions: The results of EQA should be clearly documented. Any nonconformance should be managed in real-time with a documented root cause investigation and suggested corrective and preventative actions.

Table 3-1 Overview of HPV Interlaboratory and External Quality Assurance schemes

Scope	Provider	Weblink	Comments
International	**Quality Control in Molecular Diagnostics (QCMD)**	http://www.qcmd.org/ last accessed March 1, 2024	Distribution worldwide. Accredited to ISO 17043
	College of American Pathologists Quality Solutions (CAP)	https://www.cap.org/laboratory-improvement/proficiency-testing last accessed March 1, 2024	Participation in some of the schemes may be limited to US Accredited to ISO 17043
	International HPV Reference Center	https://www.hpvcenter.se/proficiency_panel, last accessed March 1, 2024	Distribution worldwide. Screening Panel initiated in 2022
	Quality in Pathology "QUiP"	https://qualityinpathology.com, last accessed 19 Sep 2023	Submitted for accreditation to ISO 17043
	UK National External Quality Assurance Service (UK NEQAS)	https://uknegasmicro.org.uk, last accessed Nov 10, 2023	Distribution worldwide. Accredited to ISO 17043
	LABQUALITY	https://labquality.fi, last accessed Sep 19, 2023	Accredited to 17043 (PT02/FINAS) Distributions to Europe, Middle East and Asia
	Instand	https://www.instand-ev.de/en/instand-eqas/eqa-program/offer/virus-genome-detection-human-papilloma-viruses/ last accessed March 10, 2024	Distribution worldwide Accredited to ISO 17043

Table 3-1 (Cont.) Overview of HPV Interlaboratory and External Quality Assurance schemes

Scope (Cont.)	Provider	Weblink	Comments
Regional / National / Local	**EQA in Shangai, China**	Wang X, et al. Clin Chem Lab Med. 2017[7] Wang X, et al. Clin Chem Lab Med. 2019 [8]	40 laboratories (1st round) and 44 (2nd round) from Shangai in 2015 64 laboratories from Shangai in 2019
	Inter-laboratory study in Norway	Engesæter B, et al. BMC Infect Dis 2016[9]	4 laboratories from Norway, as part of the quality assurance programme of the implementation
	Pilot proficiency program in Australia	Costa AG, et al. Pathology 2018[10]	18 Australian and 2 New Zealand laboratories
	Inter-laboratory studies in Argentina	IPVC 2023 (page 485 in the Abstract e-book)[11]	30 laboratories from Argentina

3.5.5 Test Material for quality purposes

Table 3-2 shows an overview of material types that may be used for IQC and EQA. The type of material used (for IQC) and scheme joined (for EQA) will of course depend on the activities and scope of the lab. Clearly it is possible to engage in more than one EQA scheme and this is recommended if a laboratory has responsibilities for testing different biospecimen types and/or if a laboratory performs a variety of tests some of which report at a qualitative level and others a type-specific level.

Table 3-2 Overview of material types suitable for IQC and EQA.

	Types of control materials	Comments
Internal Quality Control	IQC samples can be produced by each lab or obtained from external sources (e.g. reference labs, commercial providers) Positive and negative HPV control materials can be generated in different ways: -pooled from residual cervical samples -cervical cancer cell lines in cytological media -specimens representing individual HPV type in a liquid, lyophilized, freeze-dried formats.	The control materials should ideally: - resemble the biomatrix of samples - be prepared in sufficient quantity to last ideally at least one year - be stable for the period of use - be aliquoted for convenient use - ideally be subjected to the whole procedure (from extraction to detection).
External Quality Assessment	Panel of variable number of samples that represent clinical materials, with different kind of biomatrices (e.g. cervical cells, formalin fixed paraffin embedded tissues, HPV recombinant plasmids) and transport media (Thinprep, Surepath, Preservcyt, STM, among others).	-The panel should be selected according to the specimens routinely used by each lab. - Often have a cost (not affordable for all settings). -Require import logistics (may be difficult for many settings) -National/Regional initiatives may facilitate the access. -Residual material from EQA panels can support reagent- acceptance testing and re-verifications.

3.5.6 Assay validation

The key issue for HPV molecular testing in cervical screening is its ability to detect viral infections associated with cervical intraepithelial neoplasia (CIN) grade 2 or higher (CIN2+), and to separate cervical lesions requiring further clinical intervention from transient infections that only require follow up. Thus, high-analytical sensitivity is not the aspiration, rather, it is the ascertainment of clinically relevant levels of HPV that makes a test fit for purpose in screening.

Meijer et al established international guidelines and minimum requirements for novel HPV tests regarding sensitivity, specificity, and reproducibility.[12] Of the hundreds of HPV tests available, relatively few have been validated according to these criteria although many more are under evaluation.[13,14] The international initiative VALGENT (VALidation of HPV GENotyping Tests) also provides a framework to the performance of HPV tests by use of stored samples on which disease status is known.[15]

The Meijer 2009 guideline based on reproducibility and non-inferior accuracy to a comparator/reference test represented a milestone in HPV based cervical cancer screening.[12] However, the guidelines would benefit from an update to a) incorporate assays that target other molecules than viral DNA, b) include a component for typing c) consider operational requirements including sample handling & automation d) include further comparator tests.

Laboratory professionals, clinicians, and public health decision makers should be careful to choose assays associated with robust clinical validation and performance data (as described) and these decisions may clearly be influenced by the regulatory status of an assay. This said, not all laboratories will deliver HPV testing for cervical screening purposes, and some may conduct surveillance following vaccination. Surveillance usually requires assays with a higher analytical sensitivity, detecting and identifying a broader range of types (including low and high-risk HPV). This said, HPV tests used for surveillance purposes should be shown to be fit for purpose through a process of validation and/or verification (see section 3.5.7 below).

3.5.7 Assay Verification

The implementation of a new assay has to undergo appropriate verification prior to routine use, even for commercially HPV assays. (https://www.iso.org/obp/ui/en/#iso:std:iso:15189:ed-4:v1:en, last accessed March 10, 2024).[16] Assay verification is the process of testing and reviewing an assay's performance in the hands of the reporting laboratory to ensure the anticipated performance (as stated in the instructions for use) are in fact evident in the local laboratory setting.[17] Verification reports should detail the process used to assess performance with criteria for "success" clearly stated. Ongoing verification is also required, at least annually to ensure the test is performing in a stable way. However, a verification may be triggered in the event of a significant repair and/or a move of the associated testing equipment.

In the case of commercial assays, if the user laboratory modifies or deviates from the instructions for the intended use, including for pre-analytical (for example, specimen type, collection method and media, extraction method) and analytical aspects, it should fully assess and validate how the changes impact test performance. Again, a report which details the methods used for assessment and the criteria for success should be completed.

Note that sometimes the terms "verification" and "validation" are used interchangeably between countries and settings.

3.5.8 Use of Endogenous Controls

Most HPV assays contain an endogenous control which frequently amplifies a housekeeping gene present in all human cells as a control of extraction and inhibition.[18] While they can be helpful to confirm the presence of human cells, they do not confirm that relevant cervical cells are necessarily present [17] but they protect, to an extent, against the possibility of false negatives due to acellular samples.

3.5.9 Assay run validation and result interpretation

In each run, the clinical samples are processed along with the kit's own controls and IQC. [1,18] The run is validated by the analysis of:

- Kit’s own controls (following the manufacturer`s instructions) and
- IQC (according to acceptability criteria documented).

If the control results are outside the acceptable range the run should be discarded. If controls are acceptable, the results obtained for the clinical samples analyzed may be interpreted according to manufacturer's instructions.

3.6 PERSONNEL

3.6.1 Staffing structures and levels

An organizational structure of the staff team(s) relevant to a laboratory service should be created and made available to staff (and users) in the form of a diagram. The structure should make management and responsibility lines clear. For example, it is feasible that HPV laboratories may function as independent units or form part of a larger screening or molecular service. In any case, staffing levels should be sufficient to allow the different roles and activities of the laboratory to function effectively and safely. Given that the responsibilities and size of an HPV laboratory will differ, there is no target or minimum staffing complement, although there should be a recognized head of service who will delegate section-responsibilities. For laboratories that offer a screening/diagnostic service then a quality manager is required.

It is recommended that all staff (scientific, administrative, managerial) should have:

- An up to date and accurate job description, including how the position fits into the wider laboratory/organization and the knowledge and skills required to do the job
- Contract of employment
- Yearly appraisal, with agreed objectives
- Clear line management and support
- Access to training and professional development opportunities

Personnel files should be stored in a secure location and contain core documentation (including references, qualifications required to do the job, appraisal paperwork, record of leave etc.). Additionally departmental staff lists should be comprehensive and up to date

3.6.2 Staff training and continued professional development

Staff should undergo mandatory training relevant to the policies of the employing organization as well as training relevant to HPV specific practices. For example, there may be core health and safety and governance training relevant to all staff who are not necessarily laboratory based.

A structured record of training should be created to support the trainee with an expectation of how long training should take to complete for a particular process. Training records should signpost relevant documentation including SOPs. The detail and length of training records will reflect the grade and responsibilities of the staff member. Training records should include clear evidence of training (e.g. a successfully completed assay-run, a record of question and answers relevant to the process). Staff should maintain a training folder so that records can be accessed easily and the templates for training records should be document controlled. Audits to determine appropriate provision of training documentation and completion can help identify areas for improvement.

Staff should endeavor to engage in continued professional development (CPD) to support the quality of their day-to-day practice and career development. CPD can include activities that will benefit the individual as well as the service. External training courses and meetings are worthwhile of course but can be challenging to resource, so local support for education and development is important. Organized, departmental seminar series, training courses and “journal clubs” are valuable in this regard. A document that outlines laboratory training policies including access to further education can support equity of access.

Progress in training should be documented during staff appraisal. Appraisals should be yearly at a minimum and include objective-setting as well as a review of objectives from the previous year. Appraisees should be given time to prepare before the appraisal and an accurate record of the discussion and associated actions should be maintained.

3.6.3 Competency assessment

In addition to comprehensive training, a review of staff competency for a particular technique /process is valuable and indeed mandatory for accredited laboratories. Frequency of competency review should reflect the complexity of the task and how often it is performed. Competency reviews can also help support staff who have been trained but who have not performed the task due to a period of absence.

3.7 INSTRUMENTS, EQUIPMENT AND MAINTAINENCE

It is essential for equipment (large and small) to be well managed and maintained. Failure to do so could have serious negative implications for user safety and the quality of results. All equipment should:

- Be listed in a laboratory inventory with core details (name, date of acquisition, date of installation, model, manufacturer, serial number, location, technical-support details).
- Be included in a schedule for key maintenance procedures with a record of when this was performed.
- Be managed by a named member of staff to prevent lapses in maintenance (although all users have a responsibility to ensure it is well maintained).
- Have accessible contemporary instructions for use (in the form of manufacturer instructions and/or SOPs).
- Be accommodated in a laboratory area that supports its robust and safe use

Any device that is relied on for weights and measures (including balances and pipettes) should be calibrated. Maintenance may be planned and preventative or performed in reaction to a real-time problem. The nature of “maintenance” will be affected by the piece of equipment and what it is used for and can range from daily cleaning to a full annual preventive maintenance performed by an external engineer. When a large piece of equipment (e.g., an automated extraction system or an HPV analyser) has been moved, had a substantial repair or yearly maintenance, documented demonstration that it is working as expected should occur before it is put back into routine use (see section 3.5.7).

Staff should be trained in safe and effective equipment use including maintenance and calibration procedures where relevant. This should be integrated into training plans. Where equipment is multi-user, logbooks which detail day-to-day issues can support communication between users who may be working different shifts. Where possible and affordable, equipment should be supported by maintenance contracts.

3.8 SUPPLIES

3.8.1 Reference Materials

Reference materials can be used to help validate/verify an assay and ascertain its ongoing performance. Reference materials may be sourced from external (including commercial) providers. Some material will be relevant for the amplification part of an HPV assay (e.g., plasmids) whereas other types may act as a proxy of a clinical sample (e.g. HPV containing cell lines). Some reference materials are calibrated to international units such as the WHO international HPV standards. Said standards are ”freeze-dried, cell-free preparations of purified recombinant plasmid formulated in a background of human genomic DNA”. [3]

A register of reference materials should be created which includes details of the supplier, lot reference, name of material, date of preparation/reconstitution, number/ID of aliquots made, storage location and storage conditions/expiry. Additionally, a clear record of testing and test results should be maintained. The quality and performance of reference materials should be reviewed yearly as a minimum. However, if real-time issues arise and material is not functioning as anticipated an investigation should occur which may mean materials are retired.

3.8.2 Reagents

Reagents are chemical or biological materials that are required for laboratory processes (including sample reception, sample testing and general laboratory maintenance). They include commercially available kits/assays, buffers and solutions that may be required for sample processing and HPV testing (but which are not necessarily included in commercial HPV assay-kits) and cleaning/decontamination solutions. A specific SOP should be created that reflects the general processes for reagent receipt and handling in the laboratory. This should include how reagents are initially deemed fit for purpose on arrival (i.e., seals intact, no evidence of damage), how they should be stored and who has responsibility for their management.

An inventory of reagents should be created which details:

- Reagent name. Using the accurate terminology to avoid ambiguity.
- Supplier. Again, using accurate consistent terminology.
- Lot number. So, any variability in performance that may be associated with lot can be tracked.
- Required storage conditions. To ensure adequate, safe, and appropriate storage can be identified and maintained.
- Expiry. As well as ensuring expiry dates are not exceeded, they help in maintaining adequate levels of stock.
- Storage location. To ensure stock is well and appropriately maintained.
- Confirmation of receipt in good condition. Any issues with damaged stock should be reported to the supplier in real time.
- Reference to Material Data Safety Sheet. To comply with safe handling of the material.
- Date of first use (see later section on batch acceptance). To track and ensure performance is adequate.

Material data safety sheets include details on handling and storage, physical and chemical properties, toxicological information and disposal considerations. They are generally accessible online or through direct interaction with the manufacturer. SOPs for laboratory processes/assays should also include reference to the relevant and contemporary Material Safety Data Sheet (MSDS).

A key stock list should be created to ensure that appropriate and sufficient stock levels are maintained. Minimum levels of stock should be agreed with the laboratory lead (or delegate) based on frequency of reagent use, anticipated or known expiry and (importantly) anticipated delivery time of a reagent to a particular setting. Regular stock checks should occur, this may be performed by the stock manager or delegate.

3.9 BATCH ACCEPTANCE OF REAGENTS INCLUDING KITS

To ensure new lots of reagents and kits are functioning as anticipated, they should be tested before being put into routine use.

Batch acceptance testing records should include:

- details of the kit including manufacturer, product code and lot number.
- condition on arrival (acceptable or not).
- details of how the item was deemed fit for purpose; this could include re-testing previous samples or testing a panel of material with a known/anticipated result.
- details of any further actions/escalation in the event the acceptance was not successful.
- Signature and date of assessment by the technical operator.

3.10 LABORATORY SAFETY

Laboratories should have a health and safety manual to support safe working. The 4th edition of the WHO Laboratory biosafety manual includes core information on biosafety, chemical, fire and electrical safety requirements to ensure staff, users of the service, the local community and the environment are safe.[3] Safety should be a core part of mandatory training for all those that work in laboratory teams and not just confined that those who perform bench-work.

The head of the service/laboratory (often through delegation to a health and safety committee) is responsible for implementing a programme of work, with checks, to ensure health and safety in the working environment. However, all staff are obliged to be familiar with and work to safety standards. Some core aspects to ensure safe working are:

- Access to the laboratory is restricted.
- A health and safety manual is made available to all staff.
- Formal training on health and safety procedures is provided to staff relative to their role and responsibility.
- Personal protective equipment is made available to staff and staff are aware of its appropriate use.
- The laboratory is well maintained and operates to a cleaning and maintenance schedule.
- Daily temperature monitoring is performed, including of refrigerators and freezers.
- There is a waste management policy.
- SOPs integrate and/or reference processes and protocols to ensure safe working.
- Risk assessments are performed for procedures which represent a potential chemical or biological or physical hazard.
- A register/inventory of materials (including clinical samples) is accurate and complete and includes the nature of the material and storage location.
- The laboratory has a SOP that details retention and disposal of samples.

3.11 AUDITS

Audits are designed to evaluate whether a process/quality activity in fact complies with established documentation (or quality standard) and to confirm whether these activities are sufficient and appropriate to achieve the desired objectives. Audits can:

- Help identify gaps, problems and ambiguity in systems and processes
- Act as a key driver of quality improvement

Laboratories should work to an internal audit schedule as this way problems and issues can be identified and resolved in a timely way. Frequency of audit will depend on how critical the process is and should be agreed with the quality management team. Those who perform audit should be sufficiently trained so they understand the expectations of the quality standard and/or documentation. Findings from the audit should be clearly documented and a timed action plan for resolution agreed.

Note that audits can be broad ranging (e.g. an audit of whole quality management system), relate to a particular element of the system (training, equipment, suppliers) and of course relate to a particular test/process. Audits generally involve:

- a review of documentation
- an initial meeting between the auditor and section “under audit” to agree timing, activities
- Direct observation of the process (although sometimes audits are “paper only”)
- A review meeting to discuss the observations and agree the actionable findings
- Creating a report which documents both the findings and the actions/resolutions applied
- Reschedule of a subsequent audit to review actions, the timing of which may depend on the nature and significance of any findings.

External audits (sometimes referred to as visits or inspections) also occur in laboratories that are accredited to a particular standard (e.g. ISO15189) to ensure that the standard is being maintained. Such visits are performed by independent authorized agencies/bodies. Laboratories that act as WHO prequalification laboratories are also subject to inspection by the WHO according to an agreed schedule.

3.12 REFERENCES

1. Bustin SA, et al. The MIQE guidelines: minimum information for publication of quantitative real-time PCR experiments. Clin Chem 2009;5:611-22.

2. Hawkins R. Managing the pre- and post-analytical phases of the total testing process. Ann Lab Med 2012;32:5-16.

3. WHO Laboratory quality management system: handbook. 2011 ISBN 978 92 4 154827.

4. Cuschieri K, Schuurman R, Coughlan S. Ensuring quality in cervical screening programmes based on molecular human papillomavirus testing. Cytopathology 2019;30:273-280.

5. Saunders N, Sharp I. Validation of Molecular Diagnostic Assays and Quality Assurance and Control in the Veterinary Laboratory. In: Cunha MV, Inácio J, eds. Veterinary Infection Biology: Molecular Diagnostics and High-Throughput Strategies. Vol 1247. Methods in Molecular Biology. Springer New York; 2015:77-105.
6. Carozzi FM, Del Mistro A, Cuschieri K, Frayle H, Sani C, Burroni E. HPV testing for primary cervical screening: Laboratory issues and evolving requirements for robust quality assurance. J Clin Virol 2016;76:S22-S28.
7. Wang X, Liu F, Jiang L, Bao Y, Xiao Y, Wang H. External quality assessment for human papillomavirus 16/18 DNA detection and genotyping in Shanghai, China. Clin Chem Lab Med CCLM 2017;55.
8. Wang X, et al. Results of the second external quality assessment for human papillomavirus genotyping in Shanghai, China. Clin Chem Lab Med 2019;18;58:e14-e17.
9. Engesæter B, et al. Quality assurance of human papillomavirus (HPV) testing in the implementation of HPV primary screening in Norway: an inter-laboratory reproducibility study. BMC Infect Dis 2016;24;16:698.
10 Costa AG, Escott R, Garland SM, Byers D, Tabrizi SN. Development of a pilot proficiency program for human papillomavirus DNA detection. Pathology 2018;50:659-664.
11. Basiletti JA, et al. Evaluation of the Clinical Detection of Human Papilloma Virus using Two Validated Platforms: Second Interlaboratory Study in Argentina. IPVC 2023, Poster 1655, Abstract e-book Page 485.
12. Meijer CJ, et al. Guidelines for human papillomavirus DNA test requirements for primary cervical cancer screening in women 30 years and older. Int J Cancer 2009;124:516-20.
13. Arbyn M, et al. 2020 list of human papillomavirus assays suitable for primary cervical cancer screening. Clin Microbiol Infect 2021;27:1083-1095.
14. Poljak M, Oštrbenk Valenčak A, Cuschieri K, Bohinc KB, Arbyn M. 2023 global inventory of commercial molecular tests for human papillomaviruses (HPV). J Clin Virol 2024;172:105671.
15. Arbyn M, et al. VALGENT: A protocol for clinical validation of human papillomavirus assays. J Clin Virol. 2016;76:S14-S21.
16. Cuschieri K, et al. Quality assurance in human papillomavirus testing for primary cervical screening. Int J Gynecol Cancer 2023;33:802-811.
17. Wallace P, McCulloch E. Quality Assurance in the Clinical Virology Laboratory. Encyclopedia of Virology 2021:64-81.
18. Cuschieri K, et al. The challenges of defining sample adequacy in an era of HPV based cervical screening. J Clin Virol 2021;137:104756.