5 Quality management of point-of-care testing devices

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Summary

Quality control (QC) testing and proficiency testing (PT) are integral components of a quality system to monitor analytical performance in the laboratory and at the point of care. These two processes check the quality of a device's performance by comparing observed results of QC testing or PT with a target with pre-set specifications. QC testing provides an immediate check of quality, while PT provides a delayed, peer-reviewed, external assessment of quality. However, many modern POCT devices now feature sophisticated in-built quality checks within their single use, disposable testing units. A tailored, flexible and balanced approach to quality surveillance is therefore required, taking into account the degree of the device's technological sophistication, practicality, cost of QC/PT and size/scope of POCT networks.

INTRODUCTION

In the laboratory setting, analytical quality is usually monitored by two equally important and complementary processes called quality control (QC) and external proficiency testing (PT). PT has a wide variety of synonyms that are used by different professional bodies and providers of PT programs around the world, including external quality assurance (EQA) and external quality assessment schemes or programs (EQAS). Table 5.1 provides working definitions of terms related to quality and quality systems.

The aim of conducting QC and PT testing is to monitor an analytical measurement system and to alert the operator when a change to the system has occurred that

Table 5.1. Distinction between terms used to describe quality (Source: adapted with permission from Shephard *et al.* 2012)

Term	Definition
Quality management systems (QMS)	A systematic approach to document the quality principles used by a POCT facility.
Quality assurance (QA)	An over-arching term to describe all activities to improve or maintain quality of POC tests and testing.
Quality control (QC)	The routine testing of sample(s) with known concentrations or reactivity to ensure the POC test device is performing to analytical expectations.
Proficiency testing (PT); also known as external quality assessment schemes (EQAS) or external quality assurance (EQA)	The periodic testing of a panel of samples containing a range of concentrations or infectious loads. The test results of the samples are unknown to the tester and the results obtained are submitted to the PT provider for peer assessment.

may compromise the integrity of the patient result and potentially lead to a medically important error (Ehrmeyer and Laessig 2001).

These two processes check the quality of a device's performance by comparing observed results of testing samples with differing concentrations or infectious loads to a target with pre-set specifications. Although the underlying principle of these two forms of testing is the same, there are some fundamental differences between QC and PT.

For QC testing, samples (often in a kit form) are usually provided by manufacturer of the device, but can also be supplied by a third-party provider or be produced in-house by the laboratory. One to three levels of QC are generally provided for testing, with the manufacturer or the POCT Coordinator setting the 'target' values (and the limits for acceptable performance) for these QC materials. These values are known at the time of QC testing and therefore an immediate assessment of the quality of the device's performance can be made. QC testing is often termed 'internal' QC testing.

PT samples (for laboratory and POCT programs) are provided by recognised and, preferably accredited, proficiency testing providers. Selected examples of PT providers from Australia, USA and the UK are listed in Table 5.2. These providers support a range of specific POCT programs (and linked laboratory-based PT programs) that can assess the quality of testing on POCT devices.

PT samples have multiple levels of test concentrations or infectious loads, with accurate target values and acceptable limits (because the PT material is manufactured to tight specifications set by the PT provider). With PT samples, the true result is not known at the time of testing and the operator sends the result to the PT provider. The PT provider returns a report that documents how close the observed result for that sample was to the target value and how the results from that testing facility (laboratory or POCT) compare with all other (de-identified) facilities in the program.

Table 5.2. Examples of external PT program providers to support POCT

PT provider	Website
National Serology Reference Laboratory (NRL)	www.nrl.gov.au
RCPA Quality Assurance Programs	www.rcpaqap.com.au/poct
College of American Pathologists	www.cap.org
Wisconsin State Laboratory of Hygiene	www.slh.wisc.edu/proficiency
American Proficiency Institute	www.api-pt.com
United Kingdom National External Quality Assessment Service (UKNEQAS)	www.ukneqas.org.uk
Wales External Quality Assessment Scheme (WEQAS)	www.weqas.com

Thus QC provides an immediate check of quality, while PT provides a delayed, peer-reviewed, external assessment of quality. Table 5.3 summarises the main differences between QC and PT testing.

For analytes with quantifiable concentrations, repeated testing of QC and PT samples at defined time intervals enables statistical measures of the accuracy and imprecision (reproducibility) of testing to be calculated, which determine whether the testing device is performing to acceptable analytical standards. QC is generally used for monitoring the imprecision of a device's performance, because that same QC material is tested repeatedly across time and therefore the variability of those repeated measurements can be calculated. Testing of QC samples can also be used to monitor accuracy, although the target values set by the manufacturer are generally not as tightly assigned as the targets set by the PT provider. PT therefore delivers a more robust measure of accuracy, while PT samples can also monitor imprecision if the same samples are provided and measured several times across a testing period.

Ideally, sample matrices for QC and PT material should be the same as that of the patient sample being tested. In practice, this is often not the case, because the quality samples need to have long stability across their intended period of use (often 1 or 2 years). PT materials are often provided as freeze-dried (lyophilised) human blood or urine that requires reconstitution, as clear liquids, or as swabs coated with dried, inert bacteria or virus. Consideration of the sample matrix and the type of patient sample being routinely tested is required when choosing an appropriate QC or PT material for a laboratory or POC testing program (Shephard *et al*. 2012).

MONITORING THE ANALYTICAL QUALITY OF POC TEST SYSTEMS

QC and PT provide a formal means of monitoring the analytical quality of a device. Without quality testing:

Table 5.3. Main differences between quality control testing and proficiency testing

Parameter	Quality control testing	Proficiency testing
Assessment and reporting	Internal, immediate	External, delayed, peer-reviewed
Supplier	Manufacturer or third party	Accredited PT provider
Samples tested	Usually one to three levels	Multiple levels
Target values	Known by operator when tested	Not known by operator when tested
Testing frequency	Frequently: checks quality over time	Periodic: checks quality at a set point in time
Performance indicator assessed (quantitative tests)	Reproducibility (Precision)	Accuracy and precision
Interpretation	Assesses performance of 'your' device only	Compares performance of 'your' device with other participants using the same device

- How can an operator know that their device is working well?
- How can the operator know with any confidence that the test has been performed correctly?
- How can the operator know that a patient's test results are appropriate and safe for their clinical care?

Although these quality processes have served the laboratory well and are available to support POCT programs, a key issue that continues to be debated worldwide is: 'Are these traditional QC and PT processes relevant, transferable, practical and cost-effective for monitoring analytical quality on POCT devices?' (Bullock 2004; Gill and Shephard 2010; Martin 2008). There is no simple answer or solution to this question. In attempting to consider the issue, it is necessary to:

- understand the total patient testing process
- understand the difference between laboratory and POCT systems
- assess the degree of technological sophistication that individual POC devices/test systems have, particularly their 'in-built' quality checks
- find the appropriate balance between ensuring safety and analytical quality of POCT and implementing a quality framework that is practical, achievable and cost-effective in a primary care setting.

THE TOTAL PATIENT TESTING PROCESS

The total testing process includes pre-analytical, analytical and post-analytical phases.

The pre-analytical phase of testing generally includes patient sample collection, labelling and handling. Pre-analytical steps are the most difficult to control, and errors in sample collection can lead to grossly misleading results. Training and competency assessment for device operators is perhaps the best form of 'control' of pre-analytical errors, where it is crucial that operators fully understand the errors that will occur if the sample is collected improperly.

Analytical steps generally involve calibration, sample preparation and delivery, reagent preparation and delivery, reaction between sample and reagent, and measurement of a signal and conversion to an analyte concentration.

The post-analytical phase of testing involves manual transcription or electronic transmission of the result into the patient record.

A sound quality management system should incorporate procedures to check all steps of the total testing process (Fig. 5.1).

DIFFERENCES BETWEEN LABORATORY AND POCT DEVICES

Most laboratory instruments are closed or self-contained and have the ability to measure large numbers of samples in batches throughout the day. For these types of analysers, the testing of multi-level QC throughout the day combined with monthly PT testing and regular maintenance is considered standard practice.

In contrast, many POC test systems comprise a disposable single-use testing unit with or without a reading device (NCCLS 2002; Phillips 2004). For qualitative tests, the sample is added to the testing unit, the analyte is measured and a negative or positive result is generated. For quantitative tests, the reaction process takes place in the testing unit and the reader converts the signal generated into a numeric result.

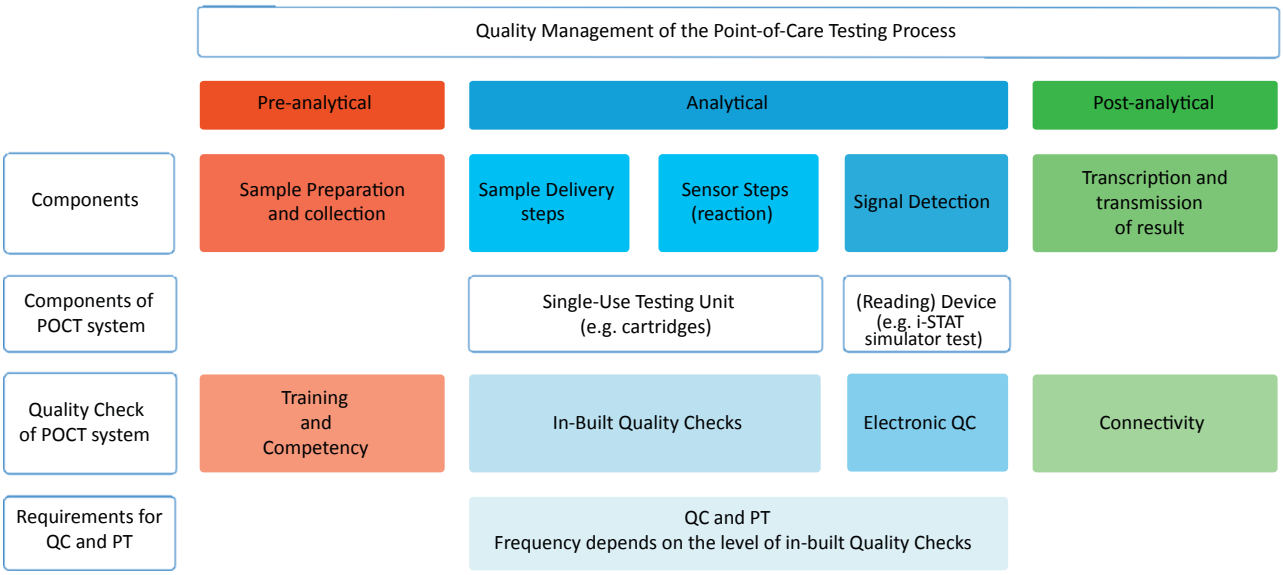

Fig. 5.1. Schematic representation comparing aspects of quality management using POCT-based single-use testing systems.

An argument can be mounted that traditional QC and PT processes are not necessarily applicable to these types of POC test systems because each testing unit is discrete and disposable, and checking the performance of a single testing unit does not guarantee with any certainty the quality of the next testing unit. How then have manufacturers of such systems approached the problem of quality management?

QUALITY CHECKS FOR POC TEST SYSTEMS

With most modern POCT devices, there has been significant technological investment by manufacturers in the development of sophisticated in-built quality checks within the testing unit itself (these checks have been described variously as 'on-board QC', 'intelligent QC' and 'internal checks'). Manufacturers have recognised that the main consumers of POCT in the future will be health professionals from a non-laboratory background and they have tried to make the devices as simple as possible for the operator and well controlled internally.

The Abbott i-STAT® cartridge has a calibration solution contained in a pouch in every cartridge and performs a calibration before each sample is tested. In-built checks of the calibration fluid include that it is free of bubbles, has not burst in the handling process and is present at the correct concentration. Every Roche CoaguChek XS® test strip has in-built control checks for strip deterioration due to exposure to excessive temperature and humidity. The Abbott Piccolo® rotor quantifies interferents such as haemolysis, lipaemia and icterus and suppresses results when interference limits are exceeded. It also validates the composition and delivery of all reagents, confirms correct sample and diluent volumes have been delivered and verifies the presence of diluted sample in all reaction cuvettes. The Cepheid GeneXpert® performs a 'sample adequacy control', which is designed to detect the presence of a single copy human gene per cell to ensure that the sample contains human cells and that the cells are adequately lysed to extract nucleic acids. A negative sample adequacy control indicates that no human cells are present in the sample due to insufficient mixing, inadequate sampling or inefficient lysis. The GeneXpert® system also performs a 'sample processing control' and a 'probe check control'.

Manufacturers of qualitative rapid POC tests based on lateral flow technology often state that their devices include an in-built 'quality control' check. What in fact they mean is that there is simply a check of the flow of liquid from the sample application area to the strip's end.

Many POCT devices incorporate quality checks by which signal generation is monitored. These are known as electronic QC checks (Westgard 2001). The Abbott i-STAT® has an electronic simulator that specifically measures electrical signal generation and ensures that these signals are within tight specification limits. Electronic QC should not be considered a surrogate for traditional QC because this only checks signal generation and does not monitor the analytical reaction process (Fig. 5.1).

The best single-use POCT systems are those with the highest degree of in-built quality checks to monitor the analytical steps.

FINDING THE BALANCE

Given this level of technological sophistication with most POCT devices today, the role of traditional QC and PT has come under question in some quarters. A training manual for a widely used POCT device recently contained the following statement: 'Quality control and system checks using control test solutions that you may be familiar with from other systems are no longer required …' Certainly this is not the view of the authors. There unquestionably remains a continuing place for traditional QC and PT as an independent check of the quality of POCT systems, but one needs to tailor the degree of technical sophistication of the device with a QC/PT frequency regimen that is cost-effective and practical.

There is no 'one size fits all' policy that can be applied universally across all POC test systems in terms of frequency of QC/PT testing. Ideally QC samples should be tested with each group of patient tests performed, but this may be impractical. As a minimum requirement, QC testing should be conducted once a month, when a new delivery of reagents is received, when there is change in reagent lot number, when a patient result does not fit the clinical presentation, or following a major maintenance or repair procedure for a POCT device (Gill and Watkinson 2010). Beyond these scenarios, frequency of QC testing in particular should take into account the actual volume and nature of patient testing conducted in the field. Many clinical chemistry and haematology PT programs provide samples for testing on a monthly or bimonthly basis, while infectious disease PT programs provide panels of samples to be tested at selected testing events or 'challenges' two to four times per year.

The cost of purchasing QC and PT materials is of relevance for small primary care settings with limited financial budgets for conducting POCT and for large POCT networks where costs of conducting QC and PT at every site can potentially become a large percentage of the consumable budget.

An alternative to traditional PT testing is 'parallel' or 'split' patient sample testing, in which the same patient sample is tested by a POCT site and by the laboratory and then results are compared. Potential advantages of parallel patient sample testing are: like PT, it provides a delayed external check of quality; testing uses a sample of identical matrix (e.g. whole blood) to that of the routine patient samples rather than a lyophilised or liquid PT material; with samples equivalent to routine specimens, parallel patient testing can check the pre-analytical component of testing; and parallel patient testing can be a cost-effective external assessment of quality. Potential drawbacks include: this mode of external assessment only tests a limited range of concentrations compared with PT, which can assess an analytical method across a wide range of concentrations; parallel patient testing does not involve peer comparison; there is a need to define appropriate acceptability criteria that recognise measurement uncertainty; and there can be problems associated with the transport and delivery of patient samples to the laboratory from geographically isolated rural and remote locations.

In terms of practicality in the field, we should never lose sight of the complexities faced by a POCT operator performing QC and PT in a non-laboratory environment. Operators in primary care facilities may be required to conduct POCT on multiple levels of QC and PT samples each month and work with a range of different sealed vials, liquid solutions and pipetting equipment to fulfil their quality testing requirements. The realities of busy health professionals who are not familiar with laboratory practice, but are required to conduct POCT in the field, are often overlooked or misunderstood (Fig. 5.2).

AN EXAMPLE OF QUALITY TESTING IN PRACTICE

The next section provides a brief practical example of the quality testing system employed by the national QAAMS HbA1c POCT program for diabetes management operating in Indigenous medical services in Australia (Shephard *et al.* 2015; Shephard and Gill 2005, 2006, 2010). This example illustrates how this quality program operates in practical terms; one that has now been successfully translated across different primary care settings, different countries and different clinical scenarios (Motta and Shephard 2015; Shephard *et al.* 2009, 2014).

Quality control testing in the QAAMS program

In the QAAMS program, device operators are required to test one set of QC materials, comprising two levels of HbA1c (reflective of a patient with optimal and poor glycaemic control) every month across the calendar year.

Fig. 5.2. An array of different quality control solutions and associated consumables for use with the DCA Vantage and i-STAT devices, exemplifying the realities of conducting QC testing in the field.

With the support of the manufacturer, an annual batch of QC kits with the same lot number is ordered and stored specifically for use by the participating QAAMS health services (which now number 190). The use of a single lot number of QC enables the program management team to monitor the imprecision of QC testing more efficiently than if there were multiple lot numbers.

Device operators are provided with a colour-coded QC result sheet on which to record their monthly QC results. The colour codes are designed to mimic a 'traffic light' system (i.e. a QC result in the green zone means 'go', orange means 'proceed with caution' and red means 'stop'); this system provides device operators with a practical and user-friendly method of interpreting their QC results on-site and making an informed decision to accept the QC results and proceed with patient testing or reject the QC results and cease testing patients until the reason for unacceptable performance has been investigated and corrected (with the assistance of the POCT Coordinator).

QC results can be entered electronically by the operator into the 'QC Results' section of the QAAMS website, where the site's imprecision is automatically updated and results can be reviewed by the POCT Coordinator.

Proficiency testing in the QAAMS Program

At the beginning of each calendar year, the QAAMS PT provider (the Royal College of Pathologists of Australasia's Quality Assurance Programs Pty Ltd) sends a PT kit containing 24 lyophilised PT samples (each numbered and dated for the next year of the program), together with vials of reconstitution fluid and a Quality Testing Calendar, to each participating service. Two samples per month are made up and tested by the participants (according to the calendar) across two 6-monthly testing cycles per year (January–June and July–December). Each sample has a target value and a limit for acceptable performance set by the PT organisers. The material provided (and acceptable performance limits set for QAAMS) are identical to those used by the PT provider for their HbA1c program for Australasian laboratories, which enables direct comparison between the two programs. The samples for each cycle comprise six paired and linearly related levels of analyte across a range of HbA1c values from 5 to 14% (31 to 130 mmol/mol). The use of paired samples enables calculation of imprecision for PT testing on the POCT device for both individual services and the group as a whole.

The HbA1c results obtained for the two PT samples tested for that month can be entered electronically onto the PT section of the QAAMS website. Within a week after the due date for the return of results for that month, the PT provider sends a report to each participating service.

Monthly scientific meetings between the QAAMS POCT Coordinator and a scientist from the PT provider are held to discuss and review all QC and PT results returned by services for that month. These QC/PT review meetings enable poor analytical performance and/or non-compliance with QC and/or PT testing schedules to be actioned and fixed in a timely fashion.

As discussed later in the book, this quality framework has been robust and sustainable for more than 16 years, with the long-term analytical performance for both QC and PT testing in the QAAMS POCT program consistently meeting analytical benchmarks for quality recommended by the Australian Government and expected of Australasian laboratories.

INFECTIOUS DISEASE POINT-OF-CARE TESTING

Testing for infectious diseases is prone to variation, whether the test is laboratory-based or a POC test. Some of the sources of variation experienced in each setting are the same, but there are sources of variation unique to the POCT setting. Even though POC tests are designed to be robust and easy to use, testing errors still occur (Wolpaw *et al*. 2010). Although the sensitivity and specificity of POC tests for HIV antibodies have been reported as being as high as 100% under well-controlled evaluations (Motta *et al*. 2013), evidence indicates that the performance in the field is often much poorer (Bloch *et al*. 2014; Learmonth *et al*. 2008; Plate *et al*. 2007; Wolpaw *et al*. 2010). Therefore, it is important that facilities using POC tests for infectious diseases participate in well-designed and ongoing quality testing processes to ensure test results are accurate. Knowledge of the sources of variation is beneficial when designing and implementing quality materials for infectious disease POC tests because each variable can be targeted and so minimise the potential effect it has on patient test results.

Sources of variation in infectious disease POC tests

Many health professionals using infectious disease POC tests are not necessarily expected to have strong scientific or technical knowledge and may be unaware of the influences that sources of variation may have on the test results (Constantine *et al*. 2005). These variables may include: environmental changes, reagents, equipment and processes, as discussed in the following sections.

Environmental changes

POCT kits are usually transported and stored refrigerated or at room temperature. However, environmental conditions such as extreme temperature and/or humidity may have an adverse effect on performance (WHO 2005a). If stored refrigerated, results from a test that is undertaken before the reagents can equilibrate to room temperature may be incorrect. Test kits or reagents that are stored refrigerated need to have their storage conditions monitored. Any unidentified, intermittent changes in refrigeration temperatures may adversely affect the performance of the test kit. Some nucleic acid tests (NAT) used at the point of care or in remote facilities require reagents to be stored frozen. If stored in an automatic defrost freezer, the reagents may undergo inadvertent and damaging freeze–thaw cycles.

Reagents

Test kits sold into countries with *in-vitro* diagnostic device (IVD) regulations such as Australia are manufactured under strict conditions. In some regulated countries, each new lot of test kits is tested to ensure the quality of its performance (lot release testing). However, reagent lots will occasionally display sub-optimal performance when used to test patient specimens in testing facilities if issues are not detected in lot release testing. Some POC tests require reagents not provided in the test kit. Even basic reagents such as water may be contaminated or at a grade unsuitable for use.

Equipment

Many infectious disease POC tests require little or no equipment or have equipment such as disposable plastic pipettes provided in the test kit. Other more sophisticated POC tests may require readers or even, in the case of NAT POC tests, small-scale instrumentation. Failure of equipment or instrumentation may affect results. For example, plastic pipettes that dispense incorrect volumes of samples or devices that fail to allow the flow of sample may report incorrect results.

Processes

Each POC test is provided with instructions for use. These instructions guide the user through the testing process

and highlight critical steps, such as time to reading the results after the addition of the patient specimen. POC test instructions are usually simple and user friendly; however, some steps are critical and must be adhered to. If manufacturer instructions at critical steps are not followed, false positive or negative results may be reported.

Quality management systems for infectious disease POC tests

The results of POC tests can have a significant impact on a patient's wellbeing, especially when testing for infectious diseases such as HIV or syphilis (WHO 2015). A false positive result will cause unnecessary further testing, counselling and anxiety for the patient as they await confirmation of the result and lead to a lack of confidence in the testing. A false negative result may give a patient a false sense of security, delay treatment and expose the community to the spread of disease. The testing facility should minimise the risk of false results by developing and adhering to strict procedures and employing quality management measures that are designed to detect unexpected changes in the testing process (Constantine *et al*. 2005; Yao *et al*. 2010). These include quality control and proficiency testing.

Proficiency testing for infectious disease POC tests

PT is a quality management service where testing facilities are provided with a panel of samples periodically throughout the year. The reactivity of the samples is unknown to the facility participating in the program. The participant tests the samples as they would a patient specimen and reports the results and any associated data (e.g. test kit name, lot number and expiry dating) to the PT provider. The PT provider analyses the results, usually by comparing the submitted results with a reference result, and writes a report, which is sent back to the testing facility. A distribution of samples is often defined as a 'challenge'. The purpose of PT is to monitor the test system from the receipt of the sample to the reporting of results.

Testing facilities can use PT results as objective and independent evidence of the quality of testing. PT can be used to periodically assess the competency of the user and identify training needs. The results allow the monitoring and comparison of the performance of testing facilities and the test kits used. Any errors or anomalies arising from PT participation must be investigated. The root source of the problem should be determined, actions to remove that source of variation implemented and resolution of the problem confirmed. In this way, a continual improvement cycle can be put into effect.

Participation in a PT program for all medical testing, including POCT, is mandatory in most developed countries (Valenti 2003). When selecting a PT provider, it is important to take several issues into account. The PT provider should be compliant with ISO 17043: 2010, General Requirements for Proficiency Testing – an international standard for PT providers. Accreditation to this standard provides evidence that the PT provider has robust sample preparation, shipping, analysis and reporting processes and has undertaken extensive testing to prove the PT samples are homogeneous and stable (Shephard *et al*. 2012).

A PT provider should supply sufficient samples to maximise the chance of detecting testing errors. Ideally, each person performing a test on a patient specimen should participate in at least one PT challenge per year. If too few samples are sent to participating facilities, errors inherent in the testing process may not be detected (Constantine *et al*. 2005). NRL recommends that PT challenges have at least five samples and that there are at least three challenges per year. The PT samples provided should reflect, as closely as possible, patient samples (Shephard *et al*. 2012). Where possible, the PT samples should also occasionally challenge the POCT with well characterised but rare genotypes/serotypes or other samples that may be encountered in a testing facility. PT also assesses the administration processes in the testing facility, with a view to emphasising the importance of these processes in ensuring that the correct test is performed on the correct sample and reported on the correct patient. The PT challenge should be designed to ask a question.

The analysis of PT results relies on reviewing results from peer groups; that is, testing facilities that test the panel samples using the same brand of POC test kit. Maximising the number of participants in peer groups allows the PT provider to employ more powerful statistical methods and have greater confidence in the conclusions drawn.

The PT provider should report the results of the analysis back to the participants quickly so that errors detected can be investigated expeditiously. An extensively delayed report may allow testing facilities to continue using poor testing procedures or reagents. The reporting process can be facilitated by the use of internet-based software, which allows the participant to enter test results directly into the database. The automatic analysis and reporting of PT results allows the PT provider to issue reports to participants quickly.

Alternatives to traditional PT

Sometimes it is impractical to conduct PT using real samples due to sample stability, importation difficulties or geographical challenges. Although less valuable, alternative methods of monitoring parts of the testing process may be substituted in these situations. However, it is not recommended that alternative PT methods are used if traditional PT is available.

Laboratory-based PT for infectious disease POCT

There are numerous providers that offer PT for laboratory-based infectious disease testing. These schemes usually provide plasma or serum-based samples in liquid, frozen or freeze-dried (lyophilised) form. If a whole-blood PT product is unavailable, these PT programs may be a suitable alternative. A small selection of laboratory-based infectious disease PT providers is presented in Table 5.2.

Photography

Some infectious disease PT providers have reported using photographs of patient's POC test results and asked that the participants read the result from the photograph (Chiu *et al*. 2011; Learmonth *et al*. 2008). This method has the advantages in that all participants receive exactly the same photographs and therefore their results can be meaningfully compared. Photographs are easily provided via email or the internet, thereby removing importation or shipping barriers. However, this PT method does not assess the pre-analytical or the analytical stages of the POCT process: only the ability of a participant to read and interpret the test result. The ability of the participant to accurately read the result is dependent on the resolution of the photograph. The PT program must also be POCT device-specific.

Alternatively, an assessment of a facility's staff to read results accurately may be assessed by the facility referring photographs of patient results to a third party for a 'second read'. This may be useful in providing oversight of a remote facility, but it will only assess the ability to read the result rather than the complete test process.

Sample re-test

Some infectious disease networks or facilities employ a re-test protocol where a defined percentage of patients, often 5–10%, have an additional sample taken and referred to a centralised reference laboratory. The reference laboratory re-tests the sample and compares the result with the original POCT result. This system has limitations (WHO 2005a). It is labour intensive, creates delays and, in low volume testing facilities, a very large percentage of POC tests would need to be re-tested in order to detect errors. This method of PT is not suited to developed countries, and its utility in resource-limited countries is questionable.

Quality control testing for infectious disease POC tests

Whereas PT assesses the performance of the POC test and the processes of a testing facility several times per year, QC provides ongoing and frequent monitoring (Shephard *et al*. 2012). QC for infectious diseases involves the testing of the same sample with known reactivity on a frequent (e.g. daily) basis or every time testing is performed. As mentioned previously, the purposes of PT and QC are different, but complementary. Whereas participation in PT is mandatory in most regulated jurisdictions, the use of QC is highly recommended.

In-built control checks

Most POC tests for infectious diseases employ a method of test validation through the use of an in-built control. Generally, this is in the form of a control band or spot built into the device (WHO 2005b). In some POC tests, the in-built control changes colour with the addition of any human sample, indicating that the sample has flowed past the control line. Other POC tests, however, change colour with the addition of any fluid, even water. Either type of in-built control of flow has little value because they are non-specific and monitor the mechanical aspect of the device rather than the analytical performance.

'Third party' quality controls

Some infectious disease POCT manufacturers provide a positive and negative quality control but most do not. Manufacturer-provided QC material should be tested as specified by the instructions for use.

Irrespective, it is beneficial to test a 'low positive' QC sample from a third party (non-manufacturer) to monitor test performance because this QC can often be used over a long period of time (Shephard *et al*. 2012). Running a 'negative' third-party control is also recommended (WHO 2015). A well-designed third-party QC program will provide access to sufficient QC sample vials so that the same QC lot can be used over an extended period of time (e.g. 6–12 months). In this way, the facility can monitor variation that may be attributed to changes in test kit lots (Shephard *et al*. 2012).

Like PT, the QC sample type should preferably reflect the sample type being tested. Infectious disease POC tests may be validated for several different sample types such as serum, plasma, whole blood and/or saliva (CDC 2003, 2007; North Carolina HIV Prevention Program 2015). Generally, commercial third-party QC samples are made of plasma. To date, there are no whole blood QC samples for infectious disease POC tests. A plasma-based QC sample will monitor the performance of the POC test and the testing processes used, and is generally appropriate for the purpose. Sometimes the procedures for testing plasma and capillary blood are different; this needs to be considered when testing a QC sample.

At a minimum, a 'low positive' third-party QC should be tested in the following circumstances (CDC 2003, 2007; WHO 2005a) before testing patient samples:

- by a new user to assess competency
- when a new test kit lot is opened
- when a new shipment of test kits is delivered
- when storage conditions fluctuate outside specified limits.

The NRL suggests that a third-party QC is tested daily if patient testing is performed daily. If patient testing is performed infrequently, the third-party QC should be tested on each day that patient testing is performed. WHO recommends testing a QC sample at least once per week (WHO 2005a). The frequency of testing should be determined by the facility manager.

It is important to ensure third-party QC samples are stored and used as described in the instructions for use. Commercial third-party QC samples may be considered prohibitively expensive or be unavailable for certain analytes. In these situations, an in-house or locally made QC sample may suffice (WHO 2005b). The development of an appropriate in-house QC sample for infectious disease POCT requires significant expertise. Variability inherent in a QC sample may mask variability in the test kit, or be misinterpreted as poor performance of the test kit. An in-house QC sample must also be proven to be homogeneous and stable over time. The storage conditions must be validated and instructions for use developed. Long-term storage at –20°C may be effective to maintain stability but repeated freeze–thaw cycles should be avoided. If being provided beyond one's own facility, the QC sample must be validated on all POC tests it is being used to monitor. In countries with stringent regulatory systems, the use of commercial QC sample is recommended if available.

Because infectious disease POC tests are generally qualitative – that is, provide positive or negative results – it is not possible to plot QC results on a graph. However, QC test results should be recorded in a systematic manner, each time detailing the date of test, person testing, test name and kit lot number, identification of any critical equipment or instrumentation if applicable along with the QC test results (CDC 2007). The use of a –, +/–, +, ++, +++ system of recoding results may be useful, but it is important to assure standardisation of interpretation between operators (Shephard *et al*. 2012). These records should include any QC test results that fail, because this will aid in determining the frequency of failures and in troubleshooting. All failures of QC should be brought to the attention of the POCT Coordinator or POCT site supervisor. In the case of QC failures, remedial action will need to be determined and whether it is safe to test patients using the test kit in which the QC sample failed.

Table 5.4. Suggested checks that can be implemented in the case of unexpected proficiency test (PT) or quality control (QC) results for infectious disease POC tests

Proficiency testing	Quality control
Check the results sent to the PT provider for errors in transcription.	Check the expiry date of the POCT reagent kit used to test the QC sample.
Check the expiry date of the POCT reagent used to test the PT samples.	Re-test the QC sample using the same and a different operator to rule out operator error.
Re-test the PT samples if possible; the PT provider may be able to supply additional samples.	Review the storage conditions of the POC test and the QC.
Check the instructions for use for the POC test to ensure the test has been performed correctly.	Repeat the QC test using a new lot of QC and a new lot number of reagent.
Check the PT report from the provider to determine whether other facilities using the same POC test also obtained an incorrect result.	Check the instructions for use for the POC test to ensure the test has been performed correctly.
Review the PT provider's instructions.	
Review the storage conditions of the POC test kits and the PT samples.	
Check for a change in critical reagents.	

The recording of QC test results should be documented with a written procedure that includes the processes employed when QC failures occur.

Corrective action

Participation in PT and QC programs provides facilities with mechanisms to detect error or deviation in infectious disease POC testing systems. The records of PT and QC should be reviewed periodically (e.g. monthly) by the POCT Coordinator or POCT site supervisor. The reviewer should sign and date the reviewed documents as evidence of oversight. When errors or deviations are identified, corrective action should be implemented (CDC 2007; Constantine *et al.* 2005; WHO 1996).

A documented action plan will assist site operators when corrective action is warranted. A flow chart is a convenient way of displaying required troubleshooting actions. The facility should be responsible for drafting the plan. Without being exhaustive, some considerations for each of PT and QC are presented in Table 5.4.

Ideally, the source of the incorrect test result should be determined and rectified. In the case of QC, the investigation should be undertaken and a valid QC test result obtained before testing patient samples.

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