Behind the scenes of EQA - Characteristics, Capabilities, Benefits and Assets of External Quality Assessment (EQA)

Part I - EQA in general and EQA programs in particular

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Statement

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Abstract

This paper is the first in a collection of five manuscripts that detail the role and substantial impact that external quality assessment (EQA) and their providers‘ services play in ensuring in-vitro diagnostic (IVD) performance quality. The aim is to give readers and users of EQA services an insight into the processes in EQA, explain to them what happens before EQA samples are delivered and after examination results are submitted to the provider, how they are assessed, what benefits participants can expect, but also who are stakeholders other than participants and what significance do EQA data and assessment results have for them.

This first paper presents the history of EQA, insights into legal, financing and ethical matters, information technology used in EQA, structure and lifecycle of EQA programs, frequency and intensity of challenges, and unique requirements of extra-examination and educational EQA programs.

Introduction

This is Part I of a five-part series of articles describing the principles, practices and benefits of External Quality Assessment (EQA) of the clinical laboratory. Part I describes historical, legal and ethical backgrounds of EQA and the properties of individual programs. Part II deals with key properties of EQA cycles [] (ref). Part III is focused on the characteristics of EQA samples [] (ref). Part IV summarises the benefits for participant laboratories [] (ref), and Part V addresses the broad benefits of EQA for stakeholders other than participants [] (ref).

Medical laboratories and point-of-care testing (POCT) sites located around the world serve a critical role in medical care by providing objective evidence for disease diagnosis, prognosis, monitoring of development, and therapy success. They are expected to provide quality services

and information characterised by accuracy, timeliness and reliability to their users, and must usually conform to national and international quality standards. Participation in External Quality Assessment (EQA) programs serves to monitor the quality of analytical and diagnostic services.

EQA is a procedure for interlaboratory comparison in which the analytical performance of participant laboratories is evaluated primarily using predetermined criteria. In each cycle, the EQA provider distributes samples with the same characteristics to participating laboratories simultaneously, giving them the conditions to achieve comparable analytical results. Within a specified period, participants analyse concentrations of measurands in or the properties of samples and submit quantitative, ordinal (semi-quantitative) and/or qualitative (nominal) results to the EQA provider. Target values are established either by Reference Measurement Procedures (RMP), by consensus of results obtained by expert laboratories, or by consensus of all reported results; for details see Part III, chapter "Determination of the target value" [] (ref). Individual results are evaluated by comparison with the target (or assigned) value and the results of other laboratories, assessed against established analytical performance specifications for accuracy, and participants receive feedback on their performance. EQA programs usually consist of several individual cycles per year, and the number of samples in individual cycles varies depending on the provider. As required by ISO 15189:2022, they cover all phases of the entire laboratory examination process - from pre-examination to examination and post-examination - and allow laboratories the opportunity to identify weaknesses or potential errors in every single step of the examination process. (Figure 1)

EQA providers are impartial expert organisations that pursue either commercial or non-profit objectives. Their services cover far more than their name suggests: they not only organise and supervise EQA schemes, but they are also the point of contact for medical and technical

enquiries. They also serve as a network centre connecting laboratories, experts, health authorities and many more.

EQA programs and their providers play a crucial role in medical care, as they are quality partners to every discipline in medical laboratory diagnostics. By assessing the analytical performance of diagnostic laboratories, they not only support participant laboratories but also provide benefits for patients and their clinicians, for in-vitro diagnostics (IVD) manufacturers, the scientific community, regulators, notified bodies, accreditation bodies, national health organisations and policymakers, and public health authorities.

The International Federation of Clinical Chemistry and Laboratory Medicine (IFCC) guidelines define proficiency testing (PT) as *"laboratory performance evaluation for regulatory purposes"* and EQA as *"laboratory performance and method evaluation with a focus on education and support purposes"* [1]. Nevertheless, there is a lack of conformity amongst the practice community about the definitions of the terms "PT" and "EQA" and they are mainly used interchangeably - maybe with a preference of "EQA" in Europe and "PT" in North America [2]. For purposes of this paper series, we use the term "EQA" to refer to all evaluation processes about interlaboratory comparison, as defined by the applicable standard ISO/IEC 17043:2023 [3].

Basics and general information about EQA

History of EQA

Though the US military conducted regular surveys of syphilis serology laboratory competence in the 1930s, the first published surveys of chemistry and haematology assays were in the late 1940s in the USA and the UK in the early 1950s. These demonstrated wide (2- to 4-fold)

variation in results between laboratories, not attributable to the methods used, even with aqueous solutions containing the pure substance of interest. However, on average, there was no evidence of bias. Sporadic surveys, published and unpublished, continued during the 1950s and 1960s, with similar findings. Most were geographically limited, in their scope in terms of analytes, especially in the challenges of producing reports within a meaningful timescale. These surveys were, however, instrumental in raising awareness of the need for quality assurance and stimulating the development of internal quality control (IQC) techniques adapted from the manufacturing industry.

However sophisticated the application of IQC, it became obvious that EQA was essential to attaining and maintaining comparability of results among laboratories. This led to the establishment of national or regional programs in the UK, USA and other countries in the late 1960s and early 1970s. These took advantage of advances in data processing technology to provide timely reports, and emphasise the frequency of distributions, the number of analytes and specimen numbers. The ethos differed between countries, with some driven by legislative requirements (e.g. the Clinical Laboratory Improvement Act (CLIA) in the USA and the Calibration Law in West Germany). Most, however, followed policies of voluntary participation with the aim of self-improvement based on scientific principles. Though program designs varied across countries, the objectives were to deliver regular services with frequent multi-specimen distributions and rapid feedback through reports, including scoring systems. However, some were restrained by the resources available from the government or the professional societies responsible for delivery [4].

There remained some confusion in terminology; however, there was a misconception that external programs could provide an element of 'control' despite their retrospective nature. This was dispelled by the publication of the outcome of a consensus conference that not only clearly defined the relative roles of quality assurance (QA), IQC and EQA but also outlined substantial

agreement on desirable aspects of program design [5]. By the mid-1980s national EQA services had been established in most countries in the developed world. Programs continued to develop in succeeding decades, increasing the scope of analytes surveyed and the sophistication of their designs in delivering information helpful to their participants in improving their performance.

Legal background to participation in EQA

A study on the impact of regulatory requirements on EQA failure rates shows that different countries have very different regulations and recommendations for participation in EQA schemes in general and the frequency of participation (Table 1) [6]. In most of the 33 countries reported in this regard, there is a clear legal obligation to participate in EQA; to a lesser extent, authorities or other official bodies, such as medical associations, review the participation and performance of individual laboratories in EQA or the EQA provider reports incorrect results to them; to a small extent there are (at least potential) sanctions of a financial nature or by restricting the authorization to carry out examinations with failed EQA.

Financing of EQA programs

Providing an EQA service can be expensive due to the procurement of material, analysis of material, the need to verify stability and homogeneity, logistic issues both in sample production and dispatch and the support for educational activities to complement the EQA program. The funding source may, therefore, hinder what a particular program can offer and restrict the range of measurands or breadth of challenges.

EQA providers can be classified in terms of their funding as either not-for-profit, usually a professional/medical association or a government agency, or for-profit, usually a commercial

organisation. Mixed models, like foundation, medical association plus individual person ownership, government plus professional/medical association are also possible. What laboratories pay and if they have a choice of provider can also vary by country and depends on whether or not a government agency, a not-for-profit organisation or a commercial company provide the EQA. In many countries, EQA participation is mandatory.

There are also fundamental differences in classifying EQA providers on the basis of whether they are regulatory or educational. These include if they provide programs outside their country of origin, the ownership (professional organisation, private), type of organisation (not-for-profit or for-profit), the range of programs they offer by discipline, measurand, and the level of support they provide to their participants. For an EQA provider to be sustainable it must be able to finance all activities within its goals fully. These include all resources - personnel and material requirements - for program delivery and customer support activities such as education and troubleshooting assistance.

Sources of income may include subscription fees for programs and income from additional material, income from webinars and conferences, grants and, in some cases, direct financial support from the government.

For some EQA organisations, lack of sufficient funding constrains the development and structure of EQA programs. Funding also influences the educational activities that can be provided and the cost to participants. The ability to provide verifiable commutable material or to have reference method target value assignment may be limited because of the funding model.

EQA and ethics

The introduction of personalised medicine requires laboratory medicine to enter the era of precision diagnostics, setting clinical performance specifications to develop and evaluate assays for clinical use [7]. It is the role and ethical obligation of EQA providers to employ contemporary methods that can identify examination procedures capable of meeting analytical performance specifications, and to enable laboratories to determine whether they meet these requirements and whether the analytical service is beneficial for the patient. The applicable standards refer to ethical requirements for the laboratory towards its patients and the EQA scheme provider towards its participants in points 4.1 "Impartiality" and 4.2 "Confidentiality" of ISO 15189:2022 and ISO 17043:2023 and for the laboratory additionally in 4.3 "Requirements for patients" of ISO 15189:2022 [3,8].

EQA is a cornerstone for ensuring the precision and reliability of laboratory diagnostics. The role of policymakers and regulatory authorities is pivotal in championing and bolstering EQA programs, thereby ensuring their widespread adoption and effectiveness. These programs evaluate laboratory performance by providing standardised samples and comparing results across different institutions, thereby ensuring the accuracy and consistency of patient test results. Laboratories' participation in EQA programs is underpinned by several ethical considerations. These include ensuring patient safety, maintaining accountability and transparency, upholding professional integrity, fostering continuous quality improvement, promoting equity and fairness, and protecting patient confidentiality. Laboratories that actively engage in EQA programs demonstrate their commitment to these ethical principles, thereby enhancing the quality and reliability of medical care. Ethical participation in EQA programs strengthens the credibility of laboratories and reinforces public trust in the healthcare system, ultimately benefiting patient outcomes.

The primary ethical obligation of clinical laboratories is to safeguard patient safety. Accurate and reliable test results are imperative for correct diagnosis, treatment, and disease monitoring. Participation in EQA programs helps laboratories identify and correct errors, enhancing the precision of patient test results. Laboratories that consistently perform well in EQA programs demonstrate their commitment to maintaining high standards, essential for patient safety and welfare.

Ethical practices in clinical laboratories demand transparency and accountability. EQA programs provide an external assessment of a laboratory's performance, fostering a culture of accountability. The requirement for laboratories to disclose their performance in these programs promotes transparency, keeping all stakeholders informed and involved. This openness is critical for maintaining public trust in the healthcare system. Patients and healthcare providers rely on the assurance that laboratories undergo rigorous external evaluations and are dedicated to continuous improvement.

Laboratory professionals adhere to ethical codes emphasising professional integrity, and participation in EQA programs reflects a laboratory’s commitment to uphold these standards and its dedication to excellence. It demonstrates a willingness to undergo external scrutiny to ensure the highest quality of patient care. In contrast, laboratories that avoid EQA programs may be perceived as lacking in integrity, potentially undermining their credibility. Additionally, as the medical field continually advances with new technologies and methodologies, EQA programs ensure the precision and reliability of patient test results while encouraging laboratories to stay current with these advancements and continuously enhance their testing procedures. This commitment to continuous quality improvement is an ethical imperative, fostering a culture of learning and development and ensuring that laboratories provide the best possible care to patients.

Ethical principles of equity and fairness are paramount in EQA programs. These programs play a crucial role in promoting inclusivity and equal opportunities for all laboratories, regardless of their size or location. By ensuring uniform standards of patient care, EQA programs mitigate disparities in healthcare quality and ensure all patients, irrespective of geographical location, receive accurate and reliable test results.

Ensuring the confidentiality and protection of patient's rights in using their samples is paramount. Similarly, the results of EQA programs must be treated with the utmost confidentiality to prevent data misuse. This commitment to patient and participant confidentiality is critical to the ethical conduct of EQA programs [9].

Information management systems in EQA

EQA requires software with various functionality to manage and administer programs and participants effectively. This functionality may be provided by bespoke development or commercial solutions as a single system or by multiple systems connected to perform specific tasks. Information systems used by EQA providers should be validated to ensure that they are fit for purpose and operate as intended. Data integrity must be ensured, data manipulation or loss must be prevented, and the accuracy of test results must be maintained. To ensure that detailed audit trails, role-based access control, and regular, verified data backups are just as required as redundant systems and infrastructure with regular monitoring and proactive maintenance to prevent disruptions and ensure continuous data access to authorised users. Additionally, as the software may be accessible from the internet for data entry and can also be interfaced with external laboratory information systems (LIS), robust cyber security measures are essential to protect data and systems from malicious attacks, threats, and breaches. Since

the structure of software for EQA also provides a good overview of processes running in parallel, software features generally required for most EQA programs are listed in Table 2.

Regulatory and educational/aspirational purposes of EQA

EQA serves different purposes, namely regulatory and aspirational/educational [1,10]. While the primary regulatory purpose is to identify poorly performing laboratories, the leading educational/aspirational purpose of EQA is to improve the quality of laboratory examination. Regulatory EQA activities usually have wide tolerance limits, whereas for educational EQA activities, these are generally tighter and may be based on clinical outcome data, biological variation or "state of the art" [11]. EQA programs may offer combinations of performance specifications that relate to either regulatory/aspirational or educational aims. Because of the different tolerance limits, a laboratory can have acceptable performance in one (regulatory) challenge and unacceptable performance in another (educational) for the same measurand.

EQA for regulatory purposes

The primary purpose of challenges intended for regulatory purposes is to identify poorly performing laboratories, and this can shape the design of the EQA program (e.g., the number of samples, the frequency of the EQA cycles and the performance expectations [11]. Laboratories that persistently are outside acceptance limits will usually receive some form of punitive outcome in the form of external inspection or loss of public funding. Using broad acceptance criteria ensures most laboratories do meet the required criteria. Furthermore, failure to achieve these criteria may result in significant consequences for the laboratory's licence to practise. These criteria may include compliance with international standards such as ISO

15189:2022 and/or superseding national guidelines and laws such as those determined by a nation's quality regulators, e.g. CLIA in the USA [12] or the Guidelines of the German Federal Medical Society for the Quality Assurance of Laboratory Medical Examinations (RiliBÄK) [13]. The RiliBÄK stipulates that reimbursement for laboratories that fail consecutive EQA cycles for the same measurand is suspended until the assessment is successfully passed again in a subsequent cycle. The responsible third party payers execute the suspension of reimbursement. With a mandatory program, there may be unintended consequences on sample handling such as laboratories treating these EQA specimens differently from patient specimens to ensure acceptable performance. Though these programs may be perceived as more stable, they may not be adaptable to meet the evolving needs of the profession [14].

EQA for educational purposes

The second purpose of EQA programs, best described as 'aspirational' or 'educational', is to improve the quality of laboratory examination through the provision of educational and scientific principles and sometimes research input as well as the assessment of regular EQA samples.

This distinction from wholly regulatory programs encourages the inclusion of more challenging samples (e.g. extreme concentrations to challenge the limit of detection, presence of interfering substances to challenge assay selectivity, rare microorganisms to assess the competence of the laboratory staff in this regard) and sometimes more stringent acceptance limits. This comes with an increased risk of 'failure', and emphasises the improvement of both individual and collective laboratory performance through the sharing of best practices. Within the laboratory, EQA provides an essential educational function through the review of reports (especially those with educational commentary or extended educational content integrated into a traditional EQA program), the use of EQA cases (e.g. in morphology) for staff training and competency

assessment, reflection on performance in seminars and training sessions and support from the EQA provider to troubleshoot non-conformances [14]. The EQA provider may publish data and questionnaire responses from the EQA program, evaluating the state of the art in performance and shaping best laboratory practices. Some countries have a formal EQA oversight structure and mechanisms to share best practices for patient safety.

Many EQA programs occasionally distribute samples that are primarily for educational purposes and may be excluded from regular performance assessment. These might include interfering substances (e.g. glucose in creatinine assay, heterophilic antibodies in immunoassays) intended to identify differences in selectivity between methods or IVDs.

In recent years, EQA programs with an exclusive educational focus have been established to supplement traditional services. These may assess the performance of an individual practitioner or provide competency assessment and/or continuous professional development (CPD) activities for laboratory professionals.

The organisation and design of educational programs are varied and the laboratory must consider the most appropriate program to support their needs. This is particularly true when the laboratory wishes to enrol a staff team for competency or professional development, in which case an effective management interface is essential for registration and monitoring the staff compliance. Programs that encourage or allow group registration by an employer are highly effective in terms of staff engagement, since the employer takes the responsibility for payment and management. Educational programs may include interpretive case studies, in which each participant views the same case with a patient scenario and patient results; morphology skills-based programs; guideline-based case generation, where each participant receives different cases generated by artificial intelligence etc. Where guidelines are established and effective, e.g. in blood transfusion practice, performance evaluation against guidelines is an unambiguous

performance comparator; however, this may provide challenges where guidelines differ regionally or nationally.

Without rigorous professional guidelines, the provider must consider how the 'correct' answer is determined. It is relatively straightforward to assess the participant's response against the whole participant group and even to rank the participant on that basis. Still, this type of analysis may be overly simplistic. Ideally, there should be peer group related analysis to reflect different experience levels in participants in the feedback to the end user; secondly, and perhaps most importantly, the most common response or observation may not be the most clinically significant. Therefore, providing expert commentary, either from a recognised authority in the field, the professional submitting the case or from a panel of experts, has the most effective educational impact. Where the performance of the individual participant is scored against the expert answer or by an expert panel, the expert panel and markers must have a demonstrated track record in the field, that membership is refreshed periodically, and members operate against objective criteria. Other features of the program to consider are whether the cases remain open indefinitely as a library or bank of cases or have a closing and reporting schedule; whether participants have single or multiple attempts at the cases; the complexity and range of cases provided and whether this is indicated; whether the program encourages reflection on what has been learnt from the cycle; whether resources informing the case are all made available at the same time or released in a staged fashion.

EQA programs

The life cycle of an EQA program

All EQA programs have to start somewhere. Once established, the EQA program usually operates on a continuous basis, and on rare occasions, a program is terminated. Whether the EQA service is pre-examination, examination or post-examination, or requires the distribution of physical specimens, or covers derived examinations based on analytical results and an algorithm, EQA service providers are continually looking to expand and improve their services to meet the needs of their users better. Providers' development and implementation of EQA programs is an intentional undertaking requiring significant resources, considerable research and development, and follows a stepwise process, as illustrated in Figure 2.

(a) Conception

EQA programs are born from a multitude of routes. These include feedback from service users / other stakeholders, EQA provider horizon scanning etc. However, there needs to be a demand that can be derived from different reasons. (Table 3) Once the requirement for an EQA program is in place, the EQA provider needs to ensure that it has both the scientific and technical capabilities to design, grow and then maintain the EQA service.

The scientific and/or technical expertise could be provided by external scientific advisors or steering committees, or it could be subcontracted. Program design and evaluation (performance assessment) remain the responsibility of the program organiser and cannot be subcontracted. This is a requirement to ensure compliance with ISO/IEC 17043:2023.

(b) Program design

Good program design is crucial for an effective EQA program. Many factors contribute to this, including but not limited to the type of material that will be distributed, the number of specimens, frequency of specimens, concentration range that will be covered, assigned values, scoring systems, report design etc. Each program will be overseen by and be the responsibility of a program organiser. EQA program design is an area that is not covered in depth in ISO/IEC 17043:2023, nor is it an area that is harmonised between different EQA providers offering EQA services for the same measurand [3]. This variation in design does allow laboratories the option to participate in EQA programs that suit their needs; however, it is up to the participant to review the program design of each provider to ensure that they meet the requirements as a supplier for the clinical services that are provided at an individual participant's laboratory.

Based on experience, for EQA to be effective, participants must have confidence in the program design. Thais can be achieved by providing information on key data and facts as shown in Table 4. Though all evidence of the effectiveness of EQA is necessarily circumstantial, these principles have been tested through changes in program design [15].

(c) Growth, Development and Maintenance

An EQA program may start as a simple survey of practice and incorporate some EQA samples, followed by a pilot phase that may run for several cycles. This allows both the EQA provider and the participants to fine-tune the design before the EQA program enters routine operation. More experienced EQA providers may launch an EQA program based on their existing experience and infrastructure for delivering EQA services.

(d) Evaluation of programs

EQA is more than an assessment of a laboratory's performance, and it also has the potential to offer post-market surveillance, provided that some prerequisites are met. At the cycle's close, the program organiser / EQA provider will review the overall performance of all methodologies. Changes in performance and/or changes in market/clinical requirements may lead to the adaptation of the EQA services by the EQA provider or discussions between the EQA provider and manufacturer. Depending on the nature and extent of the issue, and local/national regulations, the EQA provider may be required to take further action. Significant changes to EQA program design may not be covered under the scope of an EQA provider's ISO/IEC 17043:2023 accreditation. Further assessment may be required by their local accreditation body. EQA program review and development are all part of ongoing quality improvement.

(e) Termination

It would be wrong to assume that an EQA program exists 'forever'. The program design may evolve over the program's lifetime, but in some cases, the EQA program may need to end. Several factors that may lead to this, like measurands no longer required by clinicians, or impossibility to acquire appropriate EQA materials (Table 3).

In all cases where an EQA program is coming to an end, there will be processes that need to be followed to ensure that all relevant stakeholders, including participants, suppliers, the accreditation body etc., are informed. The end of an EQA program is a time for reflection on how EQA has supported the provision of specific services and what can be learnt and utilised for future programs.

Frequency and intensity of EQA

Only a few guidelines exist regarding the frequency and intensity of EQA, for example, for screening of donated blood for transfusion-transmissible infections (at least two cycles per year [16]) or blood lead (three samples every two months [17]). One of the reasons for a lack of harmonisation in this area is that ISO 15189:2022 suggests that EQA providers should be accredited in compliance with ISO/IEC 17043:2023, which specifies the criteria and procedures the EQA providers are to follow [18]. The choice of frequency by the EQA organisation may be influenced by existing information regarding results accuracy and/or harmonisation, the availability and price of control materials and the cost of the examination in laboratories. Consequently, EQA providers design their programs with different frequencies of cycles [19].

Laboratories are ultimately responsible for deciding which EQA program they use for their service. The laboratory should take into account the type of service that they are providing (prognosis, diagnosis, screening), the prevalence of the disease and the number of investigations undertaken by the laboratory (workload), the analytical complexity, the error rate of the investigation and the specialist nature of the investigation [20]. The laboratory can then choose an EQA program that meets these requirements. A review of 22 organisations representing 407 programs showed that the median for all examined disciplines was 4 cycles per year. The responses of this survey were categorised into scientific disciplines, i.e. biochemistry (6 cycles per year median), haematology (three cycles per year median), haemostasis (4 cycles per year median), and microbiology (median 3 cycles per year). As the authors concluded, the number of EQA cycles (and number of samples) varied widely per year within and between each discipline. Furthermore, there is a consensus that error rates and testing volume play an essential role in establishing the frequency of EQAs [20].

One study has tried to develop a framework for evaluating the frequency of EQA challenges [21]. The aim was to demonstrate the impact of the correlation of EQA data between different samples on the information that can be extracted from EQA results, such as the evaluation of laboratory or method performance. It was shown that the assessment of performance was flawed by the presence of a correlation between EQA results from different samples. Therefore it becomes less beneficial to send more samples per EQA cycle or organise more EQA cycles within a time interval. The authors concluded that there will always be a tension between resources (cost of the program, time to run and analyse the results) and value of appropriate intervention on problems that may increase the risk to patients [21].

The "ideal" frequency of EQA in the context of medical laboratories can vary greatly depending on the specific service a laboratory provides [22]. Both a higher and a lower number of individual samples per cycle seem to have advantages and disadvantages (Table 5). While a higher frequency seems to have more advantages in terms of analytical quality, the advantages of lower frequencies are more economical. The disadvantages seem to be the other way around [21].

Extra-analytic EQA

ISO 15189:2022 requires that the EQA program selected by the laboratory be used to check pre-examination, examination and post-examination processes [8]. Although most errors happen within the pre-examination and post-examination processes, far less emphasis has been put on their quality control and improvement, compared to the analytical parts [23]. The reason might be that pre- and post-examination processes can appear to be particularly hard to control since, contrary to the analytical phase, most steps occur outside of the laboratory.

Another issue with regard to pre-examination and post-examination quality control are difficulties in the acquiring and documenting of such errors and the lack of universally standardised quality indicators (QIs) for evaluating, monitoring and improving these steps within the total testing process [24]. Several organisations provide information and platforms for QI acquisition, documentation and benchmarking [25,26]. Many existing laboratory information systems (LIS) do not come with a pre-built functionality of recording QIs, making this process partly / mostly a manual one (which is both time consuming and error prone); however, LIS are constantly improving, so potentially, data collection will be easier. Additionally, current coding systems, such as the Logical Observation Identifiers Names and Codes (LOINC) [27] or the Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT) [28] are focussed on intra-laboratory (analytical) processes and initiatives like the Standard Preanalytical Code (SPREC) [29] systems are currently used only for biobanking purposes. This makes extra-analytic quality benchmarking intentions almost impossible. Finally, no acceptance criteria have been defined for most - if not all - extra-analytical QIs, leaving laboratories collecting and documenting such data to evaluate them like they would do with an IQC by looking out for drifts and variations of recordings over time.

Currently, most EQA providers who provide pre-examination programs are either 1) surveying the procedure and checking the knowledge of participating laboratories or 2) sending out samples designed to test pre-examination systems (e.g. for serum indices detection, RNA/DNA extraction, etc), or pre-examination case-reports with either real or fictional data [30-33]. Recently, a new type of EQA program has been introduced, aimed at improving / maintaining quality of samples sent to the laboratory via pneumatic tube transport [34-36]. Post-examination data may be collected within examination EQA programs by asking for interpretation of reported results, collection of reference range information or answering a series of case study questions.

Pre-examination and post-examination programs are designed to look specifically at quality indicators not only facing challenges with data collection, but also evaluating data and reporting meaningful information back to laboratories. A number of EQA providers use a sigma metric approach. A risk-based scoring system allows laboratories to prioritise action.

Developing specific EQA programs for each extra-analytic error possibility seems unfeasible [37]. Nevertheless, such programs are vital for quality maintenance and improvement. Therefore, it seems reasonable to focus on extra-analytical errors with the highest frequency and/or patient safety risk while considering their applicability. An alternative could be a mandatory constant documentation of selected QIs. Although no QIs are specifically mentioned, the ISO 15189:2022 standard stipulates that pre- and post-examination QIs should be regularly recorded, documented and evaluated. Currently, most laboratories are collecting information on only a few QIs, if any [23,38,39], demonstrating once more that there is room for improvement regarding quality management of the extra-analytical phases.

In some cases, it is possible to combine pre-analytical, analytical and post-analytical EQAs where case reports together with control material are circulated, and both pre-analytical, analytical and post-analytical responses are registered, ending up with a diagnosis and how this is reported to the clinicians. This is often done for rare diseases [40].

Patient-based EQA programs as a supplement to traditional EQA

Patient based quality control programs can be used both as an IQC program and as a supplement to EQA. An emphasis on the last approach will be given here. A patient-based EQA program can be defined as an EQA program asking for population-based parameters from a defined patient population. Setting up a patient-based EQA program is perceived as a complex and challenging task. The most important factors are the ability of laboratories to transfer and send

data to the EQA provider, the patient population from which the parameters are calculated, knowledge of pre-analytical factors, methods- and instruments, the analyte in question, and calculations, diagrams, and alarms or warnings. The main reason for setting up a patient-based EQA program is the shortcomings of regular EQA programs, mainly the lack of commutability or the lack of testing for commutability of many materials distributed in regular EQA programs [41,42]. Suppose the result report from the laboratory to the EQA provider is automatized. In that case, a patient-based EQA program may also be less labour-intensive and cheaper compared to conventional EQA programs.

Several techniques can be used for a patient-based quality control program, and examples of parameters are the average of normal (AoN), moving average (MA) and the moving median [43]. As far as possible, the chosen parameter should not be affected by the variation normally found in the selected patient population, and the chosen statistical approach should filter out noise. Usually, the purpose of a patient-based EQA program is i) to monitor the performance of the examination procedure of the laboratory ii) to compare the results between laboratories using the same examination procedures, and iii) to illustrate equivalence between different examination procedures.

The rationale behind using patient specimens as EQA [44,45] is that population-based parameters such as the AoN, MA or moving medians for a defined patient population, e.g., the out-patient population, typically are stable over time, and any change is usually due to pre-analytical or analytical instability or error. If all pre-analytical and patient-related factors are known and equivalent, monitoring the population-based parameters for an instrument group or a method can be useful to verify comparability between different measurement procedures (MPs).

A program based on patient results is sensitive to many factors, and when results are interpreted, many variables can affect the interpretation [46,47]. To optimise the outcome of a program

based on, e.g. patient medians it might be necessary to take the pre-analytical factors into consideration when results are grouped, for example, it can be useful to register if the laboratory results are from fasting or non-fasting patients and if the sample material is serum or plasma. If there is a worldwide participation, the lifestyle and diet of patients from which the patient medians are calculated vary. For some analytes, it adds value to group results according to country or geographical regions [2].

As for conventional EQA programs, the performance limits are determined and set by the EQA provider, but a patient-based EQA program can't be used to establish the trueness for a MP, but only the equivalence between MPs. The quality of the EQA program depends on the laboratory reported data, the group size, and the method- and instrument grouping, and an optimised version of a patient-based EQA program can be an essential tool for surveillance and for monitoring the outcome of ongoing harmonisation and standardisation work. An example based on results from a patient-based EQA program [48] is given in Figure 3, showing the daily median and the moving median for different IVD medical devices (IVD-MD) based on results reported to the program during 2022.

Conclusion

EQA has been routinely available and covers many laboratory functions for over 50 years. Though the core principles have remained the same over this time, the EQA profession has and continues to evolve to meet the needs of the participants. EQA is a critical component within a laboratory's quality management system. It is incumbent on EQA providers to ensure that laboratories are fully aware of the information they have available to them so that they understand what they are participating in.

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Abbreviations

AoN	Average of normal
CLIA	Clinical Laboratory Improvement Act
CPD	Continuous professional development
EQA	External Quality Assessment
GDPR	General Data Protection Regulation
IFCC	International Federation of Clinical Chemistry and Laboratory Medicine
IQC	Internal quality control
ISO	International Organization for Standardization
IVD	In-vitro diagnostic
IVD-MD	In-vitro diagnostic medical device
LDT	laboratory-developed test
LIS	Laboratory information system
LOINC	Logical Observation Identifiers Names and Codes
MA	moving average
MP	Measurement procedure
POCT	Point-of-care testing
PT	Proficiency testing
QA	Quality Assurance
QI	Quality indicator
RiliBÄK	Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen (Guidelines of the German Federal Medical Society for Quality Assurance of Laboratory Medical Examinations)
RMP	Reference measurement procedure
SNOMED-CT	Systematized Nomenclature of Medicine Clinical Terms
SPREC	Standard Preanalytical Code

Table 1: National regulations on EQA participation

Country	EQA participation required by law	Authorities informed about incorrect results	(Impending) financial consequences of EQA performance[1]
Australia	yes	yes	yes
Austria	yes	no	no
Belgium	yes	yes	yes
Brazil	yes	yes	no
Canada	yes	yes	[2]
Chile	yes	yes	no
Croatia	yes	no	no
Czech Republic	no	no	[2]
Estonia	yes	no	no
Finland	no/yes[3]	no	no
France	yes	yes	yes
Germany	yes	yes	yes
Greece	yes	no	no
Hungary	yes	no	no
India	no	no	no
Ireland	no	no	no
Italy	yes	[2]	no
South Korea	no	no	no
Lithuania	yes	no	no
Malaysia	yes	no	no
Mexico	no	[2]	[2]
Norway	no	no	no
Netherlands	no	no	yes
Romania	no	no	yes
Saudi Arabia	yes	no	[2]
Slovak Republic	yes	yes	yes
South-Africa	yes	no	no
Spain	no	no	no
Sweden	no	no	no
Switzerland	yes	no	no
Thailand	no	yes	no

Turkey	yes	no	[2]
United Kingdom	no	yes[4]	no
USA	yes	yes	yes

Legend: Adapted from Buchta et al. [6]
[1] Financial consequences of EQA performance are, for example, approval to carry out analyses or their reimbursement in the event that the EQA was passed or (possibly limited in time until the passing of a later EQA cycle) prohibition of further carrying out the analysis or suspension of reimbursement.
[2] data not available / not uniform for the whole country
[3] In Finland, approval is needed by the Regional State Administrative Agencies to perform laboratory diagnostics of infectious diseases and it includes mandatory participation in EQA programs for each examination procedure used.
[4] It is not mandatory for EQA providers to escalate poor performance

Table 2: Characteristics and modules of software for EQA

Participant Management The software should have features to securely manage participant information, demographics, contact details, and history. It should enable enrolment in EQA programs and cycles and provide tracking and communication with participants. EQA providers should have processes to manage general data protection regulation (GDPR) and privacy requests from other jurisdictions. Where redaction or deletion is required, the software should enable this.
Specimen Management The software should provide a mechanism to track specimens from collection through storage and assignment to an EQA cycle. Homogeneity testing data should be linked to the specimens assigned to a program so that they are identified in the event of specimen integrity issues. Safety testing results should also link to the specimen, and sample dispatch should be prevented unless safety testing is complete and the samples have passed. The software may also manage the homogeneity testing schedule and randomisation of the samples tested.
Test Design and Management The software should allow the creation and management of test items/questions. It should support the display of patient history and demographics, different question formats, scoring mechanisms, embedded multimedia, and the ability to generate customised request forms for each participant. The software should allow measurands for each sample/cycle to have assigned values set and enable multi-level assessment criteria, including fixed and percentage measurements depending on the measurand concentration.
Cycle Notification The software should provide a platform to notify participants of open EQA cycles and provide reminders if results for a cycle have not been submitted. Participants may also access functionality to track specimen delivery and view and print sample storage, handling, preparation and submission instructions.
Result Collection The software should accurately capture analytical methodology and default the methodology and units of measure whenever possible. Where results are entered using a web interface or electronic form, appropriate decimal precision should be enforced, and consideration should be given to allow customisation of the form to match the result sequence of the analyser or LIS to reduce errors. The system should provide feedback that results were successfully submitted and allow the participant to view a summary of submitted results and a history of any alterations made. Where results are submitted using an electronic interface, there should be a mechanism to ensure acknowledgment of successful electronic submission and a notification if an electronic submission has failed or results have not been submitted. The software should allow the review of electronic submissions and maintain an audit trail.
Result Analysis The software should securely store examination results and provide an audit trail of activity taken against a result. It should provide appropriate unit conversion and offer robust data analysis tools to generate statistical reports, perform analysis, identify trends, and measure participant performance against the defined allowable limits of performance. The software should display outliers to the EQA staff analysing the data and provide real-time feedback to the group statistics where outliers are included or excluded. An individual participant's previous performance should be available during the result analysis.
Result Reporting The software should be able to generate comprehensive and customisable reports for individual participants and specific groups, including manufacturers. These reports may include performance

summaries, scores, graphical representations, and feedback on areas of improvement. Accessibility should be considered where colour is used in either web or printed reports. The software must have the ability to track report versions at a participant level and should be able to re-issue amended reports at a participant or program level. The system must be able to display the reason for the amendment and what was amended.
Communication and Collaboration The software should facilitate effective communication between the EQA provider, participants, and relevant stakeholders. This may include features like email notifications, dashboards, browser or text messaging systems, and discussion forums. The software must allow participants to opt out in accordance with relevant privacy legislation.
Security management The software should be able to protect against unauthorised access, data breaches and cyber threats. This can be achieved by robust authentication methods (multi-factor authentication for all user accounts), strong access controls , encryption protocols, continuous monitoring, automated backups and disaster recovery plans. Encrypting data ensures that even if accessed without authorization, they remain unintelligible. As shared infrastructure risks in multi-tenant cloud environments can lead to data leakage, using virtual private clouds (VPCs) and network segmentation can help to isolate sensitive EQA workloads.
Audit Trail and Compliance The software should maintain an audit trail of activities and changes made within the system. It should also support compliance with relevant accreditation standards, including ISO/IEC 17043, jurisdiction regulatory requirements, and industry best practices.
User Support and Training The software should be comprehensively documented, including user guides and training materials for EQA staff and participants. These guides should be made available at the point of use, and technical support should be available to address issues or questions that may arise.

Table 3: Reasons to initiate or terminate an EQA program

Initiation of a new or adapted EQA program	Termination of an EQA program
● Development of a new biomarker - as was the case for SARS antigen and antibody detection ● Change in examination procedure's usage or application that may require a more regular and structured EQA program than basic interlaboratory comparisons ● An EQA provider looking to expand their repertoire of the services that they provide, which could be for well-established examination procedures that they don't yet cover, or enhance their existing EQA programs ● Government requirement	● The measurand is no longer required by clinicians, or is replaced by another service. ● It may not be viable for the EQA provider to continue providing the service. This could be due to insufficient numbers of participants or the EQA provider not being able to acquire relevant material to prepare samples. In this case the EQA provider will work as much as possible with laboratories to maintain the service, either with collection of material, or in some cases can support a simple specimen exchange program for interlaboratory comparisons, or cooperate with other EQA providers ● The EQA provider may wish to consolidate services either in-house or with another EQA provider ● An EQA provider may terminate a scheme in the case where a joint decision was made that other EQA providers are better suited to handle this scheme. In some countries, the different EQA providers have specialities shared between them so that all providers do not need to cover all measurands

Table 4: Requirements and success factors of EQA programs

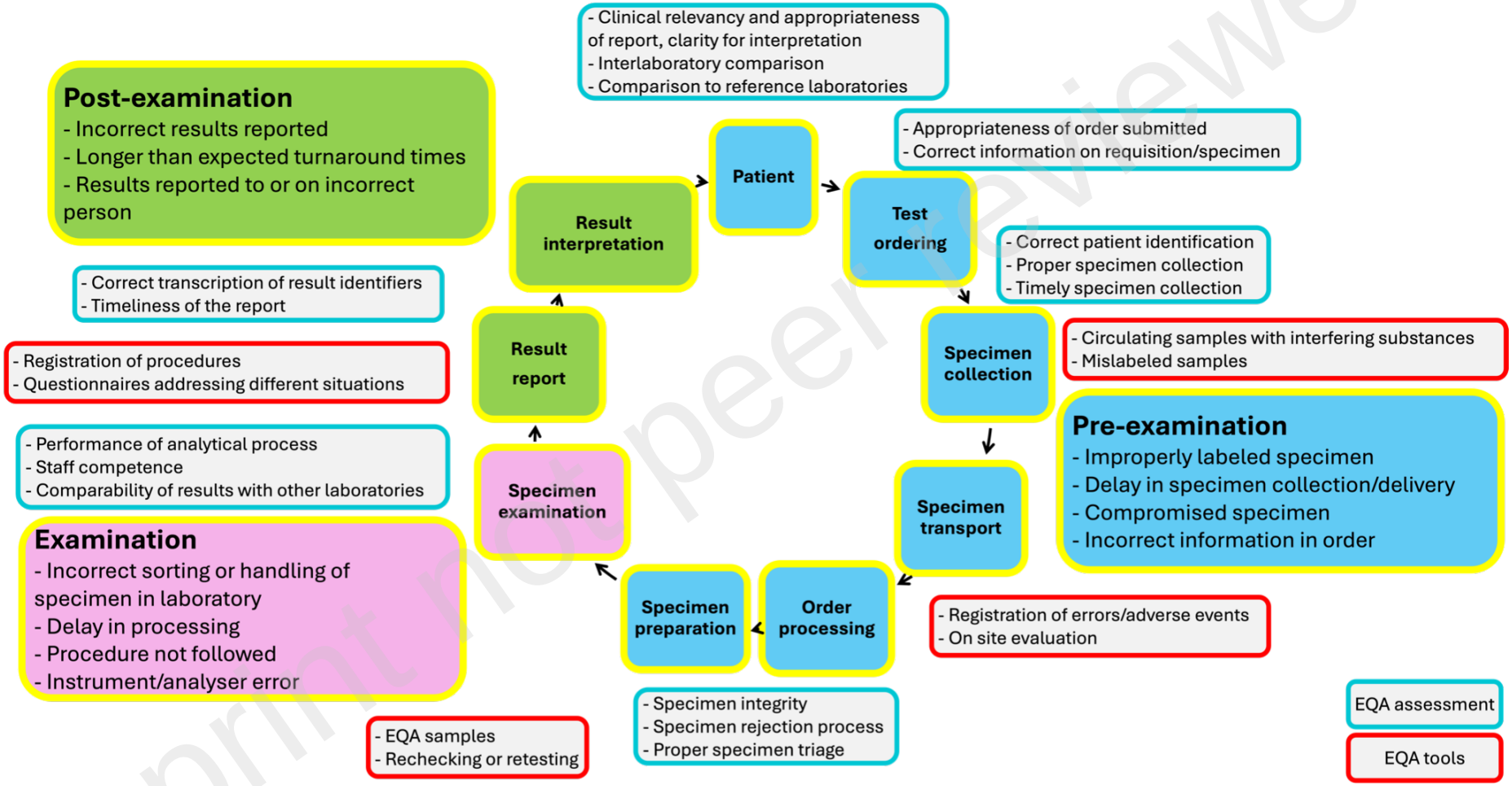
1. **Samples that**
   - are as close as practicable in composition to clinical specimens
   - cover clinically relevant concentrations
   - are stable and homogeneous
   - are probing for the assay system i.e. contain interferents
2. **An appropriate basis for assessment, through**
   - reliable and valid assigned values
   - robust statistics and scoring criteria
3. **Effective communication of performance data, using**
   - structured, informative and intelligible reports
   - a running scoring system
4. **Sufficient recent data from**
   - adequately frequent distributions
   - timely feedback of information

Legend: adapted from [15]

Table 5: Advantages of higher and lower frequency and intensity of EQA

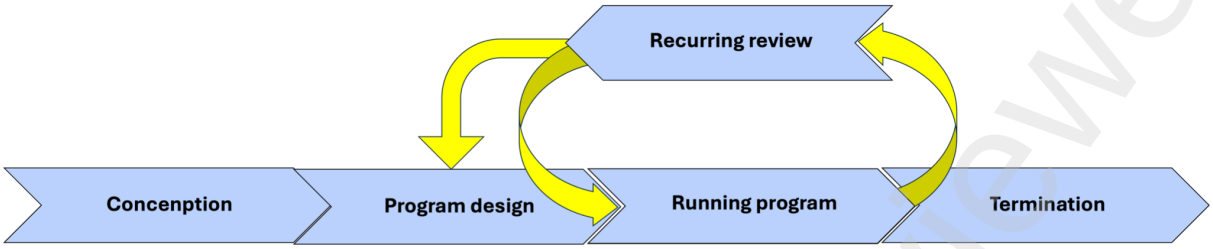
Advantages of higher frequency and intensity	Advantages of lower frequency and intensity
● a broader range of sample concentrations that might allow testing at extremes of clinical need or specific scientific studies ● improved reliability of the statistical assessment of assay performance components at the end of an EQA cycle ● earlier assessment of corrective actions ● potentially fewer patients that are affected by undetected changes in assay performance ● allows inclusion of 'educational' samples without disrupting routine assessment	● reduced costs due to reduced prices of programs ● reduced reagent costs ● reduced cost due to reduced time in handling EQA results ● reduced costs to EQA organisers ● suitable in the event of supply difficulties (rare materials)

Figure 1: EQA in the total testing process



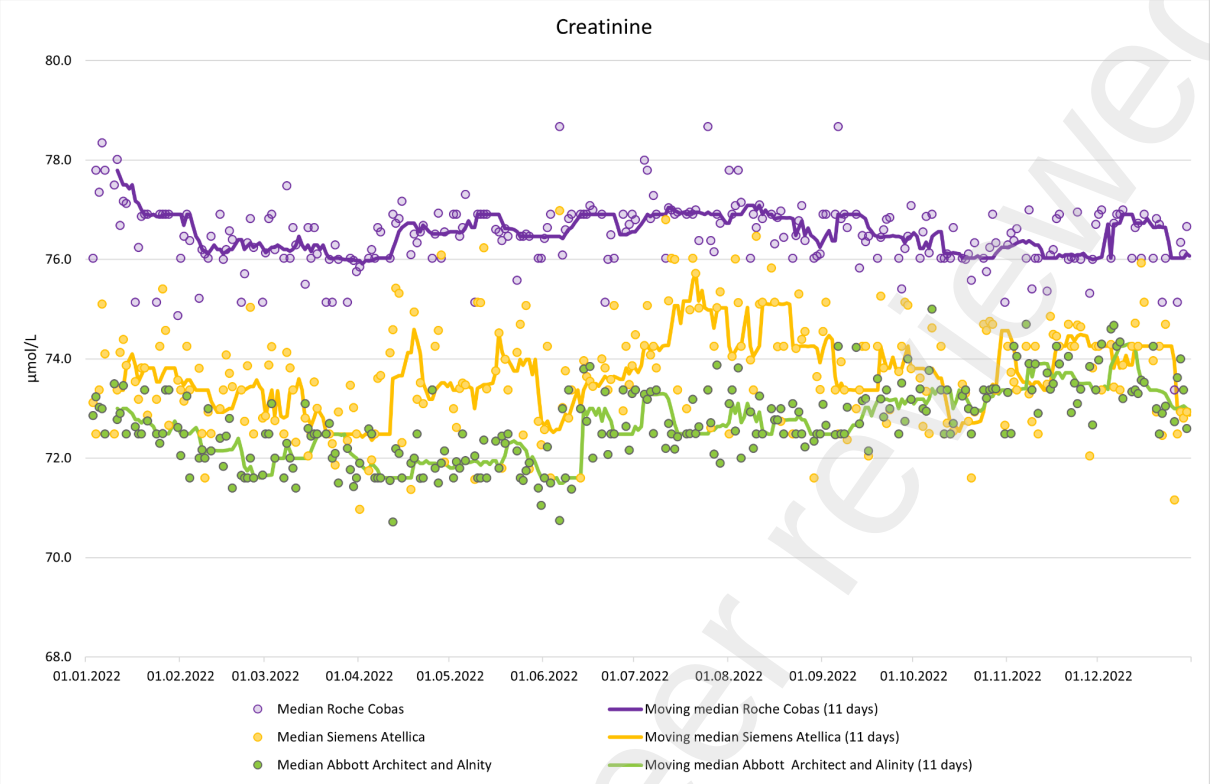
Legend: This schematic representation of the laboratory total testing process (TTP) shows the critical steps of the life cycle of a diagnostic test on a patient. Several processes take place before (pre-examination) and after (post-examination) the examination process. The process of EQA participation can help elucidate points in the TTP where error can occur, especially the value of EQA in the examination phase (pink boxes). The EQA process involves several steps along the TTP, shown as blue framed boxes "EQA assessment", while red framed "EQA tools" are that kinds of EQA that can be employed in addition to assessment of the examination process and which can help detect errors in the pre- and post-examination phases.

Figure 2: Life cycle of an EQA program



Legend: After conception and design, an EQA program comes into its routine run. Ongoing programs regularly present challenges to registered participants in the form of EQA cycles. The performance of individual EQA programs is evaluated on a regular basis and, if necessary, details of programs are adapted to match the needs of participants and technology. However, an EQA program may also reach the end of its life cycle, either because the included measurands have lost their clinical relevance or because the EQA provider decides to close it for various reasons.

Figure 3: Example on results of a patient-based EQA program for creatinine



Legend: The date is on the x-axis and the y-axis shows the concentration of the measurand. The dots represent the *daily* creatinine medians calculated from all instruments in the same MP. The lines are the *moving* medians for the creatinine MPs calculated from the last 11 medians. The overall median for the Roche Cobas group is 76.6 µmol/L (n=59847), Siemens Atellica 73.4 µmol/L (n=4620) and Abbott Architect and Alinity 72.5 µmol/L (n= 14885).