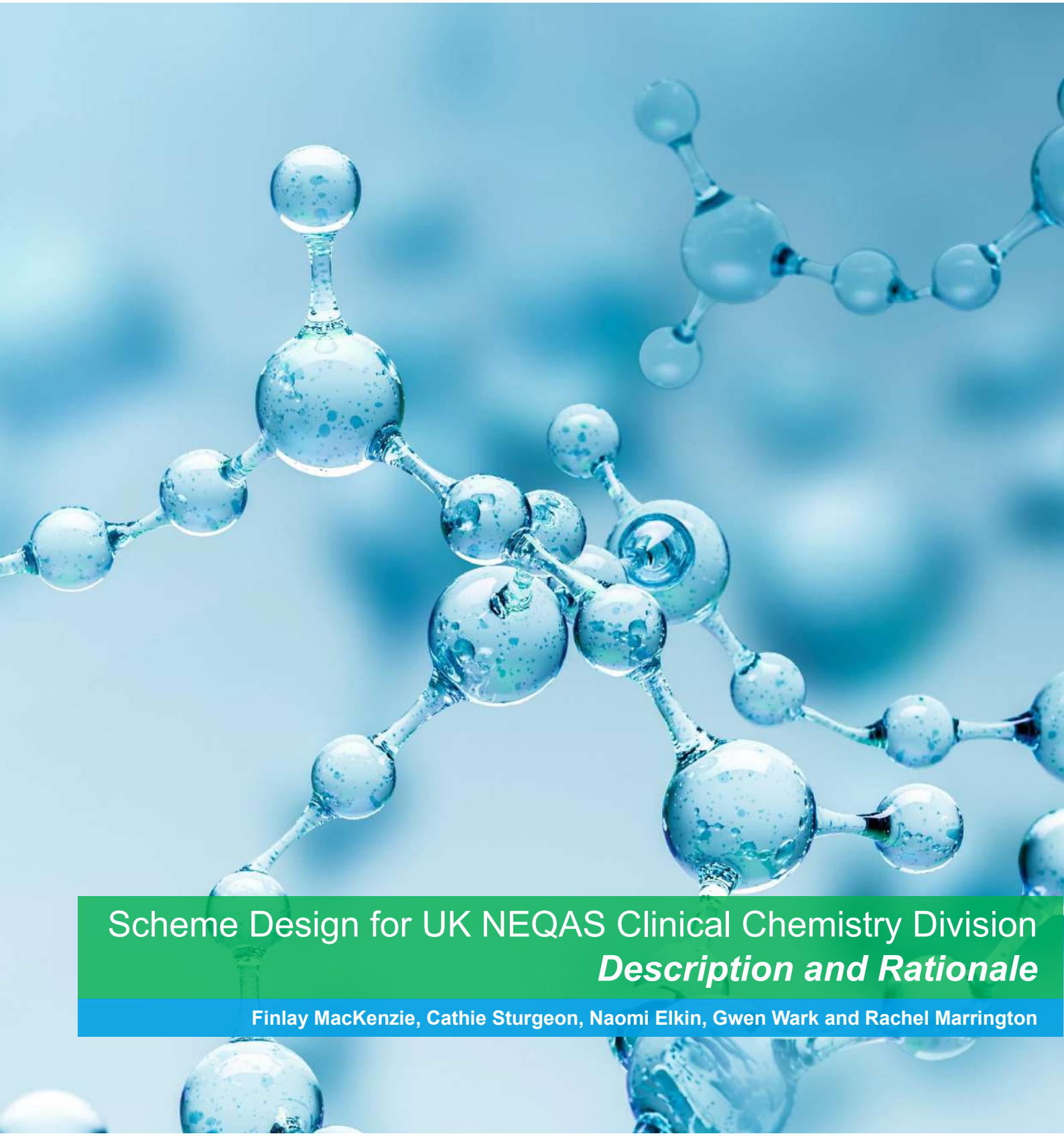
UK NEQAS
Clinical Chemistry

NHS



Scheme Design for UK NEQAS Clinical Chemistry Division
Description and Rationale

Finlay MacKenzie, Cathie Sturgeon, Naomi Elkin, Gwen Wark and Rachel Marrington

Birmingham Quality

UK NEQAS Cardiac Markers | UK NEQAS Edinburgh Peptide Hormones | UK NEQAS Guildford Peptide Hormones | UK NEQAS Trace Elements

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Table of Abbreviations

BIAS/VAR	Alternative to B- and C-Score
B-Score	Bias Score
C-Score	Consistency of Bias Score
EQA	External Quality Assessment
ISO	International Organisation for Standardisation
KPI	Key Performance Indicator
MHRA	Medicines and Healthcare products Regulatory Agency
NQAAP	National Quality Assurance Advisory Panel
QAPC	Quality Assurance Pathology Committee
UK NEQAS	UK National Quality Assessment Services
z-score	Scoring system used in analytical chemistry

Aim

The aim of this paper is to provide an overview of what laboratories should consider when reviewing and selecting External Quality Assessment (EQA) providers. The paper describes the Scheme Design adopted by the five UK NEQAS Clinical Chemistry centres, which is supported by evidence and experience from over 50 years.

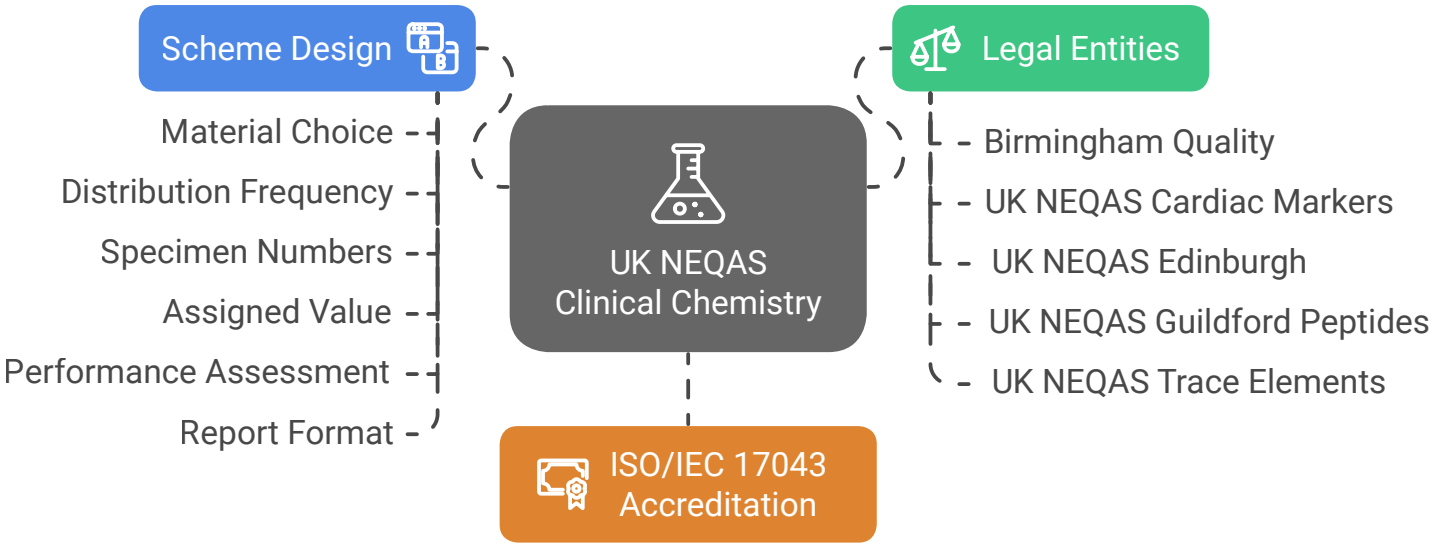
We hope to show that what we already do meets and surpasses what would be required for a clinical laboratory to adhere to as part of their own ISO 15189:2022 services.

Background

The UK National External Quality Assessment Service (UK NEQAS) was established by the Department of Health in 1969 with a remit to improve the agreement between laboratories for core clinical chemistry and haematology analytes, following individual hospital led initiatives. Birmingham was one of the first UK NEQAS Centres and much of the Scheme design currently in use in the UK was designed and developed in Birmingham. UK NEQAS is not a single entity but is comprised of 18 centres providing EQA services within different host institutions, which are the legal entities responsible for services provided.

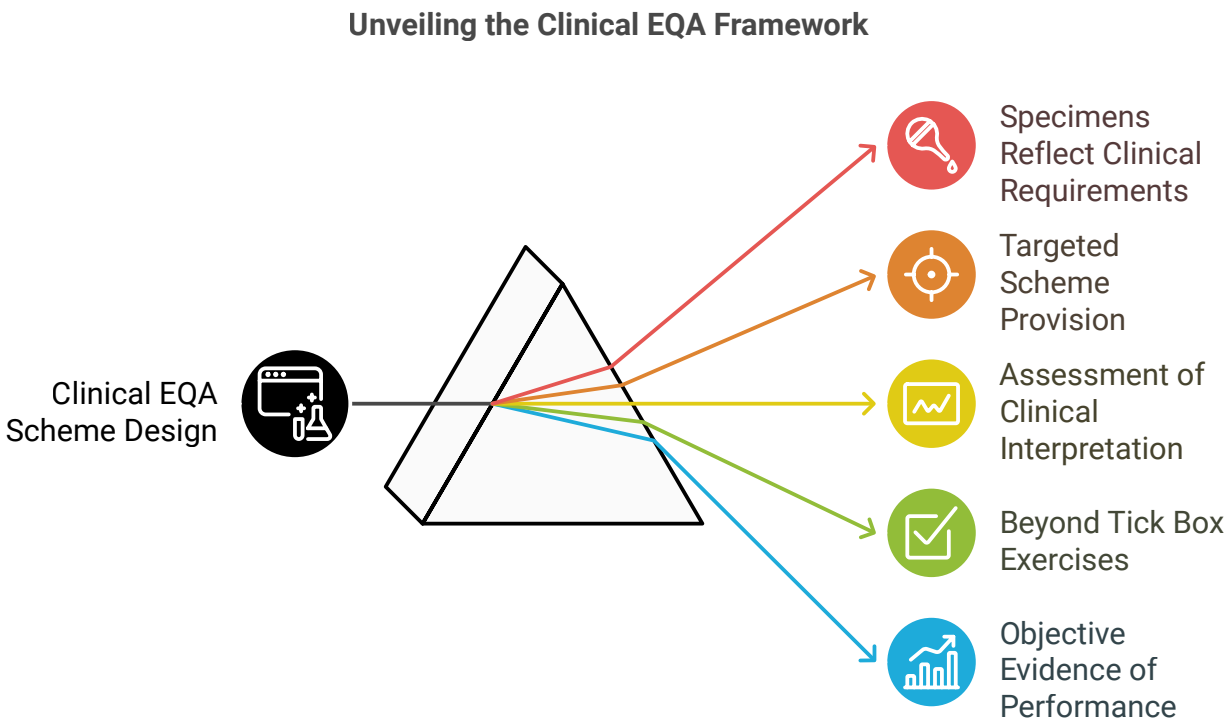
The legal entities for the five UK NEQAS Clinical Chemistry centres are NHS Trusts (Health Boards in Scotland): Birmingham Quality (University Hospitals Birmingham NHS Foundation Trust), UK NEQAS Cardiac Markers (NHS Greater Glasgow and Clyde), UK NEQAS [Edinburgh] (NHS Lothian), UK NEQAS Guildford Peptides and UK NEQAS Trace Elements (Frimley Health NHS Foundation Trust).

The centres are all accredited to the ISO Standards for Proficiency Testing [ISO/IEC 17043] (1). However, ISO/IEC 17043 does not include specific guidance relating to EQA Scheme Design. There are a number of publications relating to scheme design, which varies considerably depending on the EQA provider. Differences in scheme design include choice of material (*e.g.* commutable vs non-commutable), frequency of distribution and numbers of specimens (*e.g.* one specimen per year or four specimens monthly), assigned value, performance assessment criteria and report format and content. This document describes the Scheme Design adopted by the UK NEQAS Clinical Chemistry centres, which has previously been described (2).



Clinical Basis of Scheme Design

- *Specimens reflect clinical requirements.* The role of an EQA provider is to issue specimens that mimic routine patient samples as well as to issue more challenging specimens that probe the analytical systems and processes used. Both types of specimens provide valuable information to participants that is applicable to the service provided by their laboratory. We provide material that covers clinical decision points as well the analytical range and analytical specificity. Our EQA raises awareness of the impact of interferents as well as adding to the evidence base for quality improvement.
- *Scheme provision is targeted to the clinical application.* EQA designed to be most appropriate for individual analytes is provided, including calculated parameters with graphical representation where this facilitates interpretation. Where required, schemes specifically designed for users at point-of-care are available.
- *Clinical interpretation is assessed.* Assessment of clinical interpretation is undertaken when feasible, whether in all distributions (e.g., for haematinics or maternal serum screening) or as occasional surveys accompanied by clinical vignettes relating to the specimens issued. Close collaboration with clinical stakeholders helps to ensure that the schemes accurately assess how well current analytical requirements are met, particularly with respect to clinical guidelines.
- *Schemes are not just a tick box exercise.* Participants should be aware that as well as providing an indication of how well their results agree with those of other laboratories, scheme reports provide valuable information that should be used to ensure the service they offer is fit for purpose and to minimise the risk of adverse patient outcomes (3). Such risk assessments include for example the impact of method-related biases in relation to decision points in clinical pathways.
- *Schemes provide objective evidence of performance achievable in the real world.* Scheme data can helpfully inform selection of key performance indicators (KPIs) as well as supporting the development of tender specifications.

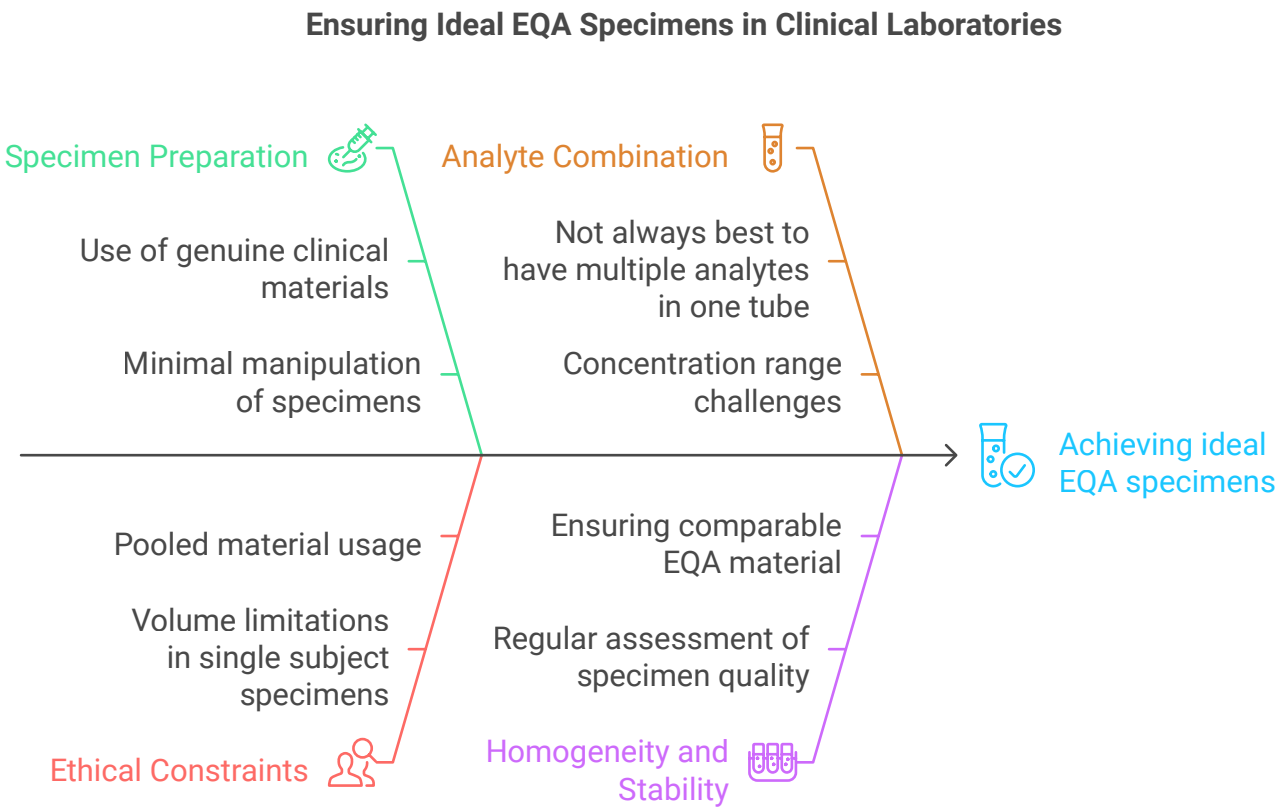


Composition of specimens distributed

The 'ideal' EQA specimens should resemble as closely as possible specimens received in a routine clinical laboratory (2, 3). They should be representative clinical material from an individual subject with or without disease and should be distributed to participants without manipulation, thus assuring commutability of the specimens issued.

In order to achieve this, UK NEQAS Clinical Chemistry centres distribute specimens prepared from genuine clinical material (serum, plasma, urine, faeces or body fluids) with minimal manipulation (3). Where feasible, specimens are prepared from a donation from one subject, but for some schemes the volume of sample required for each specimen and ethical constraints make this impossible, and samples are prepared from pooled material. For some analytes (e.g. tumour markers, cardiac markers and drugs) it may be necessary to add endogenous materials in order to achieve appropriate concentrations. For others, as well as for recovery studies, use of exogenous (purified) materials may also be required. Homogeneity and stability of specimens are regularly assessed to ensure that every participating laboratory receives comparable EQA material to test.

When appropriate, specimens contain more than one analyte for assessment. Such combination is particularly appropriate where those analytes would usually be measured in the same specimen in a clinical laboratory. This is not always practicable as it can be difficult to achieve concentration ranges appropriate for all analytes in a single specimen without additional undesirable manipulation. This may adversely affect assessment of performance for individual analytes and complicate post-market surveillance. The UK NEQAS Clinical Chemistry centres do not, therefore, combine assessment of multiple analytes in a single specimen except as described above.



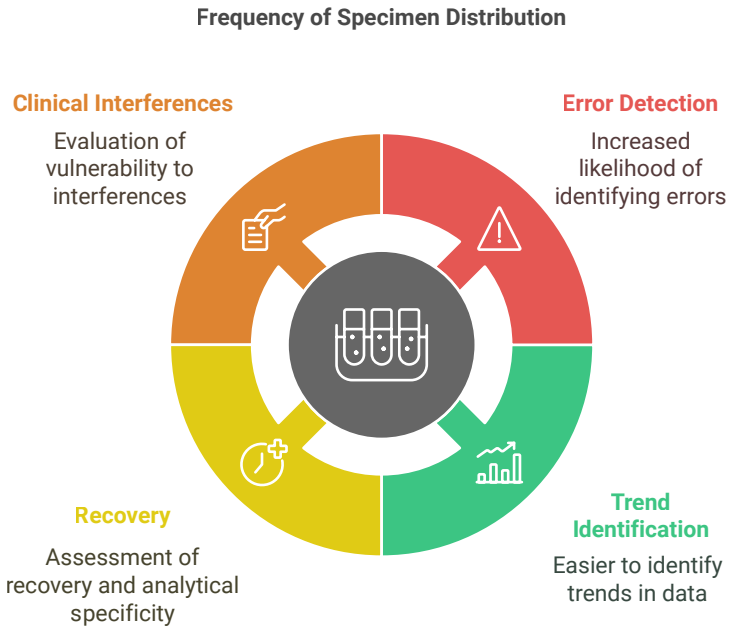
In summary, for schemes provided by the Clinical Chemistry centres,

- *Minimal manipulation of UK NEQAS specimens ensures that the specimens behave as similarly as achievable to clinical specimens and are likely to be commutable, assuring the robustness of the data. Commutability of the specimens is assessed when feasible.*
- *The key feature of using clinical material is that if an assay is non-specific, EQA specimens will show that the assay is non-specific. The same specificity issues that are observed on patient samples will be seen on a commutable EQA specimens. Therefore, differences between methods are not due to the EQA material but reflect what you see in your clinical samples. For example, Jaffe Creatinine assays display bias patterns that differ from sample to sample and this will be seen when single donation EQA specimens are used (4).*
- *Assessment of performance of more than one analyte in a single specimen is only undertaken when this can be done without prejudicing assessment of each individual analyte's performance and when appropriate analyte concentrations can be issued for each analyte.*
- *Regular testing ensures the homogeneity and stability of specimens issued to participants.*
- *Method performance issues observed for UK NEQAS specimens should reflect what is happening with clinical specimens, reflecting differences in performance of the assay systems used.*
- *UK NEQAS specimens are provided in sufficient volume for at least one replicate measurement of all required assays.*

Frequency and number of specimens issued

At least three specimens are distributed monthly for most analytes, with a few exceptions including the trace element and some point of care schemes. This enables annual distribution of specimens that cover clinically relevant concentration ranges and within-distribution issue of specimens designed to assess recovery, analytical specificity and vulnerability to clinically relevant interferences. The likelihood of detecting errors that may compromise clinical results is higher when specimens are distributed more frequently and the EQA data are more robust.

We use three specimens to allow trends to be more easily identified. The number of specimens and EQA frequency is based on clinical risk and relevance. We can more easily probe recoveries, linearity, inter-related materials and the like. Our view is that one specimen does not provide sufficient information if there were to be a random error. Even with two specimens it is not possible to determine which specimen is incorrect if result biases are different.



Pre- and Post-examination evaluation

Assessment of aspects of pre-analytical service provision is provided where feasible, for example in the UK NEQAS for Serum Indices. Similarly, assessment of interpretation is embedded in some schemes, including opportunities to submit clinical interpretations, for example total B12 results in the UK NEQAS for Haematinics. Occasional Surveys of Practice and Interpretative Exercises are also undertaken through the schemes. These additions to the EQA service provided are intended to provide participants with information that may support or challenge existing practice, encouraging improvement where required.

Target or assigned values

The target or assigned values used in EQA schemes should represent the 'best estimate of the truth'. Ideally these values should be independently validated with demonstrated traceability to a recognised Reference Method Procedure as outlined in ISO 15189:2022 (5). While a laudable aim, this is currently not feasible for many analytes used in clinical laboratories, either because reference methods do not exist or, where they are available, due to the cost and time involved in establishing the target values.

Consequently, target values used within the Clinical Chemistry centres are generally validated all laboratory trimmed consensus means. Where reference method procedures are available, these may be used periodically to validate the consensus mean target value used. This is the case for creatinine, for which the target value is the enzymatic method mean. Some assurance of the validity of consensus mean target values is also provided by assessing the stability of the target value on repeated distribution of the same pool, the linearity of the target value on issuing specimens containing different volumes of the same endogenous pool diluted in a second endogenous pool and recovery of relevant International Standards where available. When methods are recognising different molecular forms of the same analyte, target values specific to different methods or method groups may be used or results for a method group may be removed from the target value. Participants are always kept informed of such changes.

Participants occasionally request that results are compared to those of their peer group or their method mean rather than to the consensus target value. This makes between-method comparison of results and monitoring of method drift more difficult and does not help to encourage improved standardisation of methods by manufacturers. The Clinical Chemistry centres therefore do not use peer group or method mean target values unless unavoidable. Participants can compare their results to those of their peer group as this information is readily available on all the monthly reports.

Approach for Validating Target Values in Clinical Laboratories



Consensus Mean Validation

Provides a practical and widely applicable method for establishing target values





Peer Group Comparison

Offers insights into comparative performance but hinders standardisation

Scoring systems used and performance monitoring

The ‘ABC of EQA’ scoring system, developed 25 years ago in Birmingham, is used for most schemes provided by the Clinical Chemistry centres. The A score element is not used for some analytes. For analytical troubleshooting only the Bias (B-score or BIAS) and Consistency of bias (C-score or VAR) are considered. All reports provide information at the specimen and distribution level, and graphically depict trend data over a six-month time window. [The UK NEQAS for Trace Elements uses z-scores, which are not discussed further here].

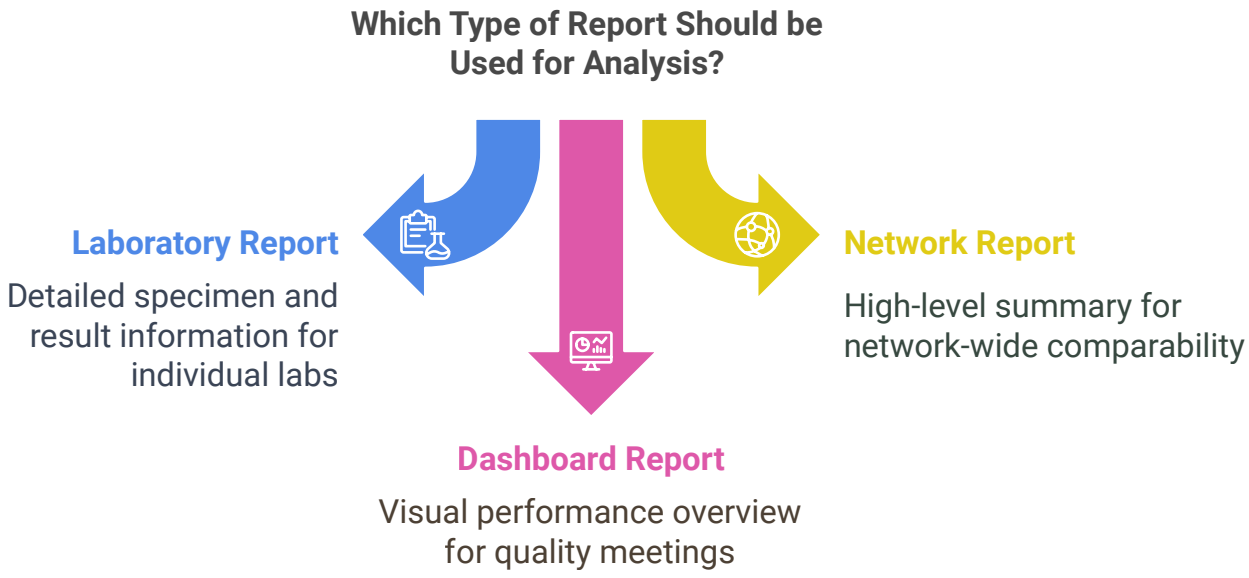
EQA target values and performance criteria are independently established and should not be changed. Participants are welcome to implement internal systems with tighter criteria, but limits of acceptable performance should never be widened. Where appropriate, performance surveillance is facilitated by the use of “Red-Amber-Green” (RAG) ratings. Participants should act on these without waiting for formal notification, which may be via the Feedback page or Comments section in some reports, and should contact the relevant EQA centre as appropriate. Escalation by e-mails to the head of department or via the NQAAP structure is rarely required.

Performance criteria are applied with some discretion by the Clinical Chemistry centres, as it is appreciated most issues of poor performance are assay-related rather than due to laboratory error. Participants are encouraged to contact the manufacturers about such issues, with copies to the relevant EQA Centre welcome.

Reports

Reports should be intuitive and easy to interpret, with different styles of report appropriate for different users (e.g., clinical laboratory vs point-of-care site). Available report formats include the following:

- Laboratory report — Provides detailed description of specimens and results in a single distribution, including method-specific information, together with performance data over a six-month window.
- Network report — Provides a high-level summary of data for all laboratory registrations within the network, enabling laboratories to assess the comparability of results across the network.
- Dashboard report — Provides a visual view of analytical performance across multiple schemes and analysers at both individual laboratory and network levels. Available only for schemes using the “ABC of EQA” scoring system, they are best suited for review in Quality Meetings.



Responsibilities of Participants

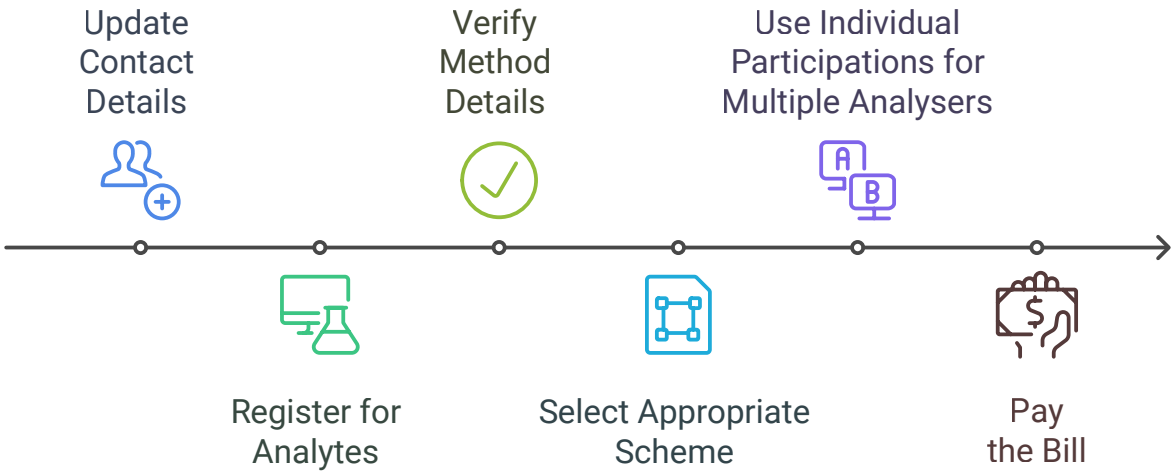
Participants should ensure that contact details are up-to-date to ensure specimens are addressed correctly and the appropriate colleagues can be contacted if required. Details can be updated at any time by contacting the appropriate centre.

Participants should also ensure that they are registered for the required analytes and that method details are correct and up-to-date. The latter is important as EQA data contributes to post-market surveillance.

Occasionally for scientifically valid reasons, analyte performance is assessed in more than one scheme (e.g., creatinine within the UK NEQAS for Acute and Chronic Kidney Disease). Where this is the case, participants should select the scheme best suited to the clinical application.

When there are multiple analysers, individual participations for each instrument are recommended as this allows trends on each analyser to be identified. This is also the case for derived analytes such as eGFR or AKI as how variation in analytical performance impacts derived results is being assessed as well as equation performance.

Responsibilities of UK NEQAS Clinical Chemistry Participants When Belonging to a Scheme



Governance

All UK NEQAS Clinical Chemistry centres have access to independent Specialist Advisory Groups and work with experts in the field if there are specific analytical or clinical issues that need to be addressed.

When necessary, poorly performing laboratories are reported to the NQAAP for Chemical Pathology (Microbiology or Haematology, as appropriate). Method-related issues are discussed with the relevant manufacturer and escalated to the Medicines and Healthcare products Regulatory Agency (MHRA) if required. However, provided methods are working within the manufacturer's specifications, action that can be taken by the MHRA may be limited. Participants are also encouraged to contact manufacturers regarding assay-specific issues.

Accreditation

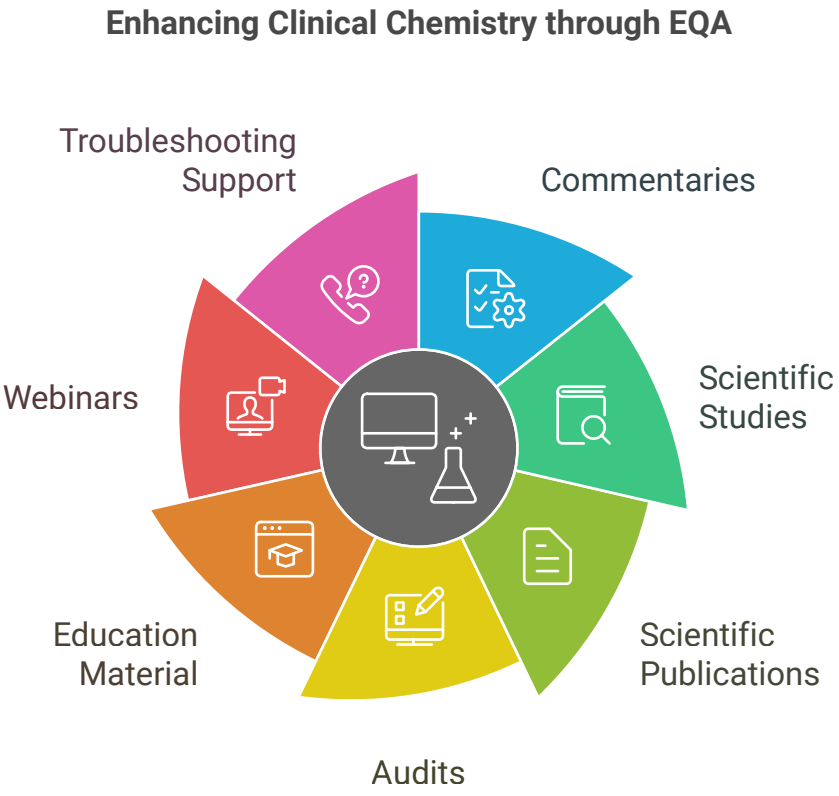
UK NEQAS Clinical Chemistry Centres are accredited to ISO/IEC 17043 for all schemes other than those in development. Such Pilot schemes and analytes added to existing schemes are submitted for accreditation

when sufficient supporting data are available. In the interim these schemes are run following the same procedures as for accredited schemes.

Educational and Scientific Aspects

The major remit of the UK NEQAS Clinical Chemistry centres is to assess the quality of results that participants obtain and encourage improvement where necessary, but the Clinical Chemistry centres are also committed to providing “value added EQA” through educational and scientific initiatives. These include -

- Commentaries, including surveys of recent relevant publications, that accompany many reports and are available to participants on the Results & Reports web page. Participants are welcome to share these with relevant stakeholders.
- Involvement in scientific studies (“research in practice”) for which EQA schemes can rapidly provide valuable “real world” data (e.g., evaluation of new candidate reference preparations, assessment of robustness to clinically relevant interferences).
- Scientific publications describing data from the schemes. As EQA data provides a “snapshot” view of performance at a given time point, these may be reviews, complementing (but not replacing) the more detailed information that is available to participants.
- Audits of current laboratory practice through Surveys of Practice and Interpretative Exercises.
- Provision of educational material (available via the Education Button on the Results & Reports web page).
- Provision of monthly webinars for participants registered in the Birmingham Quality schemes.
- Access to advice and repeat specimens from all centres if help with troubleshooting is required.



Conclusion

Staff in clinical laboratories are committed to making the best use of the resources available to provide accurate and timely results to clinicians. As laboratories invest considerable time and money in the EQA services used, it is important to ensure optimal use of available data and information. This can be used to support specifications for laboratory services, as a basis for discussion with relevant stakeholders and in regular communications with users of the service, e.g., to highlight any limitations in the service. Staff in the Clinical Chemistry centres are also always pleased to hear from participants as we all share the same goal — improved patient care.

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