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UK EXTERNAL QUALITY ASSESSMENT SCHEME FOR IMMUNOASSAYS IN ENDOCRINOLOGY

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Summary. - *UK EQAS provide the UK with a comprehensive system for EQA in endocrinology, as well as in other aspects of clinical chemistry and laboratory medicine. UK EQAS in endocrinology are scientifically designed to yield an objective assessment of participants' performance and stimulate improvements in between-laboratory agreement. The design uses appropriate specimens, based on liquid human serum and prepared with minimal processing and additives in the organising centres to enable detailed study of recovery and other important factors. Target values are validated by reproducibility on repeated distribution and by recovery and parallelism studies. Reports are presented informatively, and emphasise the cumulative scoring system (bias and variance) for performance assessment. Computerised data processing and data presentation form an integral part of these schemes, and a common core computing system is in use throughout these UK EQAS. Participants receive advice and assistance in the interpretation of performance data and, when appropriate, in the resolution of problems.*

KEY WORDS: external quality assessment, immnuoassay, endocrinology.

Riassunto (Gli schemi di valutazione esterna di qualità per i dosaggi di interesse endocrinologico nel Regno Unito). - *Gli schemi di valutazione esterna di qualità (VEQ) nel Regno Unito rendono disponibili sistemi valutativi di vasta applicabilità in endocrinologia e in altri settori della chimica clinica e della medicina di laboratorio. I programmi di interesse endocrinologico sono concepiti su base scientifica per condurre ad un giudizio oggettivo sulle prestazioni dei partecipanti e per indurre a migliorare la concordanza fra i laboratori. La struttura del programma prevede l'uso di campioni opportunamente scelti, basati su siero umano liquido, preparati presso i centri organizzatori con un minimo di trattamenti e di aggiunte per consentire uno studio approfondito del recupero e di altri fattori importanti. I valori "bersaglio" sono convalidati in base alla riproducibilità per distribuzioni ripetute di campioni e a studi di recupero e di parallelismo. Nei rapporti, presentati in maniera informativa, una grande attenzione viene attribuita al sistema di punteggio cumulativo (inaccuratezza e imprecisione) per la valutazione delle prestazioni. Il trattamento automatico dei dati e la presentazione dei dati sono parte integrante dello schema; un sistema di calcolo centralizzato è utilizzato per tutti i programmi di VEQ nel Regno Unito. I partecipanti ricevono consigli e assistenza per l'interpretazione dei dati di prestazione e, se è il caso, per la soluzione dei problemi.*

PAROLE CHIAVE: valutazione esterna di qualità, dosaggio immunologico, endocrinologia.

Introduction

The concept of external quality assessment (EQA) in general clinical chemistry was established in 1969 [1], but much of the pioneering work on EQA of hormone assays in the UK was undertaken by Hunter *et al.* from the Royal Infirmary, Edinburgh [2, 3]. Historically, the specialised nature of and expertise required for hormone assays led to their centralisation in a small number of regional centres [4]. To ensure comparability of results between centres and to assess the state of the art, the Edinburgh group began a series of specimen distributions for growth hormone in 1975. Other groups developed schemes for thyroid hormones at the same time [5] and the coordination and integration of these individual initiatives led to the development of national EQA schemes (EQAS) for hormones by the early 1980s.

Organization of UK EQAS

Currently there are three main centres for endocrine EQA in the UK, with local or individual expertise: these are in Birmingham (thyroid hormones), Cardiff (steroid hormones) and Edinburgh (peptide hormones). These are supplemented by several smaller centres, thus including all the most widely performed hormone analytes [4, 6].

This paper covers the three main schemes drawing specific examples from the UK EQAS for Thyroid-related Hormones [7].

A system of UK EQAS covers all laboratory medicine disciplines [4, 6], organised by laboratory professionals, sponsored and coordinated by the UK Government Department of Health (DH). A small number of committees, each with a specific but distinct remit, interact with the Scheme Organisers to provide a coordinated strategy and approach for all schemes, to maintain and improve laboratory performance. The three main endocrine schemes are operated by clinical scientists with a background in clinical chemistry and endocrinology who now provide an EQA service as their primary job function.

The Advisory Committee on Assessment of Laboratory Standards (ACALS) is concerned with quality assessment in pathology laboratories in all disciplines in the UK and advises the DH [6]. ACALS is concerned with policy, and ensures comparability of standards and encourages interchange of ideas between different schemes. It also terminates or creates new schemes in response to changing clinical and laboratory practice and needs.

The National Quality Assurance Advisory Panel (NQAAP) for each discipline is responsible for the maintenance of satisfactory standards of work in clinical laboratories and assesses the performance levels of individual laboratories. These small groups of experts are nominated by professional groups. The NQAAP for Chemical Pathology, which is responsible for the endocrine schemes, has nominees from the Royal College of Pathologists (RCP), Association of Clinical Pathologists (ACP), Association of Clinical Biochemists (ACB) and Institute of Medical Laboratory Sciences (IMLS), thus having medical, scientific and technical input.

Steering Committees for each discipline or sub-discipline are responsible for scheme policy, and decide together with the scheme organisers the way in which schemes are designed and data presented. The Scheme Organiser has day-to-day control of and responsibility for the scheme operation.

The Joint Working Group on Quality Assurance is a "watchdog" group, independent of the DH, which represents professional bodies across all laboratory disciplines.

The interplay between the different committees, each with its own priorities, ensures that all groups have an input in EQA, and it thus becomes easier for the Scheme Organiser to operate with the backing of all parties.

Though participation is voluntary, over 99% of NHS (public sector) and the great majority of private laboratories participate. The role of UK EQAS has always been educational and, unlike other European countries, the schemes have never been used for licensing purposes [4, 6]. As part of a wider Governmental policy covering all aspects of healthcare, it is expected that some form of accreditation will soon be instituted, and as a consequence of this, a laboratory would have to participate actively in all recognised EQAS. Release of performance details to any third party, without the participant's consent, would not be contemplated.

Scheme design

Since EQA specimens should reflect as closely as possible the behaviour of clinical specimens UK EQAS use liquid human serum specimens. Serum is a "cleaner" matrix than plasma, and liquid material is used because the aim is to manipulate the material as little as possible. The material is filtered through progressively smaller pore sizes down to 0.22 μm, and sodium azide (final concentration 15 mmol/l) is added as a bacteriostat. Additions of pure hormone, normally of international standard (IS) or international reference preparation (IRP) for peptide hormones or the pure chemical in the case of thyroid and steroid hormones, are made to adjust the analyte levels to concentrations at important clinical decision levels or to assess recovery. To assess the baseline security of assays, it is often desirable to distribute material with "zero" analyte concentration. Such materials are preferably obtained by physiological means, e.g. serum from individuals who have taken 20 μg T3 (4 times a day for 5 days prior to donation of blood) for "zero" TSH (T3-suppressed serum) or dexamethazone suppression for "zero" cortisol. By carrying out all stages of sample production, not only is there complete control over analyte concentration and relative frequency of distribution, but specific probing experiments can be carried out. As well as undertaking the familiar recovery and parallelism type experiments it is possible to look at the effect of interfering substances, e.g. heterophilic antibodies [7, 8], and cross-reactants, with only a short lag time between experimental design and analysis, which again would not be possible using commercially-prepared sera. Material from individuals with defined clinical conditions is used less frequently than previously due to the difficulty of obtaining consent to testing for antibodies to human immunodeficiency virus (HIV), which is undertaken at the individual donor stage on all materials distributed by UK EQAS.

The three schemes employ the survey approach, with monthly distributions comprising 4-6 specimens. Some analytes may be measured in the same specimens, e.g. in the thyroid scheme, while others provide separate specimens for each analyte, e.g. the steroid scheme. A laboratory has three weeks to analyse the specimens and to return results to the organising centre on the results document provided, which only shows those analytes assayed by the laboratory. The laboratory is identified by a code number, common to all UK EQAS in clinical chemistry, and so confidentiality of participation is ensured. The results received are entered into the EQA computer system and a comprehensive personalised report is generated and returned to the laboratory with the next set of specimens. The exact details of the data handling and report format differ slightly depending on the analytes involved, but the introduction of a common EQA computer package developed at the Wolfson Research Laboratories in Birmingham [9] has encouraged the centres to move towards a common output and greater harmonisation of the schemes, e.g. in adopting a common procedure for outlier result elimination [10].

Data processing and presentation

In January 1989, the UK EQAS for Thyroid-related Hormones became the first UK EQAS to use the new generalised EQA computer package [9]. This "core system" was developed in response to hardware, software and personnel difficulties experienced by several UK EQAS. It was designed to improve scheme resilience, to lessen dependence on the programming skills of individual Scheme Organisers, and to facilitate the introduction of new schemes. The system is adaptable and can be used readily by any EQAS organiser, in any discipline, without programming knowledge, for any EQAS involving distribution of test materials, processing of results data and generation of text and graphical reports. It also provides simplified database interrogation for handling queries from participants and allows more complex data retrieval for research purposes.

The monthly report, which is the participant's regular contact with the scheme, has a clear and concise format designed to give a thorough presentation of data in a readily comprehensible way [7]. The first page summarises the participant's own distribution-specific data (results, targets and biases) and cumulative scores (see below) for each analyte, and describes the specimens constituting the current distribution and whether portion of these pools have been distributed previously. The analyte-specific pages provide information on the participant's performance compared with the consensus values and a comprehensive analysis of the method-specific performance using both distribution-specific and cumulative data; analyte-specific comments are included to inform or clarify. The table of method-related median and interquartile ranges of *BIAS* and *VAR* (see below) shows at a glance the relative performance of methods in routine use.

Periodic graphical output and summary reports are used to show performance trends for an individual laboratory, to reinforce educational messages and to report the state-of-the-art in the individual schemes (Figs 1-3). Changes in participation, methods and performance over time give valuable information that would not be available from any other source; we believe that demonstration through the scheme of the superiority of immunometric methods for TSH has contributed to their current dominance (Fig. 4). By highlighting strengths and weaknesses of different assay systems, UK EQAS should lead as well as reflect current practice [7, 11]. Where appropriate, interpretation of results are assessed by UK EQAS, e.g. in the scheme for Neonatal Blood Spot TSH for those laboratories involved in screening for congenital hypothyroidism.

Performance assessment

The approach in the UK has always been that rigorous internal quality control procedures best address imprecision while EQA should be used to improve interlaboratory agreement and inaccuracy [4, 12]. In the hormone schemes accuracy is assessed by comparison of laboratory results against a target value, according to the formula:

$$\text{bias} = \frac{(\text{result-target}) \times 100\%}{\text{target}}$$

This target value is usually a consensus mean, the "all laboratory trimmed mean" (ALTM), validated where possible by reproducibility, recovery, parallelism and baseline security studies [7, 8, 11, 12]. For some analytes, because the ALTM is not stable (which may be due to the dependence on relative method usage, and where no independent reference method is available), a "grouped laboratory trimmed mean" (GLTM) is used as target. GLTMs are used for example for free T4 [7], where the relative numerical results from assay systems based on different analytical approaches depend on the analyte concentration and pool matrix; the numbers of users of the increasing variety of methods is still in a state of rapid flux. This

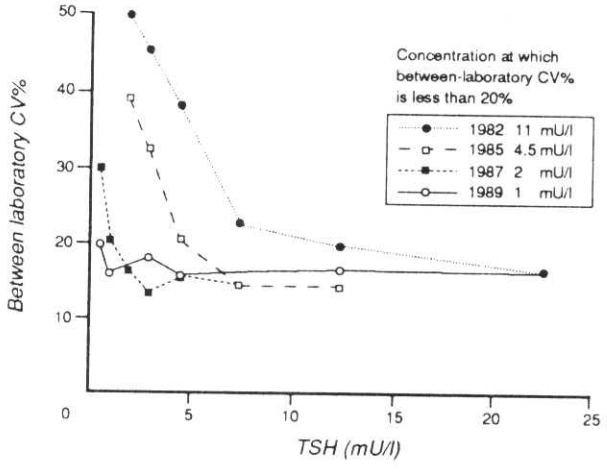

Fig. 1. - Between-laboratory imprecision profiles for TSH from 1982 to 1989, as assessed by the UK EQAS for Thyroid-related Hormones.

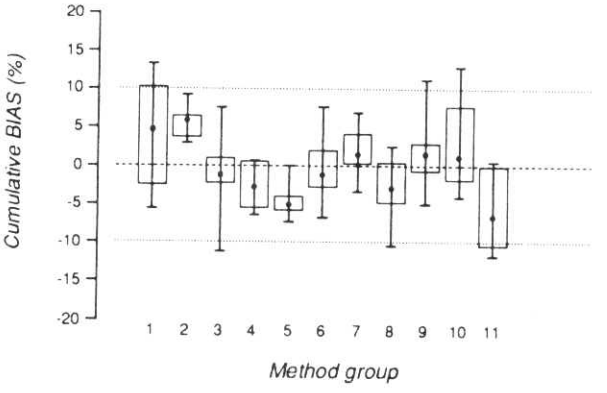

Fig. 2. - Method-related *BIAS* for total thyroxine at July 1990. The median (filled circle), interquartile (box) and extremes of range (vertical tails) for each method group are shown; the limits of acceptable performance are indicated by dotted lines.

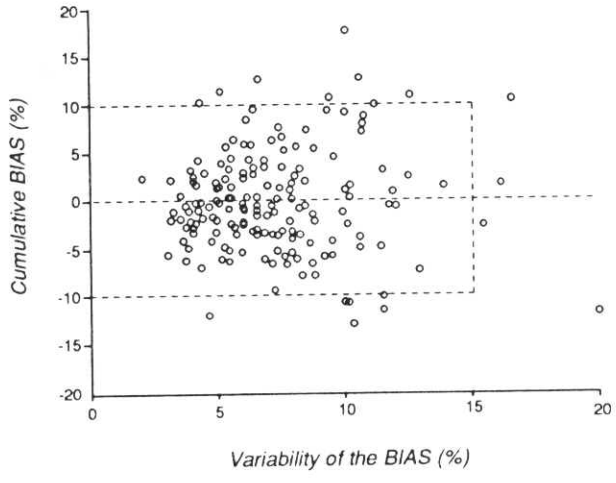

Fig. 3. - Scattergram of individual laboratories' *BIAS* and *VAR* for total thyroxine at July 1990, showing the limits of acceptable performance (*BIAS* 10%, *VAR* 15%).

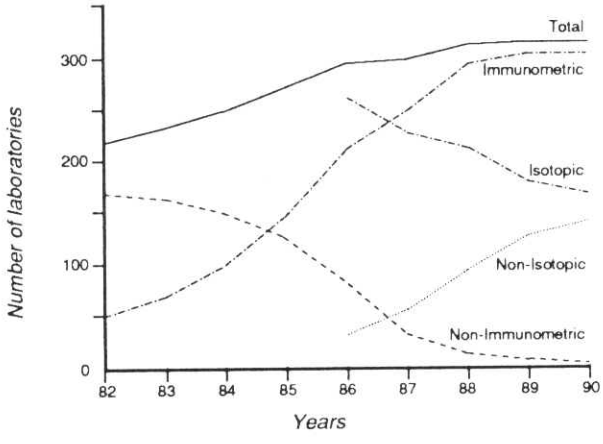

Fig. 4. - Trends in participations and methods for TSH in the UK EQAS for Thyroid-related Hormones from 1982 to 1990.

pragmatic approach has been taken so that laboratory performance can be assessed, even if only against other users of the same method.

Cumulative scoring has been used with some success in all hormone schemes to assess laboratory performance. Derivation of the cumulative bias *(BIAS)* and cumulative variability of the bias *(VAR)* for each analyte over a fixed time window has been described elsewhere [3, 11] and is summarised below. In the thyroid scheme, for example, the *BIAS* is essentially the trimmed geometric mean of the most recent 30 biases and the *VAR* is the geometric coefficient of variation of this calculation (for analytes, e.g. steroids, where the results are not logarithmically transformed, the *BIAS* and *VAR* are the arithmetic mean and standard deviation respectively). Although imprecision is a component of *VAR*, there are also contributions from dose-dependent or time-dependent bias. Thus a laboratory using a method which is calibrated inappropriately (proportional error) will have a large *BIAS* but should have a small *VAR*. Similarly, a laboratory using a system with poor specificity may have a positive bias at low concentrations but be relatively unbiased at high concentrations; this would give a large *VAR* and a small *BIAS*.

The NQAAP, in consultation with the Steering Committee, assign limits of acceptable performance based on *BIAS* and *VAR* [7]. In setting these limits many factors are taken into account, including the best possible "state-of-the-art" performance, the performance attainable by most laboratories, the validity of the target value, and the clinical requirements of the analyte.

High cumulative scores alert the Scheme Organiser to laboratories apparently experiencing difficulties. After a detailed examination of the laboratory's results and performance history, the Scheme Organiser may notify the laboratory of its current performance, ask for comments and offer help and advice. If a laboratory fails to respond after repeated attempts to contact it, and its performance shows no sign of improving, the Scheme Organiser will write a formal letter to the laboratory director to try to establish a dialogue. Should this fail, or if no progress is made, as a last resort the NQAAP would be asked to intervene [6, 7].

Though one role of UK EQAS is to identify laboratories with problems and to offer advice, the emphasis is on self-education. It is therefore encouraging that most laboratories which fall outside these limits do so only transiently and revert to acceptable performance without any direct intervention from EQAS. Referrals to the NQAAP are extremely infrequent.

Comment and conclusions

UK EQAS in endocrinology are scientifically designed to yield an objective assessment of participants' performance and stimulate improvements in between-laboratory agreement. This design is based upon appropriate specimens, enabling detailed study of recovery and other important factors, validated target values, informative report presentation, and a cumulative performance scoring system. Computerised data processing and data presentation form an integral part of the schemes, and a common core computing system is in use throughout these UK EQAS. Participants receive advice and assistance in the interpretation of performance data and, where appropriate, in the resolution of problems. Overall, UK EQAS provide the UK with a comprehensive system for EQA in endocrinology, as in other aspects of laboratory medicine.

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