Biological variation and quality for POCT

June 2001

Callum G. Fraser
Biochemical Medicine
Ninewells Hospital and Medical School
Dundee DD1 9SY
Scotland

The results of laboratory tests are used in many clinical settings. In the main, results obtained in point-of-care testing (POCT) are used either in monitoring or in diagnosis. Analytical quality does affect outcomes in these clinical situations.

Numerical estimates of the quality required for laboratory tests to ensure satisfactory outcomes in both of these settings are necessary, particularly for precision and bias. Recently, the available approaches have been fixed into a hierarchical framework agreed by experts in the field to be the best current approach to a global strategy.

They should be incorporated into quality planning strategies everywhere irrespective of the settings in which laboratory medicine is practiced, including POCT. The best general approach, directly related to clinical outcomes in general, is to base quality specifications on components of biological variation.

Many easily available data exist to facilitate this widely accepted strategy.

Introduction

Clinical laboratory test results are used in many clinical settings including screening, case finding, teaching and training, plus research and development.

However, most are used in monitoring individuals over time and in the diagnostic process. There is considerable evidence that the performance characteristics of the tests do affect clinical outcomes in both of these situations.

Performance characteristics involve both practicability and reliability characteristics.

The former include skills required, speed of analysis, plus volume and type of sample required.

The latter include precision, bias, limit of detection, and measuring range. It is often suggested that, for POCT, turnaround time is the most important performance characteristic.

However, quality specifications for the reliability performance characteristics, particularly precision and bias, are vital for creation and management of the analytical quality that impinges on test result interpretation.

However, it is given that quality specifications should be firmly based upon medical requirements, useable in all laboratories irrespective of size, type or location – including POCT, generated using simple-to-understand models, and generally supported by professionals in the field.

For about 40 years, there has been a steady stream of publications concerned with the generation and application of quality specifications [1].

There appeared to be a real conflict about how to set quality specifications, but a decisive recent advance was that a consensus was reached in 1999 on global strategies to set quality specifications in laboratory medicine [2].

This consensus was based upon a hierarchical approach published just prior to the consensus conference [3].

The hierarchy is shown below (**Table I**). All the approaches have advantages and disadvantages, but quality specifications based on components of biological variation (**strategy 2A**) seem very widely favored and will be discussed in detail in this contribution.

The effect of analytical performance on general clinical outcomes

The second strategy in the hierarchy is the creation of quality specifications based on components of biological variation – within-subject (CVI) and between-subject (CVG) variation.

These are directly related to outcomes in monitoring and diagnosis.

1. Assessment of the effect of analytical performance on specific clinical decision-making	Quality specifications in specific clinical situations
2. Assessment of the effect of analytical performance on general clinical decision-making	2A. General quality specifications based on biological variation 2B. General quality specifications based on medical opinions
3. Professional recommendations	3A. Guidelines from national or international expert groups 3B. Guidelines from expert individuals or institutional groups
4. Quality specifications laid down by regulation or by external quality assessment scheme (EQAS) organizers	4A. Quality specifications laid down by regulation 4B. Quality specifications laid down by EQAS organizers
5. Published data on the state of the art	5A. Published data from external quality assessment and proficiency testing (PT) schemes 5B. Published individual methodology

TABLE I: Hierarchical approach to classification of strategies for setting quality specifications.

Monitoring

Considering monitoring first, probably no one would disagree that analytical random variation must be kept low so that any changes seen in test results in an individual over time are clinically interesting.

In other words, we need to see the "signal" (real change) and not just the "noise" (analytical random variation – precision). For POCT, this is really important because, historically, the analytical performance achieved in alternate sites was not so good as in laboratories and, in consequence, the signal-to-noise ratio was rather low. In consequence, results obtained in POCT settings were of less than desirable quality.

This is important, because it is often said that an advantage of POCT is that patients can be monitored closely and frequently.

Monitoring involves comparison of serial test results from an individual over time. In the simplest model, changes in serial results can be due to:

- the patient improving
- the patient deteriorating
- preanalytical variation
- biological variation (within-subject) and
- analytical variation – mostly inherent random variation, measured as precision (CVA)

If preanalytical sources of variation are made as small as possible, then, to assess whether change has occurred, it must exceed the inherent variation due to biological and analytical variation which is now best termed the "reference change value"(RCV) which can be calculated as:

$$RCV = 2^{½} \cdot Z \cdot (CV_A^2 + CV_I^2)^{½}$$

where Z is the number of standard deviates appropriate to the probability selected (for example, 1.96 for $P < 0.05$ and 2.58 for $P < 0.01$).

Calculation of the effect of precision on medical decision-making is straightforward. If we investigate cholesterol (CV_I ~ 6 %) as one example of a widely done POCT procedure in pharmacies, clinics, physician's offices and other alternate sites, the change required for significance (at $P < 0.05$) increases with precision as shown in **Table II**.

Precision (CV, %)	RCV (%)
2	17.5
4	20.0
6	23.5
8	27.7
10	32.3

TABLE II: Effect of precision on reference change value for serum cholesterol at $P < 0.05$.

The quality specification advocated for precision is that the analytical variation should be less than one-half the average within-subject biological variation [4]. The rationale for this was expounded by Harris who showed that, if $CV_A < 0.50CV_I$, then the amount of variability added was about 10 % – said to be "reasonable" [5].

This proposal has been very widely accepted by professionals. This concept has been expanded more recently. Three classes of analytical quality (optimum, desirable, and minimum), based upon different fractions of within-subject biological variation, have been proposed as shown in **Fig. 1** [6].

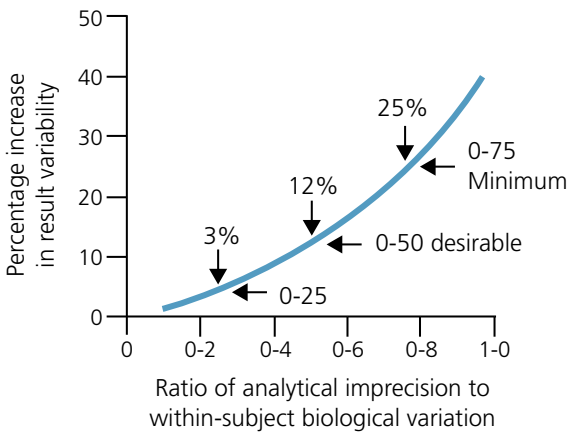

FIG. 1: Percentage increase in test result variability due to analytical precision (expressed as a ratio of analytical-to-within-subject biological variation) showing three possible quality specifications based on within-subject biological variation. From Fraser CG *et al*. Ann Clin Biochem 1997; 34: 8-12 (shown with permission).

Diagnosis

Interpretation of numerical laboratory test results in the diagnostic setting can be aided by: use of locally agreed

protocols for clinical action; values proposed by expert individuals, groups or committees; values based on outcomes, for example risk such as for cholesterol; and multiples of the upper reference limit. However, many use population-based reference values.

Patients often have tests done in various locations such as the emergency room, the outpatient clinic, the ward – in which POCT may be used – and in the laboratory.

Test results should be comparable over location. Surely then, all testing sites serving a homogeneous population should all use the same reference values. For this to be achieved, it has been shown [7] that bias should be less than one-quarter of the group biological variation (that is, $B < 0.25(CV_I^2 + CV_G^2)^{½}$).

Again, three classes of analytical quality, optimum, desirable and minimum, based upon different fractions of within- plus between-subject biological variation, have been proposed as shown in **Fig. 2** [6].

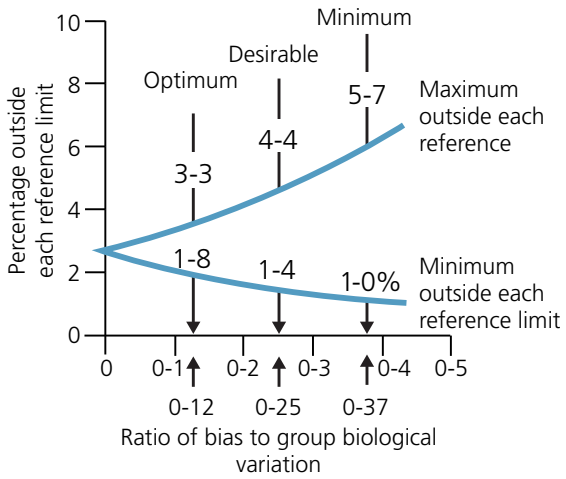

FIG. 2: Percentage of results outside reference limits due to analytical bias (expressed as a ratio of analytical-to-group (within- plus between-subject) biological variation) showing three possible quality specifications based on biological variation. From Fraser CG *et al*. Ann Clin Biochem 1997; 34: 8-12 (shown with permission).

The advantages of biological variation-based quality specifications

These strategies, directly related to the clinical uses made of test results, have many merits. Data on biological variation are available for more than 300 quantities. A recent compilation in the easily available literature and on the Internet makes the data easy to obtain [8].

The data seem independent of study location, number of subjects, length of study, analytical methodology, age of subjects, or whether they are in a state of health or have a stable, but chronic disease.

Moreover, data on components of biological variation have been used to define quality specifications for other characteristics and in other laboratory settings [9]. The models are simple. The strategies appear to be widely supported by professionals. Their use in quality planning is advocated, including for POCT.

References

1. Fraser CG. Quality specifications in laboratory medicine. Clin Biochem Revs 1996; 17: 109-14.

2. Consensus statement from "Strategies to set global quality specifications in laboratory medicine". Stockholm, April 24-27, 1999. Available at www.westgard.com.

3. Fraser CG, Hyltoft Petersen P. Analytical performance characteristics should be judged against objective quality specifications. Clin Chem 1999; 45: 321-23.

4. Cotlove E, Harris EK, Williams GZ. Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. III. Physiological and medical implications. Clin Chem 1970; 16: 1028-32.

5. Harris EK. Statistical principles underlying analytic goal-setting in clinical chemistry. Am J Clin Pathol 1979; 374: 72-82.

6. Fraser CG, Hyltoft Petersen P, Libeer JC, Ricos C. Proposals for setting generally applicable quality goals solely based on biology. Ann Clin Biochem 1997; 34: 8-12.

7. Gowans EMS, Hyltoft Petersen P, Blaabjerg O, Horder M. Analytical goals for the acceptance of common reference intervals for laboratories throughout a geographical area. Scand J Clin Lab Invest 1988; 48: 757-64.

8. Ricos C, Alvarez V, Cava F, Garcia-Lario JV, Hernandez A, Jimenez CV, Minchinela J, Perich C, Simon M. Current databases on biological variation: pros, cons and progress. Scand J Clin Lab Invest 1999; 59: 491-500. Available at www.westgard.com/guest17.htm.

9. Fraser CG. Quality specifications in laboratory medicine – current consensus views. Accred Qual Assur 1999; 4: 410-13.