The Establishment and Dissemination of Quality Goals

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Abstract: Many strategies have been proposed for the setting of quality goals in laboratory medicine. Traditional strategies are based on the use of reference intervals, opinions of clinicians, the state of the art, opinions of experts, assessment of the effect of error on clinical characteristics of tests, and biological variation. All have advantages and disadvantages but the use of data on biological variation appears to have many telling merits. The database is large and within-subject biological variation appears generally constant. Goals based on biology are available for bias as well as imprecision and the same theories can be used to generate goals for drug assays. A variety of proposals has recently been advanced for general models involving analyzing the effects of errors on diagnostic efficiency and sensitivity and a model for the allowable difference between two methods; it is of much interest that all of these generate quality goals based upon fractions of biological variation. Although in the U.S., it appears as if the advent of CLIA'88 has caused many concerns, in Europe there has been much recent rediscussion on goal setting. Approaches based on biology are much favored and, in essence, recommendations are that: desirable imprecision is less than or equal to one-half of the average within-subject biological variation, desirable bias is less then or equal to one-quarter of the group (within- plus between-subject) biological variation, and desirable difference between methods (or drift during monitoring) is less than one-third of the average within-subject biological variation. It is important to recognize that imprecision and bias must be considered together and that, when imprecision approaches the goal, bias must be small, and vice versa. Disseminating goals must be more actively pursued by all involved in laboratory medicine including journal editors and referees, industry, and organizers of PT and EQA schemes.

Introduction

Quality management processes, including the essential components of control, assessment, assurance, planning, improvement, and audit, have pervaded manufacturing and service industries in both private and public sectors, including all aspects of health care. However, to use such quality tools correctly, it is necessary first to define the standards of quality required. Perusal of the literature might suggest that problems are few because there are many

papers, reviews, and book chapters dealing with the generation and application of quality goals in laboratory medicine [1]. It does appear, however, that many still have difficulties in deciding the standards which should be attained by laboratories, ideally for all performance characteristics, but particularly for the important reliability characteristics of precision and bias (accuracy). There are plausible reasons for this including the facts that:

- tests are used in many clinical situations and it might be that there is no single set of goals which would make a method suitable for all purposes,
- there are many recommendations in the literature and it might be difficult to choose the most appropriate,
- new recommendations continue to appear, suggesting that there is no professional consensus on the topic,
- there appears to be no evidence that patients have been harmed by current performance,
- in countries which have legislation involving proficiency testing, the focus might be simply on achieving the standards required to pass, and
- industry does not appear to use professionally set goals as major considerations either in development or marketing.

In view of the apparent lack of ubiquitous use of numerical quality goals, these will be briefly critically reviewed here and then the widely accepted current recommendations documented.

Traditional strategies for setting quality goals

Traditional approaches for setting goals for precision (often used for total error, however) are based on use of (I) reference values, (ii) the opinions of clinicians, (iii) the state of the art, (iv) views of expert individuals and groups, (v) analysis of the effect of error on the clinical utility of tests, and (vi) biological variation. All have advantages and disadvantages which have been discussed in detail previously and are only summarized here .[2] Reference intervals are available for most quantities and the strategy is simple, but the fractions of the reference interval chosen to set goals are empirical, and reference intervals depend on the precision and bias of the analytical procedure, the population studied, and the statistical technique used for data reduction. The opinions of clinicians have been mainly obtained by questionnaire involving clinical vignettes but, *inter alia*, the difference between two results (or a result and a reference limit) are not due only to random analytical error as generally supposed but also to within-subject variation and pre-analytical variation, the use of the median result satisfies only half of the respondents, and the probability with which decisions are made is not always $P < 0.05$. The state of the art, even of a selected group of better laboratories, changes with time, laboratories may adopt special techniques in the analysis of samples circulated in proficiency testing (PT) or external quality assessment (EQA) schemes from which the state of the art is usually derived, and the matrix of the samples may not be the same as samples from patients. The views of expert individuals and groups, although interesting,

are often subjective and contradictory. Analyzing the effects of increasing errors on nosological characteristics such as sensitivity and specificity seems appropriate when a test is used in a single well-defined clinical situation. Problems arise, however, in generating clinical guidelines for the use of such test results in that there are often many guidelines for the use of a single test, these guidelines may become outdated or be corrupted in local practice, and they may create an unresponsive attitude to new developments or inhibit new thinking. Goals based upon biology are favored by many and are based upon the postulate of Cotlove et al [3] who suggested that: analytical error < 0.5 biological variation. This concept was expanded at the 1976 Aspen Conference of the College of American Pathologists [4] and it was suggested that, for diagnosis and monitoring - $CV_{analytical} < 0.5\ CV_{within\text{-}subject}$, and for screening - $CV_{analytical} < 0.5\ (CV_{within\text{-}subject}^2 + CV_{between\text{-}subject}^2)^{½}$; the formula in parentheses will be denoted henceforth simply as CV_{group}. This proposal was then accepted by the Sub-Committee on Analytical Goals in Clinical Chemistry of the World Association of Societies of Pathology in 1978.[5] Thus, more than two decades ago, the consensus was that quality goals were best based on biological variation.

The advantages of the approach based on biology

Goals based upon biological variation seem to have become generally accepted, but only slowly. The reasons for this might include the facts that, at least originally, (I) the database encompassed only a few quantities and the experimental work had been done on young healthy subjects, (ii) some of the calculated goals appeared too strict to be achieved with available technology and some appeared too loose, (iii) goals were not available for bias, (iv) goals were not available for exogenous quantities such as drugs, and (v) these goals were based upon statistical considerations and not on the clinical use of tests. These supposed demerits have been negated with the passing of time. Now, good data are available on the biological variation of many quantities, and the estimates seem generally constant and therefore ubiquitously applicable.[6] When goals appear too strict, these should be viewed as worthy targets, other objective goals used as interim measures, and strategies to provide quality laboratory practice, appropriate internal quality control, quality improvement, or investigation of alternative methodology instituted; when goals seem too loose, quality planning and appropriate quality control will save resources. Goals for bias based on biology have been proposed;[7] they showed that, to allow the use of common reference values, bias (as % deviation) < $0.25\ CV_{group}$, if the precision was negligible. Goals for drugs can be calculated [8] using a similar model based on pharmacokinetic theory as:

$$CV_{analytical} < 0.25\ \{[2^{T/t} - 1]/\ [2^{T/t} + 1]\}_{*}100$$

where T is the dosing interval and t the half-life.

Goals based upon recent models

In spite of the work done to refute the alleged criticisms of setting goals using data on biological variation, further general models have been proposed. Harris [9] expanded his earlier work to include bias and suggested that $CV_{analytical} < R(1/80 - 4/5\ bias^2/R2)]$ where R is the reference interval; he suggested as a rule of thumb, however,

that, in the absence of bias, $CV_{analytical} < 0.25$ $CV_{within\text{-}subject}$ for monitoring and $CV_{analytical} <$ 0.1R for diagnosis. Ross[10] considered the effect of errors on loss of diagnostic efficiency as a means of setting goals; it was suggested that, for individual testing, $CV_{analytical} < 0.64$ $CV_{within\text{-}subject}$ and, in further work,[11] it was proposed that $CV_{analytical} < 0.5$ $CV_{within\text{-}subject}$ and that bias < 0.25 to 0.33 $CV_{within\text{-}subject}$. Klee[12] proposed that an error budget, the squared sums of the imprecision and bias, be set to allow less than a 50% increase in the false-positive rate for classification of healthy subjects; the budget was allocated as allowable precision and bias of < 0.18 CV_{group} and < 0.36 CV_{group} respectively. It has also been suggested[13] that the allowable difference between methods used in the same laboratory for a single quantity can be calculated as < 0.33 $CV_{within\text{-}subject}$.

It is interesting that all these models, although none has yet been widely used, propose that analytical goals be based on fractions of biological variation.

Current consensus views

In the U.S., there appears to be much concern with the problems created by introduction of CLIA '88. It is considered that it would be a retrograde move if the standards laid down in this legislation became the analytical goals deemed suitable for use in laboratory medicine. In contrast, in Europe there has been a great interest in the harmonization of all kinds of activities, including the practice of laboratory medicine, and several groups have considered setting quality goals. A working group of the European Group for the Evaluation of Reagents and Analytical Systems in Clinical Chemistry[14] used the concepts based on biology and the need for interim goals for quantities for which these are currently unattainable to present numerical goals for commonly assayed quantities. After due consideration of all available models, it was recommended that: precision should be < 0.5 $CV_{within\text{-}subject}$ or less than the precision attained by the best 0.20 fractile of laboratories, whichever was the less stringent - the latter could be used when data on biological variation were unavailable; bias should be < 0.25 CV_{group} or < R/16 when data on biological variation were unavailable or < $CV_{within\text{-}subject}$ when these goals appeared unattainable with present technology. A further working group organized under the auspices of the European External Quality Assessment Organizers' Group has recently published [1] their views which show the renewed trend towards using biology; it was proposed that, for monitoring patients, $Sd_{analytical} < 0.5$ $SD_{within\text{-}subject}$ when changes in bias were negligible and bias < 0.33 $SD_{within\text{-}subject}$ when precision was negligible, and, for diagnostic testing, $Sd_{analytical} < 0.58$ SD_{group} when bias was negligible, and bias < 0.25 SD_{group} when precision was negligible. It is important to recognize that this working group considered that precision and bias ought to always be considered together and that, when large precision was present, only a small bias was acceptable, and *vice versa*.

Dissemination of quality goals

Although much work has been done on the generation and application of goals, which has been mainly disseminated through the publication of papers, letters, reviews, book chapters, and conference proceedings, there is no doubt that the correct application of goals could be encouraged. The authors of manuscripts concerned with evaluation of new methods, reagent kits, or analytical systems that do not use objective quality

goals as criteria of acceptability ought to be encouraged to apply these by journal editors and referees; moreover, journals could incorporate the use of quality goals as requirements in their instructions to authors. Industry could not only use objective goals to assist in the identifying the quantities for which improvements in methodology are badly needed and to use in method development, but they could assist very much in the disseminating information on quality goals by documenting these in their labeling just as the performance characteristics and reference values are currently included. Organizers of PT and EQA schemes could have a vital role in encouraging the use of objective quality goals through using these as the fixed limits for assessment of laboratory performance and through highlighting acceptable and unacceptable methodology using these criteria.

Concluding remarks

Setting quality goals has been the subject of much discussion for over three decades. There is no doubt that the current consensus is that goals for precision and bias are best based upon biological variation data and that these should be more widely used in many aspects of laboratory medicine. This is not to say that there are no unanswered questions and much work is still required on many topics including goals for tests done close to the patient, for tests done frequently, for other performance characteristics, and for qualitative and semi-quantitative tests. It is to be hoped that these challenges will be actively pursued by professionals in laboratory medicine rather than imposed by legislators.

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