Commentary

The Management of Post Analytical Correction Factors

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Abstract
Clinical laboratories may systematically apply factors to assay results after analysis, but before reporting, in order to facilitate comparison of data from different methods. This may be done to align with other patient results, reference intervals or clinical decision points. These factors, which we term Post Analytical Correction Factors (PACF), may be applied to all types of results derived from the method, i.e. quality control (QC) and external quality assurance (EQA), as well as the patient results. As the principal use of PACF is comparing patient results, it is important that the laboratory use commutable materials (i.e. patient samples) and a formal process to establish, apply and manage PACF. We report on preliminary guidelines for PACF from a recent workshop.

Introduction
In October 2015 the Australasian Association of Clinical Biochemists (AACB) conducted a Workshop on Quality Control, where the topic of post analytical factors was discussed and a consensus statement was prepared. We will call these factors ‘post analytical correction factors’ (PACF) and report on how to effectively manage them, particularly with the passage of time or the maintenance of them in a large network. We present an approach to the rational management of PACF which are commonly used in laboratories and have not as yet received any attention.

A range of different instruments and methods may be required to meet clinician and patient needs. Under accreditation standard ISO 15189, laboratories have an obligation to not only meet those needs but also to have reports that are clear and not confusing. PACF are one way laboratories can align results to facilitate comparison of patient results across different methods and with common reference intervals and decision points.

Because PACF are used for patient comparison, materials used to establish PACF must be patient-based and commutable between methods. Commutability of QC and EQA materials generally cannot be guaranteed, and so these are unsuitable for establishing PACF. PACF should never be established to align QC or EQA results for two reasons, firstly because the bias assessment tool should be separate from the calibration tool, and secondly as the QC or EQA materials are usually not commutable, and alignment with these targets may not represent effects on patient result.

When selecting instrumentation, pathology laboratories are required to consider analysers with features that best meet the different circumstances of their patient mix and laboratory locations. These factors include such factors as paediatric patients, point of care testing, specialty clinics or remote laboratories. The consequent mix of instrumentation may be from different manufacturers, use different principles of analysis, or have different sensitivity and interferences. This often produces minor differences in reference intervals for different instruments from the one manufacturer, and can reveal biases between methods from different manufacturers. Management of QC on multiple instruments measuring the same measurand either at the same site or in a distributed network has been discussed by Kuchipudi et al.1

Laboratories must also ensure that reports are not confusing for the clinicians using their results. PACF are used to align patient results so they are comparable across a laboratory network and can be compared to a common reference interval, simplifying the reporting and interpretation. The importance
of pathology results in patient care means that PACF should only be used to align results from assay methods with stable, reliable performance, and a predictable correlation based on patient results.

Laboratories use PACF in a variety of situations, including the following:

1. To align patient results from different instruments in the network, so that a patient receives the ‘same’ result regardless of which part of the network analyses that patient’s sample.

2. To allow patient results to be compared to a reference interval which may have been developed for another method. This may be considered when the results from the two methods differ significantly enough to warrant a new reference interval or decision point determination but the laboratory chooses to maintain the original reference interval, a decision which may have been driven by referrers. The move towards harmonisation of reference intervals\(^2\,^3\) has led to a need for some methods to have a PACF to correct for inherent bias compared with other methods. Managing these PACF can be problematic as factors get added to existing factors and the original reference interval determination process becomes unclear.

3. EQA results may have a factor applied by the laboratory before submission to align the results with other instruments in a network. As a general approach EQA should be unfactored if EQA is used to assess instrument performance, but factored if EQA is used to assess patient results. Unfactored results may be the most appropriate if EQA material is not commutable between the relevant instruments, as otherwise the factors relevant for patient samples may not be appropriate for the EQA material.

Guidelines for the Use of PACF

The following guidelines for managing PACF Factors were based on the consensus meeting of the AACB.

1. One instrument, or a group of identical instruments, should be designated as the reference instrument(s). This instrument must have documented stability over time demonstrated by internal QC and, where available, external QA.

2. PACF should only be applied where the analytical specificity of the reference instrument and the factored instrument are the same.

3. Due to the significance of PACF in interpreting patient results, it is essential the PACF be managed in a systematic controlled manner.

4. PACF can be used when different instruments are used to report results for an analyte where the difference in absolute value of results from the different instruments is clinically significant, i.e. significant bias compared to the analytical or clinical goal.

5. Determining PACF

   a. PACF must be determined using patient samples covering the concentration range expected in the patient population.

   b. PACF must not be determined using QC, EQA or other materials unless they are verified as commutable for the relevant methods.

   c. PACF should include sufficient samples for statistical validity to verify performance. The number of samples will depend on the precision of the assays, the spread of sample concentrations and the required accuracy of the results.

6. Monitoring PACF

   a. PACF must be reviewed regularly, the interval being dependent on the capability of the assay.

   b. Different samples must be used to check the accuracy of PACF from those used to establish them.

   c. Review must be based on patient samples run on the reference and factored analysers. Care must be taken to avoid relevant pre-analytical factors (e.g. exposure to light for bilirubin, exposure to air for bicarbonate).
d. The review must be performed in a systematic manner. This includes testing at a defined frequency (which may be based on time or other factors, such as new lot numbers of calibrators or reagents), systematic assessment of results with performance criteria and graphical analysis to allow assessment of proportional and absolute differences.

e. The performance of the PACF may be supported using data on patient means, if there are sufficiently large numbers of samples (note that this generally only checks the effect of the factors at one concentration).

(The above description of the review process shares many features with an EQA program and can be correctly termed an Internal QA program.)

7. PACF should be re-established when the reference instrument is changed.

8. EQA should generally not have PACF applied as EQA is commonly used to compare with peer group instrument performance.

It has been argued that EQA plays a role in the standardisation process and should be used to measure consistency of results from different methods. This requires that EQA results do not have factors added but is confounded by the non-commutability of most current QA material. As described above, patient samples should be used to confirm result consistency. EQA providers should consider ways of identifying results with and without PACF to ensure the validity of within method comparisons.

Laboratories using PACF must be aware of their presence and where in the system they are applied. For example, if they are applied in middleware or in the laboratory information system, the raw results from the analyser should not be provided to doctors over the phone. In this setting the internal QC results will also be unfactored. In contrast, if the factors are applied on the instrument, then all results (patients, QC and EQA) will be factored. In this setting QC targets from an instrument or QC manufacturer may not be appropriate for assessing performance. A PACF may also be viewed as an in-house in vitro diagnostic medical device (IVD) or laboratory modification of a manufacturer’s instructions and may therefore require a formal assessment, review and authorisation process.

The application of PACF raises a number of risks for a laboratory. If errors are made with setting or reviewing factors, a large number of erroneous results may be issued.

The protocols to establish, apply and review PACF must be sound with appropriate checks in the processes.

Competing Interests: None declared.

References
1. Kuchipudi LS, Yundt-Pacheco JC, Parvin CA. Designing QC rules for multiple instruments: should a QC rule be centered on individual instrument means or on a fixed mean? Should the limits be based on individual instrument SD’s or on a fixed SD? [Abstract B150]. Clin Chem 2014;60:S174.