Title: Blood Sciences Uncertainty of Results

No.of copies :	2
Location of copies :	1. QPulse
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1. Introduction

The laboratory strives to maintain a high standard of performance. Good laboratory practice and effective quality control procedures are invaluable at maintaining this position. However it should be understood that there is an inherent degree of uncertainty in any laboratory investigation. The level of uncertainty is a combination of three factors; pre-analytical influences, analytical variation and biological variation. This 'uncertainty' means that if a series of samples are taken from one individual, for any particular laboratory test, then the results will not be exactly the same.

Although some of the uncertainty can be controlled by the laboratory it is important for users to recognise the effect of pre-analytical and biological variation when they interpret laboratory tests and to understand the changes in values that must occur before they can be regarded as significant.

The following information regarding laboratory uncertanity of results is available to users on the Pathology Website.

2. Uncertainty of laboratory results

All assays carry an inevitable degree of uncertainty. The Uncertainty Policy in Pathology (QU-COM-D-32) identifies the risks/uncertainties with all the steps in the pre-examination, examination and post examination phase and the control measures that are used to ensure that variation and possibilities for error are minimised. These factors are well recognised but some occur by random error alone. A random error is associated with the fact that when a measurement is repeated it will generally provide a measured value that is different from the previous value. It is random in that the next measured value cannot be predicted exactly from previous such values.

Within the laboratory we monitor analytical imprecision by a variety of methods:

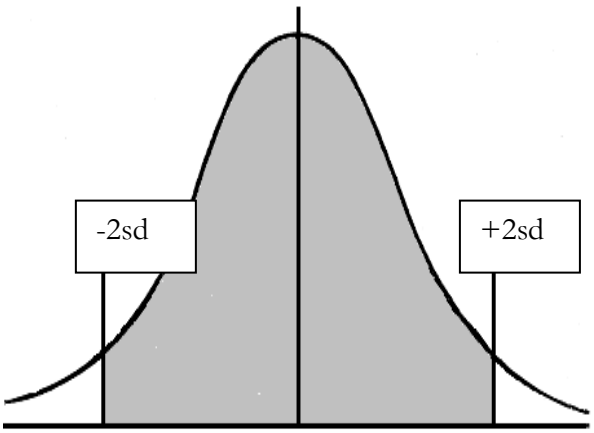
2.1 Qualitative tests

Some laboratory results require 'intrepretative' assessments i.e. Positive or Negative or subjective analysis e.g.. microcytic ++. There is an inevitable degree of observer bias in these assessments. However, internal quality schemes are designed to minimise this variability but observer bias will always be a factor.
Not only should users bear in mind these uncertainties when interpreting any laboratory value, but they should also be cautious when attempting comparisons between different laboratories.
Specific information for qualitative tests can be found in the individual test SOPs.

2.2 Quantitative tests

Analytical variation can be divided into random error (precision) and systematic error (bias). For the monitoring of a patients' condition both most be controlled and maintained at an acceptable level. This level may vary from analyte to analyte due to the nature of the assay but can be controlled by the laboratory.
The Blood Sciences Quality Control Procedure (SOP-BS-076) outlines how it utilizes both Internal QC and External QA schemes within procedures to monitor performance.
Regular review of External QA samples offers reassurance that accuracy and consistency are being maintained through peer group analysis.

Day to day assurance is provided by repeated analysis of internal quality control material. This analysis occurs at timed intervals. The time period will between analysers or specific tests due to manufacturers guidelines or the experience; backed up by statistical data; of the laboratory staff. This data is reviewed regularly for trends and required action.
Using a basic interpretation of method mean and Standard Deviation cut off at + and – 2 intervals (see figure 1, below), we are able to access bias and uncertainty for parameters run on these analysers. Additional Westgard statistical rules may also be applied to aid the laboratory to spot biases and trends.
Figure 1; Typical normal distribution around a mean with cut off points at + and – 2 standard deviations



All staff members are trained in Quality Control procedures to recognise a deterioration in performance of an assay (for more information please see Qpulse reference HR-TR-CB-TUT-043; Quality Control Tutorial) and have procedures to follow in case more guidance is required (e.g. Qpulse reference SOP-CB-D-1; Biochemistry Quality Control Review and Interpretation).
Senior staff review this data regulaly for trends in performance.

As a laboratory generally employs a measurement procedure for long periods of time, the uncertainty of measurement information most relevant to interpreting its test results against fixed reference values is the imprecision of the test results across as many routine operating conditions as possible (for example; multiple calibrator and reagent batches, multiple operators, equipment maintenance, summer/winter etc). With the caveat that quality control materials may not totally reflect the analytical behaviour of patient specimens, this imprecision is most easily derived from long-term internal quality control (QC) data, calculated as standard deviation (SD) or coefficient of variation (CV%). For the purpose of recording estimates of uncertainty of measurement the imprecision should be documented as the 95% confidence interval (± 1.96 SD; or ± 1.96 CV%).

3. **Performance Requirements for the Measurement of Uncertainty**

Once the level of uncertainty has been calculated for each assay the laboratory compares the calculated imprecision values to quoted target values to assess the assays suitability. The quoted targets can be obtained from several sources including:

- Westgard biological variation data – this data is calculated from the summary reports from available studies to give a desirable assay imprecision score (for more information please see https://www.westgard.com/guest17.htm);
- Quoted imprecision values from manufacturers instructions for use (these are used where Westgard information is not available).

The laboratory use the Westgard desirable assay imprecision score as the primary target of choice (ref. BRILS Cross site Biochemistry Meeting; October 10th 2018).

Comparison of the performance of each assay will be included in appendix 3 and reviewed during analyser ongoing verification, performed on an annual basis for all the analysers that the assay is performed on (please see Maintenance of ongoing validation/verification status; TEMP-D-84 for more information). All assays that fall outside of the desired criteria will be investigated. It should be noted however that assay imprecision does vary through out the assay range, with poorer performance recognised as each assay reaches their limits of detection. Many required parameters (e.g. rule in rule out) may occur at these limits and therefore a clinical perspective has to be applied to the assay and comparison of the target to the more stable portion of the assay linearity may be more applicable to assess suitability. The quoted Westgard and or IFU values are 'desirable' therefore any assay that is performing above the target, but within an acceptable limit, may also be designated as acceptable. In addition the laboratory is often confined to practical constraints during assay selection i.e. the laboratory may be restricted to the assays supplied by their manufacturer of choice, with not all assays performing to the same levels of performance. Also as a guide based on experience the Biochemistry laboratory at Barnsley uses the following imprecision levels to assess acceptable assay performance at the most stable fraction of assay linearity;

- Immunoassay (including EMIT spectrophotometry assays) - CVs of 10% or less
- Ion selective electrodes - CVs of 1.5% or less
- Routine Biochemistry spectrophotometry assays - CVs of 4% or less
- HPLC - CVs of 4% or less

Where the assay is used on more than one platform the mean of the selected systems is used

4. Summary of revisions

Version	Summary of change
1	Not applicable – first issue.
2	1. Changed to include full range of Chemistry assays 2. Changed to reflect measurement of uncertainty
3	Further information on the calculation of results Addition of manual ESR
4	Addition of serum osmolality range and QC details
5	Addition of uncertainty for manual differential. Inclusion of IQC review information.
6	Updated for 2017 data
7	Updated aCCP date and statement in the introduction that information available on Pathology Website
8	Added PTH data
9	Updated for 2018 data
10	Levels added to cover range of the Biochemistry assays as suggestd in UKAS finding. Assays include; AFP, alcohol, ALT, aCCP, AST, Ca125, Ca199, Cholesterol, CEA, CRP, Glucose, GGT, HDL, paracetamol, prolaction, PSA, Rf and TNI Section 5. Performance Requirements for the Measurement of Uncertainty with data in Appendix 3 added
11	Data for Actin FS APTT assay included
12	New CEA lite reagent and hs TNI
13	Removal of specific Chemistry and Haematology aspects so these can be managed independently due to a variation of review periods. Change the review time to 3 years.