Best practices to recover from an out-of-control event

Quality Control

Questions and Answers

1. **I know QC is used to identify issues, but can patient samples be used instead of QC to identify issues?**
   Patient Based Real Time QC Monitoring is a complimentary technique that can be used in addition to performing routine QC. The laboratory can also consider maintaining a reference sample set consisting of patient samples or patient sample pools that have been previously analyzed (and value-assigned) when the measuring system is performing as expected. The samples can be used as routine QC materials using a multi-rule strategy, or to assist with investigation when routine QC results exceed the acceptable range. Limitations of using patient samples as routine QC include sample volume limitations and different stability characteristics as compared to commercial QC products. The laboratory should ensure that the patient samples are stable under the intended storage conditions and storage duration, and any potential freeze/thaw effects have been investigated if the samples will be stored frozen.

2. **Is PBRTQC like "moving Averages"?**
   Use of moving averages applied to patient sample results is one of the data analysis approaches used for Patient Based Real Time Monitoring, so it can be considered a type of PBRTQC. Other data analysis approaches for PBRTQC include use of moving patient result medians, exponentially weighted means, cumulative sums or other types of algorithms.

3. **Which criteria would you use to determine if repeat results match?**
   Criteria for repeat results can be based on allowable Total Analytical Error (TEa), which is the magnitude of error that can be tolerated without an adverse impact on patient care. TEa can be determined using clinical outcomes studies, biological variation studies or assay analytical performance characteristics.

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4. **When repeating QC after an out-of-control flag, do you recommend repeating just the QC level(s) out or all levels of QC?**
   If only one level of QC fails acceptability criteria and other levels are not near the acceptance limit (about to fail), then it is likely OK to begin troubleshooting by repeating only the level that was out-of-control. However, if an out-of-control condition for the measuring system is identified and corrective action is implemented such as recalibration, then all levels of QC need to be analyzed, before resuming patient sample testing, to verify that the measuring system meets performance expectations after corrective action.

5. **Which frequency do we need to test the calibrator?**
   Quality control materials should be analyzed after every calibration and at the minimum frequency for QC analysis established by the laboratory. One of the primary reasons to analyze QC is to verify that the calibration of the measuring system is acceptable. Some regulatory agencies require periodic "calibration verification", which means verification that the measuring system response is linear over the analytical measurement range. For example the College of American Pathologists (CAP) accreditation criteria require calibration verification to be performed every 6 months. Our laboratory also verifies new lots of calibrators by analyzing the new lot as unknown samples and comparing the measured values to the target values established by the manufacturer.

6. **What do you mean with pre-analytical pbrtqc?**
   Patient Based Real Time QC monitoring utilizes patient sample results to evaluate analytical performance in real time (e.g. through the use of moving averages, cumulative summation or other modeling techniques). An advantage of this type of quality assurance approach is that the pre-analytical phase of testing is monitored because the approach uses actual patient samples that are subjected to components of preanalytical processing (e.g. centrifugation) that routine QC materials are typically not subjected to.

7. **In doing a look back of patient results to be repeated, where do we begin - samples after the time of the last good QC or samples prior to the time of the failed QC?**
   The most effective approach would be to start with repeating sets of patient samples just prior to the time of the failed QC, and work backwards in time, to the point of the last acceptable QC. This approach would reduce the number of patient samples that need to be repeated if the out-of-control condition occurred at a time point close to when the out-of-control event occurred.

8. **At what point in the process do you recommend repeating with backup QC material?**
   The first step in the investigation process is to repeat the analysis using a fresh vial of the same lot of QC material. If the result does not pass acceptability criteria, then a measuring system problem should be investigated. If the laboratory would like to try an alternate lot of QC material or use a different manufacturer's QC product, the laboratory would need to verify that there is no measuring system problem first because use of a new lot or different QC material would require validation of the QC target mean, which typically requires 10 day's worth of data. A preliminary target mean for a new lot or different QC material could be set if needed, but the laboratory would need some other means of verifying that the measuring system itself is performing as expected. An alternate lot or alternate QC material can be used to investigate and out-of-control event only if the target mean has already been established prior to the out-of-control event.

9. **Can you please explain the formula to calculate the TEa based on biological variation estimates?**
   The equation is allowable total analytical error = 1.65 x 0.5 CVi + 0.25 (CVi2 + CVg2)1/2, where CVi is the intra-individual biological variation and CVg is the inter-individual biological variation. There is a good explanation of the components of the formula in Fraser CG. General strategies to set quality specifications for reliability performance characteristics. Scand J Clin Lab Invest 1999;59:487-490.

10. **You mentioned that repeating patient results depending on what QC level fails as one method for troubleshooting. For example if the lower level failed then repeating the lower test results instead of all patient results could be done. Can you explain this method again?**
    The example showed a scenario where you may not need to repeat all patient sample concentrations if only a single level of QC fails. For example, LV1 QC was acceptable, but the LV2 QC failed high. The Root Cause was found to be calibration drift due to the fact that the calibration frequency was insufficient. Since LV1 QC was not affected, and LV2 QC failed high, you would only need to repeat patient samples with concentrations greater than the target mean for LV1, and you would not need to repeat values less than the target mean for LV1, because those results would not have been affected by this error. You need to be very careful using this strategy because it depends on which QC levels were affected, on the magnitude of the error, and the direction of the error.

11. **When should we take action for trending QC points which are still within 3 SD?**
    The specific combination of multi-rules used depends on the allowable total analytical error for the assay. A good resource to learn more is Clinical and Laboratory Standards Institute (CLSI). Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions. 4th ed. CLSI guideline C24. Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2016.

12. **How can I apply rules to 4 levels of Quality Control for 21 biomarkers run on a 96 well plate based assay?**
    The multi-rule strategy can be used for any number of QC levels for each analyte. A discussion can be found in Westgard JO, Westgard SA. Quality control review: implementing a scientifically based quality control system. Annals of Clinical Biochemistry 2016, Vol 53(1):32-50. A multi-rule strategy can be applied to each individual biomarker, because each biomarker tested is considered a separate assay. Therefore, the laboratory is actually testing 21 different analytes and separate QC multi-rule sets or a separate QC strategy is needed for each.

The following questions were asked during the presentation. Please see the webinar recording for the responses.

13. **When results have not yet been reported, would you suggest to repeat all patient results and change them or would you also use the approach to just correct results with differences greater than the Total Allowable error?**

14. **Do you have any recommendations for what to do if your QC is out of control for an extended period (for example when a QC shifts due to a Reagent lot change) but you still need to process patient samples?**

15. **How often should QC be performed? Once a day or several times?**

16. **What should we do with some analytes which don't have biologic variability?**

17. **I was wondering if you could comment on QC tips for qualitative (yes/no; pos/neg) lab assays?**