Best Practices to Recover from an Out-of-Control Event

Lorin Bachmann, PhD, DABCC
Virginia Commonwealth University, United States
lorin.bachmann@vcuhealth.org

Disclosures

Bio-Rad – speaker honorarium

Thermo Fisher Diagnostics – research grant funding and travel support

Abbott Laboratories – research grant funding

CLSI – Chair, Expert Panel on Chemistry and Toxicology, volunteer
Learning Objectives

1. Identify the first steps to take after an out-of-control event

2. Discuss how to evaluate patient results after an out-of-control event

3. Outline approaches to not only correct patient results but also to implement preventative actions

Primary reference

CLSI C24

- Design an effective QC strategy
- Select QC materials and QC frequency
- Establish QC target means and SDs
- Troubleshooting
- Recovery from out-of-control events
Laboratory errors cause harm to patients and increase cost

Mistakes in a stat laboratory: types and frequency

Mario Plebani* and Paolo Carraro

Clin Chem 1997; 43(8): 1348-1351

40,490 laboratory results = 0.47% error rate
[1/200 results]

6.4% → wrong care or inappropriate treatment
19.0% → unnecessary work-up, increased cost

Types of laboratory errors

Categories of Laboratory Errors

Phases of testing
Pre-analytical: 46-68%
Analytical: 7-13%
Post-analytical: 19-47%

Analytical error types
Instrument: 14.2%
Calibration: 9.0%
Reagent: 3.3%

Routine QC evaluates the analytical phase of testing

Laboratory Medicine 2012; 43(2): 41–44
Arch of Pathol Lab Med Dec 1996; 120: 1094-1101
Common causes of QC failures

- **Problem with the QC material itself** – improperly reconstituted, improperly stored, wrong QC material analyzed, inappropriate QC target mean or SD
- **Problem with reagents** – improper formulation or preparation, onboard degradation, altered shelf life, improperly stored, inappropriate QC target mean for a new reagent lot
- **Problem with calibrator** – improper formulation or target value assignment, improperly prepared or reconstituted, improper calibration frequency
- **Instrument problem** – lamp degradation, leak in tubing or damaged pipettor seals, mixer failure, pump failure
- **Inadequate maintenance** – inadequate cleaning or decontamination, wearing of parts
- **Improper procedure** – failure to follow SOP, inadequate SOPs or training program
What steps should be taken when a QC out-of-control event occurs?

Steps to recover from an out-of-control event: PHASE 1

1. DETECT the analytical measuring system error (QC alert)
2. STOP reporting patient results
3. INVESTIGATE to determine the ROOT CAUSE of the problem
4. IMPLEMENT CORRECTIVE ACTION to correct the problem
Steps to take after an out-of-control event: PHASE 2

5. EVALUATE IMPACT on previously reported PATIENT RESULTS

6. Take steps to MITIGATE PATIENT HARM

7. IMPLEMENT PREVENTATIVE ACTION to prevent recurrence of the problem

Be sure to Document the entire process.

---

**DETECT the analytical measuring system error**

Establish an effective QC program

- Set QC target means (20 days) and target SDs (several months)
- Establish automated QC multi-rules (ex: 1,3s; 2,2.5s (within and across control), 8_{1.5}s, R4s)
- Routinely review Levey-Jennings charts
Immediately take measuring system (or assay) out of service, turn off auto-verification

Check other levels of QC

Check QC on other analyzers performing the same assay

Check QC for other analytes

STOP patient result reporting

Analyzer 1
QC ALERT

Analyzer 2
[ABOUT TO FAIL]

INVESTIGATE to determine the ROOT CAUSE

Review Records to get started

Any developing QC trends?

Any recent changes to the assay – ex: new reagent lot, new calibrator lot?

Any recent maintenance issues or parts replaced?
Tools to evaluate recent assay performance

Levey-Jennings charts and QC multi-rules - daily, weekly, monthly

Routine laboratory records – calibration records, lot changes, maintenance logs, temperature charts

Other laboratory QA records – 6 mo linearity checks, among-instrument comparisons

Peer Group QC data

Patient Based Real Time QC (PBRTQC) monitoring

Steps to recover from an out-of-control event: PHASE 1

1. DETECT the analytical measuring system error (QC alert)

2. STOP reporting patient results

3. INVESTIGATE to determine the ROOT CAUSE of the problem
Repeat QC analysis using a fresh container of control material

Repeat QC OK?

YES

NO

Is repeat QC near limit of acceptable range?

YES

NO

Root cause not determined
Continue to investigate

ROOT CAUSE
Problem with QC material itself (or QC acceptance criteria)

- QC material evaporated or improperly stored
- QC material nearing expiration
- Wrong QC level analyzed
- Damaged shipment of QC material
- Using incorrect target mean for a new lot of QC material

4.8
5
5.2
5.4
5.6
5.8
6
6.2
Calcium QC LV1

ROOT CAUSE
Degradation of the QC material was the problem

CORRECTIVE ACTION
Use a fresh container of QC material
Steps to recover from an out-of-control event: PHASE 1

1. DETECT the analytical measuring system error (QC alert)
2. STOP reporting patient results
3. INVESTIGATE to determine the ROOT CAUSE of the problem
4. IMPLEMENT CORRECTIVE ACTION to correct the problem

Implementation of corrective action is NOT THE END of the recovery process!!

Steps to take after an out-of-control event: PHASE 2

5. EVALUATE IMPACT on previously reported PATIENT RESULTS
6. Take steps to MITIGATE PATIENT HARM
7. IMPLEMENT PREVENTATIVE ACTION to prevent recurrence of the problem
EVALUATE IMPACT on patient results

Measuring system was actually performing as expected

QC Chart

ROOT CAUSE:
Problem with QC material itself

No need to repeat patient samples

PREVENTATIVE ACTION
Modify QC material open-vial stability

Glucose QC LV1

Target Mean

-3 SDI

+3 SDI
Repeat QC OK?

NO

Replace reagent wedge

Repeat QC OK?

NO

Recalibrate with freshly prepared calibrator

NO

Repeat QC OK?

Root Cause
Instrument pump seal leaking

Call Technical Service

A problem with the measuring system is likely

Do not just repeat QC until it passes

Target Mean

-3 SDI

-2 SDI

-3 SDI

+2 SDI

+3 SDI

1

2

3

4

5

6

7

8

9
### EVALUATE IMPACT on patient results

- **ROOT CAUSE**: Problem is measuring system related
- **Patient results may be erroneous**
- **Patient samples must be repeated**

**QC Chart**

- **Patient specimens**
- **QC specimens**

Measuring system was NOT performing as expected

### EVALUATE IMPACT on previously reported patient results

Determine the date/time of the last acceptable QC
Determine number of samples analyzed since the last acceptable QC

**Repeat ALL patient samples** or **Repeat SUBSETS of patient samples**

**Patient specimens**
**QC specimens**

- N=10
- N=10
- N=10
May not need to repeat all patient sample concentrations if only a single level of QC fails.

**ROOT CAUSE**
Error due to calibration drift - calibration frequency inadequate, corrected by recalibration.

QC LV1 had no effect, Only repeat patient samples with original result > 59 mg/dL

---

Do corrected reports for patient result repeats need to be issued?

**Allowable Total Analytical Error (TEa)**
Limit for acceptable imprecision and bias for the result of a single measurement.
Clinical outcomes – allowable TEa based on change of analyte concentration in disease or for therapy; professional practice guidelines, clinical trials studies

Biological variation – biological variation studies; databases (EFLM, Westgard QC)

State-of-the-art (assay performance) – manufacturer’s package insert, laboratory’s validation data


EFLM Biological Variation Database: https://biologicalvariation.eu/

Glucose (serum/plasma)

Between-individual (CV$_g$): 8.1%

Within-individual (CV$_i$): 5.0%

References

<table>
<thead>
<tr>
<th>Reference</th>
<th>Estimate of CV$_g$</th>
<th>Estimate of CV$_i$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-term, within-person variability in clinical chemistry test results, Edelstein J, Chemiseaux U and Shek Y, 1994, Arch Pathol Lab Med, 118, 496-500</td>
<td>4.2</td>
<td>7.8</td>
</tr>
<tr>
<td>Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. Harris RF, Kenorley R, Strachan J, and Cotlove E, 1972, Clin Chem, 18, 1922-7</td>
<td>5.6</td>
<td>7.8</td>
</tr>
<tr>
<td>Biological and analytic components of variation in long-term studies of serum constituents in normal subjects. IV: Results of a study designed to delineate long-term analytic deviations. Young DG, Harris RF, and Cotlove E, 1971, Clin Chem, 17, 409-10</td>
<td>8.8</td>
<td>2.7</td>
</tr>
<tr>
<td>La variabilidad biológica intraindividual como objeto de calidad analítica. Roda C, Codina R, 1995, Rev Esp Quimioter, 38, 34-6</td>
<td>10.8</td>
<td>10.8</td>
</tr>
</tbody>
</table>
TEa = 1.65 \times 0.5 \text{CV}_i + 0.25 \left( \text{CV}_i^2 + \text{CV}_g^2 \right)^{1/2}

CV_g: 8.1%  
CV_i: 5.0%

Calculates TEa based on biological variation estimates

%Total Error Specifications

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>9.8</td>
<td>6.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>

https://biologicalvariation.eu/search?q=glucose

TAKE STEPS TO MITIGATE HARM – issue corrected reports to providers

<table>
<thead>
<tr>
<th>Original Result Glucose</th>
<th>Repeat Result</th>
<th>Unit Diff</th>
<th>% Diff</th>
<th>Issue Corrected Report?</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>91</td>
<td>-11</td>
<td>-10.8</td>
<td>YES</td>
</tr>
<tr>
<td>78</td>
<td>65</td>
<td>-13</td>
<td>-16.7</td>
<td>YES</td>
</tr>
<tr>
<td>225</td>
<td>221</td>
<td>-4</td>
<td>-1.8</td>
<td>NO</td>
</tr>
<tr>
<td>110</td>
<td>89</td>
<td>-21</td>
<td>-19.1</td>
<td>YES</td>
</tr>
<tr>
<td>68</td>
<td>56</td>
<td>-12</td>
<td>-17.6</td>
<td>YES</td>
</tr>
<tr>
<td>367</td>
<td>350</td>
<td>-17</td>
<td>-4.6</td>
<td>NO</td>
</tr>
<tr>
<td>98</td>
<td>90</td>
<td>-8</td>
<td>-8.2</td>
<td>NO</td>
</tr>
<tr>
<td>121</td>
<td>105</td>
<td>-22</td>
<td>-17.3</td>
<td>YES</td>
</tr>
<tr>
<td>280</td>
<td>266</td>
<td>-14</td>
<td>-5.0</td>
<td>NO</td>
</tr>
<tr>
<td>325</td>
<td>311</td>
<td>-14</td>
<td>-4.3</td>
<td>NO</td>
</tr>
<tr>
<td>97</td>
<td>85</td>
<td>-12</td>
<td>-12.4</td>
<td>YES</td>
</tr>
<tr>
<td>101</td>
<td>82</td>
<td>-19</td>
<td>-18.8</td>
<td>YES</td>
</tr>
</tbody>
</table>

Develop tools to enable expedited review and automated decisions
Approaches to mitigate patient harm

- Develop data entry templates to quickly identify patients that require corrected reports
- Call in extra staff to assist with patient sample repeats and provider phone calls
- Issue memos to clinical staff in real time
- Engage Risk Management or institutional Safety Teams

Steps to take after an out-of-control event: PHASE 2

5. Evaluate Impact on previously reported patient results

6. Take steps to MITIGATE PATIENT HARM

7. Implement Preventative Action to prevent recurrence of the problem

PREVENTATIVE ACTION
Implement more frequent preventative maintenance including pump seal replacements
Approaches for PREVENTATIVE ACTION

Increased frequency of QC analysis

- If assay is unstable
- For large testing volumes
- For results with immediate clinical intervention
Establish QC rules based on method performance relative to TEa limits

\[ \text{Sigma}_{(x)} = \frac{(\text{TEa}_{(x)} - |\text{Bias}_{(x)}|)}{\text{SD}_{(x)}} \]

\[ \text{Sigma} = \frac{\text{TEa}_{(x)}}{\text{SD}_{(x)}} \]

- More conservative SDI criteria needed to keep assay in control
- Use QC Multi-rules (1, 3s; 2, 2.5s within and across, 8, 1.5s, R4s)

· A small bias can be tolerated
· Larger SDI criteria can be used (1, 5s)

Slide courtesy of Greg Miller
Peer Group QC programs

Lot 1088
Peer group size
L1 = 1367
L2 = 1368
L3 = 1370

Acceptability criteria: within ±3SDI and CV < 1.5x group CV

Historical performance data for current lot and previous lots included

Peer Group QC programs

Peer Group Blood Gas
Program: O2HB
Reagent Lot#: 15208016-7, 15208019-815208016-9

<table>
<thead>
<tr>
<th>Test</th>
<th>Lab Mean</th>
<th>Group Mean</th>
<th>Group SD</th>
<th>Group SDI</th>
<th>Notes</th>
<th>SDI Range</th>
<th>SDN</th>
<th>Group CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>O2Hb LV1</td>
<td>81.8</td>
<td>82.3</td>
<td>0.46</td>
<td>1.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2Hb LV2</td>
<td>51.4</td>
<td>48.5</td>
<td>0.61</td>
<td>4.75</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O2Hb LV3</td>
<td>22.7</td>
<td>20.4</td>
<td>0.80</td>
<td>2.88</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Results can be submitted in real time, peer group data provided
- Can review peer group QC values for new lots of reagent, calibrator, assay reformulations
- Can be used by manufacturers to assist with troubleshooting
- Can facilitate faster identification of the root cause of the issue
**Patient-based real-time QC (PBRTQC)**

Means, medians, exponentially weighted means, cumulative sums (or other metrics) are calculated every N patient sample results.

Metrics compared against acceptability criteria limits (based on: SDI, RCV, TEa, modeling approaches) and alerts generated.

**Variables that influence effectiveness:**

- Number of patient results to average
- How to identify outliers and extreme values - subgroups needed, not useful for all analytes
- What magnitude of error should trigger an alert

![PBRTQC Accuracy Plot](image)

**Responding to an out-of-control event:**

- Review records
- Run assay QC immediately to confirm alert
- Run previously analyzed patient samples to confirm alert
Cumulative Summation – can be used for QC or patient samples

SDI to trigger calculation: 0.5
CUSUM value to fail rule: 3.0

Slide courtesy of Greg Miller
Comparison of PBRTQC to standard statistical QC

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Standard QC</th>
<th>PBRTQC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>1-3x per day</td>
<td>After a defined # of patient samples</td>
</tr>
<tr>
<td>Phases Tested</td>
<td>Analytical</td>
<td>Pre-analytical, Analytical, Post-analytical</td>
</tr>
<tr>
<td>Commutability Characteristics</td>
<td>Not commutable (for most)</td>
<td>Commutable</td>
</tr>
<tr>
<td>Type of Error Detected</td>
<td>Systematic, Random</td>
<td>Systematic</td>
</tr>
</tbody>
</table>


Steps to respond to an out-of-control event:

- **PHASE 1:** Detect Error, Stop Patient Testing, Investigate and Identify Root Cause, Implement Corrective Action
- **PHASE 2:** Evaluate Impact on Patient Results, Mitigate Patient Harm, Implement Preventative Action

TEa should be used to evaluate the impact on patient results after an out-of-control event, and also for designing an effective QC program that will prevent errors.

Additional tools are available that can improve ability to DETECT errors and PREVENT them from reaching clinical significance.