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 SDs or on a Fixed SD?**

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**Abstract**

**Background**

Objective – Compare performance of QC strategies centered on the individual instrument mean versus a fixed mean and limits based on individual instrument SD versus a fixed SD when applied to multiple instruments testing the same analyte.

Relevance – Using a fixed mean and SD appears to be a common practice when multiple analytic units evaluate the same analyte. The comparative efficacy of this approach has not been formally evaluated. We compare the expected number of unreliable final results reported due to the occurrence of an out-of-control condition, E(Nuf), when the QC rule means are centered on the instrument means versus a fixed mean and when the QC rule limits are established based on the instrument SDs versus a fixed SD.

**Methods**

We consider 4 analytic units in the laboratory evaluating the same analyte. We assume each instrument evaluates 2 QC levels using a 1:3s/2:2s/R:4s QC rule every 100 patient examinations. The fixed mean is set to the average of the instrument means. The fixed SD is set so the overall false rejection rate across the 4 instruments is 0.0097. We investigate a range of means and SD’s for the 4 instruments. The resulting instrument CV and bias combinations have sigma values \((TEa – bias)/CV\) ranging from 3 to 6. We determined the maximum value for E(Nuf) and area under the E(Nuf) curve for the 4 different cases:

1. QC rule means centered on instrument means and QC rule limits based on instrument SDs
2. QC Rule means centered on a fixed mean and QC rule limits based on instrument SDs
3. QC rule means centered on instrument means and QC rule limits based on a fixed SD
4. QC rule means centered on a fixed mean and QC rule limits based on a fixed SD

In each of the above cases we design the QC rules so the overall false rejection rate across the 4 instruments = 0.0097, which is the false rejection rate for the 1:3s/2:2s/R:4s QC rule.

**Results**

Tables of results are computed for the simulations. In general, the maximum E(Nuf) and the area under the E(Nuf) curve were lowest for rules using a fixed mean and fixed SD for the instruments.

**Conclusion**

Using a fixed mean and fixed SD for the QC rule had the best performance. The fixed mean appears to balance the risk of reporting unreliable results across multiple instruments while the fixed SD allocates more false rejection rate to poorer performing instruments resulting in a lower overall risk of reporting unreliable results when individual instruments have moderate to good process capability (3-6 sigma).
Introduction

There is substantial guidance on QC design when an analyte is evaluated on a single instrument, but there is little guidance on QC design when an analyte is evaluated by multiple instruments (or analytical units) that perform the same assays.

Some laboratories approach QC design for an analyte evaluated on multiple instruments the same as a single instrument, using the instrument mean for the QC mean and setting the QC limits using the instrument SD.

Other laboratories use the same QC mean and SD for all instruments (a fixed mean and a fixed SD).

We are interested in the impact these different design approaches have on patient result reliability.

We assume the instruments all use the same QC material and that they are expected to produce the same results for each QC material.

We compare the expected number of unreliable patient results due to the occurrence of a persistent out-of-control condition, E(Nu), for the 4 possible combinations of using individual instrument parameters versus a single fixed parameter:

- Individual instrument means, individual instrument SDs
- Single fixed mean, individual instrument SDs
- Individual instrument means, single fixed SD
- Single fixed mean, single fixed SD

Methods

In this study we make the following assumptions:

- 4 instruments (analytic units) in the laboratory evaluating the same analyte
- 1:3:2:2/4:4 QC multi-rule
- 2 concentration levels of QC material examined at each QC event
- Bracketed QC testing where patient results are not reported until a QC event is accepted
- Equal numbers of patient examinations between QC events for each of the 4 instruments (100)
- An allowable total error specification, \( TE_a = \pm 20\% \)

We studied different ranges of bias and CV among the 4 instruments (Table 1).

<table>
<thead>
<tr>
<th>Instrument Mean</th>
<th>Instrument SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-4%, 4%)</td>
<td>(3.8%, 4.2%)</td>
</tr>
<tr>
<td>(-4%, 4%)</td>
<td>(3.8%, 4.4%)</td>
</tr>
<tr>
<td>(-6%, 8%)</td>
<td>(3.2%, 4.8%)</td>
</tr>
<tr>
<td>(-6%, 8%)</td>
<td>(3.2%, 4.4%)</td>
</tr>
<tr>
<td>(-8%, 8%)</td>
<td>(3.2%, 4.8%)</td>
</tr>
<tr>
<td>(-8%, 8%)</td>
<td>(3.2%, 4.4%)</td>
</tr>
</tbody>
</table>

The process capability of a test can be represented by the sigma value:

\[
\text{Sigma} = \frac{\text{TE}_a - \text{Bias}}{\text{SD}}
\]

For the bias and CV range combinations in Table 1 we randomly generate 4 instrument means and SDs uniformly over the respective ranges. The instrument QC means and CVs produced give sigma values that approximately span 3 to 6 (Table 1).

For each set of instrument means and SDs we define QC rules based on:

- QC rule means set to instrument means, QC rule SDs set to instrument SDs
- QC rule means set to a fixed mean, QC rule SDs based on instrument SDs
- QC rule means set to instrument means, QC rule SDs set to a fixed SD
- QC rule means set to a fixed mean, QC Rule SDs set to a fixed SD

In each case, QC rule means and SDs are set so the overall false rejection probability across the 4 instruments is equal to 0.0097 (the false rejection probability for the 1:3:2:2/4:4 multi-rule).

When all QC rules use the same fixed mean, but QC SDs are based on instrument SDs, the individual instrument SDs are set so the false rejection probability, \( P_f \), for each instrument equals 0.0097.

When all QC rules use the same fixed SD, the SD is determined so the average false rejection probability across the 4 instruments is equal to 0.0097.

The expected number of unreliable patient results reported due to the occurrence of an out-of-control condition, E(Nu), is computed using the formula given in the appendix of Clin Chem 2008; 54:2049-54.
Results

Table 2 gives an example of 4 different instruments that examine 2 different concentrations of the same QC material.

<table>
<thead>
<tr>
<th>Instrument QC Mean, Instrument SD</th>
<th>Fixed QC Mean, Instrument SD (adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument Mean 1 Mean 2 SD1 SD2</td>
<td>Mean 1 Mean 2 SD1 SD2</td>
</tr>
<tr>
<td>1 78.5 143.3 3.25 5.93</td>
<td>80 146 3.48 6.35</td>
</tr>
<tr>
<td>2 79.3 144.8 3.10 5.66</td>
<td>80 146 3.15 5.76</td>
</tr>
<tr>
<td>3 80.4 146.6 3.15 5.74</td>
<td>80 146 3.16 5.78</td>
</tr>
<tr>
<td>4 81.8 149.3 3.30 6.03</td>
<td>80 146 3.62 6.60</td>
</tr>
</tbody>
</table>

The upper left corner shows QC rule means and SDs based on individual instrument means and SDs.
- The instrument means differ within a range of approximately ±2%
- The instrument CVs range approximately between 3.8% and 4.2%

The upper right corner shows QC rule means and SDs when a fixed mean is used for instruments, but QC limits are based on individual instrument SDs.
- Note instrument SDs in the upper right corner are slightly higher than the instrument SDs in the upper left corner
- This increase is required to keep the overall average false rejection probability at 0.0097 (Table 3)

The lower left corner shows individual QC means and a fixed SD.
The lower right corner shows a single fixed mean and SD used for all instruments.

Table 3 gives the false rejection probabilities for the QC rules defined in Table 2.

<table>
<thead>
<tr>
<th>Instrument Mean Instrument SD</th>
<th>Fixed Mean Instrument SD</th>
<th>Instrument Mean Fixed SD</th>
<th>Fixed Mean Fixed SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Instrument Mean 1 Mean 2 SD1 SD2</td>
<td>Mean 1 Mean 2 SD1 SD2</td>
<td>Mean 1 Mean 2 SD1 SD2</td>
<td></td>
</tr>
<tr>
<td>1 0.0097 0.0097</td>
<td>0.0128 0.0147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 0.0097 0.0097</td>
<td>0.0077 0.0097</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 0.0097 0.0097</td>
<td>0.0079 0.0047</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 0.0097 0.0097</td>
<td>0.0104 0.0147</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Average 0.0097 0.0097</td>
<td>0.0097 0.0097</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

When a QC rule is based on a fixed QC mean and instrument SD if the fixed mean value differs from the instrument’s mean the false rejection probability of the QC rule will increase. Therefore, each instrument’s SD was increased by the appropriate amount (see Table 2) so the false rejection probability was maintained at 0.0097.

When a fixed SD is used for all instruments, the false rejection probabilities of the instruments vary. Instruments with lower imprecision have a lower false rejection probability compared to instruments with higher imprecision.
- Instruments 1 and 4 have false rejection probabilities greater than 0.0097
- Instruments 2 and 3 have false rejection probabilities lower than 0.0097
- The overall (average) false rejection probability is 0.0097
Figure 1 plots the expected number of unreliable patient results, \( E(N_u) \), due to a systematic error (SE) out-of-control condition as a function of the magnitude and direction of the out-of-control condition. Each curve is associated with one of the instruments represented in Tables 2 and 3:

- Instrument 1: red curve
- Instrument 2: purple curve
- Instrument 3: green curve
- Instrument 4: cyan curve

**Figure 1.**

### Table 4: Maximum and Average \( E(N_u) \) Values for the Curves in Figure 1

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Instrument Mean</th>
<th>Instrument SD</th>
<th>Fixed Mean</th>
<th>Fixed SD</th>
<th>Fixed Mean</th>
<th>Fixed SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (red)</td>
<td>1.005</td>
<td>0.129</td>
<td>0.494</td>
<td>0.111</td>
<td>0.830</td>
<td>0.105</td>
</tr>
<tr>
<td>2 (purple)</td>
<td>0.269</td>
<td>0.037</td>
<td>0.172</td>
<td>0.036</td>
<td>0.316</td>
<td>0.044</td>
</tr>
<tr>
<td>3 (green)</td>
<td>0.214</td>
<td>0.035</td>
<td>0.164</td>
<td>0.034</td>
<td>0.248</td>
<td>0.041</td>
</tr>
<tr>
<td>4 (cyan)</td>
<td>0.076</td>
<td>0.117</td>
<td>0.442</td>
<td>0.095</td>
<td>0.931</td>
<td>0.112</td>
</tr>
<tr>
<td>Max/Avg</td>
<td>1.005</td>
<td>0.080</td>
<td>0.494</td>
<td>0.069</td>
<td>0.931</td>
<td>0.075</td>
</tr>
</tbody>
</table>

From Figure 1 and Table 4 it can be seen;

- If instrument means are used for QC rule means the predicted \( E(N_u) \) due to a out-of-control condition that is in the same direction as the instrument’s bias is greater than the predicted \( E(N_u) \) if the direction of the out-of-control condition is in the opposite direction of the instrument’s bias (Figures 1A and 1C)
- If each QC rule mean is set to the fixed mean the predicted \( E(N_u) \) is independent of the direction of the out-of-control condition (Figures 1B and 1D)
- Changing from instrument SDs to a fixed SD in the QC rule reduces the magnitude of the differences between higher SD and lower SD instruments in terms of the predicted \( E(N_u) \) (compare Figure 1A to 1C and Figure 1B to 1D)
- If QC rules are based on a fixed QC mean and a fixed SD the overall predicted \( E(N_u) \) is the lowest and the differences between the predicted \( E(N_u) \) among the instruments is smallest (compare Figure 1D to Figures 1A – 1C)
Table 5 shows the impact of the range of biases and CVs among instruments on the predicted E(Nu) for the 4 different QC rule mean and SD combinations.

<table>
<thead>
<tr>
<th>Range</th>
<th>Instrument Mean</th>
<th>Instrument SD</th>
<th>Fixed Mean</th>
<th>Fixed SD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Max E(Nu)</td>
<td>Avg E(Nu)</td>
<td>Max E(Nu)</td>
<td>Avg E(Nu)</td>
</tr>
<tr>
<td>(-2, 2)</td>
<td>(3.8, 4.2)</td>
<td>1.005</td>
<td>0.080</td>
<td>0.494</td>
</tr>
<tr>
<td>(-4, 4)</td>
<td>(3.8, 4.2)</td>
<td>36.182</td>
<td>0.889</td>
<td>13.118</td>
</tr>
<tr>
<td>(-8, 8)</td>
<td>(3.6, 4.4)</td>
<td>73.603</td>
<td>1.669</td>
<td>27.094</td>
</tr>
<tr>
<td>(-2, 2)</td>
<td>(3.6, 4.4)</td>
<td>0.985</td>
<td>0.070</td>
<td>0.541</td>
</tr>
<tr>
<td>(-4, 4)</td>
<td>(3.6, 4.4)</td>
<td>8.182</td>
<td>0.325</td>
<td>3.756</td>
</tr>
<tr>
<td>(-8, 8)</td>
<td>(3.6, 4.4)</td>
<td>75.701</td>
<td>1.735</td>
<td>27.911</td>
</tr>
<tr>
<td>(-2, 2)</td>
<td>(3.2, 4.8)</td>
<td>1.009</td>
<td>0.105</td>
<td>0.978</td>
</tr>
<tr>
<td>(-4, 4)</td>
<td>(3.2, 4.8)</td>
<td>3.844</td>
<td>0.251</td>
<td>1.886</td>
</tr>
<tr>
<td>(-8, 8)</td>
<td>(3.2, 4.8)</td>
<td>37.166</td>
<td>1.091</td>
<td>14.333</td>
</tr>
</tbody>
</table>

Table entries give the maximum predicted E(Nu) for any size out-of-control condition across all 4 instruments and the average E(Nu) for all 4 instruments across the range of possible magnitudes of out-of-control conditions (-40% to 40%).

Note the first data row of Table 5 is the same as the last row of Table 4 representing the case where instrument biases range between -2% and 2% and instrument CVs range between 3.8% and 4.2%.

From Table 5:
- E(Nu) appears to be quite sensitive to the degree of bias between instruments.
- As bias between instruments increases, E(Nu) increases substantially.
- The effect on E(Nu) appears more pronounced when instrument means are used for QC rule means rather than a fixed mean.
- The range of instrument CVs appears to have less impact on E(Nu) than the range of differences in QC means.

Conclusions

If a fixed QC rule mean and SD are used across multiple instruments that perform the same assays:
- The false rejection rates will vary among the instruments.
- The predicted number of unreliable patient results due to an out-of-control error condition is similar among the instruments.
- The overall expected number of unreliable patient results due to an out-of-control condition is reduced.
- The degree of reduction increases as the differences among instrument means increase.
- The focus is on detecting medically important out-of-control error conditions.

If individual QC rule means and SDs are used across multiple instruments that perform the same assays:
- The false rejection rates are the same among the instruments.
- The predicted number of unreliable patient results due to an out-of-control error condition varies among the instruments.
- The focus is on detecting statistically significant out-of-control error conditions.

We studied multiple instruments performing the same assays that exhibit QC means and SDs that are uniformly distributed throughout a range. Our findings may not apply to situations where there are multiple clusters of instrument means and SDs or where a single instrument has a substantially different mean or SD from the rest of a group of instruments.

Our studies considered instruments with biases and SDs that gave sigma values ranging from approximately 3 to 6. Situations where the sigma values are very low (<3) or very high (>6) may show different relative performance characteristics than seen here.

For the range of situations considered here, these results suggest that setting fixed QC means and SDs for multiple instruments or analytical units that perform the same assays can provide good quality control performance characteristics from the perspective of the reliability of the patients' results.

L. S. Kuchipudi, J. Yundt-Pacheco, C. A. Parvin. 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 SDs or on a Fixed SD? Poster presented at: American Association for Clinical Chemistry; July 2014; Chicago, IL.