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ANALYTICAL PERFORMANCE SPECIFICATIONS - WHAT DOES A LIMIT OF TOTAL ERROR MEAN AND WHEN CAN IT BE USED

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Total error: what does it mean ?

Total allowable error in EQA.

$$TE_a = B_{max} + 1.65 \times CV_{max}$$

Where $CV_{max} = (0.5 \times CV_I)$ Desirable APS for imprecision

$B_{max} = 0.25 \times (CV_I^2 + CV_g^2)^{1/2}$ Desirable APS for Bias.

CV_I : within-subject biological variation

CV_g : between-subject biological variation

TE_a is available for a large set of parameters in the *EFLM website.

*EFLM : European Federation of Clinical Chemistry and Laboratory Medicine

Total error: How is it used in laboratory performance evaluation?

$$Q = \frac{X - R}{R}$$

$X \sim N(\mu, \sigma)$ ⟹ $Q \sim N(B_r, CV \times |1 + B_r|)$

$$TE = B_r + 1.65CV = B_r + 1.65CV \approx 95\ percentile\ of\ Q$$

$$TE_a = B_{max} + 1.65 \times CV_{max}$$

$|Q| \times 100 > TE_a$ ⟹ X is flagged as unacceptable

Total error: does it also mean..

If I have a value that is **WITHIN** the limits of total allowable error then

- Is my bias within the acceptable limits ? $|Q| \times 100 \leq TE_a \Rightarrow B \leq B_{max}$
- Is my variability within the acceptable limits ? $|Q| \times 100 \leq TE_a \Rightarrow CV \leq CV_{max}$
- Are both my bias and variability within their respective acceptable limits ?

$$|Q| \times 100 \leq TE_a \Rightarrow B \leq B_{max} \ and \ CV \leq CV_{max}$$

?

If this is not true for one sample

- Would this be true for 2 samples? Maybe four? Or 300?

Let us do a test

$$\boldsymbol{Albumin}: \; B_{max} = 1.43\% \quad CV_{max} = 1.6\% \quad TE_a = 4.07\% \quad RF = 5\ g/dL$$

- Variability (CV): 0 till 2 times maximum variability
- Bias (B): -3 till 3 times maximum bias
- What is the chance that I have a result within the limits of total error ?

100 values of CV

100 values of B

CV : 0 **B** : $-3 \times B_{max}$	**CV** : $0.02 \times CV_{max}$ **B** : $-3 \times B_{max}$	………	**CV** : CV_{max} **B** : $-3 \times B_{max}$	………	**CV** : $1.98 \times CV_{max}$ **B** : $-3 \times B_{max}$	**CV** : $2 \times CV_{max}$ **B** : $-3 \times B_{max}$
………	………	………	………	………	………	**CV** : $6.25E^{-5} \times CV_{max}$ **B** : $-3 \times B_{max}$
CV : 0 **B** : $-B_{max}$	**CV** : $0.02 \times CV_{max}$ **B** : $-B_{max}$	………	**CV** : CV_{max} **B** : $-B_{max}$	………	**CV** : $1.98 \times CV_{max}$ **B** : $-B_{max}$	**CV** : $6.25E^{-5} \times CV_{max}$ **B** : $-3 \times B_{max}$
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………	………	………	………	………	………	………
CV : 0 **B** : B_{max}	**CV** : $0.02 \times CV_{max}$ **B** : B_{max}	………	**CV** : CV_{max} **B** : B_{max}	………	**CV** : $1.98 \times CV_{max}$ **B** : B_{max}	**CV** : $6.25E^{-5} \times CV_{max}$ **B** : $-3 \times B_{max}$
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CV : 0 **B** : $3 \times B_{max}$	**CV** : $0.02 \times CV_{max}$ **B** : $3 \times B_{max}$	………	**CV** : CV_{max} **B** : $3 \times B_{max}$	………	**CV** : $1.98 \times CV_{max}$ **B** : $3 \times B_{max}$	**CV** : $6.25E^{-5} \times CV_{max}$ **B** : $-3 \times B_{max}$

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- What is the chance that I have a result within the limits of total error ?

100 values of CV

100 values of B

(95%, 100%)

(44%,95%)

0 % **CV** : 0 **B** : $-3 \times B_{max}$	0 % **CV** : $0.02 \times CV_{max}$ **B** : $-3 \times B_{max}$	....	44.29 % **CV** : CV_{max} **B** : $-3 \times B_{max}$	....	46.82 % **CV** : $1.98 \times CV_{max}$ **B** : $-3 \times B_{max}$	46.82 % **CV** : $2 \times CV_{max}$ **B** : $-3 \times B_{max}$
....	....	....	....	....	....	....
100 % **CV** : 0 **B** : $-B_{max}$	100 % **CV** : $0.02 \times CV_{max}$ **B** : $-B_{max}$	....	95.27 % **CV** : CV_{max} **B** : $-B_{max}$	....	76.2 % **CV** : $1.98 \times CV_{max}$ **B** : $-B_{max}$	76.2 % **CV** : $2 \times CV_{max}$ **B** : $-B_{max}$
....	....	....	....	....	....	....
....	....	....	....	....	....	....
100 % **CV** : 0 **B** : B_{max}	100 % **CV** : $0.02 \times CV_{max}$ **B** : B_{max}	....	94.76 % **CV** : CV_{max} **B** : B_{max}	....	75.09 % **CV** : $1.98 \times CV_{max}$ **B** : B_{max}	75.09 % **CV** : $2 \times CV_{max}$ **B** : B_{max}
....	....	....	....	....	....	....
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Chance of being within limits of bias, variability

- If I have a value that is within the limits of allowable total error, what is the probability that both my bias and variability are within their respective acceptable limits ?
- The answer is giving by dividing sum of probabilities in green area by sum of all probabilities.
- **Only 20%!!!!!!!!!!!!!!**

100 values of CV

100 values of B

(95%, 100%)

(44%,95%)

0 % **CV** : 0, **B** : $-3 \times B_{max}$	0 % **CV** : $0.02 \times CV_{max}$, **B** : $-3 \times B_{max}$	…………	44.29 % **CV** : CV_{max}, **B** : $-3 \times B_{max}$	…………	46.82 % **CV** : $1.98 \times CV_{max}$, **B** : $-3 \times B_{max}$	46.82 % **CV** : $2 \times CV_{max}$, **B** : $-3 \times B_{max}$
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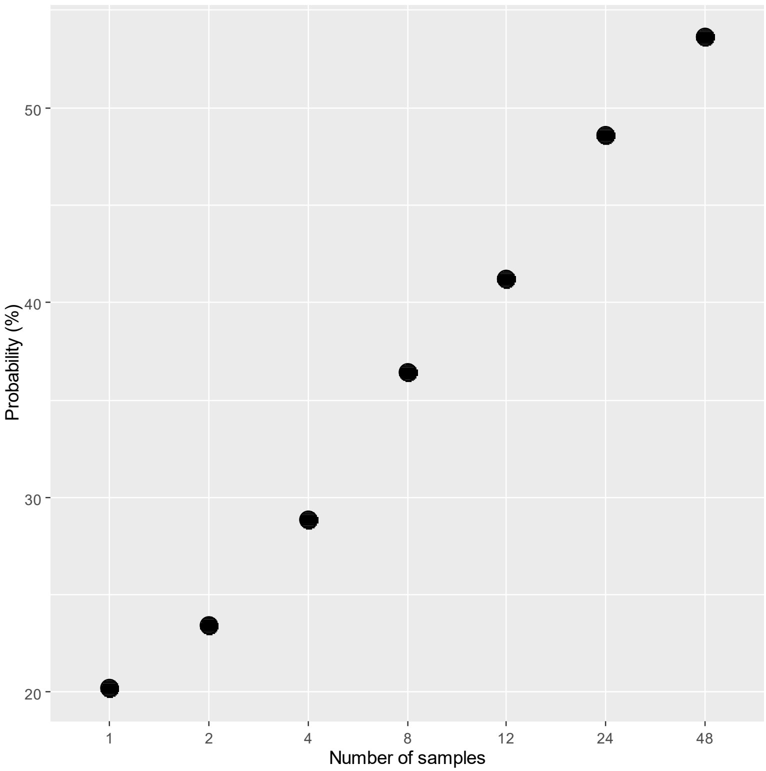
What if I have more samples ?

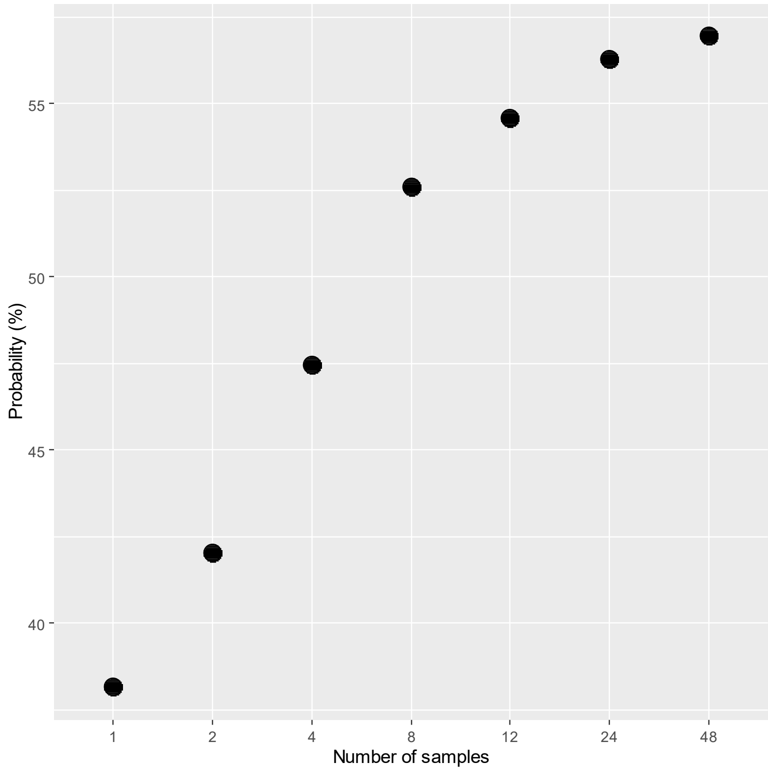
- If all my values are within the limits of allowable total error, what is the probability that both my bias and variability are within their respective acceptable limits ?



Number of samples	Probability (%)
1	20.18
2	23.40
4	28.84
8	36.41
12	41.22
24	48.57
48	53.62

What if I have more samples ?

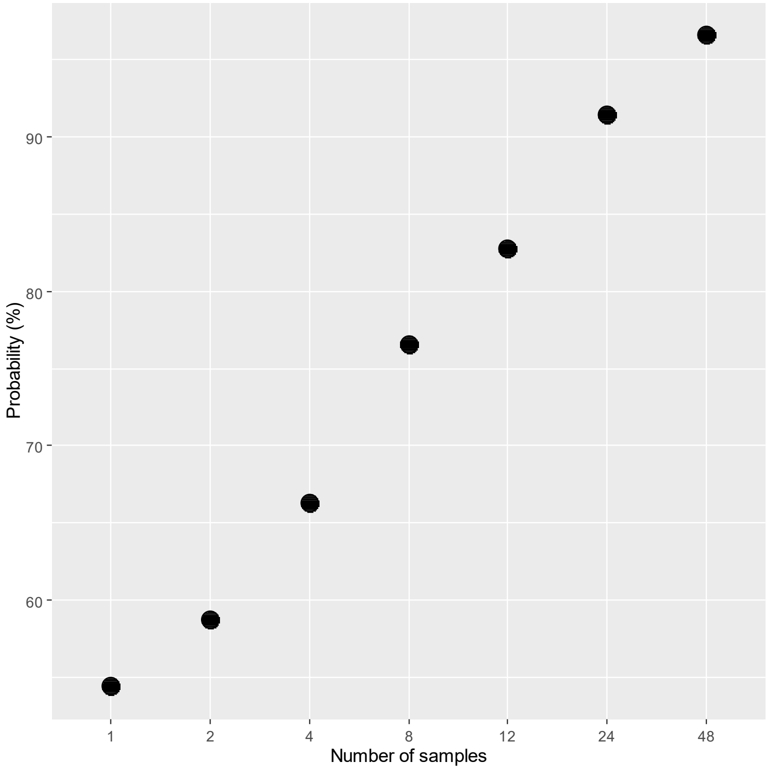
- If all my values are within the limits of allowable total error, what is the probability that my bias is within limits?



Number of samples	Probability (%)
1	38.15
2	42.04
4	47.45
8	52.61
12	54.60
24	56.29
48	56.59

What if I have more samples ?

- If all my values are within the limits of allowable total error, what is the probability that my variability is within limits?



Number of samples	Probability (%)
1	54.39
2	58.73
4	66.26
8	76.57
12	82.80
24	91.44
48	96.58

Total error: does it also mean..

If I have a value that is **OUTSIDE** the limits of total allowable error then

- Is my bias outside the acceptable limits ? $|Q| \times 100 > TE_a \Rightarrow B > B_{max}$
- Is my variability outside the acceptable limits ? $|Q| \times 100 > TE_a \Rightarrow CV > CV_{max}$
- Are bias or variability (or both) outside their respective acceptable limits ?

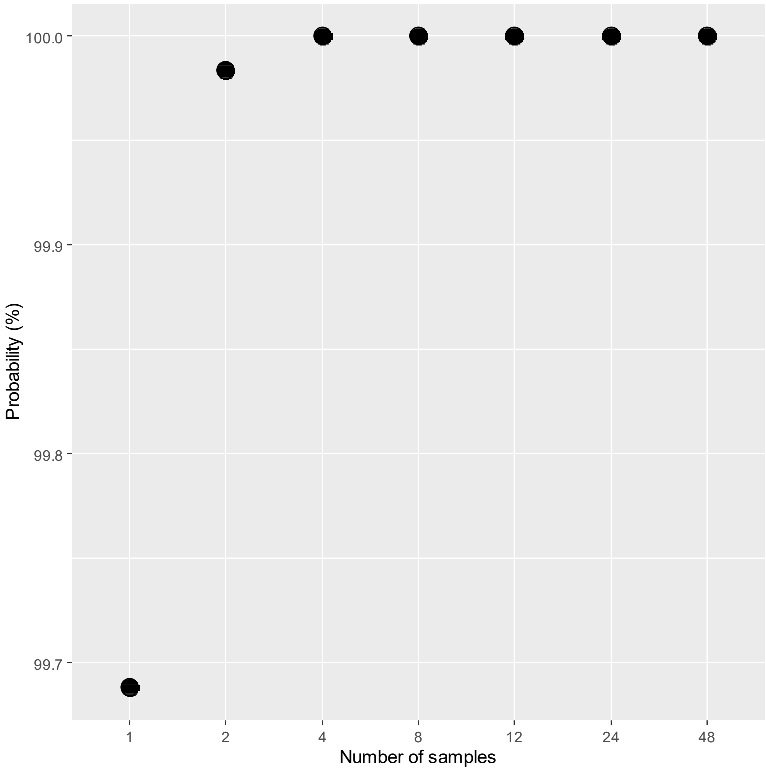
$$|Q| \times 100 > TE_a \Rightarrow CV > CV_{max} \; or \; B > B_{max}$$

If this is not true for one sample

- Would this be true for 2 samples? Maybe four? Or 300?

What if I have more samples ?

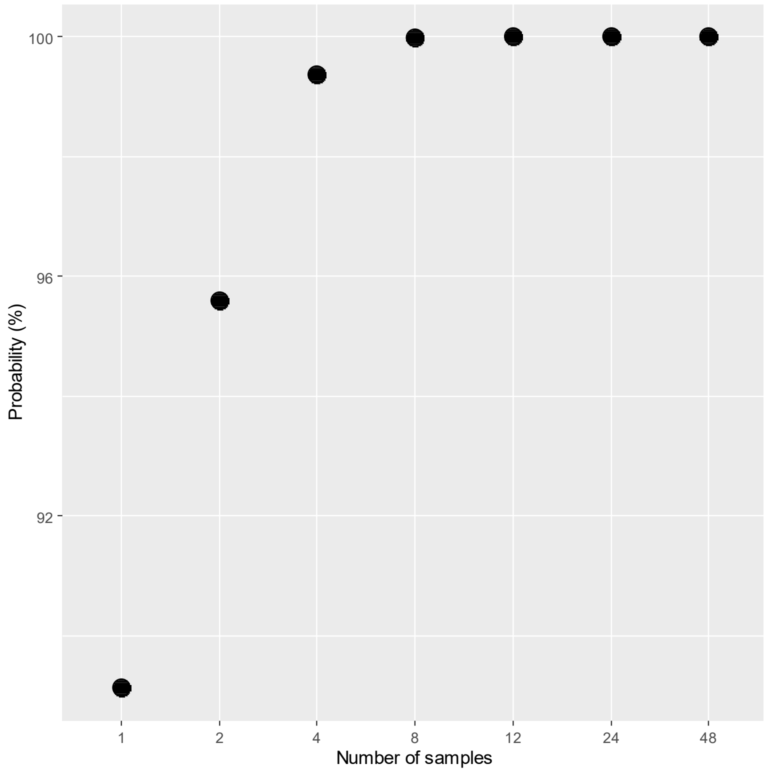
If all my values are outside the limits of allowable total error, what is the probability that either my bias or variability or both are outside their respective acceptable limits ?



Number of samples	Probability (%)
1	99.69
2	99.98
4	100
8	100
12	100
24	100
48	100

What if I have more samples ?

If all my values are outside the limits of allowable total error, what is the probability that my bias is outside limits ?



Number of samples	Probability (%)
1	89.13
2	95.60
4	99.37
8	99.99
12	100
24	100
48	100

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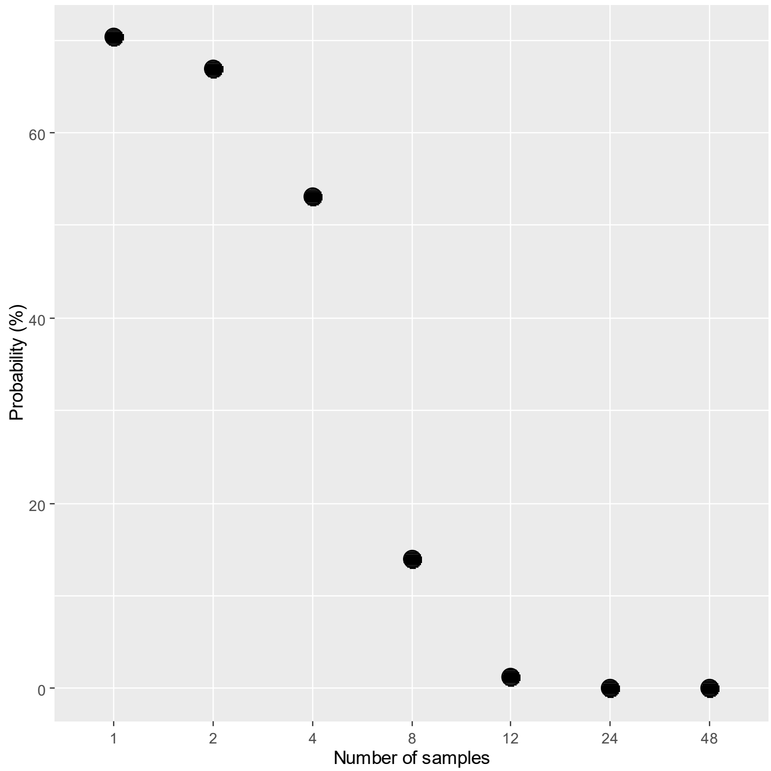
What if I have more samples ?

If all my values are outside the limits of allowable total error, what is the probability that my variability is outside limits ?



Number of samples	Probability (%)
1	70.32
2	66.87
4	53.16
8	13.93
12	1.29
24	0
48	0

Assuring bias, variability within limits

1 sample: very low probability 20%

We cannot assure a participant with acceptable Q-score that his bias AND imprecision are within limits.

Do we need more samples?

But even with more (n=12)= prob: 41.22%

At 48: only half certain

May be we can reach 100% when 1000 samples (not realistic)

The probability increases slowly with the number of samples.

But: once flagged, probability that you are outside increases fast

So, counting on number of samples within total error limits is not a reliable estimate of laboratory performance with respect to maximum variability, bias

Bias...........

What is bias ?

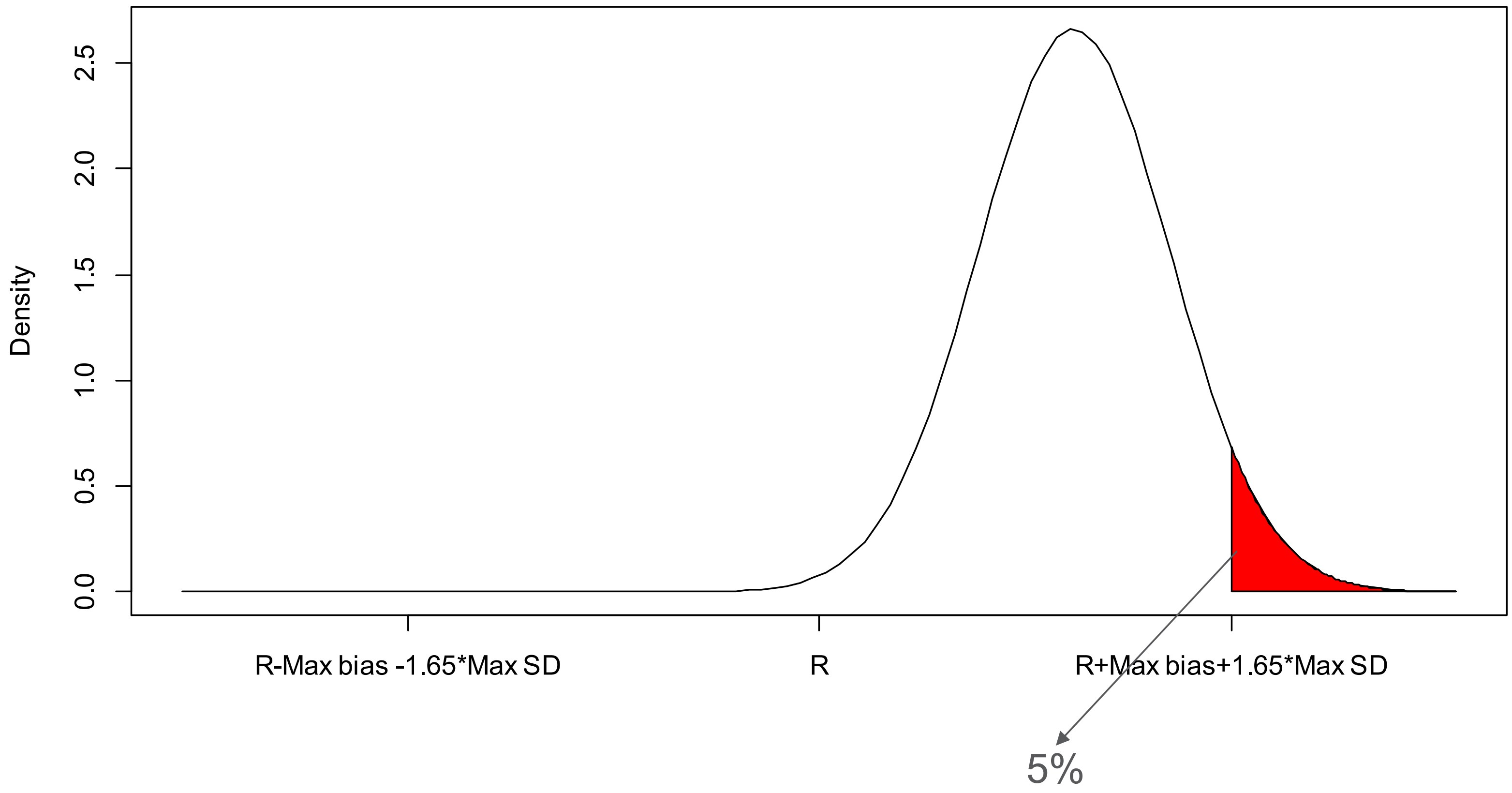
Bias with respect to consensus median ?

Bias with respect to reference value ?

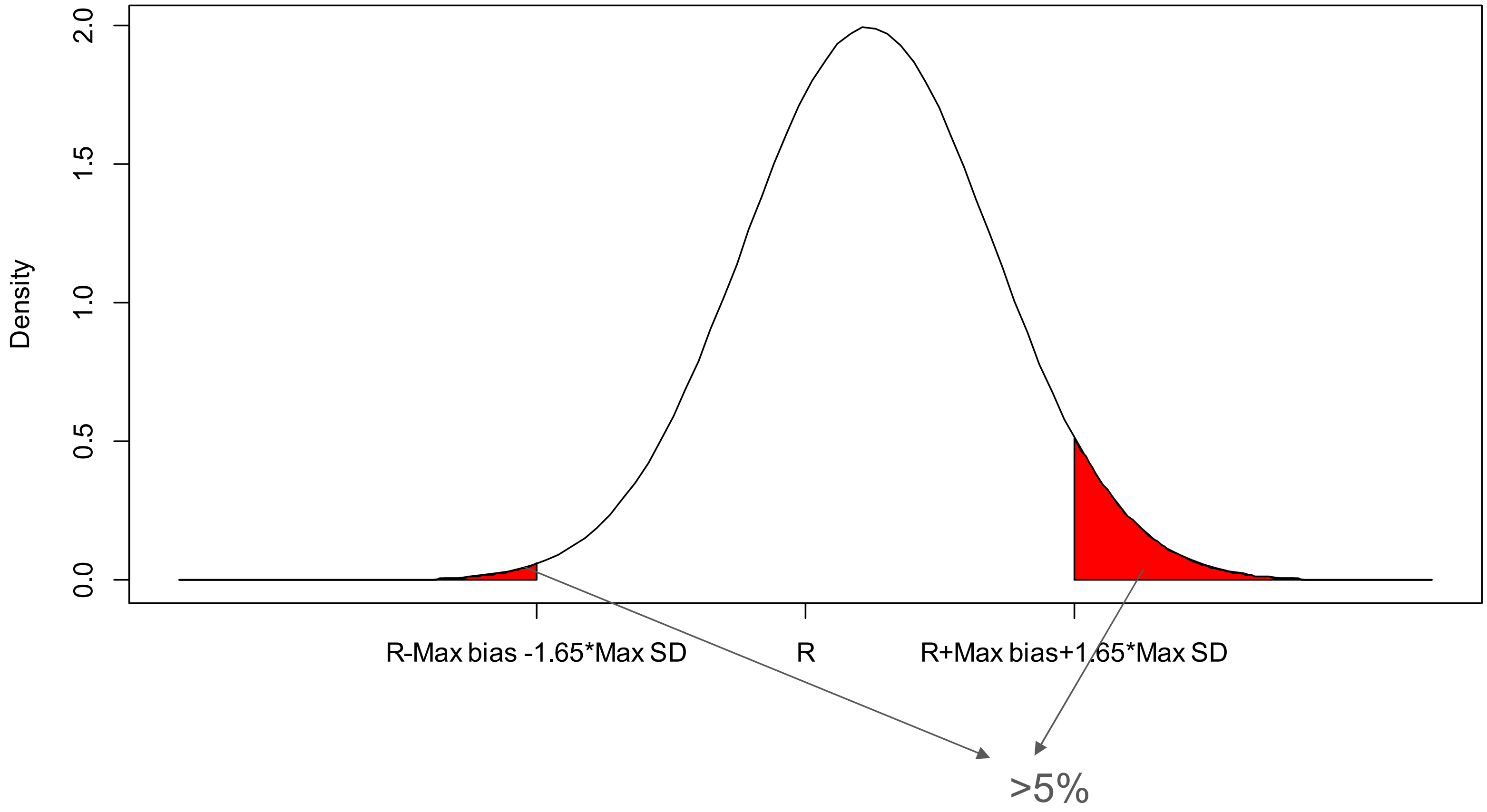
Do we allow bias with respect to peer group based consensus median ?
If so, allowed bias wrt consensus median should be different than to reference value

In our opinion, bias wrt consenus median should be 0, but we are open for discussion

Case 1: maximum allowed bias large with respect to maximum allowed variability



Case 2: maximum allowed bias small with respect to maximum allowed variability



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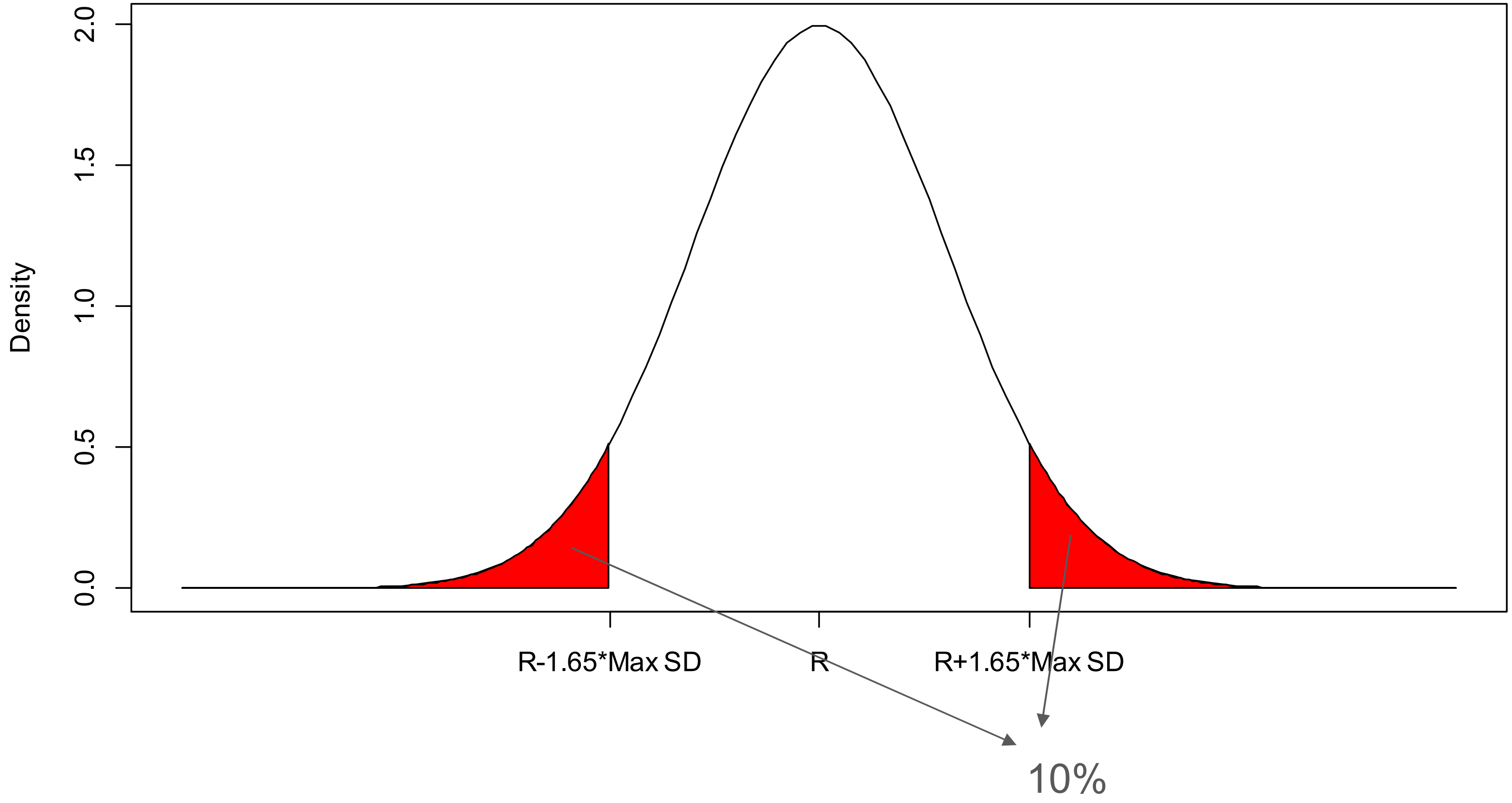
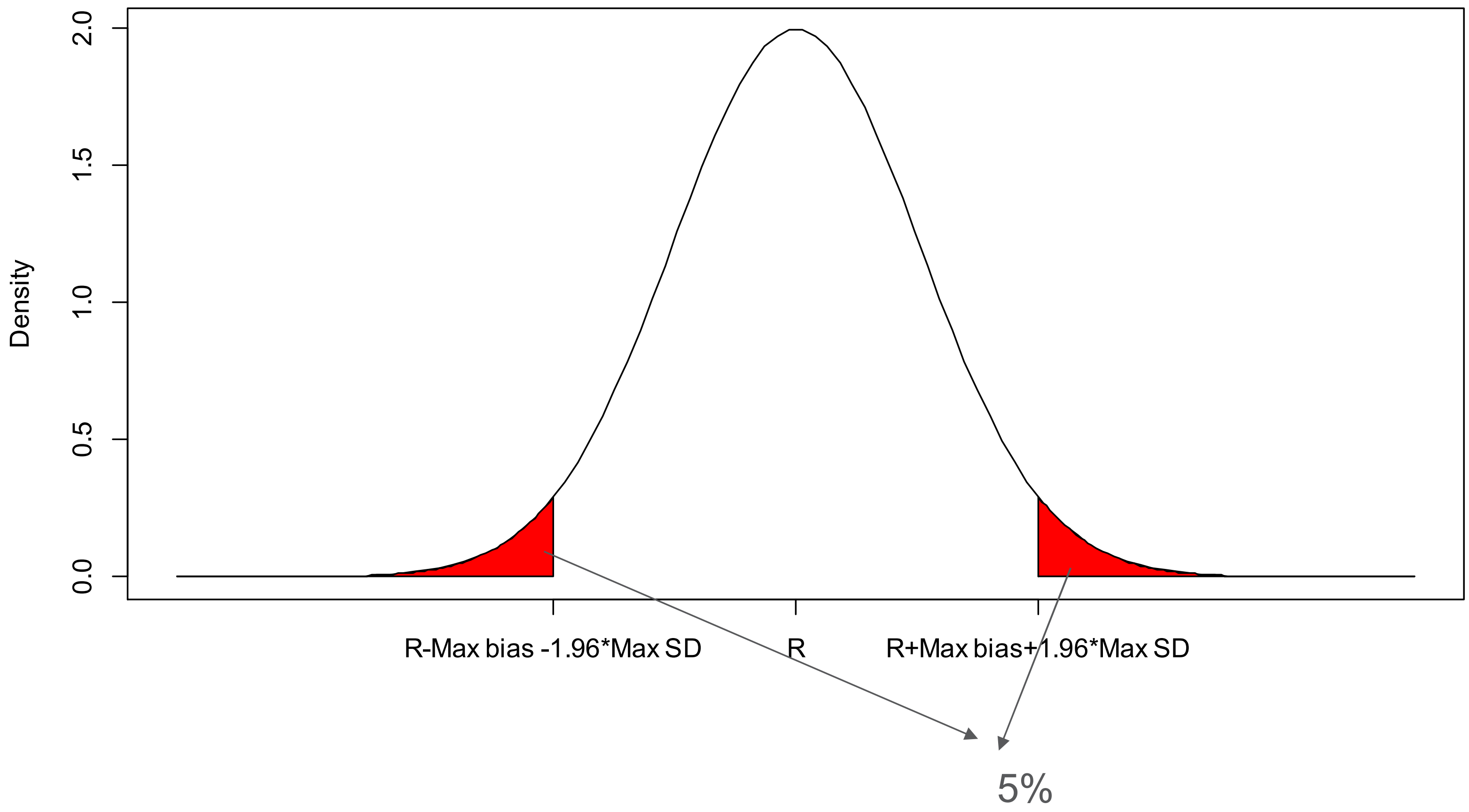
Case 3: maximum allowed bias =0, total error=0+1.65*max SD



Case 4: maximum allowed bias =0, total error=0+1.96*max SD



Are there alternatives ?

- $B \leq B_{max}$ *and* $CV \leq CV_{max}$ $\rightleftarrows$ $|Q| \times 100 \leq TE_a$

  Hence the need for a more reliable approach.

- Let $X_i \sim N(\mu_i, \sigma_i)$ $\quad i = 1, \dots, m$ be a result reported for the ith sample out the total number of samples m.

Test 1 : $\begin{cases} H_0: B \leq B_{max} \ \ and \ \ CV \leq CV_{max} \ \ for \ all \ samples \\ H_a: there \ is \ at \ least \ one \ sample \ for \ which \ B > B_{max} \ \ or \ CV > CV_{max} \end{cases}$

Test-statistic $\quad T_1 = \sum_{i=1}^{m} \left(\frac{X_i - R_i}{\sigma_i}\right)^2 \sim \chi^2_{m,\lambda}$

where $\chi^2_{n,\lambda}$ is a noncentral chi-square distribution with m degrees of freedom and noncentrality parameter λ given by $\sum_{i=1}^{m} \left(\frac{\mu_i - R_i}{\sigma_i}\right)^2$

If $\sum_{i=1}^{m} \left(\frac{X_i - R_i}{R_i \times CV_{max}}\right)^2 > p0.95\left(\chi^2_{m, m \times \left(\frac{B_{max}}{CV_{max}}\right)^2}\right)$ $\longrightarrow$ The whole “batch” is unacceptable.

Are there alternatives ?

- Let $X_i \sim N(\mu_i, \sigma_i)$ $\; i = 1, \dots, m$ be a result reported for the ith sample out the total number of samples m.

Test 2 : $\begin{cases} H_0: B \geq B_{max} \;\; and \;\; CV \geq CV_{max} \;\; for\ all\ samples \\ H_a: B \leq B_{max} \;\; and \;\; CV \leq CV_{max} \;\; for\ all\ samples \end{cases}$

MRS2

Test-statistic $\quad T_1 = \sum_{i=1}^{m} \left(\frac{X_i - R_i}{\sigma_i}\right)^2 \sim \chi^2_{m,\lambda}$

where $\chi^2_{n,\lambda}$ is a noncentral chi-square distribution with n degrees of freedom and noncentrality parameter λ given by $\sum_{i=1}^{m} \left(\frac{\mu_i - R_i}{\sigma_i}\right)^2$

If $\sum_{i=1}^{m} \left(\frac{X_i - R_i}{R_i \times CV_{max}}\right)^2 < p0.05\left(\chi^2_{m, m \times \left(\frac{Bmax}{CVmax}\right)^2}\right)$ ⟹ The whole "batch" is acceptable.

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Diapositive 22

MRS2 To discuss with Wim

Mohamed Rida Soumali; 12.10.2022

Noncentral chi-square distribution based performance evaluation :

- If my batch of results is accepted, what is the probability that both my bias and variability are within their respective acceptable limits ?

Number of samples	Probability (%)
1	29
2	60
4	/
8	/
12	86
24	80
48	74

Noncentral chi-square distribution based performance evaluation :

- If my batch of results is accepted, what is the probability that both my bias and variability are within their respective acceptable limits ?

Number of samples	Probability (%)	Probability (%) TE
1	29	20.18
2	60	23.40
4		28.84
8		36.41
12	86	41.22
24	80	48.57
48	74	53.62

Conclusions

- Total error only works if we are looking one result at a time, and only informs if we have a flagged result
  - Variability and/or bias may larger than what is allowed if a result is not flagged
  - In all other cases, total error is not informative
- For comparisons with respect to an consensus median, we should modify the total error because we cannot allow bias.
- Total error then becomes 1.96*maximum variability
- There are alternatives: noncentral chi-square distribution
- So far, results that are not flagged may still hide bias or variability that is too large.

Conclusions

- Shouldn't we approach the problem differently ?
  - Maximum deviation budget that can be consumed by bias or variability
  - If bias is large, only small variability is allowed

  - If variability is large, only small bias is allowed

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