Setting the **Global Standard for Quality** in Laboratory Testing

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19 February 2015

To: Recipients of EP09-A3

From: Jennifer K. Adams, MT(ASCP), MSHA

Subject: Errors in Table 4 and Appendix A of CLSI Document EP09-A3

This notification is to inform you of errors in CLSI document EP09-A3, *Measurement Procedure Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Third Edition,* Table 4 (page 21) and Appendix A (pages 41 to 44).

In Table 4, the ranking of samples by concentration depends on an accurate estimate of the concentration of each sample. When the average of the measurements from each measurement procedure is used in the ranking scheme as the horizontal axis of a difference plot, then the formula $(x+y)/2$ must be used. This formula was incorrectly listed as $(x-y)/2$ and would give ranking based on x to y difference rather than their average.

The corrected table is below, with the correction highlighted.

Table 4. Formulas for Creating Ranked Order Difference Plots

Horizontal Axis (z)	Vertical Axis: Difference (d) Is Constant (Constant SD)	Vertical Axis: Difference (d) Is Proportional to Concentration (Constant CV)
Samples ranked by comparative measurement procedure results	$z_k = \text{Rank}(x_i)$ $d_k = y_k - x_k$ (5)	$z_k = \text{Rank}(x_i)$ $d_k = (y_k - x_k)/x_k$ (6)
Samples ranked by average of the two procedures	$z_k = \text{Rank}([x_i + y_i]/2)$ $d_k = y_k - x_k$ (7)	$z_k = \text{Rank}([x_i + y_i]/2)$ $d_k = (y_k - x_k)/[(x_k + y_k)/2]$ (8)

Abbreviations: CV, coefficient of variation; SD, standard deviation.

In Appendix A, the technique in the original appendix for deriving the median and its confidence intervals is well described and mathematically correct. However, the additional technique is that typically used for determining the median and is in alignment with the descriptions and computations in the main body of EP09.

The beginning of Appendix A, which contains the additional technique, is reproduced below.

> In instances where the distribution of results does not follow a normal (gaussian) distribution, the median is a more robust estimator of central tendency than the mean. This section provides two procedures to compute the median and its confidence interval (CI). The first procedure is based on a normal approximation to the binomial, while the second procedure is based on the Wilcoxon distribution-free signed rank test.

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Experiment

Below is the experimental layout of a measurement procedure comparison study, where y_i is the result with the candidate measurement procedure and x_i is the result with the comparative measurement procedure.

Patient	x_i	y_i
1	x_1	y_1
2	x_2	y_2
3	x_3	y_3
…	...	...
N	x_N	x_N

Assumptions

1. Let $d_i = y_i - x_i$, for $i = 1,\ldots N$. The differences $d_1,\ldots d_N$ are mutually independent.
2. Each d_i comes from a continuous population, not necessarily the same, that is symmetrical about a common median θ. Each d_i can be expressed in units or as a percentage of the sample concentration.

Example

Table A1. Median Bias and CI Example Data

Patient	*x*	*y*	(*y*−*x*)/*x*		Patient	*x*	*y*	(*y*−*x*)/*x*
1	0.52	0.49	−5.77%		51	27.13	24.42	−9.99%
2	0.99	0.97	−2.02%		52	25.72	27.72	7.78%
3	1.49	0.66	−55.70%		53	24.45	24.17	−1.15%
4	1.99	1.87	−6.03%		54	26.39	27.65	4.77%
5	2.52	2.56	1.59%		55	28.76	28.12	−2.23%
6	3.20	2.91	−9.06%		56	26.37	29.74	12.78%
7	3.37	3.53	4.75%		57	27.63	28.28	2.35%
8	3.95	3.96	0.25%		58	28.78	27.89	−3.09%
9	4.85	4.51	−7.01%		59	27.74	29.19	5.23%
10	4.96	5.46	10.08%		60	32.59	29.34	−9.97%
11	5.33	5.85	9.76%		61	31.48	32.00	1.65%
12	6.00	5.98	−0.33%		62	30.31	31.99	5.54%
13	7.02	6.62	−5.70%		63	32.30	30.50	−5.57%
14	7.15	6.92	−3.22%		64	33.11	32.73	−1.15%
15	7.76	7.47	−3.74%		65	31.33	32.76	4.56%
16	7.71	7.56	−1.95%		66	31.45	31.62	0.54%
17	8.59	8.08	−5.94%		67	31.37	32.35	3.12%
18	9.87	8.94	−9.42%		68	33.54	33.46	−0.24%
19	8.75	9.34	6.74%		69	32.74	32.71	−0.09%

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Table A1. (Continued)

Patient	x	y	$(y-x)/x$		Patient	x	y	$(y-x)/x$
20	10.48	9.81	−6.39%		70	33.21	36.07	8.61%
21	10.16	9.78	−3.74%		71	32.57	32.26	−0.95%
22	11.17	10.91	−2.33%		72	35.85	37.90	5.72%
23	11.83	11.13	−5.92%		73	37.04	34.18	−7.72%
24	11.79	12.17	3.22%		74	35.23	36.43	3.41%
25	12.29	12.63	2.77%		75	34.54	42.28	22.41%
26	11.39	12.96	13.78%		76	35.45	35.52	0.20%
27	13.67	14.93	9.22%		77	39.35	37.29	−5.24%
28	12.93	12.91	−0.15%		78	40.13	39.27	−2.14%
29	12.83	15.35	19.64%		79	37.98	41.93	10.40%
30	16.78	14.71	−12.34%		80	41.87	42.29	1.00%
31	14.72	15.92	8.15%		81	41.14	42.46	3.21%
32	16.53	15.32	−7.32%		82	43.39	37.68	−13.16%
33	17.17	17.04	−0.76%		83	38.93	39.71	2.00%
34	16.82	15.68	−6.78%		84	43.28	42.52	−1.76%
35	18.39	18.17	−1.20%		85	42.48	46.82	10.22%
36	17.68	17.38	−1.70%		86	42.55	44.16	3.78%
37	19.30	18.82	−2.49%		87	45.17	39.29	−13.02%
38	19.53	20.98	7.42%		88	44.18	45.78	3.62%
39	19.77	18.42	−6.83%		89	45.12	41.71	−7.56%
40	20.48	18.77	−8.35%		90	40.93	46.03	12.46%
41	21.08	20.34	−3.51%		91	48.80	46.89	−3.91%
42	21.31	21.37	0.28%		92	49.47	43.86	−11.34%
43	21.64	21.21	−1.99%		93	45.21	47.88	5.91%
44	20.52	24.33	18.57%		94	48.44	46.26	−4.50%
45	24.30	23.68	−2.55%		95	45.07	43.64	−3.17%
46	21.30	21.72	1.97%		96	43.72	47.45	8.53%
47	24.13	23.59	−2.24%		97	49.74	52.83	6.21%
48	23.99	24.19	0.83%		98	47.59	54.06	13.60%
49	22.19	24.19	9.01%		99	48.61	54.09	11.27%
50	23.83	23.75	−0.34%		100	53.08	49.53	−6.69%

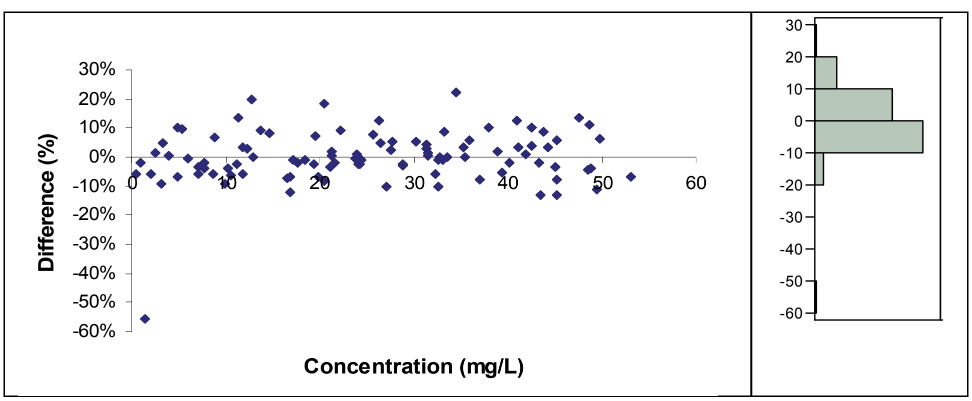

Figure A1. Proportional Difference Plot

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A1 Procedure Based on the Normal Approximation to the Binomial

The point estimator is the simple median of the differences as used in the body of this guideline.

$$\hat{\theta} = median\left(d_i, i = 1,\ldots,\mathrm{N}\right) \quad \text{(A1)}$$

For N = 100, after ranking these differences in order, the median difference is the average of the differences at positions 50 and 51 (ie, position 50.5).

From the normal approximation to the binomial, an approximate 1 − α CI for the median is obtained by counting off $1/2N^{1/2}\eta_\alpha$ where η_α is the upper 1/2α significance point of a standard normal variate. For example, for N = 100, α = 0.05, the approximation is $1/2N^{1/2}\eta_\alpha = 5(1.96) = 9.8$. Rounding out 50.5 ± 9.8, the 96.4% CI is provided by positions 40 and 61. The CI at this percentage can be provided or an estimate of the 95% CI can be obtained through interpolation. The resultant estimates from the data in Table A1 are thus:

N = 100
Median = −0.335%
96.4% CI = −2.020% to 1.590% (positions 40 and 61)
95% CI = −1.998 to 1.152 (interpolated)
94.3% CI = −1.990 to 1.000 (positions 41 and 60)

A2 Procedure Based on the Wilcoxon Distribution-Free Signed Rank Test

This procedure may give somewhat different estimates, but because more differences are included in the calculations, the CI is more robust and therefore perhaps more appropriate for smaller sample sizes (eg, 40 samples).

The following text at the end of A2 was also revised:

The following estimates, using the data in Table A1 and the plot in Figure A1, demonstrate this computational technique.

N = 100
Median = −0.05%
95% CI = −1.41% to 1.61%

If you require any additional clarification regarding this correction, please contact CLSI Customer Service (customerservice@clsi.org).

We appreciate your commitment to CLSI, and regret any inconvenience.

Minor edits were recently noted in Appendix B of EP09-A3 in the procedure for performing the generalized extreme studentized deviate technique and in Table B1. The affected text is set in bold below. Affected equations are outlined.

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c. **Corresponding to the number of test statistics (*h*), compute the following *h* critical values:**

$$\lambda_i = \frac{t_{v,p}(N-i)}{\sqrt{(N-i+1)\left(v+t_{v,p}^2\right)}}, \tag{B2}$$

where N is the initial number of samples in the dataset, and *i* = 1, 2, ...*h*,

$$v = \mathrm{N} - i - 1, \tag{B3}$$

$$p = 1 - \frac{\alpha}{2(\mathrm{N} - i + 1)} \tag{B4}$$

and $t_{v,p}$ is the **one-sided** 100*p* percentage point from Student *t* distribution with *v* degrees of freedom and probability = *p*.

d. The number of outliers is determined by finding the largest *i* such that $ESD_i > \lambda_i$. **If ESD_h and ESD_{h+1} are equal (a tie), then neither one should be seen as an outlier.**

Setting α = 0.01, with N = 100 and then *h* = 5. Table B1 lists each subsequent iteration.

Table B1. Example Results

Parameter	*i* = 1	*i* = 2	*i* = 3	*i* = 4	*i* = 5 = *h*
Average $(\bar{x})$	0.01%	0.57%	0.35%	0.15%	−0.03%
SD	9.15%	7.25%	6.94%	6.69%	6.45%
ESD_i	6.09	3.01	2.78	2.75	2.14
λ_i	**3.75**	**3.75**	**3.75**	**3.74**	**3.74**
Bias	−55.70% *j* = 3	22.41% *j* = 75	19.64% *j* = 29	18.57% *j* = 44	13.78% ***j* = 26**

Definitions: *ESD*, extreme studentized deviate; λ_i, critical value; *j*, the row in Table A1 in Appendix A where each bias was obtained; *SD*, standard deviation.

Jeffrey R. Budd, PhD, Chairholder of the document development committee for EP09-A3, provided the accompanying explanation:

"Appendix B is referenced in the document only as a way to detect data points that should be investigated. The document goes to great lengths to visually help the user find these points without the need for such a statistical outlier rule. The errors in the formula will provide only slightly different results than expected and are therefore not serious. Nevertheless, they should be addressed to accommodate other guidelines that may reference EP09-A3 as a source of such an outlier rule. In addition, the authors of EP09-A3 used the two-sided *t* distribution, while Rosner's example (now correctly replicated) uses a one-sided distribution to compute λ_i. Table B1 has been corrected."

These changes will be incorporated into the document at its next scheduled printing. Please direct any related queries to customerservice@clsi.org.