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Variations in FVC and FEV_1 Biologic Quality Control Measures in a Global Multi-Center Clinical Trial

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BACKGROUND: Although quality control standards are recommended to ensure accurate test results, the coefficient of variation for the FVC and FEV_1 biologic quality control (BioQC) is not specified. The primary aim of this study was to evaluate variations in spirometry BioQCs in a large and diverse cohort of individuals to determine an acceptable standard for the coefficient of variation. METHODS: The FVC and FEV_1 biologic control data were secondary analyses from an inhaled medication trial that was conducted over 3 y ending in 2018 that included 114 laboratories. Results were sent to a central repository for expert review. The FVC and FEV_1 coefficients of variation were based upon a minimum of 10 spirometry values annually separated by at least 5 d. A second method of computing the coefficient of variation used 10 values within 28 d. Descriptive statistics were computed. Wilcoxon signed-rank tests were conducted to compare whether the median coefficient of variation values between the 2 methods differed, tested at $\alpha = 0.05$ using SPSS. RESULTS: Of 249 biologic control participants, 170 met the first year's inclusion criteria. The coefficient of variation for the 5-d separated method was < 5% for 94.1% of FVC and 93.5% of FEV_1 values in the first year. By year 3, 90% of FVC and FEV_1 coefficient of variation values were < 4%. The medians for the 5-d separated and the 28-d measure showed no difference for either FVC coefficient of variation or FEV_1 coefficient of variation, $Z = -1.764$, $P = .78$, and $Z = -0.980$, $P = .33$, respectively. CONCLUSIONS: Interlab biologic control variation values of < 4% for FVC and FEV_1 are achievable; however, individual labs should strive to attain lower values. Acceptable coefficients of variation can be achieved within 28 d. *Key words: Forced expiratory volume; quality control; spirometry standards; reproducibility of results; coefficient of variation.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Spirometry is the most common pulmonary function test used in diagnosis, monitoring, disability and impairment evaluations, as well as research and epidemiological surveys. The basic measures of spirometry are FVC and FEV_1. An accurate interpretation of test results and clinical changes over time requires strong quality control.[1] Prior to testing patients, technologists calibrate spirometry equipment to assure the equipment displays accurate values.[2] Biologic quality control (BioQC) assessments further evaluate the entire testing system to include the equipment, the software, and procedures by technologists within the laboratory.[3] The BioQC test is performed by a healthy, nonsmoking individual with stable lung function who can conduct an acceptable and repeatable spirometry. The individual's BioQC mean value ± 2 SD establishes an expected range of values used to monitor quality control.[4]

The American Thoracic Society (ATS)/European Respiratory Society (ERS) guidelines recommend quality control standards; however, BioQC standards for FVC and FEV_1 are not clearly specified.[2] The ATS/ERS guidelines refer to the ATS Pulmonary Function Laboratory Management and Procedure Manual;[4] however, the manual does not include statements on BioQC testing frequency

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nor an acceptable coefficient of variation. The published data on coefficient of variation were measured at various frequencies (hourly,[3,5,6] daily,[7-10] weekly[5,8]), in mostly small sample sizes ($n < 100$[1,3,5-14] and $n > 100$[15]), varied smoking status (100% nonsmokers[3,6,9,14,15] and some smoking history[5,7,8,10,11]), gender (< 50% male[6,7,9,15] and < 50% female[1,3,8,10,11,13,14]), conducted by the same[3,6,9] or different technologists,[5,8,15] and with the same[3,8,9,11,13,15] or different spirometers.[1,3,13]

Stronger evidence demonstrating the acceptable spirometry variation in biologic control subjects must be evaluated in order to establish consistent targets for spirometry BioQC coefficient of variation for FVC and FEV_1. Therefore, the primary aim of this study was to assess FVC and FEV_1 BioQC coefficient of variation in a large, global multi-center clinical trial with a diverse cohort for 3 years. Additionally, the coefficient of variation changes in each of the 3 years were assessed to determine how often BioQC coefficient of variation should be evaluated.

QUICK LOOK

Current knowledge

A comprehensive spirometry quality control program includes conducting biologic quality controls (BioQCs). The first step in a BioQC program is to identify a healthy volunteer and establish the individual's coefficient of variation.

What this paper contributes to our knowledge

This paper specified a process for establishing a spirometry BioQC coefficient of variation value. This study also identified an achievable standard for interlaboratory spirometry BioQC coefficient of variation across multiple manufacturers. Further, the study indicated that coefficient of variation values were stable over 2 years.

Methods

Study Design

A retrospective analysis was performed on FVC and FEV_1 BioQC data collected from an inhaled medication study that was conducted over 3 y ending in 2018. This study was granted exemption status by the institutional review board from Rush University Medical Center.

Procedures

Onsite training on BioQC for FVC and FEV_1 testing was provided to each of the 114 pulmonary function labs (PFLs) across North America, Europe, and Israel as a part of the inhaled medication trial. These training sessions included oversight of equipment calibration procedures and process of conducting spirometry BioQC testing. The equipment that was used for the testing was routinely calibrated according to the 2005 ATS/ERS quality control specifications for spirometer accuracy and precision.[16] Five different brands of pulmonary function equipment were used in this study. The spirometers used were the Encore (CareFusion, San Diego, California), EasyOne Pro (ndd Medical Technologies, Andover, Massachusetts), Jaeger (Jaeger/Cardinal Health, Hochberg, Germany), MGC Diagnostics (St. Paul, Minnesota), and KoKo - formerly nSpire Health (Longmont, Colorado).

BioQC participants enrolled in the study were technical staff working regularly in PFLs. Participants in this study were free of any known lung diseases and were nonsmokers based on self-report. The following demographic data were collected from each subject's submitted laboratory report: age, gender, race, and height. BioQC participants underwent study-specific training or were coached by a trained technologist to perform serial FVC and FEV_1 measurements lasting from 1 y to > 3 y as part of the quality program.

Each PFL participating in this study sent spirometry test results from their BioQC subjects and mechanical quality control findings to a central repository for expert review. The expert reviewers examined calibration reports, BioQC numerical results, volume-time graphs, and flow-volume loops to assure adherence to 2005 ATS/ERS acceptability and repeatability standards.[16] The 6 reviewers were registered respiratory therapists and registered pulmonary function technologists with over 100 years combined experience working with quality control. Feedback on errors were sent back to local sites. All satisfactory BioQC test results were transferred to a spreadsheet.

The initial coefficient of variation assessment included sequential BioQC tests separated by at least 5 d. Tests measured more frequently were removed to prevent values that may create an unrealistically low coefficient of variation value. The resulting coefficient of variation comprised the 5-d separated measure. A second assessment of BioQC coefficient of variation used the first 10 values provided they occurred within 28 d to determine whether the measurement time frame affected the coefficient of variation. This coefficient of variation represented the 28-d measure. Both spirometry coefficient of variation assessments were based on the first 10 values annually. Data were transferred from the spreadsheet to SPSS 22.0 (IBM, Armonk, New York) for the statistical analysis.

Data Analysis

Descriptive statistics were reported for demographic data and outcome variables. The Wilcoxon signed-rank

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Table 1. Demographic Data

Demographic Variables	Year 1 ($n = 170$)	Year 2 ($n = 87$)	Year 3 ($n = 31$)
Gender, *n* (%)			
Female	110 (64.7)	52 (59.8)	17 (54.8)
Male	58 (34.1)	33 (37.9)	14 (45.2)
Missing	2 (1.2)	2 (2.3)	
Race/ethnicity categories, *n* (%)			
White	137 (80.6)	64(73.6)	20 (64.5)
Black	11 (6.5)	8 (9.2)	5 (16.1)
Asian	3 (1.8)	2 (2.3)	0
Hispanic	14 (8.2)	10 (11.5)	5(16.1)
Unknown	5 (2.9)	3 (3.4)	1 (3.2)
Age, y*			
Mean (SD)	46.1 (12.7)	46.6 (12.7)	51.8 (5.5)
Range	21–73	21–73	45–60
Height, cm†			
Mean (SD)	169 (8.9)	169 (10.0)	168.5 (11.4)
Range	152–191	152–191	152–188
Weight, kg‡			
Mean (SD)	75.8 (16.4)	75.7 (17.0)	78.1 (16.0)
Range	42.0–116.8	42.0–110.0	42.0–105.0
FVC, L			
Mean (SD)	4.10 (0.98)	4.09 (1.01)	3.92 (1.06)
Range	2.18–6.66	2.23–6.71	2.15–6.70
FEV_1, L			
Mean (SD)	3.24 (0.77)	3.21 (0.78)	3.11 (0.84)
Range	1.58–5.55	1.63–5.32	1.57–4.93

*Age data were available for year 1 ($n = 93$), year 2 ($n = 46$), and year 3 ($n = 11$).
† Height data were available for year 1 ($n = 115$), year 2 ($n = 54$), and year 3 ($n = 18$).
‡ Weight data were available for year 1 ($n = 110$), year 2 ($n = 51$), and year 3 ($n = 17$).

test was used to evaluate if median values of coefficient of variation for FVC and FEV_1 differed between the 5-d separated measure compared to the 28-d measure. The tests were conducted at alpha = 0.05 using SPSS 22.0. The Friedman test evaluated whether there were any coefficient of variation changes between each year, and pairwise Wilcoxon signed-rank tests evaluated the location of differences using $P = .02$ (.05/3) for a family-wise alpha = 0.05.

Results

There was a total of 249 BioQC participants enrolled in the study, of which 170 met the inclusion criteria for spirometry BioQC for the first year. There were fewer participants in the subsequent years; 87 in year 2 and 31 in year 3, respectively. The sample population included predominantly white females with the mean age of 47 y (see Table 1).

In the first year, > 93% of values for FVC and FEV_1 had a coefficient of variation < 5%. The percentage of coefficient of variation values < 5% rose in the second and third years. There were > 90% coefficient of variation for FVC and FEV_1 values that were < 4% by year 3. The values for coefficients of variation for BioQC for FVC and FEV_1 over 3 y are listed in Table 2. Figures 1 and 2 show FVC and FEV_1 BioQC coefficient of variation values for each year's first 10 data points. The determination of whether the 5-d separated measure differed from the 28-d measure showed no difference for either FVC coefficient of variation or FEV_1 coefficient of variation, $Z = -1.764$, $P = .78$, and $Z = -0.980$, $P = .33$, respectively. Only 70 (41%) of the 170 sites completed their coefficient of variation data collection within the 28-d time frame.

Analyses were conducted to see if median values of coefficient of variation differed between years. The Friedman test, $n = 28$, was significant at $P < .001$. The comparisons between FVC coefficient of variation and FEV_1 coefficient of variation between years 1 and 2 and years 1 and 3 showed statistically significant differences at a $P = .02$ (see Table 3). There was a < 1% change in median coefficient of variation differences for FVC and FEV_1 values over the 2-y period.

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Table 2. Coefficient of Variation for Biologic Quality Control for FVC and FEV_1 Over 3 Years

	BioQC Subjects, *n*	Median	Range (IQR)	Coefficient of Variation Values < 3%	Coefficient of Variation Values < 4%	Coefficient of Variation Values < 5%
Year 1 FVC coefficient of variation	170	2.42	0.59–7.08 (1.40)	71.8%	85.9%	94.1%
Year 2 FVC coefficient of variation	87	2.13	0.52–5.27 (1.15)	86.2%	94.3%	97.7%
Year 3 FVC coefficient of variation	31	1.74	0.79–4.20 (1.36)	83.9%	96.8%	100%
Year 1 FEV_1 coefficient of variation	170	2.65	0.98–10.49 (1.41)	60.6%	85.3%	93.5%
Year 2 FEV_1 coefficient of variation	87	2.14	0.83–6.21 (1.16)	78.2%	93.1%	97.7%
Year 3 FEV_1 coefficient of variation	31	2.14	0.64–4.44 (1.43)	77.4%	83.8%	100%

BioQC = biologic quality control
IQR = interquartile range

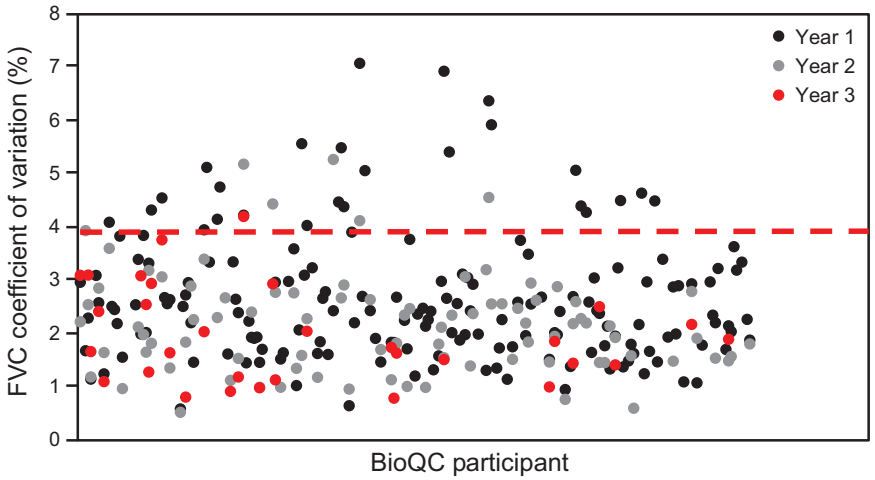

Fig. 1. FVC biologic quality control (BioQC) coefficient of variation of first 10 data points by year.

Discussion

High-quality spirometry requires careful attention to quality control practices to ensure the equipment's accuracy and precision for producing reliable test results.[2] Thus, routine performance of BioQC testing in addition to calibration procedures is vital for each PFL's quality control program to detect systematic errors that may occur with the technologist, the software, or the specific spirometer.[3,17,18] Regarding technologists, a study that compared 13 laboratories in the Denver area attributed interlaboratory variations due to differences in practices and procedures.[14] Similar findings occurred in the SAPALDIA study when different operators used the same equipment.[3] The current study had a large number of diverse individuals ($n = 170$) conducting BioQC values across a range of ages and race/ethnicity and equal distribution of sex.

The current study used 5 different brands of equipment as well as equipment at 101 different sites. Equipment variation was demonstrated by Kunzli and colleagues[3] when the same technologist measured subjects using the same versus different spirometers. The variation for FVC coefficient of variation rose from 2.2% to 2.7%, and FEV_1 coefficient of variation rose from 2.2% to 3.3% when measurements were made with different spirometers. In another study, instrumentation in a longitudinal study accounted for 13–58% of total FEV_1 variability observed in subjects.[3,14] Thus, BioQC targets need to be based on studies that include diverse equipment and sites. Further, the values must come from acceptable tests conducted on spirometers with confirmed volume linearity.

The Association for Respiratory Technology & Physiology (ARTP) recently recommended that BioQC values be

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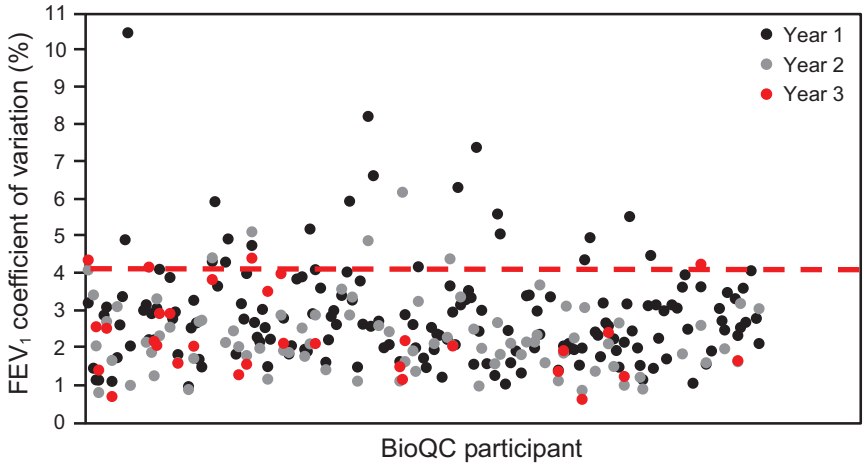

Fig. 2. FEV_1 biologic quality control (BioQC) coefficient of variation of first 10 data points by year.

Table 3. Wilcoxon Pairwise Comparisons of Median Changes in the Coefficient of Variation Between Years

	FVCYear 1 and Year 2 (*P*)	FVCYear 1 and Year 3 (*P*)	FVCYear 2 and Year 3 (*P*)	FEV_1Year 1 and Year 2 (*P*)	FEV_1Year 1 and Year 3 (*P*)	FEV_1Year 2 and Year 3 (*P*)
Median changes in the coefficient of variation between years	−0.49 (< .002)*	−0.54 (< .001) *	−0.22 (0.29)	−0.50 (.001) *	−0.47 (.003)*	0.21 (.59)

* Significant at alpha = 0.02.

computed by obtaining 10 measures over 10 consecutive working days.[18] The data from the current study demonstrated that only 41% of the BioQCs successfully completed acceptable tests to establish their baseline coefficient of variation within 28 d. This indicates that although a 10 consecutive working-day target may be appropriate it is not pragmatic for most PFLs. Computing the coefficient of variation on 10 data points within 28 d did not yield significantly different results than if the data were collected over more than 50 d.

Table 4 shows a historical summary of spirometry BioQC FVC and FEV_1 coefficients of variation including the variability in number of participants, number of sessions, the measurement frequency, the trials/session that were conducted, and whether published standards were followed. All these variables affect the resulting coefficient of variation. For example, note that the smallest coefficient of variation results from tests conducted on the same day at hourly intervals. The number of participants in each study also affects the results by reducing the coefficient of variation. The SD decreases with increasing sample size, which directly lowers the coefficient of variation.[15] This concept is highlighted clearly in a study that evaluated a single person who tested in 21 PFLs over a period of 13 y. The coefficients of variation were smallest when the number of tests was highest. Further, the interlab variability was higher than the intralab variability.[13] This finding is expected due to the variances in equipment, available training, technologists conducting the test, characteristics of BioQC individuals (smoking history), regional differences, and standards utilized.

The BioQC participants in the current study received training at the study outset on-site specific to their equipment. The proper function of their equipment was confirmed prior to data collection. Experts assured all test results met the 2005 ATS/ERS criteria.[16] The data accounted for 5 different spirometry systems across 114 labs and demonstrated that an acceptable target for the coefficient of variation was $< 4\%$. Although interlaboratory standards may be higher due to the variables identified above, each lab should have values $< 4\%$ and strive to achieve an even lower coefficient of variation to improve data integrity. For example, the British Columbia Accreditation program requires a coefficient of variation $< 3\%$ for individual labs (https://www.cpsbc.ca/files/pdf/DAP-SP-Quality-Control-Plan.pdf, *Accessed July 27, 2021*).

One additional finding that emerged from the current study was the individual's experience conducting a BioQC. Figures 1 and 2 demonstrate that the majority of BioQC values $> 4\%$ appeared in year 1. Greater reproducibility and precision are possible when PFL staff understands potential error sources and calibration standards. The smaller coefficient of variation

Table 4. Historical Spirometry Biologic Quality Control FVC and FEV_1 Coefficients of Variation

First Author	Year	FVC Coefficient of Variation	FEV_1 Coefficient of variation	Spirometer/# Devices	# Operators/ Training	# Unique Participants/# Sites	Average Number of Test Sessions	# Trials or Test Session (Standards)	Frequency of Test Sessions	Mean Age, y	% Smokers	% Male	% White
Watts[1]	2005	2.21	2.26	11 different spirometers 44	NR/NR	3/23	3	(1994 BTS Standards)	Every 5 y	NR	NR	100	NR
Kunzli[3]	1995	2.00	2.20	Sensormedics 2200 mass flow sensor/8	1/Yes	13	8	(ATS 1987 Update)	Hourly	24.0	0	53.8	NR
Kunzli[3]	1995	2.70	3.30	Sensormedics 2200 mass flow sensor/1	8/Yes	13/1	8	(ATS 1987 Update)	Hourly	24.0	0	53.8	NR
Kangalee[13]	1992	2.30	2.90	Collins Maxi System (Eagle 1 Processor)/1	NR/NR	1/1	NR	NR	Monthly	NR	NR	100	100
Kangalee[13]	1992	3.80	3.80	8 different spirometers/17	NR/NR	1/17	NR	NR	Once	NR	NR	100	100
Wanger[14]	1991	4.10	4.80	6 different spirometers/NR	NR/NR	5/13	NR	Varied per technologist	Testing over 45-d period; frequency not given	41.0	0	60.0	NR
Groth[15]	1986	4.90	4.70	Jaeger Pneumotachograph/1	2/Yes	112/1	2	3	0.5–6 mo	45.5	0	40.8	100
Rozas[9]	1982	2.14	2.80	13.5 L water seal/1	1/NR	15/1	5	3 (ATS 1979 Am Rev Respir Dis) 119:831	Daily	NR	0	46.7	NR
Lebowitz[7]	1982	3.50	3.60	Pneumotachygraph/1	NR/NR	10/1	30	5	Daily	33.7	0.3	0.2	NR
Nickerson[6]	1980	3.50	3.60	Heated Fleisch no. 3 Pnemotachygraph transducer/NR	1/NR	15/1	At least 5 flawless, < 12	5	1 d	18.0	0	46.7	NR
Cochrane[5]	1977	1.80	2.30	Ohio 840 (dry rolling seal)/ NR	2/NR	10/1	30	Mean of 3 trials; all analyses versus the "best" test	Hourly	24.1	50.0	50.0	NR
Cochrane[5]	1977	2.90	3.35	Ohio 840 (dry rolling seal)/ NR	2/NR	10/1	18	Mean of 3 trials; all analyses versus the "best" test	Weekly	24.1	50.0	50.0	NR
McCarthy[8]	1975	2.50	2.50	Wedge/1	2/Yes	12/1	10	NR	Daily	27.0	0.3	58.3	NR
McCarthy[8]	1975	6.00	7.00	Wedge/1	2/Yes	20/1	10	NR	Weekly	39.0	0.5	55.0	NR
Dawson[11]	1966	2.10	3.00	13.5-L water seal Collins spirometer/1	NR/NR	38/1	5	Best of 2	Bi-annually	35.5	47.4	100	NR
Spicer[10]	1966	8.10	NR	10-L spirometer/NR	NR/NR	11/1	21	NR	Daily	25.5	46.0	54.5	1.0

NR = not reported
ATS = American Thoracic Society
BTS = British Thoracic Society

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range by year 3 demonstrates how a user's experience lowers the range. The fact that 80% of FVC BioQC coefficient of variation values were < 3% by year 3 could have been due to combined learning about equipment and procedures. This reinforces a prior statement that improvements in BioQC testing can improve laboratory precision.[13]

Additionally, this study investigated the coefficient of variation changes in each of the 3 y to determine how often BioQC coefficient of variation should be evaluated. There were statistically significant changes in both FVC and FEV_1 between years 1 and 2 and between years 1 and 3. However, this < 1% change in medians of coefficient of variation is not practically significant. This finding suggests that the frequency of calculating the coefficient of variation depends on the experience with testing. More variability was observed in BioQC testing in the first year of the study. Technologists conducting BioQC measures mastered their skills, and less variability was noted with each year. Therefore initially, laboratories may recalculate their BioQC values annually until greater subject consistency is achieved. Once the stability of results is achieved, it might be appropriate to recalculate BioQC limits every few years due to natural lung changes. The latest 2020 ARTP spirometry statement recommends recalculations of the ranges for BioQC spirometry values and coefficients of variation at least once every 2 years.[18]

There were several limitations to this study. The main limitation is that the number of participants declined each year, making the sample size smaller for the between-year comparisons. The decreased sample size in years 2 and 3 was a result of a decreasing number of active sites and BioQCs in the clinical trial. Sites were closed as they completed the study, resulting in natural attrition for a 3-y study. The ending date for each site in the study influenced the total number of participants in year 3. Fewer participants in year 3, however, did not affect the power to find a difference between years 1 and 2 or years 1 and 3 of the study. It may have influenced finding a difference in coefficient of variation between years 2 and 3 due to the smaller effect size present between those years. Also, the majority of participants were white females. It is not known if variability would change if more men or a more diverse population participated. In addition, the smoking status and health history were based on self-report, and the measurements did not account for diurnal variation.

Conclusions

A strong spirometry BioQC program needs to adhere to current ATS/ERS spirometry standards to achieve acceptable results. The spirometry BioQC coefficient of variation values in this study came from a large and diverse cohort of individuals. These data support that FVC and FEV_1 coefficient of variation standards < 4% are achievable and should be the maximal acceptable value for a spirometry BioQC program. Initially, values should be recalculated each year until values stabilize. After coefficient of variation values stabilize, it might be appropriate to recalculate coefficient of variation limits every few years.

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