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Comparison of Spirometric Hesitating Start Criteria Using the Ratio of Extrapolated Volume to Timed Forced Expiratory Volumes

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Comparison of Spirometric Hesitating Start Criteria Using the Ratio of Extrapolated Volume to Timed Forced Expiratory Volumes

A thesis submitted to the
Graduate School of the
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in partial fulfillment of the requirements
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in the Department of Environmental Health
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by
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MD, Boston University 2002
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Abstract

Background: The origin of the hesitating start criterion was not established from a peer reviewed scientific study, but was based upon clinical opinion from expert users. The primary purpose of the current study is to investigate alternative hesitating start criteria for shorter forced expiratory times with a high degree of correlation to the currently accepted method.

Methods: A total of 1,719 workers met eligibility criteria for this study and contributed 24,945 trials. The primary purpose was to find the slope of the regression of EV/FVC on EV/FEV₁, EV/FEV₃, and EV/FEV₆.

Results: From regression analyses, the values for EV/FEV₁, EV/FEV₃, and EV/FEV₆ corresponding to the five percent EV/FVC value were determined to be 6.62%, 5.59%, and 5.25%, respectively. Application of the newly developed EV/FEV₆ hesitating start criteria to trials truncated at six seconds resulted in 125 (0.96%) fewer trials being rejected when compared to the conventional hesitating start criteria of EV/FVC of 5%.

Conclusions: A newly derived hesitating start criterion using EV/FEV₆ of 5.25% was determined. This new criterion is recommended for tracings that do not achieve a plateau, such as when a six second expiration (FEV₆) is performed. Application of this new hesitating start criterion was shown to reduce the number of maneuvers falsely rejected when a plateau is not achieved.
Acknowledgement

We thank Enas Alshaikh for her assistance with statistical analyses.
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List of Definitions

FEV₁- maximal volume of air exhaled in the first second of a forced expiration from a position of full inspiration
FEV₃- maximal volume of air exhaled in three seconds of a forced expiration from a position of full inspiration
FEV₆- maximal volume of air exhaled in six seconds of a forced expiration from a position of full inspiration
FVC- maximal volume of air exhaled with maximally forced effort from a maximal inspiration
EV- volume of air calculated at time zero using the back extrapolation method
FWMMP- Fernald worker population. FWMMP is the standard abbreviation for the Fernald Worker Medical Monitoring Program
UCPCP- University of Cincinnati Pulmonary Clinic population. The UCPCP was investigated by Lopez (1998, unpublished data).
Spirometry trial- one forced expiratory maneuver by a subject
Test session- includes all spirometry trials completed by one subject on the same day
Introduction

Pulmonary function tests (PFT) are routinely used as a screening tool to measure lung function, with spirometry most commonly performed. Pulmonary function testing standards have been established to make administration and interpretation of spirometry uniform. The American Thoracic Society (ATS) and the European Respiratory Society (ERS) issued joint statements in 2005.\textsuperscript{1-3} Test acceptability criteria and the definition of a hesitating start were adopted in 1979 by the medical community.\textsuperscript{4} However, the origin of the hesitating start criterion was not established from a peer reviewed scientific study, but was based upon clinical opinion from expert users. The primary purpose of the current study is to investigate alternative hesitating start criteria for shorter forced expiratory times with a high degree of correlation to the currently accepted method.

Measurement of forced expiratory volumes on volume-time tracings uses the back extrapolation technique to identify time zero. PFT trials with excessive hesitating starts are not representative of forced expiratory maneuvers and thus are not usable for reporting forced expiratory measurements of lung function.

A spirometry trial with a hesitating start is defined as having a ratio of extrapolated volume (EV) to forced vital capacity (FVC) greater than or equal to five percent, or an EV greater than 150 milliliters if the FVC is three liters or less.\textsuperscript{2} Achieving an acceptable FVC requires a subject to reach a plateau on volume-time tracings. A plateau is indicated by a change in volume less than twenty-five milliliters for at least one second.\textsuperscript{2} Unfortunately some subjects are unable to achieve an acceptable plateau when conducting a forced expiratory maneuver due to a variety of reasons, including medical
conditions. Failure to achieve an acceptable plateau alters the calculated ratio of EV to FVC.

Forced expiratory volume at six seconds (FEV₆) has been shown to be an acceptable surrogate of FVC.⁵⁻⁸ Exhalation for six seconds is also significantly better tolerated than complete exhalation to FVC. Tracings without a plateau underestimate FVC, elevating the calculated EV/FVC ratio and increase the likelihood of rejection due to a hesitating start. Therefore, when a plateau is not reached, the calculation of a hesitating start based on shorter forced expiratory times, rather than FVC, would appear to be more appropriate. Many patients and spirometry technicians could benefit from the development of criteria that define a hesitating start based on EV/FEV₆, rather than one based on EV/FVC.

**Purpose of the study**

The purpose of the study is to find the percentage of trials that are rejected by the current method of determining a hesitating start, based on EV/FVC greater than or equal to five percent, and accepted using new hesitating start criteria based on the ratio of extrapolated volume to forced expiratory volumes at shorter times.

**Literature Review and Significance**

Currently, the scientific literature does not contain an evaluation of hesitating start criteria for spirometry trials. To our knowledge, no published studies have evaluated hesitating start criteria for FEV₆ maneuvers. Development of hesitating start criteria based on shorter forced expiratory times may result in patients performing fewer
maneuvers, thus reducing testing time, discomfort, and perhaps risk of injury especially among the elderly and infirm. Better patient compliance with testing procedures will likely be achieved. This may improve participation rates for screening spirometry. Ultimately, this may also improve the accuracy of the diagnosis and monitoring of pulmonary disease, especially among those who have difficulty achieving a complete exhalation to residual volume.

Finally, this study has the potential to provide rationale for adding functionality to pulmonary function testing software. An early warning signal indicating a hesitating start could be implemented that is based on shorter exhalation times. If a hesitating start is detected, the operator could stop the trial immediately and prevent unnecessary effort.

Hypothesis

Hesitating start criteria based on the ratio of extrapolated volume to forced expiratory volumes at one, three and six seconds will identify spirometry trials with acceptable starts that were previously classified as having a hesitating start using the currently accepted criteria based on the ratio of extrapolated volume to forced vital capacity.

Specific Aims

1) Identify the relationship between EV/FVC and EV/FEV₁, EV/FEV₃ and EV/FEV₆ spirometric measurements of participants in the Fernald Worker Medical Monitoring Program (FWMMP) by regression analyses. Calculate the upper endpoint of a one-tailed 95% prediction interval of the (statistical) predicted values for EV/FEV₁, EV/FEV₃ and
EV/FEV₆ that correspond to the value of EV/FVC at 5%, which can be used to indicate the presence of a hesitating start on spirometry.

2) Apply the hesitating start cutoff value identified in specific aim one to the same tracings after truncating expiratory times at one, three, and six seconds. Compare the number of acceptable starts using the new cutoff values to the number of acceptable starts determined using the currently accepted method based on EV/FVC.

3) Compare the number of acceptable starts using the FEV₁ cutoff value for defining a hesitating start in the FWMMP cohort to the number of acceptable starts using the FEV₁ cutoff value calculated from a University of Cincinnati Pulmonary Clinic Population (UCPCP). (Lopez 1998, unpublished data)

**Study Methods**

This study is a retrospective cohort study of subjects who were included in the Fernald II Settlement, who participated in the Fernald Worker Medical Monitoring Program (FWMMP), and who had at least one pulmonary function test. All data was de-identified. Subjects represented a worker and former worker population at a uranium processing plant in Fernald, Ohio. Workers were followed to monitor for potential health effects from occupational exposure to uranium and radiation. A total of 1,719 Fernald workers met eligibility criteria for this study and contributed 24,945 trials.

Spirometry measurements used for this study were collected by the FWMMP between January 2000 and October 2008. Subjects were tested approximately every other
year and completed multiple trials within each test session. The spirometry tests were administered by experienced pulmonary function specialists who had completed a National Institute for Occupational Safety and Health approved training course. Computerized data was acquired according to ATS/ERS standards using OMI spirometry software (Houston, Texas) connected to an eight liter SensorMedics 922 volume spirometer (SensorMedics Inc., Yorba Linda, CA). Volume-time and flow-volume tracings were collected, which allowed calculation of FVC, FEV₁, FEV₃, FEV₆, EV and forced expiratory time (FET). Time zero was calculated using back-extrapolation. Appendix A shows a summary of ATS/ERS acceptability criteria, calculation of EV, and the method used to identify a hesitating start.

Inclusion criteria for regression analyses were 1) spirometry trials without invalid or missing forced expiratory measurements 2) spirometry trials meeting ATS/ERS acceptability criteria and 3) acceptable spirometry trials with EV/FVC less than 5%, and resulted in inclusion of 13,025 trials in the study. A total of 11,920 trials did not meet study inclusion criteria, and the vast majority of these (11,487 trials) were excluded for failure to meet acceptability criteria as defined by the spirometry software. The most common exclusion was failure to reach a plateau, as shown in Table 1. Three hundred twenty eight trials were excluded due to invalid/missing information and practice testing. These trials were performed for teaching, maintenance, calibration or contained missing/corrupted pulmonary function measurements. One hundred five acceptable trials with EV<150ml were excluded due to having EV/FVC greater than or equal 5%. Inclusion criteria for a sensitivity and specificity analysis of the EV/FEV₆ cutoff value
were 1) acceptable trials included in the regression analyses and 2) unacceptable trials
due solely to having EV/FVC greater than or equal to 5% (a hesitating start).

The UCPCP included 3,479 acceptable spirometry trials from 801 individuals
Trials were performed using an eight liter SensorMedics volume spirometer
(SensorMedics Inc., Yorba Linda, CA) connected to OMI spirometry software. The
predominant race was Caucasian and the predominant sex was male. This cohort was
used to validate the EV/FEV₁ hesitating start cutoff value developed in this paper.

The Institutional Review Board at the University of Cincinnati and the Fernald
Worker’s Advisory Group approved the study.

**Statistical Analysis**

Exploratory analyses were performed to assess worker demographics (gender,
race, age at test, body mass index, smoking status), test characteristics (maximum number
of trials per subject, number of subjects at each test session, number of trials per test
session), and the distribution of spirometric variables (FVC, FEV₁, FEV₃, FEV₆, EV,
EV/FVC, FEV₁/FVC). Kolmogorov–Smirnov and Shapiro-Wilk tests were used to test
the distributional properties of the spirometric variables. Tests and graphical displays
supported the assumption of normality of spirometric variables. Since multiple outcomes
per subject were analyzed, correlations between spirometric measures within the same
session were investigated by obtaining Pearson correlation coefficients. Repeated
measures linear regression analyses were performed to investigate the relation between
EV/FVC and EV/FEV₁, EV/FEV₃, and EV/FEV₆. The compound symmetric correlation
structure was specified, based on equal correlations between trials on the same subject within each session. Three separate regression models were analyzed using data from all acceptable trials of 1501 subjects (i.e. EV/FVC was less than 5%). In each model the independent variable was EV/FVC, dependent variables were EV/FEV₁, EV/FEV₃, and EV/FEV₆. The primary purpose was to find the slope of the regression of EV/FVC (independent variable) on EV/FEV₁, EV/FEV₃, and EV/FEV₆ (dependent variables). The estimated value of each dependent variable corresponding to an EV/FVC of approximately 5% was obtained, as well as the upper endpoint of a one-tailed 95% prediction interval on the (statistical) predicted value corresponding to EV/FVC of 5% in a similar set of data. The upper endpoint of a one-tailed 95% prediction interval of the (statistical) predicted value was then used to identify the newly calculated ratio of EV to timed volumes at one, three, and six seconds (i.e., EV/FEV₁, EV/FEV₃, and EV/FEV₆).

Secondary analyses were performed in order to investigate the effect of spirometry pattern on the estimated hesitating start cutoff values. For these analyses, subjects were classified into normal, obstructive, restrictive and mixed spirometry patterns based on Hankinson’s lower limit of normal.⁹ Again, the upper endpoint of a one-tailed 95% prediction interval on the (statistical) predicted value of EV/FEV₆ was selected as the cutoff value. In another analysis, the UCPCP was used to validate the EV/FEV₁ hesitating start cutoff value developed in this paper. An additional analysis was also performed in which the sensitivity and specificity of the new cutoff value at six seconds was compared to the currently accepted hesitating start cutoff value based on EV/FVC. All data were analyzed using statistical software (SAS version 9.1; SAS Institute, Cary, NC).
Results

Acceptable trials from 1501 FWMMP participants (13,025 trials) were analyzed. Table 1 shows the number of unacceptable spirometry trials by ATS/ERS acceptability criteria. Table 2 shows the majority of subjects were Caucasian (n=1411; 94%) with the remainder classified as Black, Hispanic, Asian or other. The mean age at test was 63 years (range 34 - 90) and 1172 (78%) were male. Former smokers constituted 49% of the cohort, while 41% were never smokers and 10% were current smokers. The mean body mass index was 29 with a standard deviation of 5. The mean FEV₁/FVC (%) was 74.5 with a standard deviation of 7.

Appendix A shows a summary of ATS/ERS acceptability criteria, calculation of EV, and the method used to identify a hesitating start. Appendix B shows the distribution of the spirometric variables FEV₁, FEV₃, FEV₆, FVC, FEV₁/FVC, EV, and EV/FVC. Appendix C shows the scatter plots of EV/FVC versus EV/FEV₁, EV/FEV₃ and EV/FEV₆. Appendix D shows the histograms of forced expiratory time (FET) of acceptable trials and all trials. The mean FET for acceptable trials was 11.9 seconds with a standard deviation of 2.9 seconds. The mean FET for all trials was 10.8 seconds with a standard deviation of 3.7 seconds. Appendix E shows the frequency distributions of the maximum number of acceptable trials per subject, maximum number of trials per subject for all trials, total number of acceptable trials at each test session, and number of subjects contributing acceptable trials at each test session.

From the regression analyses, the hesitating start cutoff values for EV/FEV₁, EV/FEV₃, and EV/FEV₆ corresponding to the five percent EV/FVC value were determined to be 6.62%, 5.59%, and 5.25%, respectively. Figure 1 shows a volume-time
tracing with the cutoff values defining a hesitating start at one, three and six seconds of exhalation.

To evaluate the newly developed hesitating start criteria, 13,025 acceptable tracings were truncated at six seconds to simulate maneuvers with early termination (i.e., no plateau). Applying the currently accepted hesitating start criterion of 5% to these maneuvers with truncated expiratory times resulted in 162 (1.2%) maneuvers being rejected. Applying the newly developed hesitating start criterion of 5.25% resulted in 37 (0.28%) trials being rejected. This means that 125 (0.96%) fewer trials would have been rejected if these tracings had their expiration stopped at six seconds and the new EV/FEV$_6$ hesitating start criteria were applied. In reality, all of these maneuvers had acceptable starts when the expiration was permitted to reach a plateau.

Acceptable trials (N=13,025) were also truncated at one and three seconds to evaluate the utility of an early warning system for identifying a hesitating start. Applying the currently accepted hesitating start criterion of 5% to maneuvers truncated at one second resulted in 1327 (10.2%) maneuvers being rejected. Applying the newly developed hesitating start criterion at one second of 6.62% resulted in 90 (0.69%) trials being rejected. Applying the currently accepted hesitating start criterion of 5% to maneuvers truncated at three seconds resulted in 424 (3.3%) maneuvers being rejected. Applying the newly developed hesitating start criterion at three seconds of 5.59% resulted in 55 (0.42%) trials being rejected.

The hesitating start cutoff values for the spirometry pattern subgroups were 5.24% (normal), 5.66% (obstructive), 5.25% (restrictive) and 5.63% (mixed). Table 3 shows the number of trials rejected after applying the EV/FEV$_6$ subgroup specific hesitating start
cutoff values to acceptable trials truncated to six seconds that were categorized by spirometry pattern. The conventional EV/FVC cutoff value of 5% and the newly calculated EV/FEV₆ cutoff value of 5.25% were also applied to each subgroup. No trials in the obstructive and restrictive subgroups were identified as having a hesitating start when the newly developed subgroup specific criteria were applied.

For a sensitivity and specificity analysis of the EV/FEV₆ cutoff value, 13,025 acceptable trials plus 511 unacceptable trials due solely to having EV/FVC greater than or equal to 5% were included. Table 4 shows the sensitivity was 99.7% and specificity was 94.9%.

Using a different clinical population, Lopez (1998, unpublished data) reported a hesitating start cutoff value based on EV/FEV₁ of 6.16%. Applying Lopez’s hesitating start cutoff value of 6.16% to acceptable trials truncated to one second from the FWMMP, 246 (1.9%) trials were rejected. In comparison, when the hesitating start cutoff value based on EV/FEV₁ from the FWMMP of 6.62% was applied to the acceptable trials truncated to one second in the FWMMP, 102 (0.78%) trials were rejected.

**Discussion**

This study identified hesitating start criteria for spirometry trials that do not achieve a plateau. This is especially useful for clinical settings where tracings are stopped shortly after six seconds, a situation where plateaus are unlikely to be achieved. In our study population, nearly sixty percent of unacceptable trials (8008 of 13,536) did not achieve a plateau, despite vigorous coaching and lengthy forced expiratory times (mean
10.8 seconds). Currently, a hesitating start is determined by the ratio of extrapolated volume to the FVC, despite whether or not a plateau is achieved.

In our study, using EV/FEV$_6$, a new cutoff value for determining a hesitating start was calculated (5.25% vs. the traditional 5% EV/FVC). Application of this new hesitating start criterion in a cohort where the forced expiratory times were truncated resulted in the acceptance of more trials than the conventional approach. When spirometry trials with prolonged forced expiratory times are stopped at six seconds, applying the new EV/FEV$_6$ hesitating start cutoff value would likely result in fewer unnecessary rejections of trials. These findings highlight the value in using the new FEV$_6$-based criterion for identifying hesitating starts in spirometry trials.

In this study, we validated the EV/FEV$_1$ cutoff value obtained in the FWMMP by the similarity to that obtained using the Lopez population. FEV$_6$ was not available at the time of that study. Based on similar results at one second, we suspect that if Lopez had analyzed EV/FEV$_6$, similar results would have been obtained. Thus, new FEV$_6$ criterion has the potential to be applicable to a wide variety of clinical populations.

The number of participants, number of trials, experience of the testing technicians and use of testing procedures that adhered to ATS/ERS guidelines are strengths of the study. Use of acceptable trials for analyses ensured tracings were free from errors and of high quality.

In the spirometry pattern subgroup analysis (restrictive, obstructive, etc.), the hesitating start criteria based on FEV$_6$, ranged from 5.24 to 5.66%. In a general population, a value of 5.25% is recommended. However, for individuals with known airway obstruction, a value of 5.66% may be more appropriate. Additional research is
needed to find the optimum value in individuals with airway obstruction because it is highly correlated with forced expiratory time. Until additional information becomes available, the more conservative value of 5.25% is recommended.

This study also has some limitations. The study population is not representative of the general population due to older age, predominance of male gender and Caucasian race and occupational exposures to uranium and radiation. While the study population is not representative of the general population, it is representative of the type of subjects (e.g., older) that may need to stop forced expiratory maneuvers at six seconds. The study population is also representative of the type of population that participates in spirometry testing for occupational exposures.

We did not show in our study whether the new hesitating start cutoff values were better or worse than the currently accepted value. We showed that the new values at shortened forced expiratory times were highly correlated to the current EV/FCV value of 5% and that the new hesitating start cutoff values could be used as a highly sensitive and specific surrogate for determining an excessive hesitating start during spirometry testing. Use of the currently accepted hesitating start criteria is still recommended for trials that achieve a plateau.

The EV/FEV$_1$ and EV/FEV$_3$ values could be used as an early warning tool in spirometry software to identify hesitating starts. Many office spirometers do not provide real-time tracings for the operator to visually recognize hesitating starts. An audible and visual warning at one and/or three seconds could alarm if a potential hesitating start was detected using the newly defined values reported in this study. The trial could be terminated quickly, thus minimizing the wasted time, discomfort, and health risk of a
prolonged exhalation in a trial that would be rejected anyway based on the hesitating start.

Conclusions

The use of hesitating start criteria based on FEV₆ would result in more trials being classified as having an acceptable start of test when a plateau is not achieved compared to the currently accepted method. This would have the largest impact on individuals with obstructive disease who frequently have prolonged expiratory times, and may have difficulty achieving a plateau. These individuals would more easily achieve acceptable trials, while performing fewer prolonged forced expiratory maneuvers, thus decreasing the physical work required for each test session. This would likely lead to improved patient compliance within each test session, decreased side effects and ultimately, increase participation in surveillance programs.

Incorporation of an early warning signal in spirometry software to alert the operator to a possible hesitating start would also be very useful. This could be done with the values obtained at one and/or three seconds. Finally, improved consistency in pulmonary function testing may lead to more accurate diagnosis and treatment of lung disease.
Bibliography

5. Jensen RL, Crapo RO, Enright P. A statistical rationale for the use of forced expired volume in 6 s. Chest 2006; 130:1650-1656
7. Swanney MP, Jensen RL, Crichton DA, et al. FEV6 is an acceptable surrogate for FVC in the spirometric diagnosis of airway obstruction and restriction. Am J Respir Crit Care Med 2000; 162:917-919
Table 1 - Number of unacceptable spirometry trials by ATS/ERS acceptability criteria

<table>
<thead>
<tr>
<th>Frequency Rank</th>
<th>ATS/ERS Criteria Not Met</th>
<th>Number of Rejected Trials (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No Plateau(^1)</td>
<td>8008 (59)</td>
</tr>
<tr>
<td>2</td>
<td>Low Peak Flow(^2)</td>
<td>3180 (24)</td>
</tr>
<tr>
<td>3</td>
<td>EV/FVC (\geq 5%), or 150mL, whichever was greater</td>
<td>1668 (12)</td>
</tr>
<tr>
<td>4</td>
<td>Cough in first second of exhalation</td>
<td>507 (4)</td>
</tr>
<tr>
<td>5</td>
<td>FET &lt; 6 sec</td>
<td>173 (1)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>13,536* (100)</td>
</tr>
</tbody>
</table>

* 11,487 spirometry trials were rejected due to ATS/ERS acceptability criteria, and 2049 of these trials did not meet more than one ATS/ERS acceptability criteria.
\(^1\) Defined as no change in volume (<25mL) for at least one second on the volume-time curve.
\(^2\) Defined as peak flow for any given trial that is within 20% of the highest acceptable peak flow. An exception is given when the highest peak flow is less than 6 liters per second. In these cases, the shape of the tracing is used.
**Table 2** – Demographic and selected spirometric characteristics of subjects contributing acceptable trials (N = 1501)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1172 (78)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1411 (94)</td>
</tr>
<tr>
<td>African-American</td>
<td>81 (5)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (.61)</td>
</tr>
<tr>
<td><strong>Age at test, yrs</strong></td>
<td>63 ± 11</td>
</tr>
<tr>
<td><strong>Body Mass Index</strong></td>
<td>29 ± 5</td>
</tr>
<tr>
<td><strong>FEV₁/FVC%</strong></td>
<td>74.5 ± 7</td>
</tr>
<tr>
<td><strong>Smoking status</strong></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>740 (49)</td>
</tr>
<tr>
<td>Never</td>
<td>613 (41)</td>
</tr>
<tr>
<td>Current</td>
<td>146 (10)</td>
</tr>
</tbody>
</table>

Data are presented as No. (%) or mean ± SD

* Total subjects vary due to missing data
Figure 1 - Volume-time tracing showing cutoff values defining a hesitating start at one, three and six seconds of exhalation for 1501 workers (n=13,025 trials)

Values reported for EV/FEV₁, EV/FEV₃ and EV/FEV₆ are the upper endpoint of a one-tailed 95% prediction interval on the (statistical) predicted value corresponding to EV/FVC of 5%
Table 3 - Number of trials rejected after applying hesitating start cutoff values for EV/FEV\textsubscript{6} to acceptable trials truncated to six seconds by category of spirometry pattern.\textsuperscript{1}

<table>
<thead>
<tr>
<th>Group</th>
<th>Number trials (%)</th>
<th>Number trials rejected using cutoff value EV/FVC = 5%</th>
<th>Number trials rejected using cutoff value EV/FEV\textsubscript{6} = 5.25%</th>
<th>Number trials rejected using subgroup specific cutoff value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal\textsuperscript{2}</td>
<td>9,848 (76)</td>
<td>120</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Obstructive\textsuperscript{3,4}</td>
<td>1,053 (8)</td>
<td>10</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Restrictive\textsuperscript{5}</td>
<td>1,810 (14)</td>
<td>28</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Mixed\textsuperscript{6}</td>
<td>314 (2)</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>13,025 (100)</td>
<td>162</td>
<td>37</td>
<td>30</td>
</tr>
</tbody>
</table>

*Subgroup specific cutoff values were 5.24\% (normal), 5.66\% (obstructive), 5.25\% (restrictive) and 5.63\% (mixed)

2. Normal defined as FEV\textsubscript{1}/FVC\% greater than LLN and FVC greater than LLN and FEF\textsubscript{25-75%} greater than LLN
3. Obstructive defined as FEV\textsubscript{1}/FVC\% less than LLN and FVC greater than LLN
4. The low frequency of obstructive trials was because many trials with an obstructive pattern did not reach a plateau and were excluded from the analysis.
5. Restrictive defined as FEV\textsubscript{1}/FVC\% greater than LLN and FVC less than LLN
6. Mixed defined as all others
Table 4 – Sensitivity and specificity of the EV/FEV₆ hesitating start cutoff value compared to the ‘gold standard’ hesitating start cutoff value of EV/FVC = 5% based on 13,536 trials

<table>
<thead>
<tr>
<th></th>
<th>EV/FVC &lt; 5%</th>
<th>EV/FVC ≥ 5%</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>EV/FEV₆ &lt; 5.25%</td>
<td>12,988</td>
<td>26</td>
<td>13,014</td>
</tr>
<tr>
<td>EV/FEV₆ ≥ 5.25%</td>
<td>37</td>
<td>485</td>
<td>522</td>
</tr>
<tr>
<td>Total</td>
<td>13,025</td>
<td>511</td>
<td>13,536</td>
</tr>
</tbody>
</table>

Note: N = 13,536 trials includes 13,025 acceptable trials plus 511 unacceptable trials with EV/FVC ≥ 5% from FWMMP.

Sensitivity (%) = (12,988 / 12,988 + 37) * 100 = 99.7 %

Specificity (%) = (485 / 485 + 26) * 100 = 94.9 %
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Appendix A
Table 1 – 2005 ATS/ERS acceptability criteria summary

Spirometry trials are acceptable if:

1. They are free from artifact
   - Cough during the first second of exhalation
   - Glottis closure
   - Early termination or cut-off
   - Effort that is submaximal throughout
   - Leak
   - Obstructed mouthpiece

2. They have good starts
   - Extrapolated volume < 5% of FVC or 150mL, whichever is greater

3. They show satisfactory exhalation
   - Duration of at least 6 seconds and a plateau in the volume-time curve or if the subject should not or cannot continue to exhale.
Appendix A
Figure 1 – Calculation of extrapolated volume and a hesitating start of spirometry

Hesitating start = EV/FVC ≥ 5%
Appendix B
Figure 1 - Distribution of FEV$_1$ (mL)

- N = 13,025 trials
- Mean = 2857 mL
- SD = 755 mL
- [Min, Max] = [484, 6104] mL
Appendix B
Figure 2 - Distribution of FEV₃ (mL)

N = 13,025 trials
Mean = 3414 mL
SD = 877 mL
[Min, Max] = [794, 7337] mL
Appendix B
Figure 3 - Distribution of FEV$_6$ (mL)

N = 13,025 trials
Mean = 3645 mL
SD = 915 mL
[Min, Max] = [849, 7798] mL
Appendix B
Figure 4 - Distribution of FVC (mL)

N       = 13,025 trials
Mean    = 3838 mL
SD      = 962 mL
[Min , Max]  = [857 , 8034] mL
Appendix B
Figure 5 – Distribution of FEV$_1$/FVC (%) 

N = 13,025 trials
Mean = 74.5 %
SD = 7.07 %
[Min, Max] = [32.21, 97.08] %
Appendix B
Figure 6 - Distribution of EV (mL)

N = 13,025 trials
Mean = 89.4 mL
SD = 43.4 mL
[Min, Max] = [0, 314] mL
Appendix B

Figure 7 - Distribution of EV/FVC (%)
Appendix C

Figure 1 – Scatter plot of EV/FVC versus EV/FEV$_6$ for random ten percent of trials obtained by linear regression (N=1303)
Appendix C

Figure 2 – Scatter plot of EV/FVC versus EV/FEV$_1$ for 13,025 trials obtained by linear regression

$$\text{EV/FEV}_1 = 0.0008 + 1.3098 \times \text{EV/FVC}$$
Appendix C
Figure 3 – Scatter plot of EV/FVC versus EV/FEV$_3$ for 13,025 trials obtained by linear regression

\[ \text{EV/FEV}_3 = 0.0003 + 1.1123 \times \text{EV/FVC} \]
Appendix C
Figure 4 – Scatter plot of EV/FVC versus EV/FEV$_6$ for 13,025 trials obtained by linear regression

\[
\text{EV/FEV}_6 = 0.0001 + 1.0458 \times \text{EV/FVC}
\]
Appendix D
Figure 1 – Histogram of forced expiratory time (FET) per trial for trials meeting ATS/ERS acceptability criteria (N = 13,025 trials)

N = 13,025 trials
Mean = 11.9 seconds
SD = 2.9 seconds
[Min, Max] = [6.0, 26.97]
Appendix D
Figure 2 – Histogram of forced expiratory time per trial (FET) for all trials (N = 24,630 trials)

N = 24,630 trials
Mean = 10.8 seconds
SD = 3.7 seconds
[Min, Max] = [0.9, 26.97]

Note: 315 trials with invalid/missing information were excluded from analysis.
Appendix E
Figure 1 – Frequency distribution of the maximum number of acceptable trials per subject (N = 1501 subjects)

Number of Subjects

Maximum Number of Acceptable Trials

N = 1501 subjects
Mean = 8.7 trials per subject
SD = 5.5 trials per subject
Appendix E

Figure 2 – Frequency distribution of the maximum number of trials per subject for all trials. (N = 1703 subjects)

Note: Most subjects contributed trials from more than one test session.
Appendix E

Figure 3 - Frequency distribution of total number of acceptable trials at each test session (N = 13,025 trials)
Appendix E
Figure 4 - Frequency distribution of the number of subjects contributing acceptable trials at each test session

Note: Some subjects were present at multiple test sessions