ATS/ERS 2019 Spirometry Standards

PSRC Annual Meeting, 08DEC2023

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PFTs are weird

- No accreditation of labs
- Important decisions are based on the results yet the tests are not covered by CLIA
  - qualification, training and competency are not standardized
- Unique interaction of operator, patient and equipment

2

We're not going to go over everything

- IMPORTANT CHANGES
  - What is most important?
- What might not be right?

3

Where can I get the standards?

- The ATS/ERS 2019 Spirometry Standards:
  - https://www.thoracic.org/statements/pulmonary-function.php
  - from there you can also access the Online Supplement
    - (good stuff here)
- The Spirometry Patient Survey:
  - https://openres.ersjournals.com/content/7/1/00712-2020

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2019 Standards; What's in it?

- Patient
- Equipment
- Operator
- Procedure
- Analysis
- Quality Assessment

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Changes from ATS/ERS 2005 Standards

- New list of relative contraindications
- Spirometers are now required to meet International Organization for Standardization (ISO) 26782 standards, but with a maximum permissible accuracy error of 2.5%
- Device quality assurance procedures updated
- Operator training and maintenance of competency addressed
- List of activities patients should avoid before testing updated
- Focus on devices that measure both expiration and inspiration
- Maneuver acceptability and repeatability criteria updated*
- Bronchodilator responsiveness vs. reversibility
- End of forced expiration (EOFE) redefined

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Changes from ATS/ERS 2005 Standards

- Requirements for spirometry systems to provide uniform cues and feedback to the operator added
- New withholding times for bronchodilators for responsiveness testing
- New grading system for assessment of spirometry quality developed
- Standardized operator feedback options that promote synoptic reporting developed
- Preliminary findings derived from an international patient survey were presented

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Quality Control

- Equipment Installation
- Equipment quality control
- Equipment and software updates

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3 Liter Syringe Calibration

- Accuracy tolerance reduced from 3.0% to 2.5%
  - when 0.5% tolerance for syringe accuracy, total tolerance is 3.0%
- Daily calibration or verification
- Syringe must be revalidated
  - manufacturers recommendation
  - when dropped

Table of Potential Reasons for Calibration Failure is in the Standards

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Contraindications

- Acute MI changed from 1 month to 1 week
- Eye surgery – 1 week
- Thoracic or abdominal within 4 weeks
- Sinus or middle ear surgery within 1 week
- Hypo- or hypertension
- Significant atrial or ventricular arrhythmia
- Non-compensated heart failure
- Uncontrolled pulmonary hypertension
- Acute cor pulmonale
- More…….

All are relative contraindications

D/C if patient experiences pain!

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Performance of Spirometry

- Patient preparation
  - meds to withhold, if applicable
- Arrival in lab
  - check for contraindications
  - meds
  - age to nearest decimal
  - shoeless height in cm to nearest decimal
  - weight in kg to nearest 0.5kg
  - birth sex and ethnicity*

Operator training and attainment and maintenance of competency must be integrated in any spirometry testing service

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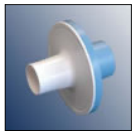
Filters, nose clips – Use them!

- Saliva can cause measurement errors; filter prevent this
- Clean exhalate during forced exhalations protects operators and patients that follow
- Use the same filter during calibration/verification



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Patient Instruction

- Demonstrate the procedure
- Emphasize posture
- Tell them what to expect
- Stay on mouthpiece and inhale back to full lungs

- Vigorously coach to full inflation; both before and after the forced exhalation
- 'Deepest breath, more, more, more…'

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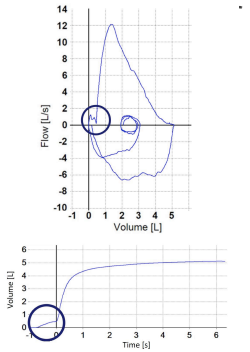
Satisfactory Start of Test

- Back extrapolated volume less than 5% is greater
- Do not pause at TLC for > 2 seconds
  - can decrease PEF and FEV1
  - so can a slow inspiration
- Rise time from 10-90% of PEF should be less than 150 msec



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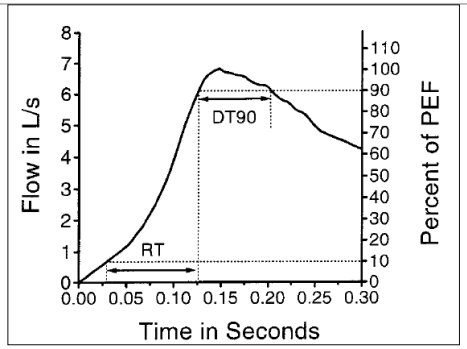
Rise Time from 10% to 90% of Peak Flow ≤ 150ms (0.15s)



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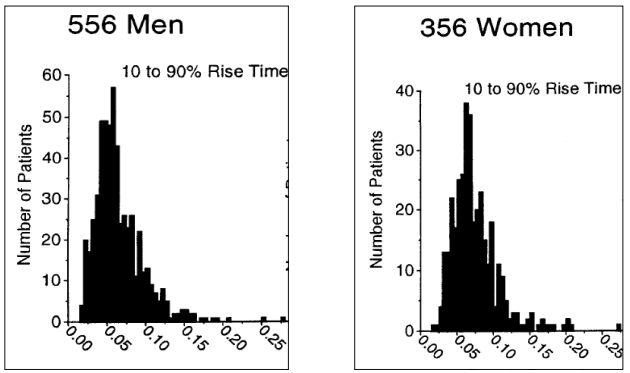
$RT_{10\%-90\%}$ in COPD and Normals



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End of Forced Expiration Criteria (EOFE)

- Obvious plateau of 1 second (no more minimum FET)
  - < 25 ml/second without glottic closure
- 15 second exhalation if no plateau
- When unable to achieve or maintain a plateau
- (e.g., children with high elastic recoil and patients with restrictive lung disease), acceptability is based on repeatability of FVC within 0.15L
- Cannot or should not continue to expire

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Summary of Acceptability, Usability and Repeatability Criteria for FVC

Acceptability and Usability Criterion	Required for Acceptability	Required for Usability
BEV ≤ 5% of FVC or 0.100L	YES	YES
No evidence of faulty zero flow	YES	YES
No glottis closure after 1st s	YES	YES
No evidence of obstructed mouthpiece	YES	YES
No evidence of leak	YES	YES
Evidence that forced exhalation was from full inflation	YES	YES
• Plateau (≤ 0.025L in last 1s) **or**	YES	NO
• FET ≥ 15s **or**	YES	NO
• FVC within repeatability tolerance of largest FVC or is > largest prior FVC	YES	NO
Evidence of forced exhalation was from full inflation	**YES**	**YES**

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BEV as FVC acceptability criterion?

- Meant to prevent reporting SVC as FVC
- No data shows BEV protects against this
- Says operator should be able to override an unacceptable rating for FVC, if appropriate.

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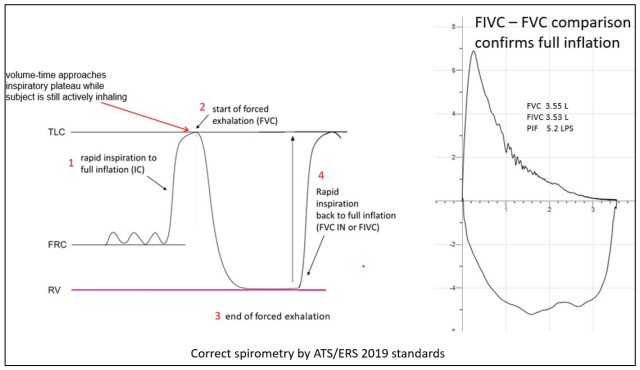
Proving the forced exhalation started from full inflation – Phase 4



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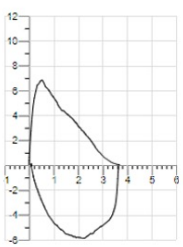
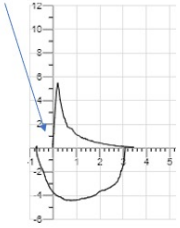
FIVC must be a maximal inspiratory maneuver



A properly performed FIVC that demonstrates the forced exhalation started from full inflation.
Note the rounded, 'upside-down haystack appearance of the inspiratory flow-volume loop.

FIVC is significantly larger than the FVC



A properly performed FIVC that demonstrates the forced exhalation started before full inflation was reached.
Note the rounded, 'upside-down haystack appearance of the inspiratory flow-volume loop.

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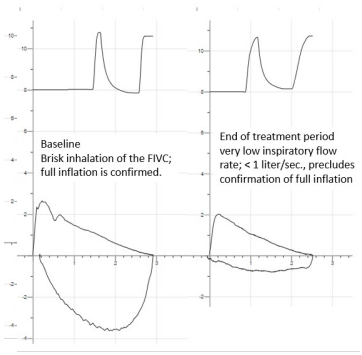
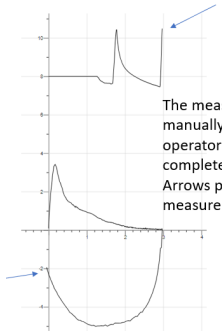
If FIVC is not maximal, might as well not do it





The measurement of FIVC was manually terminated by the operator before the patient completed the inspiration. Arrows point to where the FIVC measurement ended.

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Acceptable SOT and EOT
Two repeatable FEV1s and FVCs

Parameter	Best	Pred.	Pre.%			
Time				09:51	09:52	09:54
FEV1	1.297	3.847	33.7	1.140	1.297	1.284
FVC	2.194	4.810	45.6	1.862	2.194	2.144
FEV1%F	0.59	0.80	73.6	0.61	0.59	0.60
25-75	0.61	3.69	16.5	0.61	0.61	0.59
PEF	176.41			176.41	173.45	168.26
FETPEF	0.083			0.055	0.083	0.114
FET	7.21			6.56	7.21	6.94
VBEex	0.03			0.03	0.03	0.09
VBe%FV	1.48			1.86	1.48	4.19

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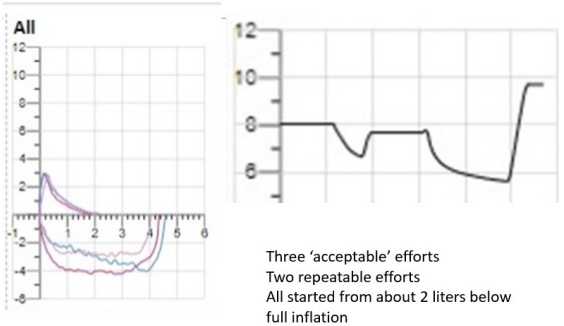
Repeatability does not mean full inflation!



Three 'acceptable' efforts
Two repeatable efforts
All started from about 2 liters below full inflation

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Grading Spirometry Quality

- Grading system adapted from ATS Recommendations for a Standardized Pulmonary Function Report (2017).
- FVC and FEV1 are graded separately.
- Based on number of acceptable efforts (for that parameter) and repeatability of two largest efforts.

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Grading System for FEV1 and FVC

Graded Separately

Grade	Number of measurements	Repeatability: age >6 yr	Repeatability: age ≤6 yr*
A	≥3 acceptable	within 0.150 L	within 0.100 L*
B	2 acceptable	within 0.150 L	within 0.100 L*
C	≥2 acceptable	within 0.200 L	within 0.150 L*
D	≥2 acceptable	within 0.250 L	within 0.200 L*
E	≥2 acceptable	>0.250 L	>0.200 L*
	OR 1 acceptable	n/a	n/a
U	0 acceptable AND ≥1 useable	n/a	n/a
F	0 acceptable and 0 useable	n/a	n/a

* Or 10% of the highest value; applies to age ≤ 6 yr only

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Standardized Operator Comments

1.Relating to Patient condition:

- No comments
- First attempt at spirometry
- Reference values are based on ethnicity that may not be suitable for this patient
- Patient used bronchodilator(s) prior to test *[prompt for drugs, doses and times used]*
- Patient smoked < 1 hr prior to test
- Patient had difficulty understanding directions
- Patient reported consumption of an intoxicant
- Observed symptoms e.g. cough, wheeze, dyspnea or cyanosis *[prompt for symptoms]*
- Other [prompt for description]

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Other:

For part 1, **Other** should include information of any deviation from standard protocol

- patient tested standing
- ulna length or arm span used to estimate height
- patient did not use nose clip
- If birth sex and/or ethnicity data are not disclosed
  - state which default values were used for calculating predicted values
  - adapters described: face mask, tubing connectors or occlusion valves (e.g. patients with tracheostomy or nasal resection), a brief description of how the spirometer was adapted, including the diameter of the smallest connector used to adapt the patient to the spirometer should be included in the notes.

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Standardized Operator Comments

2.Relating to quality of each maneuver

- No comments
- Cough during the first second of expiration
- Glottis closure
- Early termination
- Hesitant start of test
- Obstructed mouthpiece or breathing tube
- Leak around mouthpiece
- Not at TLC prior to expiration
- Operator changed maneuver designation from acceptable to unacceptable *[prompt for reason]*
- Other [prompt for description]

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Standardized Operator Comments

3.Relating to bronchodilator responsiveness testing

- Facility bronchodilator responsiveness protocol followed for type, dose and delivery method of bronchodilator and wait time before post-BD testing
- Post-BD measurements obtained using other bronchodilator(s), dose(s), delivery method or wait time. *[prompt for bronchodilator(s), dose(s), delivery method and wait time]*
- Other [prompt for description]

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Other…

- For part 3, **Other** should include any deviation from the default bronchodilator responsiveness testing protocol used by the facility that has not otherwise been entered.

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Standardized Operator Comments

- **4.Relating to quality of testing session**

  - No comments
  - Acceptability and/or repeatability criteria not met despite patient's best efforts
  - Spirometry induced bronchospasm
  - Patient was too tired to continue
  - FEV1 dropped more than 20% from baseline
  - Motivation difficulties
  - Coordination difficulties
  - Other [prompt for description]

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Standardized Operator Comments

- Spirometry system software should provide pop-up windows allowing the operator to click on the appropriate comments as follows:
  - Part 1 – when patient information is entered
  - Part 2 – at the completion of each maneuver
  - Part 3 – just prior to post-bronchodilator testing Part 4 – at the completion of the testing session

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Patient survey of 1,760 patients from 52 countries

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Most think spirometry is not so bad.

- Though many patients gave suggestions about how spirometry testing could be improved, it is important note that 90% of patients found spirometry testing acceptable and not problematic

36

Uncomfortable, but important.

- While some patients found the test to be uncomfortable, they felt it was a necessary, temporary discomfort.

37

Patients know when you are losing your patience

Patients also felt that it was important that operators did not express disappointment when patients have trouble completing the test.

38

Don’t make me ask….

- Patients would like to have water, tissues and sputum pots provided without having to ask.

39

Please don’t yell at me…..

- Though many felt encouragement or coaching is important, some patients would have preferred a gentler approach rather than shouting instructions to blow.

40

You matter to them….

- Many patients emphasized the importance of the operator. Those who have had several tests felt that it made a real difference how friendly and encouraging the operator is.

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They need your encouragement….

- Some felt that the operator needed to fulfil the role of a cheerleader and that it made a difference to their results.

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Please be kind….

- Patients also felt that operators need to "have empathy before, during and after the maneuver" and that it is important to check if the patient is ready and how they feel about performing the next maneuver.

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Why didn't anyone tell me this?

- Patients felt that it is very important to be prepared for what is going to happen during the test and then to be coached through the process.

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ATS/ERS 2019 Spirometry Standards

PSRC Annual Meeting, 08DEC2023

PHIL LAKE PHD

SENIOR DIRECTOR, RESPIRATORY SOLUTIONS, CLARIO

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Agenda

- The impact of variability in clinical research.
- The limitations of ATS/ERS compliance to determine accurate lung function.
- The potential to modify study outcomes through implausible data.

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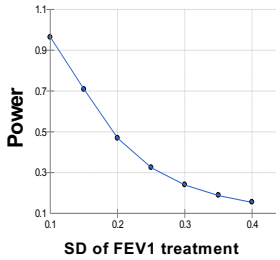
Power to Show Treatment Effect

- Regulatory studies power respiratory studies @ 80-90% power to show the desired treatment effect
- Statistical power is a function of treatment effect, patient numbers and variability
- An increase in FEV1 variability at each visit will increase SD and reduce statistical power
- All elements of variability are controlled to assist with this



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Control of variability

- Testing at same time of day within a 2hour window
- Subsequent visit testing at each visit ± set window from the baseline visit
- Washout of bronchodilators and testing at trough drug levels
- Restrictions on food and drinks likely to modify lung function
- Strict controls of concomitant medications
- Need for rest prior to testing and between efforts to minimize fatigue
- Adherence of ATS/ERS forced spirometry requirements
- Standardized equipment
- Desire to keep same LFT at all visits

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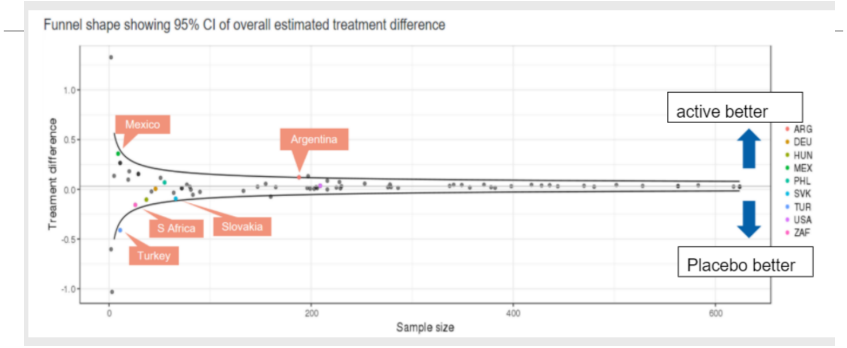
Power to show a Mean treatment effect



Low variability data can drive accurate treatment responses in fewer patients. High variability can generate a false positive or false negative outcome in smaller patient numbers

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Downside for higher variability

- Increased patient numbers required for each trial
- Higher exposure of patients to experimental drugs to prove proof of concept
- Longer drug development timelines
- Increased risk of inaccurate study data
- Inability to determine more personalised medication or characterise population most likely to respond
- Increased cost of drug development

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The case for plausibility Asthma case study

- International study where Tx was around 240ml in favour of active therapy
- Patients in South America actually declined on therapy relative to placebo
- Sponsor wanted to understand why their drug did not work in Latin America

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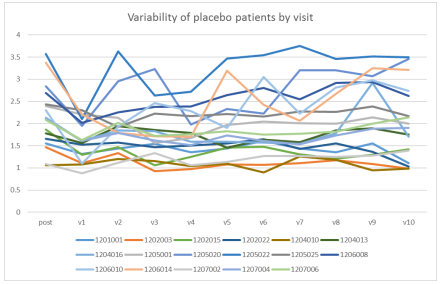
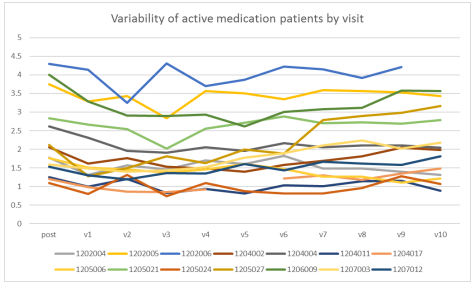
Case example Aberrant treatment effect in High variability patients

- ATS ERS compliance was high with levels of unacceptable data in less than 2% of tests
- Lung function response shows a high number of implausible changes in FEV1 over time
- By Chance, high variability appears to be focused more in placebo group patients





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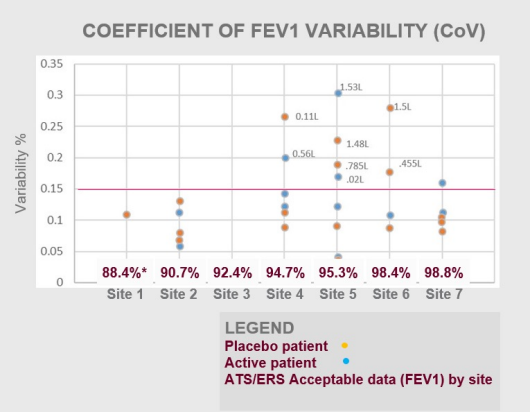
FEV1 Variability by site

- Each data point represents standard deviation of on therapy FEV1 divided by baseline FEV1 to normalise scale
- Variability above 15% appears to be more problematic
- Orange dots are placebo patients who would be expected to show little change on therapy
- Blue dots (active medication patients) are expected to show increased variability due to treatment uplift
- Outliers with variability above 15% include implausible treatment responses of up to 1.53L
- Overall ATS/ERS site compliance does not align with the presence of less variable data



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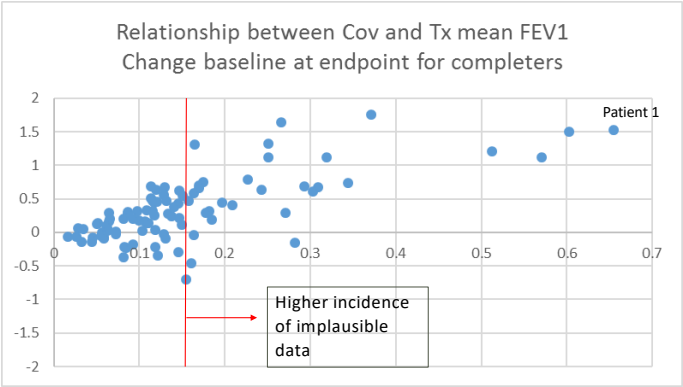
Relationship between variability and accurate treatment effect

- Highly variable patients are associated with higher incidence of implausible treatment response
- Outliers dominantly show treatment responses are modified by poor technique



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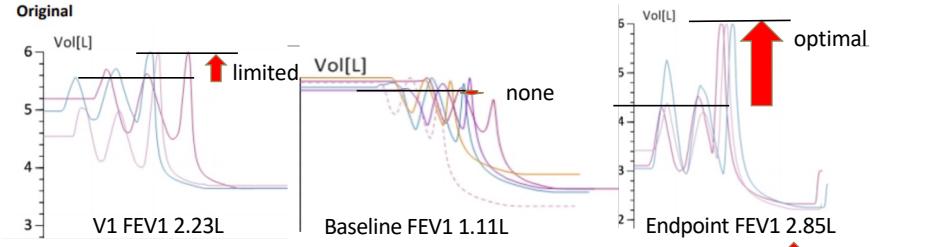
Issues with data that meets ATS 2005 standards

Reproducible data ≠ accurate or maximal data



Best FEV1 at: 10:24:56 FVC [L]: 1.535 Pred FEV1/FVC [%]: 89 QC Grade: Acceptable	FEV1 [L]: 1.138 Pred FVC [%]: 48 PEF [L/min]: 160 BTR Grade: Acceptable	Pred FEV1 [%]: 42 FEV1/FVC : 0.74 FEF 25-75 [L/s]: 0.846
Best FEV1 at: 09:49:06 FVC [L]: 1.571 Pred FEV1/FVC [%]: 84 QC Grade: Acceptable	FEV1 [L]: 1.098 Pred FVC [%]: 49 PEF [L/min]: 176 BTR Grade: Acceptable	Pred FEV1 [%]: 41 FEV1/FVC : 0.70 FEF 25-75 [L/s]: 0.658
Complete Date/Time: 07-Nov-2018 11:39:08	Revised: No	Overall Evaluation: Normal

Apparent drug effect 1.74L

FEV1 varies due to variable inhalation and not drug effect

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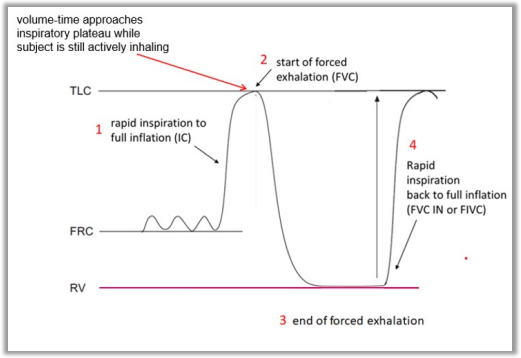
ATS 2019 focus on SIE

Updates to ATS/ERS guidance in 2019 were partially designed to highlight the issue of SIE

If FIVC matches FVC then it is likely that the initial inhalation to TLC was close to optimal



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Reassessment of ATS 2019 data with 2005 standards

Impact of incorporating the evaluation of full inflation recommended in the 2019 spirometry standards on the evaluation of spirometry acceptability

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Background

Evaluation of Full Inflation

The 2019 ATS/ERS spirometry standards update provides an objective means for evaluating whether forced exhalations began from at or close to full inflation.

At the end of forced exhalation (EOFE), the patient is coached to rapidly inspire to full inflation. The volume inhaled, the forced inspiratory vital capacity (FIVC), must be no more than 5% (or 0.100L whichever is larger) larger than the forced vital capacity (FVC) for the effort to be considered acceptable. This comparison identifies a submaximal inhalation error (SIE) – forced exhalations that start from a lung volume below full inflation.

The acceptability of spirometry measurements using the 2005 acceptability criteria was compared with the acceptability using the updated 2019 acceptability criteria, including the evaluation of full inflation. We sought to determine the prevalence of SIE in clinical trial spirometry data that was rated as QC Grade A or B for both FVC and FEV1 by the 2005 acceptability and repeatability criteria.

Methods

We reviewed 646 measurements from 162 patients in the first 4 months of a clinical trial using the 2019 spirometry standards for acceptability, including verification of full inflation were enforced. 58 operators from 39 sites made the measurements.

We also evaluated the acceptability of these measurements using the 2005 standards which do not require verification of full inflation. The two ratings were compared and the prevalence of SIE in measurements that would have been rated QC Grade A or B using the 2005 QC criteria is reported.

Main Findings

- The recommendation to compare the FIVC and FVC allows the identification of spirometry effort that did not start from full inflation.
- 12.8% of spirometry measurements in a clinical trial that required the use of Phase 4 to verify full inflation showed objective evidence of starting from less than full inflation. These were rated Unacceptable by 2019 criterial but would have been rated Acceptable by 2005 standards.
- When these measurements were evaluated using the ATS/ERS 2005 standards they were rated as high quality (acceptable and repeatable).
- These measurements were generated by 58.3% of the operators from 43.8% of the sites that contributed measurements.
- In clinical trials, the exclusion of spirometry efforts shown to start from less than full inflation will likely reduce intra-subject variability, reduce implausible treatment effects and permit determination of more accurate treatment effects.

ERT

ERS is neither responsible for/ nor endorses the data and information presented on this poster

Results

We identified 83 measurements (12.8%) that would have been rated Acceptable and Repeatable by the 2005 standards for acceptability that were rated Unacceptable by the 2019 standards because they were judged to start from less than full inflation. 28 operators from 21 sites made these measurements. This represents 58.3% of the users and 43.8% of the sites that had contributed data.

The comparison of FIVC to FVC in these measurements showed forced exhalations started from an average of 271 mL (SD 128mL) below full inflation (range 106 to 722 mL), representing an average of 8.9% (SD 3.6%) of the FVC (range 5.1 to 18.4% of FVC).

A common finding was the apparent absence of even a start of an inspiration following the EOFE in the tracing of the inspiration preceding the forced expiration. The rapid transition from inspiration to forced expiration suggests the operator was not acting on feedback from the subject to judge when the command to start the forced exhalation should be given.

Discussion

All 83 measurements were rated Acceptable, demonstrated repeatability of the two largest efforts and were thus considered QC Grade A or B for both FVC and FEV1 when evaluated by the 2005 acceptability criteria.

Repeatability of the two largest efforts has long been considered evidence that the forced exhalations started from full inflation. These findings demonstrate that repeatability cannot be used as a surrogate for objective assesment of full inflation as recommended in the 2019 ATS/ERS Update of Spirometry Standards.

More than half of the operators from nearly half of the sites contributed measurements demonstrating SIE, suggesting SIE is common.

Adoption of the evaluation of Phase 4 allows objective evaluation of full inflation. Excluding spirometry efforts that do not start from full inflation will likely reduce the intra-subject variability of spirometry results, reduce implausible treatment effects and permit more accurate determination of treatment effects in clinical trials.

Comparison of current YTD data about intra-subject variability in this study with another similar asthma study that used ATS/ERS 2005 guidelines for quality evaluation yields encouraging results:

Comparison of spirometry variability: 2005 vs. 2019 guidelines	2005 Guidelines	2019 Guidelines*
Within-visit FEV1 variability (mL, % of FEV1)	83 mL, 4.9%	49 mL, 2.4%
Coefficient of Variation on therapy	8.3%	4.6%
Percentage of patients showing >15% coefficient of variation on therapy	20.0%	2.2%

* Interim analysis

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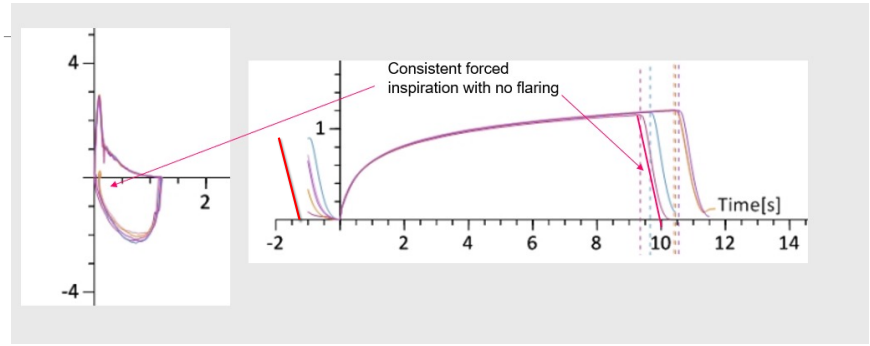
Optimal ATS ERS 2019 technique



FIVC matches FVC to corroborate the initial inhalation

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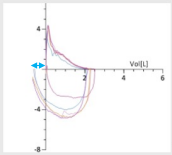
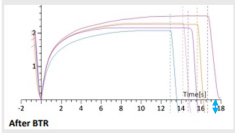
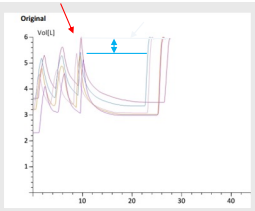
Submaximal inhalation detection with correct use of ATS/ERS 2019 standards

Submaximal data V4







Test Grade	Parameter	Pred	%Pred	Best	1st	2nd	3rd	4th	5th
	Time				10:43:39	10:45:19	10:46:49	10:48:47	10:50:20
E	FEV1 [L]	2.112	67	**1.423**	1.423	~~1.194~~	~~1.407~~	~~1.397~~	~~1.401~~
E	FVC [L]	2.679	94	**2.515**	2.515	~~2.079~~	~~2.385~~	~~2.263~~	~~2.356~~
	FEV1/FVC	0.79	71	**0.57**	0.57	~~0.57~~	~~0.61~~	~~0.62~~	~~0.65~~
	PEF [L/s]			**4.300**	4.300	~~3.656~~	~~4.000~~	~~4.180~~	~~4.340~~
	FEF25-75 [L/s]			**0.596**	0.596	~~0.556~~	~~0.676~~	~~0.740~~	~~0.806~~
	FIVC after Ex [L]			**3.015**	2.469	2.652	2.924	2.985	3.015
	VBEex [L]			**0.018**	0.018	~~0.007~~	~~0.027~~	~~0.016~~	~~0.020~~
	Risetime [s]				0.028	~~0.014~~	~~0.044~~	~~0.027~~	~~0.030~~
	Quality Data					6	6	6	6

Without full inspiration these efforts would pass as acceptable. Potentially 350ml below expected FEV1 based on FIVC and FEV1:FVC ratio

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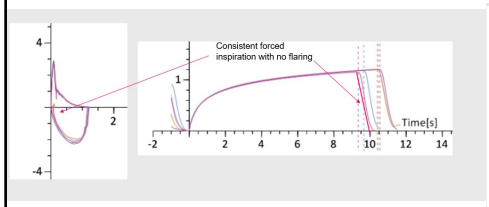
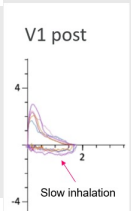
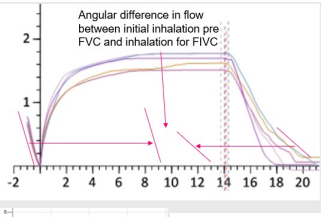
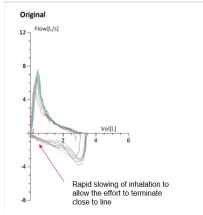
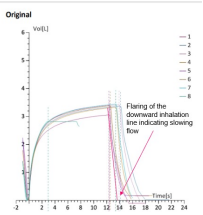
Examples Good and manually terminated FIVC collection

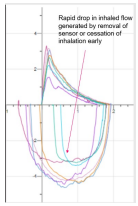


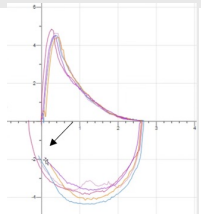












The core issue with manipulated data is that it is impossible to determine if the values are accurate.

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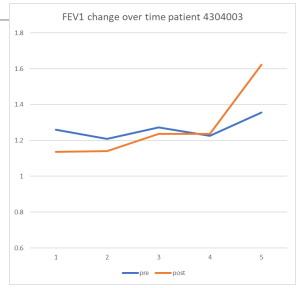
Site Manipulation case example
Why fixed FIVC issues undermine drug effect reliability

Visit	FEV1	Post FEV1	Change	% rev	Clario grade	FIVC issues
1	1.261	1.137	-124ml	-7.9%	AA/AA	Y
2	1.209				AA*	Y
3	1.272	1.236	-36ml	-2.8%	AA/AC	Y
V5	1.227				AA	Y
V8	1.357	1.623	+226ml	+19%	EA	Y



Apparent change from baseline in trough measures. +96ml Change post bd 486ml. Although data is inaccurate this would not flag for plausibility based on change from baseline or change between visits

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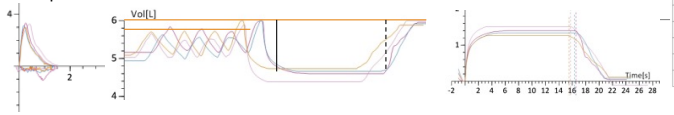
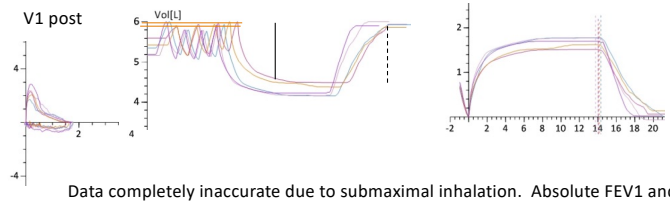
Manipulating FIVC to meet ATS/ERS 2019 system checks

V1 pre



Test Grade	Parameter	Pred	%Pred	Best	1st	2nd	3rd	4th
	Time				11:08:56	11:10:16	11:11:36	11:12:52
A	FEV1 [L]	3.185	33.45	**1.066**	1.066	0.993	~~1.038~~	0.998
A	FVC [L]	4.045	34.64	**1.401**	1.401	1.339	~~1.595~~	1.268
	FEV1/FVC	0.79	96.48	**0.76**	0.76	0.74	~~0.82~~	0.79
	PEF [L/min]			**199**	199	186	~~194~~	178
	FEF 25-75 [L/s]	2.783	29.98	**0.834**	0.834	0.728	~~1.195~~	0.893
	FIVC after Ex [L]			**1.616**	1.357	1.256	1.616	1.152
	VBExx [L]			**0.055**	0.055	0.044	~~0.071~~	0.054
	Risetime [s]				0.105	0.087	~~0.150~~	0.135
	Quality Data						2-6	

V1 post



	Time				11:39:46	11:40:57	11:42:02	11:43:26	11:44:3
A	FEV1 [L]	3.725	30.53	**1.137**	0.889	0.929	1.137	0.916	1.04
A	FVC [L]	4.750	37.39	**1.776**	1.513	1.776	1.772	1.623	1.69
	FEV1/FVC	0.79	81.37	**0.64**	0.59	0.52	0.64	0.56	0.6
	PEF [L/min]			**172**	138	103	143	124	17
	FEF 25-75 [L/s]	3.258	20.76	**0.677**	0.467	0.588	0.677	0.394	0.54
	FIVC after Ex [L]			**1.836**	1.448	1.771	1.836	1.488	1.67
	VBExx [L]			**0.018**	0.019	0.012	0.018	0.019	0.02
	Risetime [s]				0.060	0.051	0.052	0.067	0.05
	Quality Data								

Data completely inaccurate due to submaximal inhalation. Absolute FEV1 and FVC underestimated. % predicted too severe, Reversibility inaccurate.

FEV1 data will actively detract from study power.

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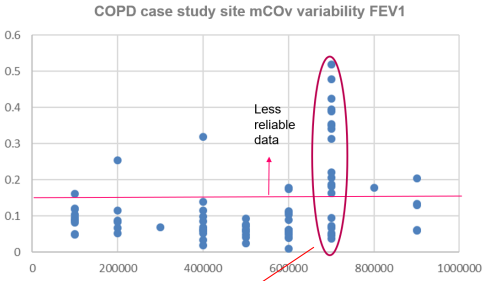
COPD example: site data variability

Problem site who appeared to switch COPD patients to healthy volunteers post randomisation has generated exceptional variability

Average study mCov= 9.3%
Average Country mCoV= 12.7%
Site mCoV average= 24.4%

Site x increases overall study Cov by 11%

ATS/ERS does not differentiate this site from the rest of the study



Problem Site

Study overall

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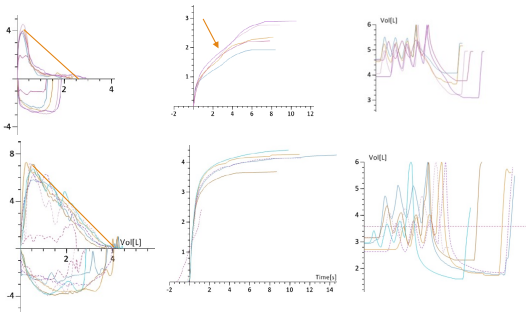
Patient switch; 64 Yr old Male COPD patient

Flow loop geometry change V2 to V3 14 days later

Parameter	Best	%Pred	1st	2nd	3rd	4th	5th
Trial Time			09:47:42	09:49:02	09:50:23	09:51:43	09:53:08
FEV1 [L]	1.266	41.75	1.082	0.976	1.089	1.118	*1.266
FVC [L]	2.905	73.88	2.232	1.920	2.768	2.355	*2.905
FEV1/FVC	0.44	55.89	0.48	0.51	0.39	0.47	0.44
FEF25-75 [L/s]	0.396	13.96	0.482	0.325	0.422	0.409	0.396
PEF [L/min]	275	56.35	118	228	*275	242	236
Error Codes						E	

Parameter	Best	%Pred	1st	2nd	3rd	4th	5th	6th	7th
Deselected by			System		System		System		
Trial Time			09:27:52	09:29:24	09:30:43	09:32:21	09:33:54	09:35:19	09:36:42
FEV1 [L]	3.332	109.87	2.127	3.058	3.255	3.266	3.137	2.918	*3.332
FVC [L]	4.401	111.92	2.439	4.252	3.400	4.258	4.146	3.688	*4.401
FEV1/FVC	0.76	97.07	0.87	0.72	0.96	0.77	0.76	0.79	0.76
FEF25-75 [L/s]	2.722	95.97	2.126	2.090	3.368	2.776	2.551	2.606	2.722
PEF [L/min]	438	89.74	128	351	432	*438	376	426	406
Error Codes	E		DEFH	E	DEF		H	E	E



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ATS/ERS compliance limitations

Generally successful at generating more consistent data in around 85% of patients

Does not pick up

Change of patient
Poor adherence to protocol washout
Site manipulation of data
Submaximal inhalation
Implausible changes to lung function

Around 15% of data classified as acceptable are inaccurate

At best if evenly distributed in patient arms this will reduce statistical significance
At worst this will generate type I or type II errors. False positive or false negative results

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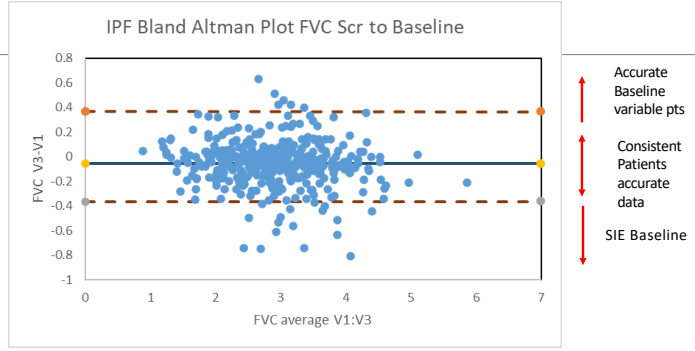
IPF Example trial 1 (Circa 400 pts)



Accurate Baseline variable pts

Consistent Patients accurate data

SIE Baseline

Change Scr to Baseline	AST 2005 1	ATS2005 2	ATS 2005 3	ATS2019
+5%	9.60%	8.2%	8.4%	9.1%
±5%	74.90%	74.4%	73.7%	65.7%
-5%	15.50%	17.4%	17.9%	25.3%

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