WEBINAR

Optimising Spirometry Endpoints in Clinical Trials

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Why this matters

- Spirometry drives endpoints
  e.g. FEV1: FVC: % Predicted

- Missing data and variability reduces statistical power

- ATS-ERS 2019 Spirometry testing guidelines - does the approach need to be disease specific?

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The hidden risk

- Are we automatically rejecting good FEV1 and FVC data that does not meet a specific ATS-ERS QA criteria due to a patient's physiology
e.g. IPF (restrictive) vs COPD (obstructive)?

- Are we creating bias from these exclusions?

- Are we unnecessarily doing repeat visits?

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Learning objectives

1. Interpret ATS-ERS 2019 Test QA criteria
2. Evaluate disease-specific risk
3. Assess limits of uniform QA
4. Apply disease-specific QA

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ATS-ERS **objective QA** test criteria errors explained

Excessive Back Extrapolation

- BEV in excess of 5% of FVC or 0.10L

Submaximal Inhalation

- Failing to reach TLC prior to forced manoeuvre.
- Submaximal effort.
- Lack of test understanding.

Cough in 1st Second

- An audible cough that raises suspicion of incorrect expiratory technique.
- A cough that is visible on the graphs which impacts the forced expiratory flow in any way.

EOFE Criteria Not Met

- Early cessation of expiration
- Failing to achieve a 1s plateau
- Failing to achieve an FVC within the repeatability criteria of other FVCs within the session.

Glottis Closure

- Visible and abrupt flattering of expiratory flow and volume on graphs which ends the manoeuvre or is followed by a second expiratory trace.

Example impact on endpoints

ISSUE	IMPACT ON FEV1	IMPACT ON FVC
Slow Start (BEV)	↓ Reduced	↓ Reduced
Glottis Closure	-	↓ Reduced
Cough (1st second)	↑ Increased	-
Submaximal Inhalation	↓ Reduced	↓ Reduced
EOFE	-	↓ Reduced

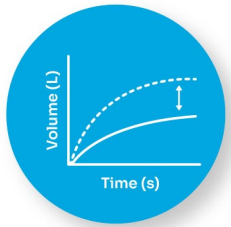
ATS-ERS **subjective QA** test criteria errors explained

Poor Coordination

- Participant struggling to perform relaxed tidal breathing following by a forced manoeuvre.

Artefact

- Any significant deviation in flow caused by cough, mouthpiece obstruction, charges in effort.



Drift

- Flow-signal error due to flow-head exposure to external airflow while zeroing.

Submaximal Effort

- Lack of test understanding
- Low expiratory effort applied in part or throughout.

Leak

- Poor lipseal
- Equipment fault or poor assembly.

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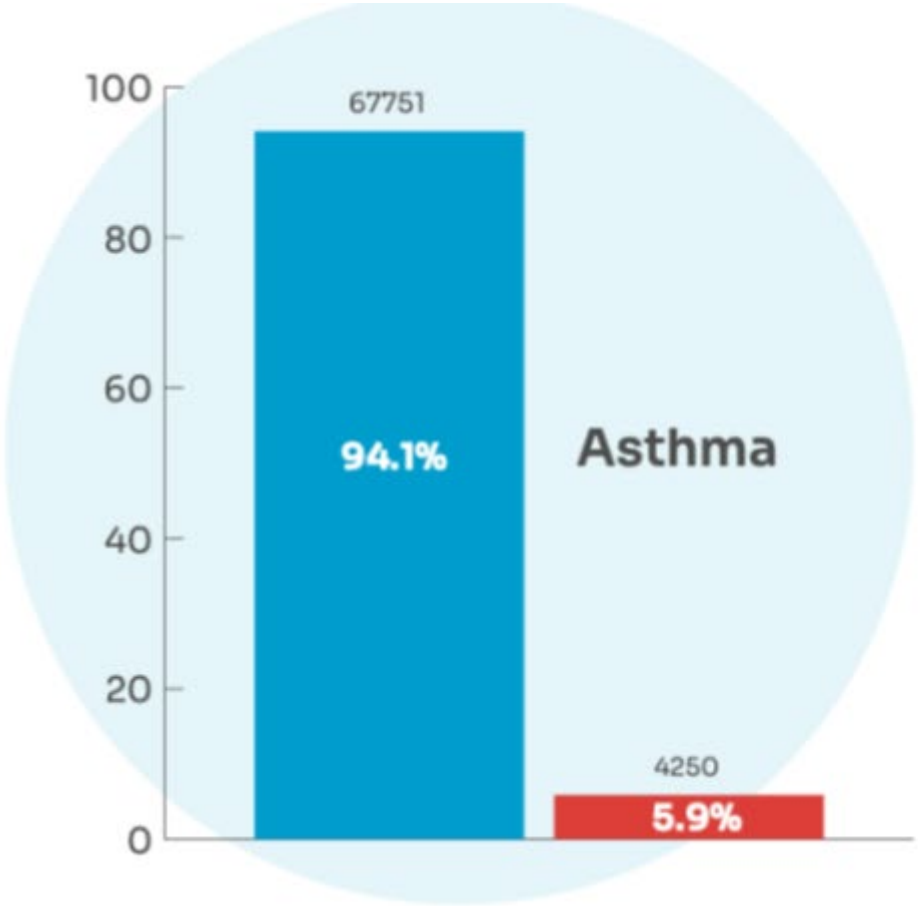
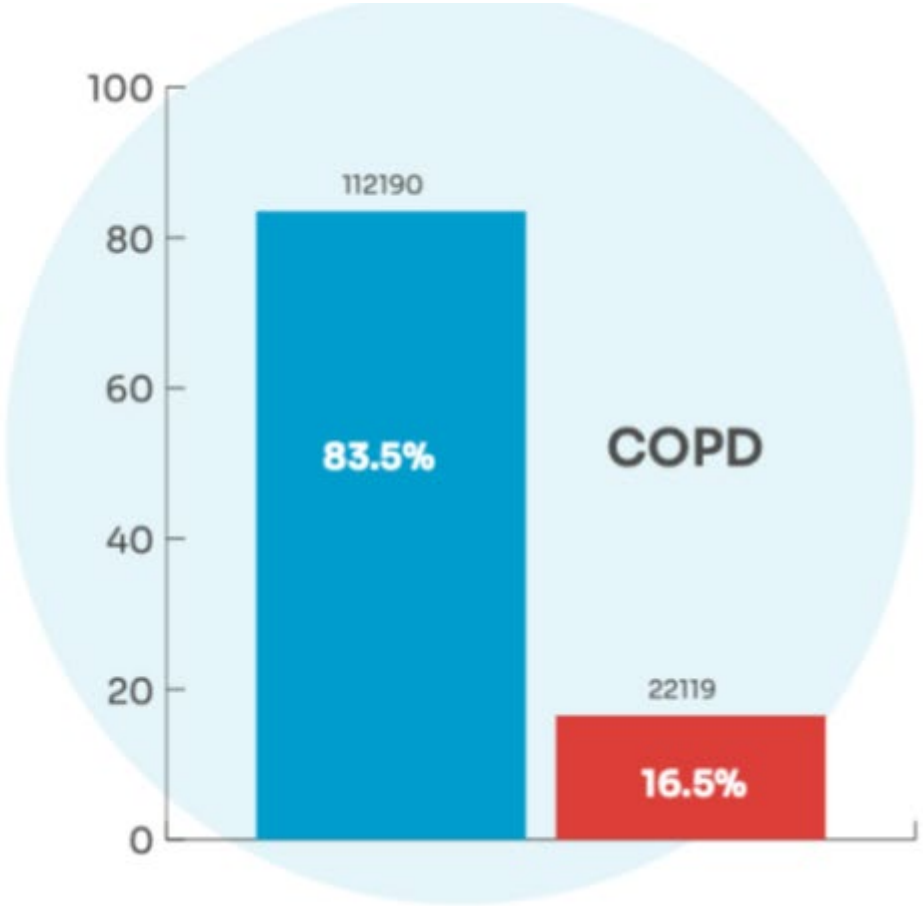
Example impact on endpoints

ISSUE	IMPACT ON FEV1	IMPACT ON FVC
Drift	↑ Artificially high	↑ Artificially high
Submaximal effort	↓ Reduced	↓ Reduced
Leak	↓ Reduced	↓ Reduced
Poor coordination	↓ Reduced	↓ Reduced
Artefact -	↑ or ↓ (High or Reduced)	↑ or ↓ (High or Reduced)

Test acceptability % by disease

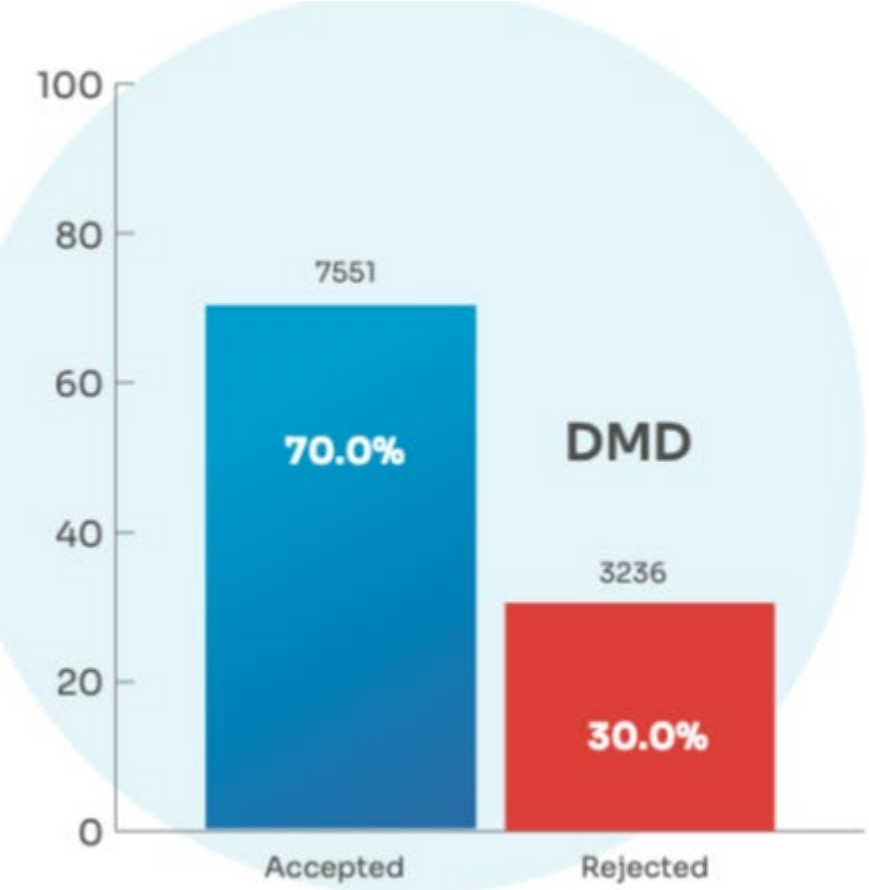
Obstructive

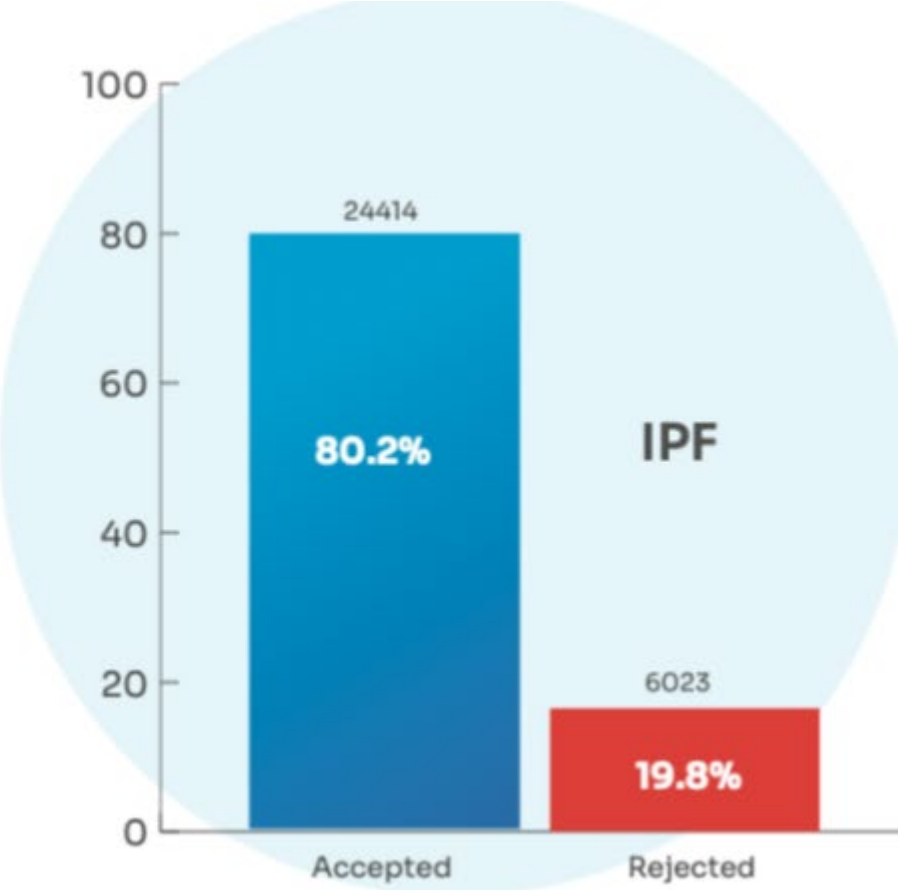




Test acceptability % by disease

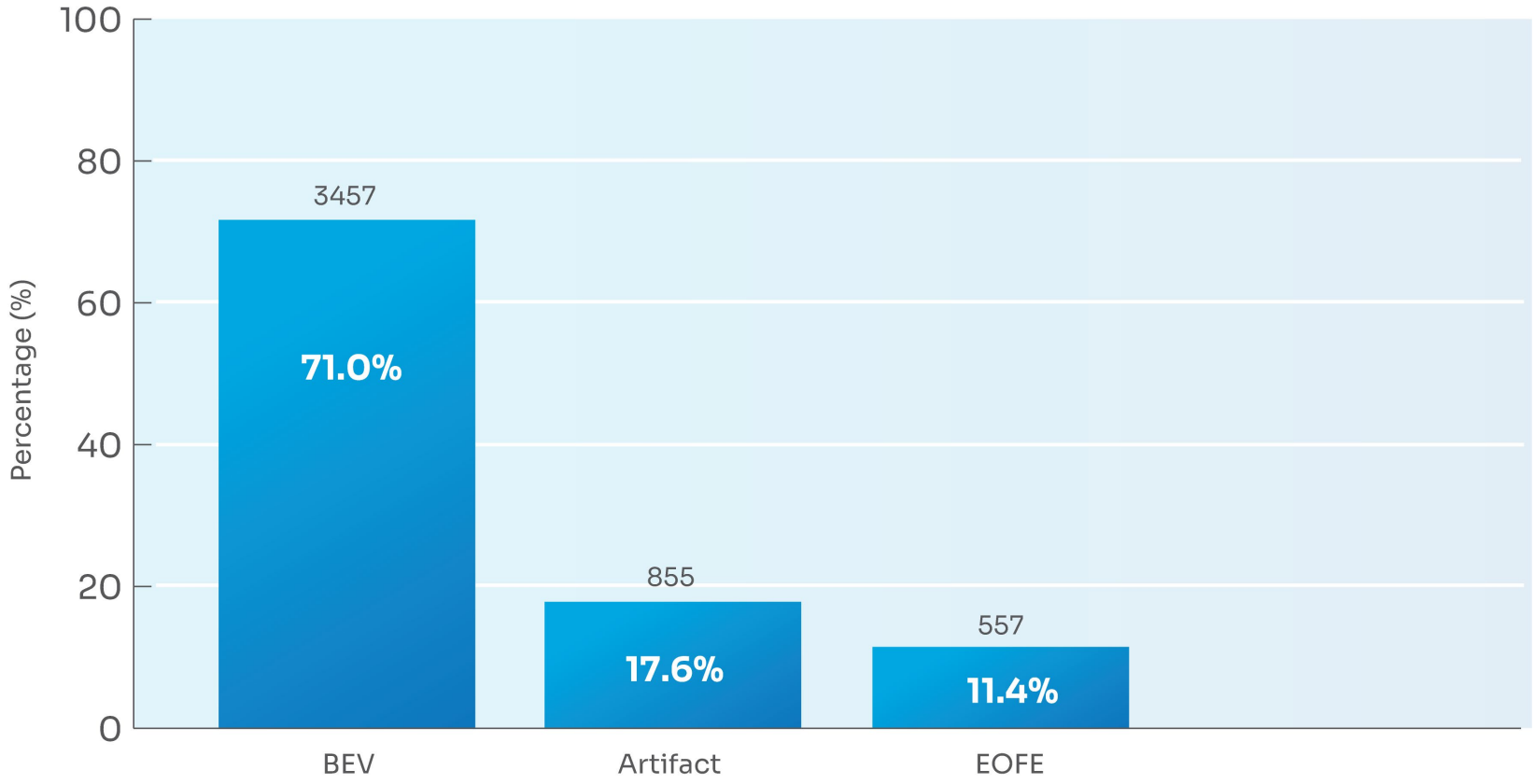
Neuromuscular and Restrictive





Comparison COPD vs IPF

Reasons for failed Spirometry tests **IPF**



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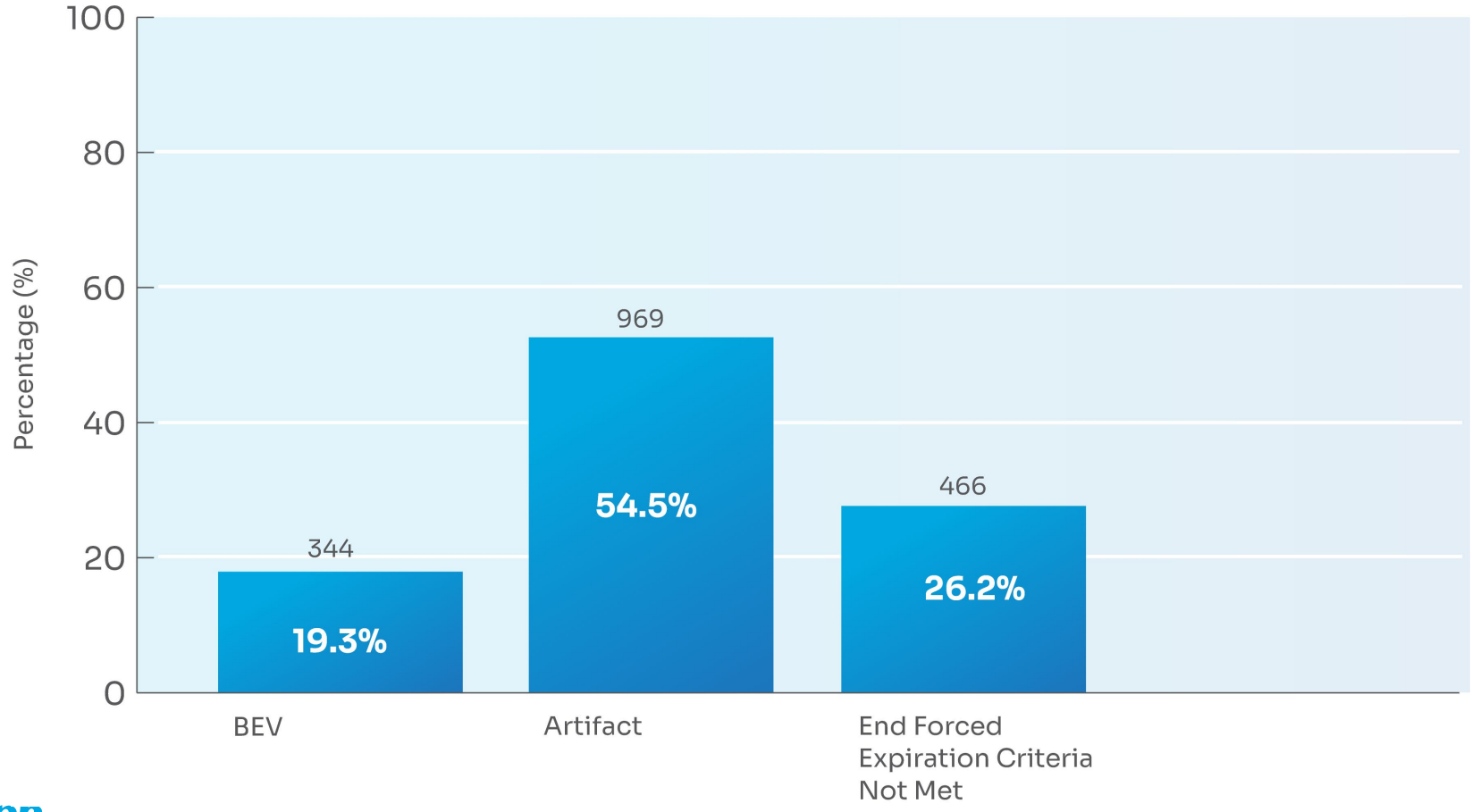
Comparison COPD vs IPF

Reasons for failed Spirometry tests **COPD**



Example disease-specific factors in patients

Restrictive >

e.g. IPF often struggle to meet the back extrapolated volume criteria due to lower FVC values.

Severe Obstructive >

e.g. COPD there was a lot of artefact particularly at the end of the test.

Neuromuscular Disorder >

Often struggle with start of test and keeping maximal effort throughout the manoeuvre.

Assessing limitations

- Are there any risks with an automated QA approach?
- Could restrictive physiology (e.g. IPF) impact a patient's ability to achieve acceptable data?

Definition of BEV (Slow-start) > Back Extrapolated Volume measures air exhaled before maximal effort in forced expiratory manoeuvres.

BEV Criterion Threshold > BEV must be ≤5% of Forced Vital Capacity or 0.100 liters, whichever is greater

Acceptability and Usability > BEV requirement applies equally to acceptability and usability for both FEV_1 and FVC measurements.

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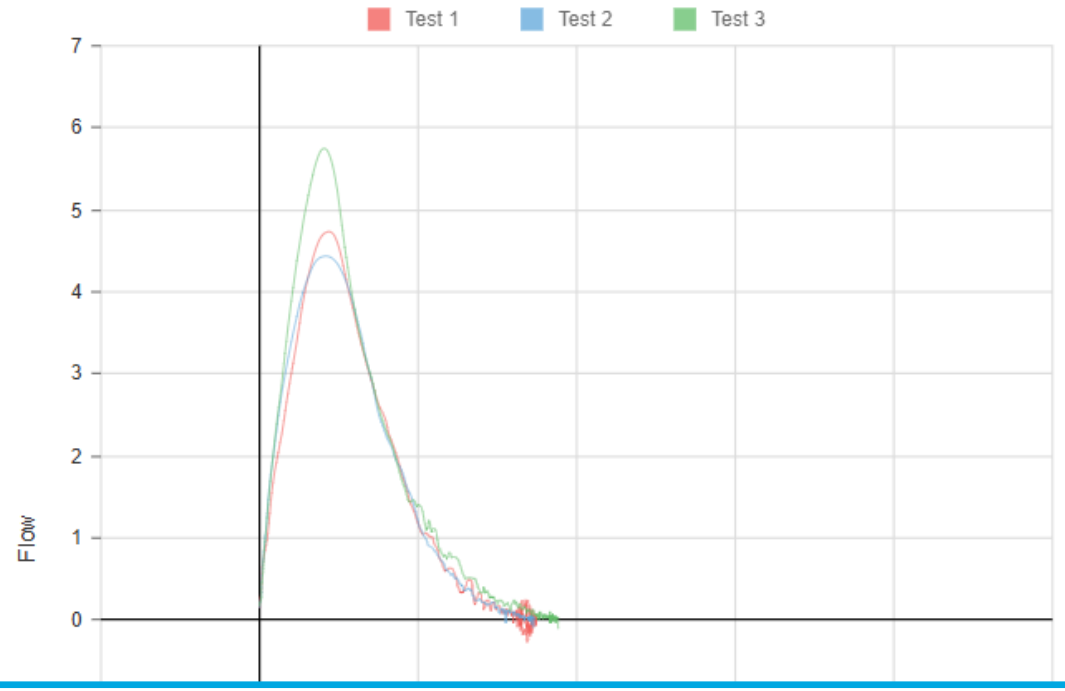
What are the risks?

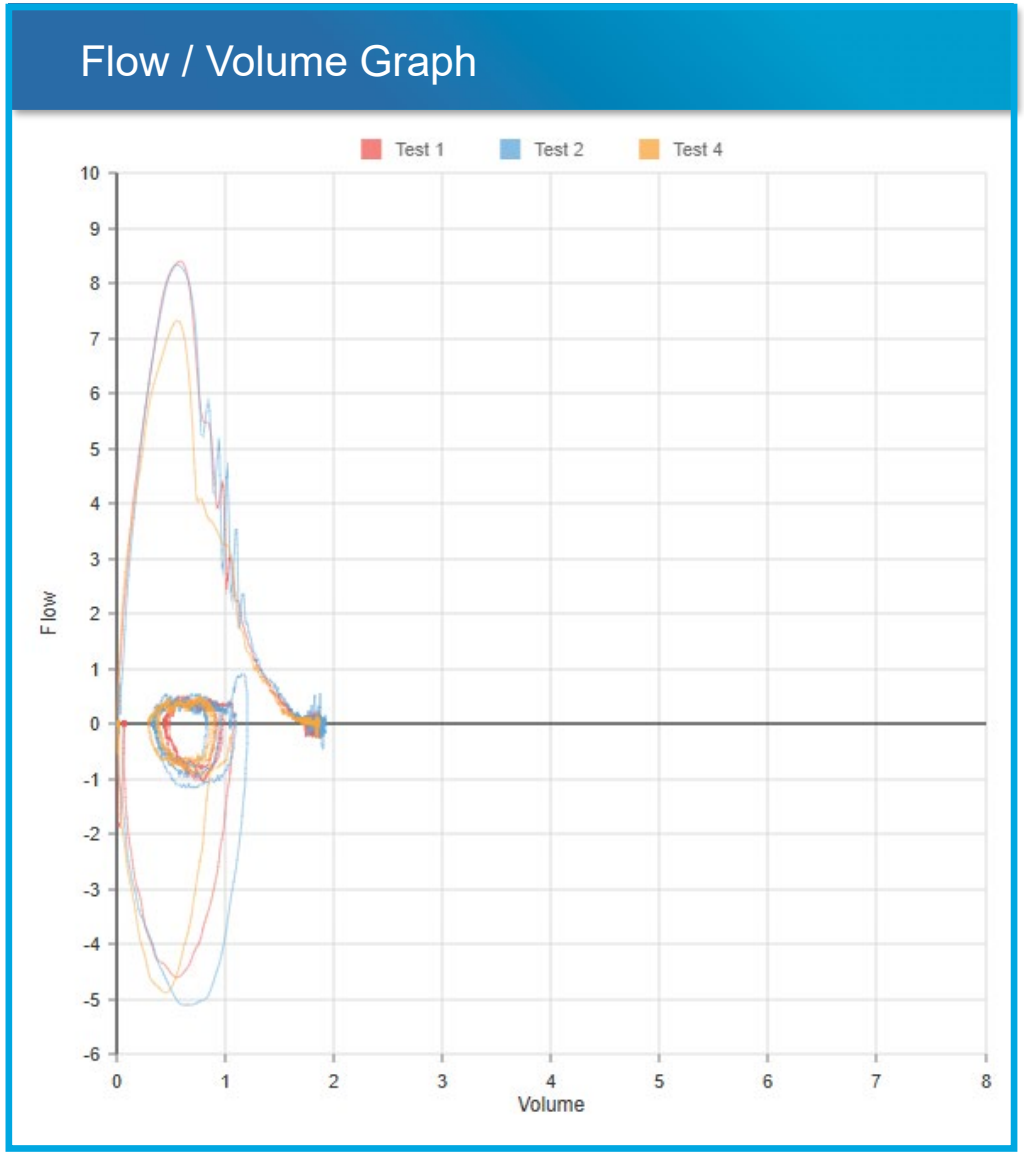
Flow / Volume Graph



PARAMETER	TEST 1	TEST 2	TEST 3
FVC (L)	1.74	1.73	1.89
FEV1 (L)	1.37	1.37	1.44
PEF (L/min)	284	266	349
BEV (L)	0.11	0.08	0.11
TPEF (ms)	145	117	111
Repeatability - FVC (ml)	-140	-150	10
Repeatability - FEV1 (ml)	-70	-70	0
Start of Test Acceptable	NO	YES	NO

What are the risks?

Is this artefact/cough consistent with the automated review?



Clinical trial impact

- Could we be missing valid or usable data by automatically rejecting tests that don’t meet a specific QA criteria without considering a patient unique physiology?

- Is there room to have a more flexible approach to apply an over-read of tests?

Applying a disease-specific approach to test QA

- Allow a human review of tests flagged as not meeting QA criteria that is disease specific.

- Flexible approach – document the scientific reasoning of why a test is acceptable despite a QA criteria not being met

Site-level changes

Tailored coaching for each patient population.

Adjust the time in-between tests to allow patient recovery.

Allow the Physiologist/ Investigator to over-ride any automated review with documented scientific reasoning.

Sponsor/CRO changes

Over-reading QA criteria

Allow for borderline test cases to be assessed by an expert.

Develop a practical spirometry QA framework

Aligned to your disease population.

Site training strategy

Adapt it to your patient population focus on the specific QA errors.

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Human over-reader QA feedback

- Can identify any patient specific physiological patterns
- Determine if an automated QA flag is disease related or a true error.
- Provide clear instructions back to site staff conducting Spirometry testing how to improve coaching based on critical thinking and not a generic guide.

Key takeaways

- ✓ Understand the specific test QA challenges for the patient population in your clinical trial.
- ✓ Errors are disease-specific.
- ✓ Develop a disease-specific Spirometry QA criteria to be applied across all stakeholders, Sponsor, CRO, Investigator Site.
- ✓ Include an element of human over-reader review with a flexible approach to FEV1 and FVC test acceptability.

Thank you

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