EasyOne Pro LAB
Measurement Technology Background

Content

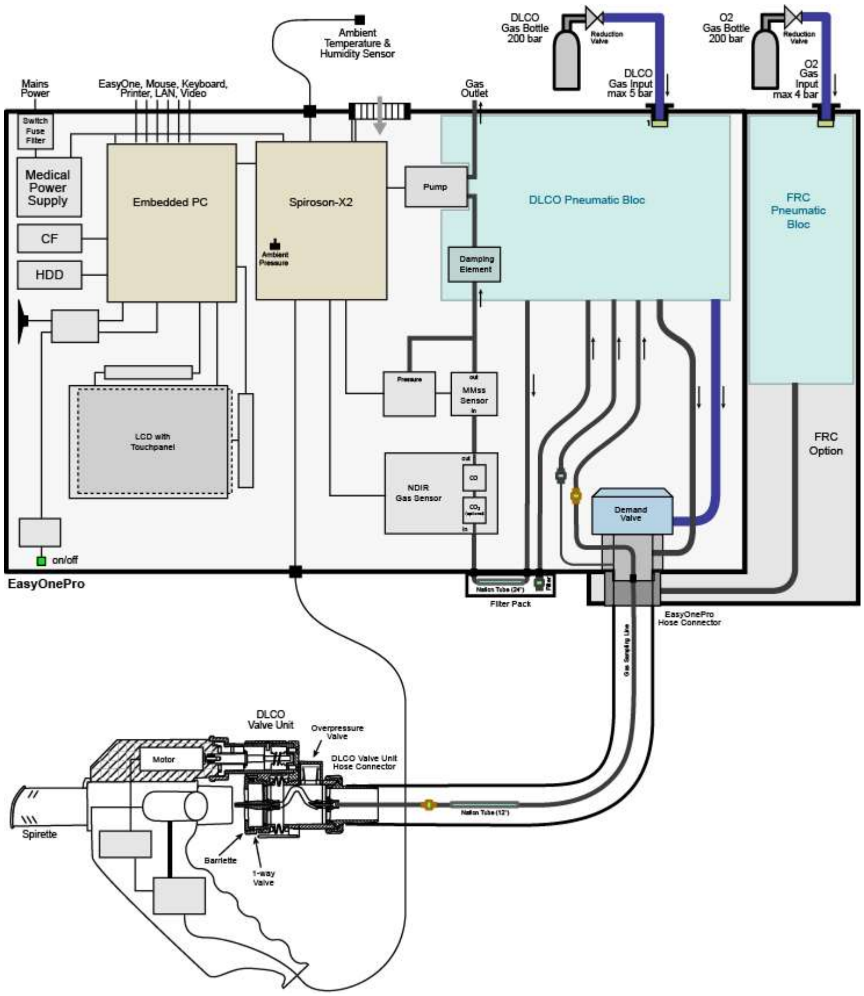
1 Introduction

This application note describes how the N_2 multi-breath washout (MBW) is implemented in EasyOne Pro LAB (EOPL). The description shows in detail the following:

- Data acquisition: Sensors used in the system and detailed specification of the sensors.
- Algorithms used to compute FRC, LCI and derived parameters.
- Validation performed with EasyOne Pro
- What has to be considered when performing MBW tests?

2 EasyOne Pro LAB System Layout

The following block diagram shows overview of the EasyOne Pro LAB system:



Sensors for flow, gas-composition and pressure are located at two different positions: The so called "main-stream" sensors are located near the patient's mouth in the hand-held unit, the "side-stream" sensors are located within EasyOne Pro device and a sampling tube moves gas at a flow rate of approx. 9 ml/s from the main-stream sensor location to the side-stream sensor location. The transport delay from main-stream to side-stream location is approx. 1000 ms; for details on the delay-time determination see below.

2.1 Main-Stream Flow and Molar Mass Sensor

The main-stream flow and molar mass sensor is the main sensor used to measure the in- and expiratory air flow rate in and out of the patients lungs. The sensor is based on ultrasonic transit-time measurement and uses a disposable breathing tube called spirette. The sensor samples flow and molar mass at 400 Hz, this data rate is converted, stored and analyzed at a rate of 200 Hz.

Sampling Rate	400 Hz (converted and stored with 200 Hz)
Flow Range	±16 l/s
Flow Accuracy	±2% or 0.05 l
Flow Resolution	4 ml/s (internally 0.625 ml/s)
Flow Resistance	0.3 cm H_2O/l/s at 16 l/s
Molar Mass Range	9 to 50 g/mol
Molar Mass Accuracy	0.01 g/mol
Molar Mass Resolution	0.005 g/mol

2.2 Main-Stream Pressure Sensor

The main-stream pressure sensor is used to measure the pressure within the ultrasonic flow sensor. The signal is only used in order to detect too low or too high pressure within the sensor.

Sampling Rate	200 Hz (converted and stored with 20 Hz for MBW tests)
Pressure Range	±100 mb
Pressure Accuracy	±2%
Pressure Resolution	0.05 mb

2.3 Side-Stream Flow and Molar Mass Sensor

The side-stream ultrasonic flow and molar mass sensor uses the same technology as the main-stream flow and molar mass sensor, it is, however, optimized for molar mass measurement.

Sampling Rate	400 Hz (converted and stored with 200 Hz)
Flow Range	±20 ml/s
Flow Accuracy	±3.5%
Flow Resolution	0.125 ml/s
Molar Mass Range	9 to 50 g/mol
Molar Mass Accuracy	0.01 g/mol
Molar Mass Resolution	0.005 g/mol
Molar Mass Response Time	100 ms (10% to 90% step response time at side-stream flow of 8.5 ml/s)

2.4 Side-Stream CO$_2$ Sensor

The side-stream CO$_2$ sensor is based on non-dispersive infrared absorption technology.

Sampling Rate	200 Hz
CO2 Range	0 to 15%
CO2 Accuracy	0.05% from 0 to 5%, 0.2% from 5 to 10%
CO2 Resolution	0.005%
CO2 Response Time	100 ms (10% to 90% step response time at side-stream flow of 8.5 ml/s)

2.5 Side-Stream CO Sensor

The side-stream CO sensor is also based on non-dispersive infrared absorption technology; it is only used for the DLCO measurement.

Sampling Rate	200 Hz
CO Range	0 to 0.35%
CO Accuracy	0.001% (10 ppm)
CO Resolution	0.0001% (1 ppm)
CO Response time	200 ms (10% to 90% step response time)

2.6 Side-Stream Pressure Sensor

The side-stream pressure sensor is used to measure the pressure at the location of the side-stream gas sensors. This signal is used to convert the partial pressure measurement of CO and CO_2 sensors into percentage gas concentration.

Sampling Rate	200 Hz (converted and stored with 10 Hz)
Pressure Range	±100 mb
Pressure Accuracy	±2%
Pressure Resolution	0.05 mb

3 Algorithm for MBW Analysis

The software installed on EOPL is called ‘EasyOne Connect’ (formerly EasyWarePro). The software can also be installed on a separate PC and can then be used to analyze data collected on an EOPL by copying the patient database to the PC. EasyOne Connect is the official software of the medical product and that software must be used for all diagnostic purposes and data analysis.

The additional ‘scientific’ software WBreath must only be used for scientific data analysis, e.g. for looking at raw data recorded with EOPL. WBreath must not be used for diagnostic purposes. WBreath matches the results of the EasyOne Connect software very closely (usually within ±0.5%) when using correct configuration settings and the correct software version. Differences in result parameters are caused by rounding differences between the two programs.

In order to compute parameters of the MBW test the N_2 concentration must be determined. The N_2 concentration is determined indirectly using the information of the side-stream molar mass sensor, the CO_2 sensor and ambient humidity. When using the WBreath program this method is selected by choosing “N2 (Side stream MM, CO2)” under Analysis / FRC Options.

The following two equations are used to compute the concentration of N_2:

1) The sum of all gas concentrations equals 100% (Dalton’s law)

$$f_{N2} + f_{O2} + f_{CO2} + f_{H2O} + f_{Ar} = 1$$

2) The molar mass of the gas equals the gas concentrations of all involved gases multiplied by the molar mass of the gas:

$$f_{N2} \cdot MM_{N2} + f_{O2} \cdot MM_{O2} + f_{CO2} \cdot MM_{CO2} + f_{H2O} \cdot MM_{H2O} + f_{Ar} \cdot MM_{Ar} = MM$$

From the above equations the following parameters are known or measured:

- MM_{xx}: The molar mass values of the involved gases (N_2, O_2, CO_2, H_2O and Ar). All molar mass values are determined using technical reference gases. The values of these constants deviate slightly from the theoretical values since the gases have different heat capacity ratios (c_p/c_v) that influence the actual molar mass value that is measured by the side-stream molar mass sensor.
- MM: The overall molar mass measured by the side-stream molar mass sensor.
- f_{CO2}: Fraction of CO_2 measured by the side-stream CO_2 gas sensor.
- f_{H2O}: Fraction of water vapor. Due to the two Nafion tubes in the patient tube and in the ‘Filter Pack’ (see system block diagram) the partial pressure of H_2O at the side-stream gas sensor position equals the ambient partial pressure of H_2O. The ambient partial pressure of H_2O can be computed using the ambient pressure, the ambient humidity and the ambient temperature. Partial pressure of H_2O is then converted to f_{H2O}.
- f_{Ar}: Fraction of Argon. Argon is not absorbed by the body, and its concentration can therefore be directly related to the N_2 concentration (i.e., $f_{Ar} = 0.0093 * f_{N2} / 0.7809$, see [3]).

Additional correction of f_{CO2} measurement

The CO_2 concentration f_{CO2} is measured by infrared (IR) absorption. However, IR based CO_2 sensors are impacted by the presence of O2 which influences infrared absorption of CO2. Due to this effect, the measured f_{CO2} concentration is converted using a correction based only on the measured f_{O2} value:

$$f_{CO2} = F(f_{CO2measured}, f_{O2})$$

This additional correction function corrects CO_2 values of 5% by approx. by 0.4% points at very high O_2 concentrations. The correction is very small at ambient O_2 concentrations.

From the two main equations above only the two gas concentrations f_{N2} and f_{O2} are unknown. Since there are two equations, these two gas concentrations can be determined by resolving the above equations for f_{O2} and f_{N2}.

By computing f_{N2} for each data point a real-time signal of f_{N2} is available (like all other data channels, this 'virtual' N_2 signal is available at a rate of 200 Hz). By multiplying f_{N2} with the main-stream flow rate the in- and expired N_2 volumes of each breath of the washout can be determined. This data can then be used to compute FRC, LCI and derived parameters.

4 Additional Considerations for MBW Analysis

In addition to the basic algorithms for MBW analysis there are additional aspects that have to be considered when performing and analyzing washout tests.

4.1 Performing the Washout Test

According to the test settings in EasyOne Connect under Utilities / Configuration / Test / FRC the washout test includes a slow vital capacity test (SVC) before or after the washout procedure. By combining the washout with an SVC test TLC and RV can be computed. In both automatic and manual washout-start mode the end of the SVC test must be indicated by the user.

In order to compute FRC it is a prerequisite that a few stable breaths are recorded before the actual washout. The number of breaths that have to fulfill the stability criteria is defined under 'Min. Number of Breaths' in the Configuration of the FRC test in EasyOne Connect. In both manual and automatic mode this minimum number of breaths has to fulfill the stability criteria before a washout starts, in manual mode the user has to indicate by a button that the test has to start.

The stability criteria for the tidal volume Vt before the washout are as follows:

	Minimum Vt	Maximum Vt
Patient Weight available:	5 ml/kg (max 350 ml)	30 ml/kg
Patient weight not available:	250 ml	3000 ml

4.2 Target Tidal Volume Range

In order to perform good quality MBW tests the tidal volume should be within limits appropriate for the person performing the tests. The target tidal volume range is indicated during the MBW test in the inspiratory volume bar graph with a shaded area. The technician should try to keep the patient breathing within the limits of the shaded area.

EasyOne Connect software V2.2 an earlier use target volume as defined in the ATS/ERS MBW Consensus Statement [3]: The adult target range is 0.95 to 1.4 liter, the pediatric target range is 10 to 15 ml/kg.

EasyOne Connect software ›V2.3 uses a target range published by E. Horton et al [4]. The target volume range is computed by determining the ideal body weight (IBW) and based on IBW the target tidal volume range is set to 8 to 13 ml/kg. The following formulas are used to compute IBW:

Men age <16 yr : $\text{IBW} = 9.278*((h/100)^3 - 1.851) + 1.992*(\ln(h/100)*(h/100)^3 - 0.3798) + 23.98$
Women age <16 yr : $\text{IBW} = 9.835*((h/100)^3 - 1.562) + 1.466*(\ln(h/100)*(h/100)^3 - 0.2322) + 21.09$
Men age ≥16 yr : $\text{IBW} = 50.0 + 0.91*(h-152.4)$
Women age ≥16 yr : $\text{IBW} = 45.5 + 0.91*(h-152.4)$

Compared to the previous version this target range is closer to ‘normal’ tidal breathing whereas the previous ranges lead to relatively large breaths.

4.3 Breathing Baseline

FRC is the volume inside the lungs at the end of a ‘normal’ expiration. Therefore stable tidal breathing is a prerequisite for determination of an accurate FRC.

According to the ATS/ERS Consensus Statement [3] the FRC is not corrected when the breathing baseline is changes before the washout test. The change of the breathing baseline during the last expiration before the washout can be monitored using the parameter ‘FRC base’. For this purpose a mean breathing baseline is determined in the following way: The mean breathing baseline is the end-expiratory volume of three breaths preceding the start of the washout and a maximum of 10 breaths following the start of the washout. The parameter ‘FRC base’ can be selected and displayed / reported similar to other parameters.

Remark: The influence of a change in FRC baseline can easily be demonstrated: Perform an FRC test, and during the last breath with room air perform a deeper expiration. In this case ‘FRC base’ will be a relatively large volume reflecting the change in breathing baseline.

4.4 Automatic Gas Sensor Delay Time Determination

The delay times of the side-stream molar mass (MMss) and CO_2 signals depend on the gas transport time from main-stream sensor to the side-stream gas sensors plus the response times of the gas analyzers. Both delay times are determined automatically for each MBW trial performed with EasyOne Pro LAB. The N2 signal is then computed based on the delay-time corrected MMss and CO2 signals.

With software release V2.1 the delay computation was strongly improved by moving from a flow based cross correlation to a volume based cross correlation. This improved the accuracy of the MBW computation strongly, especially in cases where the patient performed ‘breathing stop’.

Delay time determination is crucial to the computation of FRC. As shown in a poster presented at ATS 2012 a change in the delay time by 10 ms can already cause a change in FRC by 2%. Exact delay time determination is a unique feature of the main-stream and side-stream molar mass measurement in EasyOne Pro. Delay time determination using this method is patent-protected by ndd.

4.5 Automatic Gas Sensor Calibration

The gas sensors are automatically tested and calibrated prior to each MBW or DLCO trial.

The CO sensor is calibrated using a 5-point calibration with DLCO test-gas, room air and a mixed gas at the beginning and at the end of the test. This calibration is patented by ndd and includes a calibration of the non-linearity of the sensor and a correction of small sensor drift effects. Note: This procedure is not performed in an MBW test since the CO sensor is not used.

The molar mass sensor is 2-point calibrated prior to each trial. In case of DLCO the calibration is based on room air and DLCO test gas, in case of MBW this is room air and 100% oxygen.

The CO_2 sensor is single-point calibrated using room air prior to each MBW trial.

4.6 Automatic Drift correction

Automatic drift correction has been introduced with V1.8 of EasyOne Connect. Drift correction is performed in the following way: Drift correction is only applied to the actual washout phase, i.e. to all breaths where the valve is closed and 100% O_2 is inspired by the patient. During that phase the flow geometry in inspiratory direction is changed and the measurement of inspired gas flow velocity is affected. Drift correction adapts only the gain of the inspired flow in such a way that the drift during the washout phase is compensated.

Drift correction therefore only changes inspiratory flow (and therefore inspiratory volume), and it affects therefore the FRC, LCI (and derived parameters) only minimally, since these parameters mainly depend on the expired volume of all washout breaths. The correction has a larger influence on parameters like TLC or RV, especially when an SVC test is performed directly after the washout.

4.7 Computation of FRC, LCI and LCI5

LCI equals the Cumulative Expired Volume (CEV) at the point where the tracer concentration reaches 1/40th of the initial concentration divided by the FRC computed at this breath. More precisely the LCI breath is the first of three consecutive breaths where the end-expiratory N_2 concentration is below 1/40th of the mean end-expiratory N_2 concentration before the washout. In case of N_2 washout CEV is therefore determined at approx. 2% N_2 (initial concentration approx. 78% N_2).

Due to this definition of the LCI relatively small errors in the N_2 concentration measurement can cause relatively large errors in the computation of LCI (this limitation is independent of the method used to compute the tracer concentration and applies therefore to all devices computing LCI):

- If a large breath is just at 2.0%, a very small error in the concentration measurement can make this breath be included or not.
- The error can be even larger if this breath at 2.0% is preceded by 2 breaths that are lower than 2.0%. Then the CEV can change by 3 breaths.

If automatic test mode is selected, EasyOne Pro terminates the MBW test when it is safe to assume that 3 consecutive breaths are below 2.0% N_2 when the final off-line N_2 computation is performed. For that purpose the software checks that the on-line N_2 concentration measurement of 5 consecutive breaths is below 1.8%.

LCI5 uses the same definition as LCI, but it is computed at 1/20th of the initial N2 concentration; LCI5 is based on the FRC at the LCI5 point.

The final reported FRC value is the FRC value at the point of LCI.

Tests that do not meet the LCI ending criteria (three consecutive breaths below 1/40th of initial concentration) are marked as ‘not acceptable’. If the N2 concentration of the last breath is below 5%, however, an LCI value still reported; in this case the LCI value is calculated based on an extrapolation of the end-tidal N2 concentrations (extrapolation is based on the last 1/4th of the N2 concentration, with a minimum of 4 N2 concentration values). These LCI values of ‘not acceptable’ test, based on extrapolation of N2 concentration values, must be treated with great care.

4.8 Raw Data Storage and Export

Each test performed in the clinical software (EasyOne Connect) stores the entire raw data in the EasyWarePro database. In order to access the raw data the 'WBreath Export' command can be used and the test can then be opened in the WBreath software where all raw data channels can be accessed. When comparing FRC values between 'EasyOne Connect' and WBreath please be sure that the appropriate software versions are used.

4.9 Recalculating Existing MBW Tests

When the 'EasyOne Connect' software is updated existing tests are not automatically recomputed. This means that existing tests remain unchanged unless the user explicitly updates these tests.

In order to manually update MBW tests the following 'trick' has to be used: Go into Utilities / Configuration / General, Header and enter 'Recalculate-FRC' under 'Header 1'. After doing so, a 'Recalculate' button appears when viewing MBW tests. Existing MBW trials can be re-computed based on the installed (new) software. Please note that each trial must be re-computed individually. At the moment there is no utility to re-compute batches of MBW tests.

4.10 Software Versions

For details about software versions please refer to the software version history available from our website (http://www.ndd.ch/index/downloads-software).

5 Validation

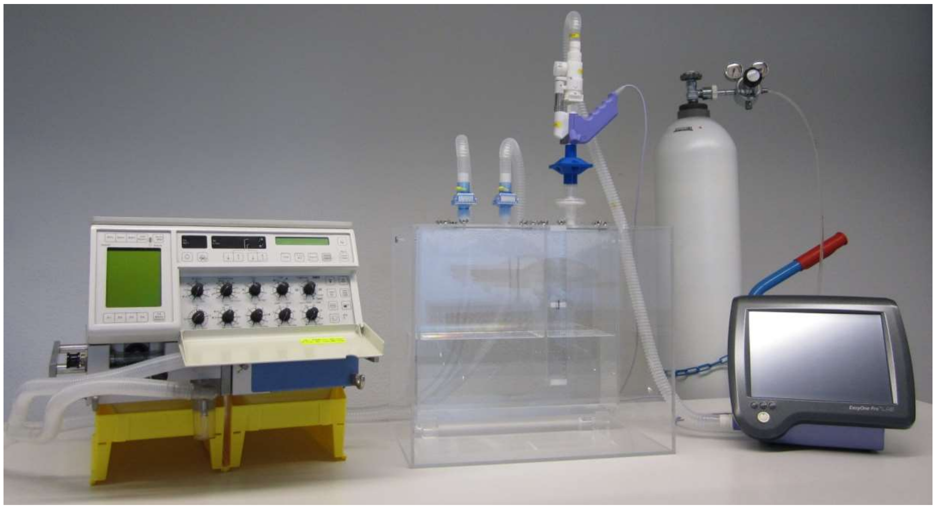
5.1 Flow

Flow (and therefore volume) has been validated by performing the standardized ATS testing. An appropriate report from the LDS hospital is available. Additional tests according to the ISO waveforms are also available.

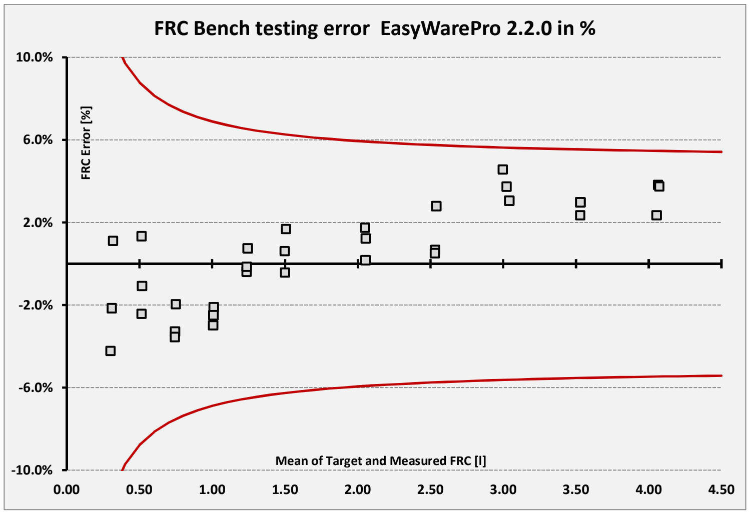
5.2 FRC

The FRC measurement by N_2 washout has been validated using a lung model proposed by Singer et al. [1]. In total 36 bench test measurements have been performed. Tidal volume (Vt) was varied between 0.4 and 1.0 l, the respiratory rate varied between 15 and 20 min^{-1}, the target FRC volume varied between 0.75 and 4.0 l.

The following picture shows from left to right the following components: Ventilator (Dräger Evita), water filled lung model, oxygen gas bottle and EasyOne Pro LAB. For the actual tests and additional heater was used to warm up the water to 37 °C.



The Bland-Altman plot shows the results of bench testing:



The two red lines in the diagram above indicate the ±5% error including an error of 1 mm in water level (water level measured visually). Only measurements above 0.75 l FRC have been performed since the error from the water level measurements exceed 50% of the 5% error margin.

The results can be summarized as follows:

- Mean value of all measurements deviates 0.32% from the target value.
- The standard deviation (sd) over all measurements is 2.29%.
- The 95% confidence interval ranges from -4.2 to 4.8%. All measurements are within ±5% of the target values.

5.3 Compliance with ATS/ERS recommendation

The following table lists the recommendations of the ATS/ERS task force for ‘Measurement of FRC using nitrogen washout’ (see [2], pages 515 to 517) and compares the recommendations to the performance and/or specifications of EasyOne Pro LAB.

ATS/ERS Recommendation [2]	EasyOne Pro LAB	Comment	Pass/ Fail
Equipment			
N2 analyzer accuracy ≤0.2%	N2 sensor accuracy 0.2%, resolution 0.1%	N2 determined indirectly using Dalton's law (sum of all gas concentration equals 100%)	Pass
Method of measuring N2 concentration	Indirect via molar mass and CO2	One of the methods described in the standard	Pass
N2 measuring range 0 – 80%	N2 range 0 – 100%	n/a	Pass
N2 resolution ≤0.01%	N2 resolution 0.1%	n/a	Pass
95% N2 response time to one 10% N2 step ≤60 ms	95% N2 response time to 80% N2 step approx. 80 ms	n/a	Pass
Flow sensor meets standardization for spirometry recommendations	Spirometry specifications are met	n/a	Pass
Sampling rate ≥40 Hz	200 Hz	n/a	Pass
Breathing valve dead space < 100 ml	10 ml	n/a	Pass
Back pressure from gas supply system < 1 kPa	0.1 kPa	O2 provided via bias flow system with very low resistance	Pass
0% and room air N2 concentration checked before each test	Automatic gas sensor calibration performed with each trial	n/a	Pass
End of test when N2 concentration <1.5%	Automatic stop at 1/40 of the tracer concentration	The ATS/ERS recommendation [3] specifies test end at 1/40 of the initial concentration (approx. 2%)	Pass
Repeated FRC measurements should agree within 10%	95% CI of in-vitro tests <5%	See also ERS/ATS Consensus Statement (below)	Pass
Quality Control			
Check of N2 sensor calibration with room air and 100% O2 (0% N2) before each test	Gas sensors are automatically calibrated before each trial	n/a	Pass
Linearity of N2 analyzer confirmed every 6 months	Molar mass sensor has a linear response over its measurement range, no linearity correction applied	n/a	Pass
Calibration check of flow sensor, including 100% O2	Flow sensor independent of gas composition	Flow measurement using ultrasonic flow sensor is completely independent of gas composition	Pass
Testing of biologic controls should be performed monthly	Monthly biological calibration check mentioned in the manual	n/a	Pass

5.4 Compliance with ATS/ERS Consensus Statement

The following table lists the requirements of the ATS/ERS Consensus Statement for inert gas washout published in the ERJ 2013 [3].

ERS/ATS Consensus Statement [3]	EasyOne Pro LAB	Comment	Pass/ Fail
Component Recommendations (see page 511, table 2)			
Flow measurement: Accuracy with 5% across range of flows during clinical testing, 3% with syringe	Flow is within ATS/ERS recommendations for spirometry (see report)	Flow accuracy exceeds those of the consensus statement	Pass
Sample flow <40 ml/min if sensor proximal to flow sensor	Sample flow is not proximal to flow sensor and is therefore not relevant	n/a	Pass
Volume drift	Volume drift is corrected automatically, a warning is shown when correction is excessive	Can be verified in research software	Pass

Gas analyzer accuracy	Tracer gas analysis based on Molar mass and CO2, automatically calibrated with each test	Can be verified in research software	Pass
Gas analyzer rise time	Molar mass and CO2 sensor have a rise time of approx. 80 ms	n/a	Pass
Data sampling frequency	200 Hz	n/a	Pass
Synchronization of flow and gas signals	Signal synchronization accuracy approx. 5ms	Automatic synchronization based and mainstream molar mass signal	Pass
Equipment related dead space < 2 ml/kg	Dead Space approx. 36 ml	Equipment should only be used for bodyweight ≥18 kg (see age limit in manual)	Pass
Equipment related resistance	Same resistance as in spirometry, large open flow path	Very low flow resistance	Pass

Overall recommendations (see page 512, table 3)			
Flow accuracy	Flow is with ATS/ERS recommendations for spirometry (see report)	Flow accuracy exceeds those of the consensus statement	Pass
95% of measured FRC values are within 5% of target volume of in-vitro device	See validation above	n/a	Pass
Quality of gas signal and gas analyzer accuracy	N2 sensor range 0 to 100%, resolution 0.1%, accuracy 0.2%	N2 signal computed based on measurement of molar mass and CO2	Pass
Recommendations for online washout software (see page 512, table 4)			
Software to display flow, volume and respiratory rate monitoring	Flow/volume graph available.	Flow rate monitoring will be added in Q1/2 2016	Pass
Graphical display of inert gas concentration	Gas concentrations displayed on-line	n/a	Pass
Accurate breath detection	Breath detection automatic for all age groups supported by device	n/a	Pass
If SnIII is measured display breath-by-breath inert gas expirogram	Research software only, expirogram displayed.	n/a	Pass
Online display should display end-tidal gas concentration	Online display of end-tidal concentrations available.	n/a	Pass
If SnIII is measured online display of FRC and lung turn-over	SnIII analysis only available in research software.	Clinical software planned for Q1/Q2 2016.	Pass
Automatic computation of parameters at end of test	All parameters available at end of test	n/a	Pass
Offline analysis	Offline analysis available with research software WBreath	n/a	Pass
Warning messages	Warning messages are automatically displayed at the end of the test	n/a	Pass
Recommendations for offline washout software (see page 513, table 5) The recommendations are only addressed in an over-all overview			
Clinical Software, EasyOne Connect	The Clinical software (EasyOne Connect) is designed for easy application in daily use in a clinical environment. The software provides a mostly automatic test procedure including automatic calibration. The software allows pooling of trials to overall tests.		
Research Software, WBreath	The research software (WBreath) allows in depth analysis of the tests performed with the Clinical software. Each trial performed in the Clinical software can be analyzed separately with the scientific software. No pooling of data possible; this can be achieved by the clinical software. The raw data signals are available and allow to check for drift, synchronization etc. For SnIII analysis the software allows to enable/disable individual breaths.		

6 References

[1] Singer F, Houltz B, Latzin P, Robinson P, Gustafsson P. A Realistic Validation Study of a New Nitrogen Multiple-Breath Washout System. PLoS ONE 7(4): e36083.

[2] J. Wanger, J.L. Clausen et al. ATS/ERS Task Force: Standardization of Lung Function Testing. Standardisation of the measurement of lung volumes. Eur Respir J 2005; 26:511-522.

[3] P.D. Robinson et al. Consensus statement for inert gas washout measurement using multiple- and single breath Tests. Eur Respir J 2013; 41: 507–522.

[4] E. Horton, R. Jensen, S. Stanojevic, F. Ratjen. Estimating physiologically appropriate tidal volume ranges for multiple breath washout tests. In press.