SPIROMICS Manual of Procedures and Data
Part 2
Pulmonary Function Testing v1.1

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Abbreviations

6MW: six-minute walk
6MWD: Six-minute walk distance
AE: Adverse event
ATS: American Thoracic Society
BTPS: Body temperature, pressure standard
CDC: Center for Disease Control
CO: Carbon monoxide
COHgb: Carboxyhemoglobin
CV: Coefficient of variation
eCO: Exhaled carbon monoxide
ERS: European Respiratory Society
eSP: Electronic short path spirometry software
FDA: Federal Drug Administration
$FEF_{25\%-75\%}$: Forced expiratory flow between 25% and 75% of forced vital capacity
FET: Forced expiratory time
FEV1: Forced expiratory volume in first second
FiO_2: Fraction inspired oxygen
FRC: Functional residual volume
FVC: Forced vital capacity
HFA: Hydrofluoroalakane propellant, HFA-134a (1,1,1,2-tetrafluoroethane)
HRCT: High-resolution computed tomography
IC: Inspiratory capacity
ISP: Communications software for the eSP KoKo spirometer
LLN: Lower limit of normal
MCID: Minimal clinically important difference
MDI: Metered dose inhaler
NHANES: National Health and Nutrition Examination Survey
PEF: Peak expiratory flow
PEFT: Peak expiratory flow time
PFT: Pulmonary function testing (spirometry)
pO_2: Partial pressure of oxygen
ppm: Parts per million
RB: Rebreathing
RV: Residual volume
SBP: Systolic blood pressure
SpO_2: Oxygen saturation measured by pulse oximetry
SVC: Slow vital capacity, may be modified as inspiratory or expiratory
TLC: Total lung capacity
VC: Vital capacity, may be modified as slow or forced
VEXT: Volume, extrapolated (spirometry)
VO_2 max: Maximum oxygen uptake

2 Pulmonary Function Testing (PFTs)

2.1 Protocol Summary

2.1.1 Background and rationale

The 2005 ATS/ERS guidelines for pulmonary function testing and interpretation will serve as the primary guidance for the conduct and interpretation of the spirometry, and if performed lung volumes and diffusing capacity.[1,2,3,4,5]

The FDA preferred primary endpoint for assessment of alteration in disease progression is serial measurements of FEV_1 over three years [6]. Other objective physiologic assessments considered by the FDA, in the draft guidelines, are RV/TLC, and exercise results such as six-minute walk. FEV_1 has been the primary outcome for most trials attempting to demonstrate disease modification for COPD. FEV_1 is also the usual outcome for studies of bronchodilation.

The between maneuver repeatability, which 90% of consecutive patients can meet, is 120 ml (6.1%) for FEV_1 and 150 ml (5.3%) for FVC.[7]. The established target is 150 ml for both measures (or 100 ml if the FVC is <1 L) [3]. The short-term (24.9±17.1 days) reproducibility in mild COPD participants is 113 ml (CV 4.1%) for FEV_1 and 150 ml (CV 3.5%) for FVC [8]. The minimal clinically significant difference for FEV_1 is about 100 ml [9].

2.1.2 Inclusion criteria specific to pulmonary function testing

- None (all included in study enrollment criteria)

2.1.3 Exclusion criteria specific to pulmonary function testing resulting in postponement or modification of testing

- Myocardial infarction, eye, chest or abdominal surgery within 6 weeks
- Upper or lower respiratory tract infections including untreated tuberculosis; chest, abdominal, oral or facial pain within 3 weeks
- Those with prior significant difficulties with pulmonary function testing
- For six-minute walk, clinically significant cardiac, orthopedic or balance difficulties or resting hypoxemia (SpO_2 <88% on room air, (on 1.5 L/min oxygen at University of Utah)).
- Recent use of bronchodilators is recorded and specific withholding is suggested but not mandatory.

2.1.4 Methods

Brief testing sequence and methods for each visit (baseline, 12, 24 and 36 months):

- Exhaled carbon monoxide will be performed using the Micro+Smokerlyzer (Bedfont Scientific, bedfontusa.com).
- Spirometry (SVC and FVC) will be performed on standardized equipment, eSP Koko (nSpire Health, www.nspirehealth.com) pneumotachometer (flow) spirometer. Centralized quality assurance will be used.
    - Slow vital capacity (expiratory vital capacity method)
    - Forced vital capacity
    - Bronchodilation with ipratropium bromide HFA and albuterol sulfate HFA 4 puffs each (30 minute waiting period before post-bronchodilator SVC or FVC)
    - Slow vital capacity, 30-minute post bronchodilator (expiratory vital capacity method)
    - Forced vital capacity post bronchodilator
- Six-minute walk with perceived breathlessness and exertion scales and pulse oximetry before and after. Recording SpO_2 every 2 seconds on a pulse oximeter such as the Onyx II 9560 (Nonin, www.nonin.com) will be implemented when available.

Safety spirometry during induced sputum and before and after bronchoscopy if performed will utilize the PiKo spirometer without central over reading.

2.1.5 Primary outcome:

- Change in post bronchodilator FEV_1 as percent reference (Hankinson 1999[10]) with baseline value (% reference) as a covariate.

2.1.6 Secondary outcomes:

- Exhaled carbon monoxide as an indicator of recent smoking
- FVC, SVC_{exp}, IC
- Bronchodilator reversibility of FEV_1 and FVC
- FEV_1 /FVC
- S_pO_2 at rest
- Six-minute walk distance

- Perceived breathlessness at end of six-minute walk
- Area above the oxygen saturation-time curve during the six-minute walk

2.1.7 Human Participants Protection

Exhaled carbon monoxide measurement requires a short breath hold followed by a slow exhalation into a disposable mouthpiece with a one-way valve and filter to prevent cross contamination. Rarely, participants may experience breathlessness, cough, fatigue or dizziness/lightheadedness (hyperventilation), all of which are brief.

PFTs are a common medical procedure of generally low risk. Some participants may experience breathlessness, cough, fatigue, dizziness/lightheadedness (hyperventilation), all of which are brief and very rarely headache, syncope, musculoskeletal chest pain, rib fractures or ear injury. A seated position has been specified to reduce risk related to dizziness or syncope. Transmission of airborne disease is rare and minimized or eliminated with single-use filters.

Instructions for withholding bronchodilator medications prior to testing will stress the continued use of rescue medication if needed. The use of albuterol or ipratropium will generally relieve any symptoms related to the trough effect of long-acting bronchodilators.

Albuterol has been reported to cause urticaria, angioedema, paradoxical bronchospasm, angina, arrhythmias, QT prolongation, hypertension, hypokalemia, seizures, tremor, nervousness, headache, tachycardia, muscle cramps, palpitations, insomnia and dizziness.

Ipratropium has been reported to cause cough, nausea, dry mouth, dizziness, headache, dyspnea, atrial fibrillation, tachycardia, paradoxical bronchospasm, laryngospasm, angioedema, anaphylaxis, hypersensitivity and exacerbate angle closure glaucoma.

The dose used in testing is twice the usual q4 hour dose of albuterol or the q6 hour dose of ipratropium used chronically. However, home management of exacerbations includes increasing the dose and/or frequency of bronchodilator therapy [11]. Doses in patients hospitalized or visiting the Emergency Department for exacerbations may be ten times the usual dose. Redosing, after at least 3 hours, is unlikely to result in any additional side effects.

The six-minute walk is self-paced, however participants are encouraged to cover as much distance as they can in six-minutes. As with any walk, the participant may stumble or fall. It is expected that more severe participants will become short of breath and may need to stop to recover before six minutes has elapsed. The walk will be stopped if the participant's SpO_2 falls below 80% when continuous oximetry is implemented.

Data transmission is FDA 21 CFR Part 11 compliant. The date of the procedure and of birth are the only HIPPA protected data to be transmitted, but the public data sharing data set will use the visit identifier and the ordinal age. The PFT software is designed to be HIPPA compliant for clinical use.

The participant may benefit from treatment or secondary prevention after study identification of unrecognized pulmonary disease. All study personnel are certified in the ethical conduct of human biomedical and genetics research and HIPPA information security.

2.2 Equipment

A standardized spirometer(s) will be leased for each site. Every effort will be made to assure the same equipment is available throughout the study.

A chair without wheels for the participant will be provided adjacent to a table for the spirometer and laptop. A medical waste receptacle will be available to dispose of any items contacting the participant's oral secretions etc (e.g. mouthpieces).

2.2.1 Supplies

Disposable low-resistance (0.5 cm H_2O at 60 L/min) filters and nose clips with extra supplies for wastage and training. Site supplied alcohol hand gel and germicidal equipment wipes will be used to meet recommended infection control measures.

2.2.2 Spirometry

The Koko spirometer (nSpire) pneumotach connects to a dedicated standard PC. The accuracy error is ≤3% meeting the ATS/ERS standards.

Rolling seal spirometers are a standard for reference laboratories and prior large epidemiologic studies such as NHANES III, Lung Health Study and MESA. The data in suggest the repeatability of the Koko (eSP, Eaglet, Legend) is comparable or superior to rolling seal spirometers (SpiroAir, SpiroAirLT , OMIS 922).

Table 1: comparison of spirometers for FEV_1

Spirometer	Repeatability		Bias		Imprecision
	ml	%	Liters	%	Liters
Koko eSP 1	0.0104	0.32	0.022±0.007	0.83±0.22	±0.046
Koko eSP 2	0.0096	0.44	0.005±0.007	0.42±0.31	±0.022
Koko eSP 3	0.0100	0.43	0.001±0.007	0.11±0.30	±0.023
Eaglet	0.0045	0.18	-0.009±0.003	-0.37±0.13	±0.020
HD3000	0.0046	0.17	0.003±0.003	0.02±0.12	±0.006
Koko Legend	0.014	0.57	-0.037±0.010	-1.38±0.41	±0.037
SpiroAir	0.016	0.68	0.001±0.011	0.05±0.58	±0.032
SpiroAir LT	0.021	0.92	-0.047±0.016	-1.19±0.65	±0.029
OMIS 922	0.028	1.22	0.004±0.020	0.16±0.86	±0.031

Repeatability: the difference between 95% of pairs of measurements is expected to be less than this value.

Bias: mean and 95% CI for the difference between measured and expected.

Imprecision: the difference between 95% of measurements and the true value are expected to be less than this value after correction for bias.

2.2.3 Spirometry data storage and back-up:

Daily data transfers from the individual sites to the over read servers at nSpire (FDA 21 CFR Part 11 compliant). Online/offline data acquisition, audit trail and remote upgrade capabilities are available. Transfers monthly to the GIC via secure FTP.

2.3 Personnel

2.3.1 Qualifications

All technicians who perform pulmonary function tests will be required to meet the recommendations for personnel qualifications for pulmonary function testing issued by the American Thoracic Society [12] and updated by the ATS/ERS Task Force.[2] Minimum requirements include sufficient education and training to assure that the technician understands the fundamentals of the tests, the common signs of pulmonary diseases and the management of the acquired pulmonary function data. Each PI will certify the qualifications of the technicians at their site. Each technician will certify they have reviewed the pulmonary function MOP. The site PI will designate a Site administrator (nSpire Investigator statement faxed to nSpire 800.916.4737) who will be responsible for creating technician accounts on the eSP Koko system.

2.3.2 Training

Two to three technicians will be trained for each site. Initial central training at a coordinators' meeting prior to beginning the study (protocol specific theory and practice) will be conducted assuming all technicians have previously performed PFTs. Additional training sessions (live and recorded) will be available online.

2.3.3 Certification

Enablement on the eSP Koko system: technicians will complete:

- Security statement
- Sample calibration
- Sample linearity check
- Sample SVC and FVC
- Technician certification checklist
- Cover sheet for fax

These items will be faxed to nSpire for review 800.916.4737. After review the technician will be enabled for testing on the local system

Certification of each technician will be based on the independent performance of PFTs on three separate individuals prior to any study PFTs (may be on pilot participants). Each technician will have the initial PFTs evaluated for quality and protocol compliance by the UCLA PFT core.

Training of new interim personnel will follow a similar plan. Site visits will include specific review of PFT quality.

Development of spirometry skills will emphasize: 1) demonstration of the FVC maneuver before participant's first attempt, 2) vigorously coaching to obtain a full inspiration followed by a "blast" at outset of maneuver and constant encouragement of complete exhalation ("squeeze everything out"), 3) observation of participant throughout the maneuver and 4) enthusiastic feedback to encourage maximal efforts. Physiology, spirometry repeatability and acceptability, calibration verification, quality assurance, infection control, troubleshooting will also be addressed.

2.4 Infection Control

2.4.1 Filters

Disposable filters/mouth pieces and nose clips will be used for each participant.[13] Materials in contact with participant mucosal surfaces will be disposed of as medical waste.

2.4.2 Cleaning

Measures will include hand hygiene (alcohol gel) and daily external cleaning of spirometer with germicidal disposable wipes. CDC guidelines do not recommend routinely sterilizing or disinfecting the internal machinery of the PFT machine.[13]

2.4.3 Hand washing

Hand washing (soap and water or alcohol based "waterless" hand cleaner) before and after each patient contact.

2.5 Calibration and Linearity Verification

Prior to calibration the nViro weather station must be plugged in to a powered USB port (any computer on at minimum to the windows prompt) for 20 minutes.

Each day of subject testing the spirometer will be calibrated at three target flows with a biologic filter in place. The tracings will be stored in a binder at the site (may be archived to a file when full). The calibration factors will be reviewed centrally.

- Low flow rate cycle (0-4L/sec)
- Medium flow rate (4-8L/sec
- High flow rate cycle (8-12L/sec).

Each week a verification of linearity will be performed with three strokes at each of the above flows. The tracings will be stored in a binder at the site (may be archived to a file when full).

2.6 Schedule of exams

Table 2: Schedule of visits

Visit	Interval	Stage	Time
1: Baseline	Exhaled carbon monoxide 1: Pre (before bronchodilators) Bronchodilator administration 2: Post (after bronchodilators) Six-minute walk	 1: SVC 2: FVC 1: SVC 2: FVC	 30-180 minutes
2: Year 1	Exhaled carbon monoxide 1: Pre (before bronchodilators) Bronchodilator administration 2: Post (after bronchodilators) Six-minute walk	 1: SVC 2: FVC 1: SVC 2: FVC	52 ± 4 weeks within 4 hours time of day from baseline visit 30-180 minutes
3: Year 2	Exhaled carbon monoxide 1: Pre (before bronchodilators) Bronchodilator administration 2: Post (after bronchodilators) Six-minute walk	 1: SVC 2: FVC 1: SVC 2: FVC	104 ± 4 weeks within 4 hours time of day from baseline visit 30-180 minutes
4: Year 3	Exhaled carbon monoxide 1: Pre (before bronchodilators) Bronchodilator administration 2: Post (after bronchodilators)	 1: SVC 2: FVC 1: SVC 2: FVC	156 ± 4 weeks within 4 hours time of day from baseline visit 30-180 minutes

	Six-minute walk		
98: Early term	Exhaled carbon monoxide 1: Pre (before bronchodilators) Bronchodilator administration 2: Post (after bronchodilators) Six-minute walk	 1: SVC 2: FVC 1: SVC 2: FVC	 30-180 minutes
99: Unscheduled	As appropriate		

Subjects in the pilot study will be assigned a unique subject number for that visit and will have visit 1 (baseline) tests performed. If they are enrolled in the study, they will receive a new subject ID and repeat visit 1. Subjects in the repeatability substudy will also be assigned new study numbers and will repeat visit 1.

The window for the annual visits is 52 weeks ± 4 weeks, for the repeatability sub study 4 weeks ±2 weeks. Ideally the spirometry will be performed at the same time of day to obviate the effect of diurnal variation, but a 4-hour window is acceptable.

2.7 Quality Assurance

2.7.1 Local

2.7.1.1 Technician feedback

Quarterly feedback on the performance of each technician will include 1) information concerning the nature and extent of unacceptable maneuvers and nonreproducible tests (goal <5%); 2) corrective action that the technician can take to improve the quality and number of acceptable maneuvers; 3) positive feedback to technicians for good performance; and 4) comments on the calibration. Immediate feedback on acceptability and repeatability will be provided by the spirometer software.

Quarterly feedback, by technician and machine, using a statistical process control approach, derived from manufacturing quality control, will be developed to further encourage the highest quality PFTs and quickly identify shifts or drift in technician or spirometer performance. Mean time to "failure" in meeting acceptability criteria will be modeled as a nonhomogeneous Poisson process and presented as "Duane" graphs to assess increasing or decreasing failure rate. [14]

2.7.1.2 Spirometry

No attempt will be made to hand calculate values from tracings. Tracings generated from digital data are unlikely to yield useful corrections or validation. Avoiding this will also shorten the training time.

2.7.1.2.1 Mechanical Standards

Spirometer/pneumotach: Daily **calibration verification** will be performed with a 3 L syringe (with a biologic filter in line) at 3 flow rates. Immediate feedback will be the ±3.5% volume at each flow rate.

A weekly evaluation of the **calibration** verification will be performed with a 3 L syringe (with a biologic filter in line) three times each at 3 flow rates. Immediate feedback will be the ±3.5% volume at each flow rate.

Long-term feedback will be developed using a statistical process control methodology in addition to the usual ±3.5% for the volume standard. Leak testing is not applicable to flow based spirometers. A careful review for zero flow state will be made. Calibration syringes will be recertified annually (3L ±15ml).

2.7.1.2.2 Repeatability Goals

A continuous feedback program to the technicians will target >95% of spirometry tests meeting the repeatability criteria (NHANES III achieved 90% for FVC and 92% for FEV_1, reported by Crapo, ATS 2005).

2.7.1.3 Entered demographic/atmospheric data:

Entered participant data (date of birth, height, sex and race) will be crosschecked against the main database. The barometric pressure temperature and humidity is transmitted directly from the nViro unit to the spirometry software. Values will be verified at the site visits by comparison to a reference barometer at site visits.

2.7.2 Central PFT Quality Assurance Core

Monthly, a database query of the centralized spirometry will evaluate the acceptability and repeatability of all spirometry.

An over read QA program will review all spirometry. A secondary review will be made of:

- Initial PFTs for each technician (certification)

- Statistical outliers at baseline of FEV_1 , FVC
- Statistical outliers in change of the same parameters (review of baseline and changed follow-up)
- Discordant changes (e.g. fall in FEV_1 and improvement in symptoms if identified by GIC analysis)
- Those flagged as poor quality by database query
- Random sample stratified by site enrollment.

Calibration records, syringe certification and mechanical standards for each site will be reviewed on a regular basis.

This core will not provide clinical interpretations.

2.7.3 Site Visits

Site visits will be made during the first year and as needed following.

2.7.3.1 Training/retraining

If remote web based training/retraining does not resolve identified difficulties, an experienced technician will visit the site for retraining. New procedures such as continuous oximetry will use a similar approach depending on the complexity.

2.7.3.2 Equipment validation

For spirometry, exchange with a new machine will be used if phone based troubleshooting is unable to resolve the problems.

2.7.3.3 Procedure verification

Visits will be reviewed for completeness and protocol adherence (e.g. eCO, SVC, FVC bronchodilator, SVC, FVC, six-minute walk)

2.8 Participant Preparation

2.8.1 Safety

PFTs will be deferred or not performed for those with: recent (6 weeks) upper or lower respiratory tract infections including TB; chest, abdominal, oral or facial pain; stress incontinence; dementia; recent myocardial infarction (6 weeks), chest or abdominal surgery (6 weeks), those with prior significant difficulties with spirometry or participant refusal.

2.8.2 Instruction

Prior to PFTs, participants will be asked to withhold/refrain from vigorous exercise (0.5 hours), smoking (1 hour), eating a large meal (2 hours), alcohol (4 hours), caffeine (6 hours), inhaled albuterol (6 hours), inhaled ipratropium (8 hours) and other bronchodilators (twice the usual dosing frequency, see Table 3). Practicality may require some long-acting bronchodilators to simply be noted rather than withheld. Instructions for withholding bronchodilator medications prior to testing will stress the continued use of rescue medication if needed. The use of albuterol or ipratropium will generally relieve any symptoms related to the trough effect of long-acting bronchodilators. Failing to withhold/refrain from the above activities will not exclude a participant from continuing with PFTs.

The PFT values after bronchodilators are the most important outcomes. Sites will vary in the ability to consent/instruct potential subjects over the telephone for withholding prior to written consent due to local IRB policies. Withholding may be different at sequential visits. Some subjects, in spite of trying, will be unable to withhold drugs prior to visits.

Table 3: Target duration of abstinence from bronchodilators

Drug	Brand names containing the drug	Duration of abstinence
Albuterol	ProAir HFA, Proventil HFA, Ventolin HFA, AccuNeb, Generic nebulizer solutions, Non-sustained release oral tablets	6 hours
Epinephrine	Epipen, Twinject, S2, generic	6 hours
Levalbuterol	Xopenex HFA, Xopenex solution, Generic solution	6 hours
Metaproterenol	Generic nebulizer solutions, Non-sustained release oral tablets or syrup	6 hours
Pirbuterol	Maxair Autohaler	6 hours
Terbutaline	Generic tablets	6 hours
Ipratropium	Atrovent HFA, Combivent, DuoNeb, Generic nebulizer solutions	8 hours
Theophylline immediate release	Elixophyllin, Theolair, Generic	12 hours
Albuterol (sustained release)	VoSpire ER, Sustained release oral tablets	24 hours
Arformoterol	Brovana	24 hours
Formoterol	Dulera, Foradil Aerolizer, Foradil Certihaler, Perforomist, Symbicort	24 hours
Salmeterol	Advair Diskus, Advair HFA, Serevent Diskus	24 hours
Theophylline extended 12-hour release	Theochron, Generic q12 hour ER	24 hours
Theophylline 24 hour release	Theo-24, Uniphyl	48 hours
Tiotropium	Spiriva	48 hours

Combination drugs are listed as the drug with the longer withholding time

Drugs available in the US (Orange Book) are listed

http://www.accessdata.fda.gov/scripts/cder/ob/docs/queryai.cfm

The FDA has announced the planned last date for the following products to be dispensed

Alupent (metaproterenol) 14 Jun 2010

Combivent (albuterol & ipratropium) 31 Dec 2013

Maxair (pirbuterol) 31 Dec 2013

Inhaled steroids, cromolyn, intranasal steroids, antihistamines, leukotriene receptor blockers (montelukast, zafirlukast, Accolate, Singulair) and 5-LO inhibiters (zileuton, Zyflo, Zyflo CR) have no withholding parameters. Beta-blockers will be noted, but not restricted. Beta-blockers will be grouped by cardioselectivity.

Table 4: Beta-Antagonists

Beta-1-Selective Antagonists

GENERIC NAME	BRAND NAME
Acebutolol	Sectral
Atenolol	Tenormin Tenoretic (combo)
Betaxolol	Kerlone Betoptic S (eye)
Bisoprolol	Zebeta Ziac (combo)
Metoprolol	Lopressor Lopressor HCT Toprol-XL

GENERIC NAME	**BRAND NAME**
Betaxolol	Betoptic S (eye)
Betaxolol	Kerlone
Metoprolol	Lopressor
Metoprolol	Lopressor HCT
Acebutolol	Sectral
Atenolol	Tenoretic (combo)
Atenolol	Tenormin
Metoprolol	Toprol-XL
Bisoprolol	Zebeta
Bisoprolol	Ziac (combo)

Other Beta Antagonists

GENERIC NAME	BRAND NAME
Carteolol (eye)	(generic)
Carvedilol	Coreg Coreg CR
Esmolol	Brevibloc (IV)
Labetalol	Trandate
Levobunolol	Betagon (eye)
Metipranolol	OptiPranolol
Nadolol	Corgard Corzide (combo)
Nebivolol	Bystolic
Penbutolol	Levatol
Pindolol	Visken
Propranolol	Inderal Inderal LA InnoPranXL
Sotalol	Betapace Betapace AF
Timolol	Blocadren Timolide 10-25 (combo) Betimol (eye) Istalol (eye) Timoptic (eye) Combigan (eye combo) Cosopt (eye combo)

GENERIC NAME	**BRAND NAME**
Carteolol (eye)	(generic)
Levobunolol	Betagon (eye)
Sotalol	Betapace
Sotalol	Betapace AF
Timolol	Betimol (eye)
Timolol	Blocadren
Esmolol	Brevibloc (IV)
Nebivolol	Bystolic
Timolol	Combigan (eye combo)
Carvedilol	Coreg
Carvedilol	Coreg CR
Nadolol	Corgard
Nadolol	Corzide (combo)
Timolol	Cosopt (eye combo)
Propranolol	Inderal
Propranolol	Inderal LA
Propranolol	InnoPranXL
Timolol	Istalol (eye)
Penbutolol	Levatol
Metipranolol	OptiPranolol
Timolol	Timolide 10-25 (combo)
Timolol	Timoptic (eye)
Labetalol	Trandate
Pindolol	Visken

Caffeine up to 200 mg (see Table 5) is permitted prior to the procedures (note the NPO requirements for the blood).

Table 5: Caffeine equivalents

Caffeine equivalent to 200 mg
- Coffee up to 16 oz
- Espresso up to 3 shots
- Energy drinks: Rock star, Amp Red Bull, Full Throttle up to 20 oz
- High caffeine cola drinks (Jolt) 24 oz
- Instant coffee or tea up to 25 oz
- Brewed tea 33 up to oz
- Vault up to 34 oz
- Non-cola soft drinks up to 43 oz
- Diet cola or Diet Dr. Pepper up to 51 oz
- Cola or Dr. Pepper up to 65 oz
- Chocolate milk up to 2.5 gal
- Cocoa (Swiss Miss) up to 83 gal
- Chocolate covered coffee beans up to 16 beans
- Chocolate chips, semisweet up to 1.75 cups
- Chocolate chips, milk up to 5.95 cups
- M&Ms, plain up to 6.87 cups
- M&Ms, peanut up to 11.76 cups
- Butterfinger bars, bite size up to 2857 bars

Small container energy drinks:
- Charge! Super Shot (200 mg/ 59 ml)
- Upshot (200 mg/ 74 ml)
- Fuel Cell (180 mg/ 59 ml)
- Ammo (171 mg/ 30 ml)
- Mana Energy Potion (160 mg/ 40 ml)
- Jolt Endurance Shot (150 mg/ 59 ml)
- NOS Powershot (125 mg/ 59 ml)
- Slam Energy Drink (107 mg/ 59 ml)
- Kore Energy Shot (100 mg/ 51 ml)
- Powershot (100 mg/ 30 ml)
- Sky Rocket Syrup (100 mg/ 28 ml)

Energy drinks over the 200 mg limit in a single container:
- Redline Power Rush (350 mg/ 74 ml)
- Wired X344 (344 mg/ 455 ml)
- Spike Shooter (300 mg/ 248 ml)
- Cocaine Energy Drink (280 mg/ 248 ml)
- Extreme Energy 6-hour shot (220 mg/ 59 ml)

For others caffeine containing drinks check

http://www.erowid.org/chemicals/caffeine/caffeine_info1.shtml#1

http://www.energyfiend.com/huge-caffeine-database

PFTs will be performed with disposable low-resistance filters, nose clips, seated in a non-rolling chair with the chin slightly up, after loosening tight or restrictive clothing and removing loose dentures.

2.9 Preparation and Calibration

Room temperature will be ideally maintained at 23 ±1.5 °C The temperature, humidity and barometric pressure will be automatically recorded by the nViro unit attached to the spirometry laptop. Allow a minimum of 20 minutes with the nViro weather station plugged in to an powered USB port for the temperature measurement to stabilize

Volume/flow verification will be performed daily with a three-liter syringe at three flow rates. The weekly linearity verification will be performed if due.

The height measured from the anthropomorphic portion of the protocol will be entered into the spirometer.

2.10 Exhaled carbon monoxide.

2.10.1 Definition/Description

Sources of carbon monoxide in exhaled air include; CO formed by enzymatic degradation of heme, non heme-related release (lipid peroxidation, xenobiotics, bacteria) and exogenous CO (see Table 6). [15] CO in the environment is primarily due to incomplete combustion (including in cigarettes). A cut off of 6 ppm separates non-smokers from smokers. The alveoli are the predominant site of exhaled CO.

Factors altering exhaled CO

Table 6: Factors Influencing Exhaled Carbon Monoxide

Disease

- ↑ Allergen challenge (early and late response)
- ↑ Asthma (mild-moderate)
- ↔ Asthma (mild)
- ↑Asthma (severe)
- ↑Atopy
- ↑ Asthma in children (persistant asthma)
- ↑ Allergic rhinitis
- ↑ COPD (ex-smokers)
- ↑ Upper respiratory tract infections
- ↑ Bronchiectasis and lower respiratory tract infections
- ↑ Interstitial lung disease
- ↑ CF
- ↑ Citically ill patients
- ↑ Diabetes, hyperglycemia, oral glucose loading

Miscellaneous

- ↑ Smoking
- ↑ Airway pollution
- ↑ Airway obstruction
- ↑ Hyperbilirubinemia
- ↑ Sex (cyclic variations in women)
- ↑ Race (↑ COHb in Japanese newborn)
- ↑ Increased heme breakdown (anemia, hematoma, preeclampsia)
- ↑ Fasting
- ↑ Dehydration
- ↑ Phenobarbitone
- ↑ Xenobiotic compounds (e.g. paint remover)

[15])*Definition of abbreviations* ↓ _ decrease; ↑ _ increase; ↔ _ no change

Due to changes in smoking topography and variable washout times, the exhaled CO is not proportional to the intensity of smoking (cigarettes per day) [16]. Even heavy traffic exposure does not increase levels above 6 ppm [17]. Non-smokers have exhaled CO < 6 ppm, but 23% of smokers will fall in this range.[18] Passive smokers have mild elevations 5.2±3.4 ppm [19]. Active smokers are typically in the high teens. Severe airway obstructions or high concentrations of CO result in underestimation of CO Hgb from exhaled CO (~3% at FEV_1 50% [20].

Measurement of carboxyhemoglobin allows for adjustment of DLCO for carbon monoxide back-pressure. Carboxyhemoglobin is elevated with recent smoking or exposure to other combustion products.

CPT codes: carbonmonoxide quantitative (82375)

2.10.2 Equipment and supplies

- Micro+Smokerlyzer exhaled carbon monoxide monitor (Figure 1, Bedfont Scientific Ltd, England, www.bedfont.com) version 1.0

Figure 1: Micro+Smokerlyzer

- D-piece filters (Figure 2) (12 per package): changed monthly as indicated by the change D-piece screen at start-up (Figure 5).

Figure 2: D-piece filter for eCO

- Flat pack paper mouthpieces (Figure 3) (50 or 250 per package): one per participant

Figure 3: Flat pack mouthpiece for eCO

- AAA batteries (3) as spares
- Cetrimide alcohol free wipes (25 or 50 per package) for weekly and as needed cleaning.
- Calibration materials (PFT over read center only)
  - 50 ppm CO balance N_2 (primary standard, blend ±5%/2.5 ppm, analytic tolerance ±1%/0.5 ppm) 150 A cylinder with adaptor for D-piece
  - CGA 350 regulator

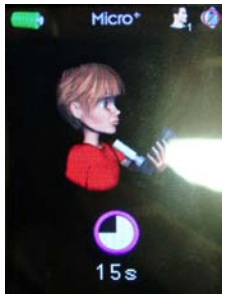
2.10.3 Method of assessment

A micro+smokerlyzer exhaled carbon monoxide monitor will be used. A new cardboard mouthpiece will be inserted on the D-filter. The monitor will be turned on (Figure 4A) auto zeroing the monitor) and the testing mode selected. (Figure 4B. center icon of person).

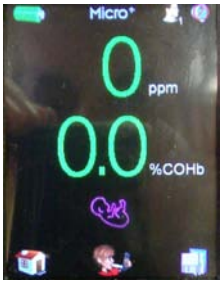
Figure 4: Micro+Smokerlyzer screen shots

A 

B 

C 

D 

E 

The participant will be instructed as follows (Figure 4C):

- At the prompt you will take a full breath in.
- Hold your breath for 15 seconds
- At the third tone you will breathe out gently and completely into the mouthpiece (Figure 4D)

The participant will complete the maneuver and the ppm recorded from the screen (Figure 4E)

The process will be repeated for a second maneuver.

Dispose of paper mouthpiece as medical waste. Do not throw away the D-filter (see maintenance).

2.10.4 Acceptability (applied to each maneuver) and Repeatability (between maneuvers for each participant):

A breath hold between 10 and 20 seconds is acceptable. Two measures within 6 ppm are sufficiently repeatable

2.10.5 Maintenance

Special cetrimide antibacterial wipes for weekly cleaning or when visibly soiled- NO ALCOHOL

Replace one-way bacteriologic filters every 4 weeks prompted by built-in on-screen reminder (Figure 5). It will appear at star-up. After replacing the D-piece filter, click the check on the screen.

Figure 5: Reminder to replace D-piece monthly

Batteries (3 AA) as indicated in upper left of home screen

Sensor replacement centrally if needed (estimated about every 3 years)

2.10.6 Quality assurance

Exchange return twice yearly

- Calibration/verification with 50 ppm CO balance N_2 (primary standard)
- Recording of sensor installation date
- Instrument calibration date
- Number of tests
- Replace batteries

A validation study will be performed to confirm the accuracy and repeatability of the eCO monitors

2.10.7 Derivation or calculation of variable

Estimation of COHb=0.63+0.16 (exhaled CO ppm) for Bedfont EC50 monitor [21]

2.10.8 Normal range, protocol limits, significant change and adverse event grading

Lower/upper limit of normal: >6 ppm is consistent with recent smoking or other exposure

Precision and units: xxX parts per million (ppm), range 0-500

Protocol inclusion criteria: none. An estimated 25% of smokers will have levels below 6 ppm due to clearance time since last cigarette.

Clinically significant change: N/A

Critical values: ≥58 ppm (~10% COHgb)

Administer oxygen. Refer to Emergency Department or consult study physician for confirmation (CO-oximetry) and further treatment

AE grade: N/A

2.10.9 Data validation

Verification and central calibration (50 ppm) every six months centrally

Correlation of self-report of smoking status with measured levels

2.10.10 Statistical plan of analysis

Smoking abstinence verification

2.10.11 Relation to specific aim/ study objective

Smoking status is an important predictor of rate of decline in lung function.

2.11 Spirometry: Slow Vital Capacity

2.11.1 Definition/Description:

Spirometry interpretation guidelines suggest referencing FEV_1 to VC to define obstruction.[4] SVC_{Insp} or SVC_{Exp} may give a "more correct" estimate of FEV_1 /VC ratio. This is a typically European approach contrasted with the US referencing the FVC. Almost all reference equations use FEV_1 /FVC; recognizing that in normals FVC, SVC_{Insp} and SVC_{Exp} are very similar. In obstructed participants, generally the SVC_{Insp} > SVC_{Exp} > FVC. The guidelines imply, but do not state, the maximal VC, by whatever method, may be the most appropriate reference for FEV_1 . IC, best measured with the SVC_{Exp} method, provides a measure, the converse of FRC, of airtrapping, which may be limiting during exercise.

2.11.2 Equipment and supplies

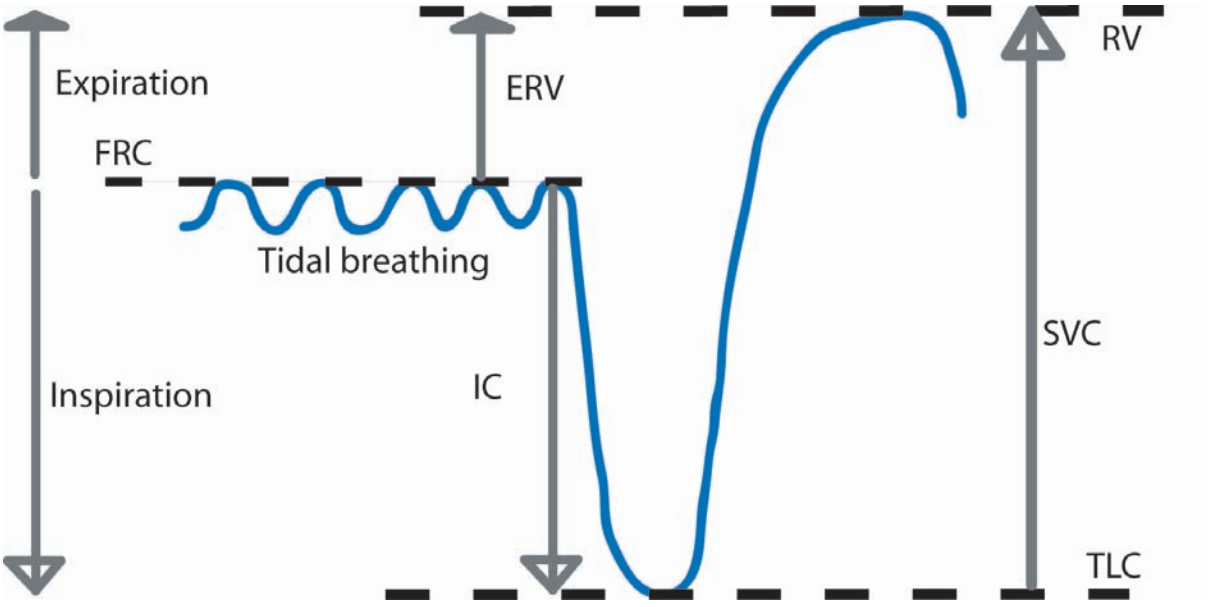
- KoKo spirometer
- Notebook computer with eSP spirometry, ISP communication, antivirus/firewall software installed
- 3-liter calibration syringe
- Participant filters and nose clips
- Ink-jet printer with cartridges and cables
- nViro weather stations
- Study specific system users guide

2.11.3 Method of assessment

Slow vital capacity will be performed with disposable low-resistance filters, nose clips, seated with the chin slightly up, after loosening tight or restrictive clothing and removing loose dentures.

The SVC_{Exp} method (Figure 6) will be used for SPIROMICS. PFT technicians will emphasize: 1) demonstration of the expiratory VC maneuver before participant's first attempt, 2) vigorously coaching to obtain a full inhalation followed by constant encouragement of complete exhalation, 3) observation of participant throughout the maneuver and 4) enthusiastic feedback to encourage maximal efforts. A minimum one-minute rest between maneuvers will be observed. A minimum of three acceptable and 2 repeatable maneuvers will be obtained. Up to 5 maneuvers are permitted to meet criteria. See study specific users guide for screen shots and step by step instructions for software.

Figure 6: SVC_{Exp} : Inspiratory capacity/Expiratory VC method



2.11.4 Acceptability (applied to each maneuver) and Repeatability (between maneuvers for each participant):

Acceptability: A minimum of five tidal breaths with a consistent (±~90 ml) end expiratory volume (FRC point), end of test criteria met (change in volume <0.025 L over 1 s and expiratory time >6s) and no cough, glottic closure, leaks at the mouth or obstruction of mouthpiece. Three acceptable maneuvers out of up to a maximum of 5 attempts will be expected.[3]

Repeatability: Difference between largest and next largest VC value <=150 ml.[3]

2.11.5 Warning messages and flags

- INVALID (Insufficient tidal stability to establish baseline)
  Message appears when subject does not perform at least 5 **stable** tidal breaths before the deep inspiration.
  Resolution: Coach subject to maintain a more stable/relaxed breathing pattern.
- INVALID (Insufficient tidal breaths)
  Message appears when subject does not perform at least 5 tidal breaths before the deep inspiration.
  Resolution: Coach subject to perform more tidal breaths before they take the deep breath in.
- INVALID (No SVC maneuver found)
  Message appears when the subject does not perform an SVC after the IC or if the space bar is accidentally hit during IC.
  Resolution: Coach subject to take a deep breath in (for IC) then exhale completely to a good plateau (for SVC)
- Warning: Negative ERV (expiratory reserve volume)
  Message will appear if subject does not perform a complete exhalation (after the IC) that goes past (above) the end tidal baseline.
  Resolution: Coach subject to exhale completely to a good plateau
- Warning: Questionable tidal stability
  Message will appear when tidal stability is not reached, i.e. there is more than 90 mls difference between end-tidal points. This is the top point of each tidal breath.
  Resolution: Coach subject to breathe at a stable rate and volume during tidal breathing

2.11.6 Maintenance

See study specific users guide

2.11.7 Quality assurance

Training and certification initially and annually or as needed for difficulties
Protocol compliance prompts in software
Quality assurance prompts in software
Central over read/QA review of each maneuver (acceptability and repeatability) and selection of best test

2.11.8 Derivation or calculation of variable

SVC_{Exp} : largest acceptable maneuver
IC (from the SVC_{Exp} maneuver above): average of 3 acceptable maneuvers which have the largest SVCs. [3]

2.11.9 Normal range, protocol limits, significant change and adverse event grading

Lower/upper limit of normal: For SVC_{Exp} , NHANES FVC values by race, sex
Precision and units: X.XX Liters BTPS
Protocol inclusion criteria: NA
Clinically significant change: unknown
AE grade: NA

2.11.10 Data validation

Electronic data transfer
Expert over read and electronic validation methods

2.11.11 Statistical plan of analysis

SVC_{Exp} , IC
FEV_1 /SVC_{Exp} compared to FEV_1 /FVC.
IC contrasted to CT measures of airtrapping

2.11.12 Relation to specific aim/ study objective

IC may be a surrogate for FRC, TLC and airtrapping

2.12 Spirometry: Forced Vital Capacity

2.12.1 Definition/Description

FEV_1 is the standard for approval of bronchodilator drugs and the most widely accepted for disease modification. Because the test is readily available and inexpensive, the results may be easily generalized.

2.12.2 Equipment and supplies

See slow vital capacity section

2.12.3 Method of assessment

Spirometry will be performed with disposable low-resistance filters, nose clips, seated with the chin slightly up, after loosening tight or restrictive clothing and removing loose dentures.

Forced expiratory vital capacity (spirometry) will be performed after completing the slow VC maneuvers. PFT technicians will emphasize: 1) demonstration of the FVC maneuver before participant's first attempt, 2) vigorously coaching to obtain a full inspiration followed by a "blast" at outset of maneuver and constant encouragement of complete exhalation ("squeeze everything out"), 3) observation of participant throughout the maneuver and 4) enthusiastic feedback to encourage maximal efforts. A minimum of three acceptable and 2 repeatable maneuvers will be obtained.

A minimum of three acceptable maneuvers will be performed. Additional maneuvers (up to 8 total) will be performed until the repeatability criteria are met or it is not safe for the participant to continue.

See study specific users guide for screen shots and step by step instructions for software.

2.12.4 Acceptability and Repeatability:

2.12.4.1 Acceptability criteria (applied to each maneuver) are listed below.

a. Back-extrapolated zero-time is less than 5% of the FVC or 150 ml (which ever is greater).
   Slow start of test. The participant did not begin his/her initial peak flow early enough; repeat, coaching for a more forceful and abrupt start ("BLAST it out").
b. Rapid rise to PEF. Time to peak <120 ms will generate a prompt to "blow harder", but will not result in the rejection of the maneuver. Rise time and dwell time will be evaluated for PEF, but are not mandated.
   Low peak flow. The patient did not achieve an adequately forceful blast. Repeat the effort, coaching to blow harder and faster.
c. Absence of leaks or obstruction of the mouthpiece.
d. Absence of glottic closure.
e. Absence of cough. Coughing causes abrupt irregularities in flow and is a reason to reject the test when it occurs during the first second of the effort. Coach the patient to make the effort without coughing. Sometimes it is helpful to have the patient blow just slightly less forcefully than the maximum to prevent a cough. Maneuvers with the cough occurring after the first second may still be usable for the FEV_1 .
f. Smooth end of exhalation (plateau on volume time curve). The change in volume is less than 0.025 L over the last second of exhalation.
   Abrupt end of test. At the end of exhalation, the patient stopped blowing out too abruptly, ending his/her effort too soon. Coach the patient to maintain his/her expiratory effort to the very end. In patients with severe COPD, the expiration often does not reach a plateau in a reasonable period of time (over 15 to 20 seconds at times), which is acceptable.
g. Minimum six-second exhalation.
   Short expiratory time. Patient did not continue his/her expiration for at least 6 seconds or did not reach a volume plateau.

2.12.4.2 Repeatability (between maneuvers for each participant)

a. FVC: the difference between largest and next largest value of FVC <150 ml (100 ml if FVC <1 L).[3]
b. FEV_1 : the difference between largest and next largest value of FEV_1 <150 ml (100 ml if FVC <1 L).[3]
c. Last FEV_1 not largest (trending up) will be evaluated, but not mandated
d. PEF: the difference between largest and next largest value of PEF < 10% (or 6.6 L/min which ever is greater)(NHANES III criteria) and not trending up over subsequent maneuvers will be evaluated but not mandated.

A minimum of three acceptable maneuvers will be expected.[3] In general, if you cannot obtain 3 acceptable and 2 reproducible tests within 8 attempts, further testing will not be productive, and may be terminated on the judgment of the technician. Many people who cannot perform spirometry, however, have either neurological or

cognitive deficits that may not otherwise be obvious. Therefore, inability to perform spirometry should be reported to the investigators because it may affect participation in the study.

The largest acceptable FVC will be reported. The largest usable FEV_1 (not necessarily meeting acceptability criteria d to g above) will be reported. The PEF and $FEF_{25-75\%}$ will be reported from the maneuver with the largest sum of FEV_1 and FVC. The FET will be reported from the largest FVC maneuver.

2.12.5 Quality assurance messages and flags

- BST - Best effort
- CON - Effort consistent with best (meets repeatability)
- AE- Abrupt end during exhalation
  Resolution: encourage the participant to exhale more completely until they reach a flow plateau. Glotic closure results in an abrupt change to zero flow which appears to meet the plateau criteria and may not be identified with this flag. Exhalation may be much longer than 6 seconds. In severe subjects, efforts beyond 15-20 seconds may not be useful and could precipitate syncope
- CG – Cough
  Resolution: try again. Cough after 1 second may produce usable FEV1 measures.
- 6 SEC - Expiration Time < 6 seconds
  Resolution: encourage the participant to exhale longer
- DIS - Discarded
- PEFT – Peak Expiratory Flow Time > 150 ms
  Resolution: encourage the participant to exhale more forcefully.
- BE – Back Extrapolation (VEXT) > 5% or 150ml, whichever is larger
  Resolution: encourage the participant to exhale more forcefully and not to hesitate after the full breath in.
- RB –Rebreathing
  Resolution: terminate the maneuver with the space bar after the inhalation following the FVC maneuver and before the participant breaths out a second time

2.12.6 Maintenance

See study specific users guide

2.12.7 Quality assurance

Training and certification initially and annually or as needed for difficulties

Protocol compliance prompts in software

Quality assurance prompts in software

Central over read/QA review of each maneuver (acceptability and repeatability) and selection of best test

2.12.8 Derivation or calculation of variable

FEV_1 , FVC, PEF, FET, $FEF_{25-75\%}$ calculated from the maneuver as for ATS/ERS standards

FEV_1 /FVC, FEV_1 /SVC_{Exp}

Isovolume FEF: Average flow over reference volume a) pre bronchodilator FVC and b) baseline visit FVC (post hoc)

For change over time:

- Absolute change: (follow-up value-baseline value)
- Percent initial value: (follow-up value-baseline value)/baseline value x100
- Percent of predicted (reference) value: (follow-up value-baseline value)/(FEV_1 or FVC reference value)

Percent reference, Z score and categorical LLN for Hankinson 1999[10])

2.12.9 Normal range, protocol limits, significant change and adverse event grading

Lower/upper limit of normal: Hankinson/NHANES[10], non-smokers by race and sex [uses race, sex, age and height see table 4 & 5 in reference]. Use Caucasian for all non- African American, non-Mexican American (Hispanic, non-African American)

Precision and units: volumes xX.XX Liters BTPS, flows X.XX L/s BTPS, ratios XX.X %,

Protocol inclusion criteria:

Ability to perform spirometry

Table 7: Study enrollment criteria and strata (Protocol table 1 &2)

	Non-Smokers	Smokers	Mild/Moderate COPD	Severe COPD

Smoking Status	< 1 pack-year	> 20 pack-years	> 20 pack-years	> 20 pack-years
Lung Function	FEV_1 /FVC > LLN FEV_1 > LLN FVC > LLN	FEV_1 /FVC > LLN FEV_1 > LLN FVC > LLN	FEV_1 /FVC < LLN and $FEV_1 \geq 50\%$ ref post ipratropium/ albuterol	FEV_1 /FVC < LLN and $FEV_1 < 50\%$ ref post ipratropium/ albuterol
Sample Size	N = 200 (6.25%)	N = 600 (18.75%)	N = 1800 (56.25%)	N = 600 (18.72%)

Clinically significant change: FEV_1 100 ml reported as clinically significant. $FEV_1 \geq 12\%$ (calculated from baseline not percent reference) and 200 ml for bronchodilation by ATS/ERS criteria.

AE grade: NA

2.12.10 Data validation

Electronic data transfer

Electronic validation methods

- Physiologically plausible human range of values in normal and disease: 15-130%
- Protocol inclusion criteria: strata above
- Change of >10% absolute/year

2.12.11 Statistical plan of analysis

Primary analysis: Change in post bronchodilator FEV_1 as percent reference (Hankinson 1999[10]) with baseline value (% reference) as a covariate.

Secondary analysis: FEV_1 /FVC

Exploratory analysis:

FEV_1 , FVC, PEF, FET, $FEF_{25-75\%}$, FEV_1 /FVC, isovolume $FEF_{25-75\%\ ,\ baseline}$, $FEF_{25-75\%\ ,\ pre\ BD}$, as 1) change in post bronchodilator percent reference with baseline percent reference as a covariate, 2) change in post bronchodilator Z score with baseline Z score as a covariate, 3) change in pre bronchodilator percent reference with baseline percent reference as a covariate, 4) change in pre bronchodilator Z score with baseline Z score as a covariate, 5) change in bronchodilator response as percent reference FEV_1 with baseline as a covariate

FEV_1 /FVC comparison to FEV_1 /SVC_{Exp} , and FEV_1 /(max SVC_{Exp} , FVC,)

Alternative reference equation Stanojevic [22], may have superior LLN and Z score characteristics

2.12.12 Relation to specific aim/ study objective

Serial measurements of FEV_1 over three years is the FDA preferred primary endpoint for assessment of alteration in disease progression [6]. Therefore, FEV_1 decline is the nominal comparator for novel outcomes

2.13 Bronchodilation

2.13.1 Definition/Description

Assessment of acute bronchodilator response timed to target the peak drug effect. In COPD subjects, 4 puffs of ipratropium CFC reached 80% of the maximal response of 8 puffs before 0.6 hours and was sustained through 6.2 hours on average [23]. In asthma subjects albuterol HFA given as 1, 1, 2 puffs at 30 minute intervals achieved 83% of the 16 puff response at 30 minutes [24].

2.13.2 Equipment and supplies

- Ipratropium bromide HFA (Atrovent HFA 12.9g (200 puff) canister NDC 0597-0087-17)
- Albuterol sulfate HFA (Ventolin HFA 18g (200 puff) canister NDC 0173-0682-20, or 8g (60 puff) NDC 0173-0682-21 or 0173-0682-24)
- Ventilator tubing (Figure 7), 15 cm (6 inches) segment used as spacer (100 feet/roll) cut with scissors

Figure 7: Ventilator tubing for use as a spacer

2.13.3 Method of assessment

Repeated SVC_{Exp} and FVC following administration of:

Short-acting ß2-agonist and anticholinergic (SAMBA): ipratropium bromide HFA (Atrovent HFA), four puffs of 21μg with spacer and albuterol sulfate HFA (Ventolin HFA) four puffs of 120μg 30-180 minutes prior to "post" spirometry or SVC.

A worksheet in the spirometry software will be used to document the time of the first puff of ipratropium. Please use the computer clock time.

- **Doses taken previously at home or other bronchodilators do not result in modification of this dose**

Good inhaler technique

- Shake
- Slow deep breathe in over 4-5 seconds
- Technician will actuate MDI at beginning of breath
- Ten second breath hold
- Relax, catch breath and repeat for next puff
- About 30 seconds total per puff

Remember many of the control participants will never have used an inhaler.

Redosing: In the event that "post-bronchodilator" studies (including 6-minute walk and HRCT) are delayed the participant may receive additional doses of bronchodilators as follows:

Table 8: Bronchodilator redosing

Time after initial dose (min)	Re/dose	Permitted testing window (minutes after re/dosing)
0 (initial doses)	4 puffs ipratropium and 4 puffs albuterol	30-180 minutes
>=165-<300	4 puff albuterol	15-180
>=300	4 puffs ipratropium and 4 puffs albuterol	30-180

Table 9: Bronchodilator redosing examples:

Initial dose	New dose time	Give	New test can start
8:00	-	-	8:30-11:00
8:00	10:45	4 puffs albuterol	11:00-13:00
8:00	13:01	4 puffs ipratropium and albuterol	13:31-16:15

For the induced sputum, 2 puffs of albuterol will be administered to all COPD participants (FEV_1 /FVC ratio< LLN) who have not had a dose in the prior 165 minutes.

2.13.4 Maintenance

Ipratropium MDI (Atrovent® HFA) short acting anticholinergic (muscurinic) four puffs of 21μg with spacer

Priming: initially and if not used for >3 days

Storage: stored in an upright position in a secure area at room temperature

Washing: weekly (or if grossly contaminated) washing of mouthpiece (never canister) with warm water. Allowed to dry completely prior to use. Cold sterilization (Cidex) should be used, if grossly contaminated.

End of canister: Puff count for canister will use a manual tally on a file card (Figure 8).

Figure 8: Atrovent HFA MDI actuation log

SPIROMICS Atrovent MDI Actuation Log

Date of first use:_____ Prime ○○ Date of canister expiration_____

Prime the ATROVENT HFA Inhalation Aerosol before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Avoid spraying ATROVENT HFA Inhalation Aerosol into eyes.

Actuations:

○○○○○○○○○○○○ ○○○○ ○○○○ ○○○○ ○○○○

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○○○○ (replace inhaler)

Expiration: expiration date on canister

Dispose of after use in accordance with local policy

Albuterol HFA (Ventolin® HFA) short acting ß2 agonist, four puffs of 108μg (90μg albuterol base) with spacer

Priming: initially and if not used for >2 weeks

Storage: stored in an upright position in a secure area at room temperature

Washing: weekly (or if grossly contaminated) washing of mouthpiece (never canister) with warm water. Allowed to dry completely prior to use. Cold sterilization (Cidex) should be used, if grossly contaminated.

End of canister: Puff count for canister will use the built in mechanical counter (stop at 0)

Expiration: expiration date on canister or 12-month limit after removal from the foil package

Dispose of after use in accordance with local policy

Spacer is a 15 cm segment of ventilator tubing, single participant use. Dispose of as medical waste after use.

2.13.5 Quality assurance

Percent completed according to protocol

Priming, expiration and end of canister
Adverse events

2.13.6 Derivation or calculation of variable

Time before post bronchodilator maneuvers

Time to first post bronchodilator SVC maneuver after administration of first puff of ipratropium. (Criteria 30-120 minutes)

Time to first post bronchodilator FVC maneuver.

For FEV_1 and FVC

Absolute change: (post value-pre value)

Percent initial value: (post value-pre value)/pre value x100

Percent of predicted (reference) value: (post value-pre value)/(FEV_1 or FVC reference value)

For $FEF_{25-75\%}$

Isovolume referenced to the pre bronchodilator FVC 25-75%

Absolute change: (post value-pre value)

Percent initial value: (post value-pre value)/pre value x100

Percent of predicted (reference) value: (post value-pre value)/($FEF_{25-75\%}$ reference value)

2.13.7 Normal range, protocol limits, significant change and adverse event grading

Precision and units:

Absolute change: xxX ml

Percent initial value: xX.x %

Percent of predicted (reference) value: xX.X%

Clinically significant change:

FEV_1 or FVC ≥12% (of baseline not percent reference) and 200 ml

<8% (or <150 ml) may be within the measurement error

2.13.8 Data validation

Spirometry software prompt for time after bronchodilator

Electronic validation methods for time between first dose of bronchodilator and SVC

2.13.9 Statistical plan of analysis

Stratification by post bronchodilator FEV_1

Bronchodilator response

2.13.10 Relation to specific aim/ study objective

Known predictor of decline in lung function

2.14 Six-minute walk

2.14.1 Definition/Description

Simple test of functional exercise capacity that relates to activities of daily living. Considered "maximal" in impaired individuals. Correlates with VO_2 max

2.14.2 Equipment and supplies

- Oximeter (Onyx II 9560, Nonin, Figure 9)

Figure 9: Onyx II oximeter

- AAA batteries (2) with replacements
- Traffic cones (2)
- 30 m tape measure
- Course markers
- Stopwatch
- Clipboard with instruction script and worksheet for counting laps
- Borg dyspnea and exertion scales
- A chair that can be easily moved along the walking course, if needed.
- Emergency equipment (according to local policy)
    - Telephone
    - Sphygmomanometer
    - Oxygen source

2.14.3 Method of assessment

Six-minute walk tests are performed in a 30 m segment of straight hallway marked at 3 m intervals. In addition to the usual ATS protocol, the patient is monitored when available with Bluetooth wireless pulse oximetry and the time and distance recorded at which they desaturate to <88%. The test is also terminated if the saturation falls below 80%. Dyspnea (Borg 0-10) and perceived exertion (Borg 6-20) scales are completed at the end of test.

Comfortable clothing and appropriate shoes for walking should be worn. Participants should use their usual walking aids during the test (cane, walker, etc.). A light meal is acceptable before early morning or early afternoon tests. A "warm-up" period before the test should not be performed. For this study the test will be performed off of supplemental oxygen.

Bronchodilator

For this study the walk will be performed after bronchodilation (as above)

Site preparation

- Layout a 30m course in an unimpeded straight hallway. Markers for the endpoints and 3 m intervals should be applied to the baseboard on one side. Try to adjust the location within the hallway to avoid the need to place markers in doorways etc. Use the provided 30 m metric tape measure.
- If a preexisting 100 foot (30.48m) course with 10 foot markers has been previously laid out, it may be used for this study
- Place the turn signs at the proximal and distal turn points of the course when in use.
- Have ready the following materials
    - Stopwatch/timer
    - Worksheet for counting laps
    - Oximeter
    - Breathlessness and exertion scales

- A chair that can be easily moved along the walking course, if needed.
- Emergency equipment (according to local policy)
  - Telephone
  - Sphygmomanometer
  - Oxygen source

Pre-assessment

- It may be simplest to use a paper copy of the data entry form to record the data while the test is in progress.
- Record any bronchodilator medications taken since the post bronchodilator spirometry
- Review blood pressure. If BP was performed more than four hours prior, repeat
  If SBP >200 mmHg or <60 or diastolic blood pressure >110 mmHg discontinue test
- Record use of supplemental oxygen for use during the test. In general, it is preferable to use room air. If the participant is on long-term oxygen therapy with a resting saturation off oxygen of <88%, supplemental oxygen **may** be used during the test. Future yearly tests should be at the same amount of supplemental oxygen if at all possible.
  The University of Utah will use 1.5 L/min by continuous nasal canula for all subjects to simulate sea level inspired pO_2 unless the subject is receiving a higher flow rate for long-term oxygen therapy **and** desaturates to less than 88% on 1.5 L/min at rest (see above). All other sites are below 300m altitude. The University of Utah is at an altitude of 1419m (the football stadium), which has a fractional atmospheric pressure of 84.3% (ICAO standard atmosphere, Geigy tables). To achieve the same inspired pO_2, an additional 3.3% oxygen would have to be added. This can be delivered at rest by 1.43 liters of supplemental oxygen (2.3%/L). It is practical to deliver 1.5 L/min throughout the walk (Table 10). It is recognized the actual inspired FiO_2 is dependant on the minute ventilation and will decrease with increased exertion.

Table 10: Standardization of inhaled oxygen for simulation of sea level while at altitude

Altitude (m)	Supplemental oxygen (L/min.)
474	0.5
969	1.0
1490	1.5
2041	2.0
2624	2.5
3243	3.0

- The flow is recorded in liters per minute. Record the type of delivery system. The usual type is a continuous flow nasal canula. Most portable concentrators use a pulse (conserver delivery), but there are also a few "mustache" type conserver devices. Oxygen is not titrated during the test. This is not intended to optimize their use of oxygen.
- Record oxygen saturation and pulse on the oxygen flow used for the test, at rest.
  If resting heart rate is >120 or <50 discontinue test.
  If the saturation is <88% the participant is not eligible to continue the test. See note on supplemental oxygen above.
- Apply and begin continuous pulse oximetry recording if available.

Instructions for challenge

- Explain use of the modified Borg scale (0-10) for assessing breathlessness.
- Explain the use of the Borg rating of perceived exertion scale (6-20) for rating of perceived exertion.
- Read the following participant instructions: "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."
- Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

- "Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready.
- Standardized encouragement read in a steady voice
    - After the first minute, tell the patient the following (in even tones):
      "You are doing well. You have 5 minutes to go."
    - When the timer shows 4 minutes remaining, tell the patient the following:
      "Keep up the good work. You have 4 minutes to go."
    - When the timer shows 3 minutes remaining, tell the patient the following:
      "You are doing well. You are halfway done."
    - When the timer shows 2 minutes remaining, tell the patient the following:
      "Keep up the good work. You have only 2 minutes left."
    - When the timer shows only 1 minute remaining, tell the patient:
      "You are doing well. You have only 1 minute to go."
    - With 15 seconds to go:
      "In a moment I'm going to tell you to stop. When I do, just stop right where you are and I will come to you."
    - At six minutes say:
      "Stop"
- If the participant stops at any time prior, you can say:
  "You can lean against the wall if you would like; then continue walking whenever you feel able."

Do not use other words of encouragement (or body language) to influence the patient's walking speed.

Accompany the patient along the walking course but keep just behind them. Do not lead them.

- If available record the distance at which the saturation drops to <88%

Post-walk-assessment

- Record oxygen saturation and pulse
- Record the Borg CR-10 scale (0-10) for assessing breathlessness.

Figure 10: Borg CR-10 breathlessness scale

"Please use this scale to indicate how **breathless** you felt during the test you have just completed. It is your own feelings of breathlessness that is important, not what other people think. Look at the scale and the expressions and indicate one of the numbers."

0	Not at all breathless
0.5	
1	Very slightly breathless
2	Slightly breathless
3	Moderately breathless
4	
5	Severely breathless
6	
7	Very severely breathless
8	
9	
10	Extremely breathless

- Record the Borg rating of perceived exertion scale (6-20) for rating of perceived exertion. A different scale forces the participant to specifically think about the symptom asked and avoids the sometimes thoughtless answer of the same level on the second question. The Borg 6-10 exertion scale is roughly proportional to the pulse. The alternative of a 100 mm visual analog scale is more cumbersome.

Figure 11: Borg perceived exertion scale

"Please use this scale to indicate your perception of **exertion** i.e. how heavy or strenuous was the test you have just completed. It is your own feelings of effort and exertion that is important, not what other people think. Look at the scale and the expressions and indicate one of the numbers."

6	Nothing at all
7	
	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

- Record number of laps and partial lap distance walked to the nearest m. If a 100 foot course was used, record the distance to the nearest foot and convert as follows:

  Feet*0.3048=meters

  Record the distance rounded to the nearest meter.

- Record Reason for stopping

  6 minutes completed
  Desaturation to <80% if continuously monitored
  Foot, knee, hip or other orthopedic pain
  Muscle fatigue or pain
  Breathlessness
  Adverse events
    Angina
    Lightheadedness
    Intolerable dyspnea requiring bronchodilators
    Leg cramps
    Staggering
    Diaphoresis
    Pale or ashen appearance
    Mental confusion or headache
    Other

- Remove the pulse oximeter 2 minutes after completion or when fully recovered.

2.14.4 Acceptability (applied to each maneuver) and Repeatability (between maneuvers for each participant):

N/A

2.14.5 Maintenance

Wipe clean the pulse oximeter window with an alcohol swab if the sensor does not pick up well

2.14.6 Quality assurance

Clinical stability at start of test (blood pressure)
Adequate effort
Absence of medical complications
Absence of technical problems
Complete data set

2.14.7 Derivation or calculation of variable

Total distance walked in 6 minutes on room air. Those with desaturation <85% prior to the test will receive a distance of 0m

Distance to desaturation on room air
Time to desaturation on room air

2.14.8 Normal range, protocol limits, significant change and adverse event grading

Lower/upper limit of normal[25]:

Men: mean= 7.57 Ht (cm)-5.02 Age-1.76 Wt (kg)-309 m
LLN=mean -153m

Women: mean= 2.11 Ht (cm)-5.78 Age-2.29 Wt (kg)+667 m
LLN =mean-139m

Precision and units: xxX meters
Clinically significant change:

6MWD increase of 54 meters may be less (35m) in severe COPD.

For Borg breathlessness MCID 1-2 units

AE grade

2.14.9 Data validation

Electronic data transfer of oximetry and answers in planning

2.14.10 Statistical plan of analysis

6MW distance and change over time will serve as a functional outcome

2.14.11 Relation to specific aim/ study objective

2.15 Safety assessment spirometry:

2.15.1 Definition/Description

FEV_1 is used to evaluate the safety of procedures (e.g. bronchoscopy, induced sputum) likely to induce bronchospasm or be unsafe if performed in participants with low values. The PiKo meets the ATS standards for FEV_1 (±3.5% or 0.1L which ever is greater). Given that FEV_1 is a maximal effort, underestimating the FEV_1 due to a poor effort would err on the side of safety. It is very difficult to get an artifactually high FEV_1 unless the mouthpiece is occluded (like blowing a trumpet). Post hoc review of the value or from another spirometer, the tracing would not improve safety. The values must be acted on as they are obtained-either to abort the procedure or administer bronchodilators.

2.15.2 Equipment and supplies

- PiKo peak flow / FEV_1 meter (nSpire, Figure 12)

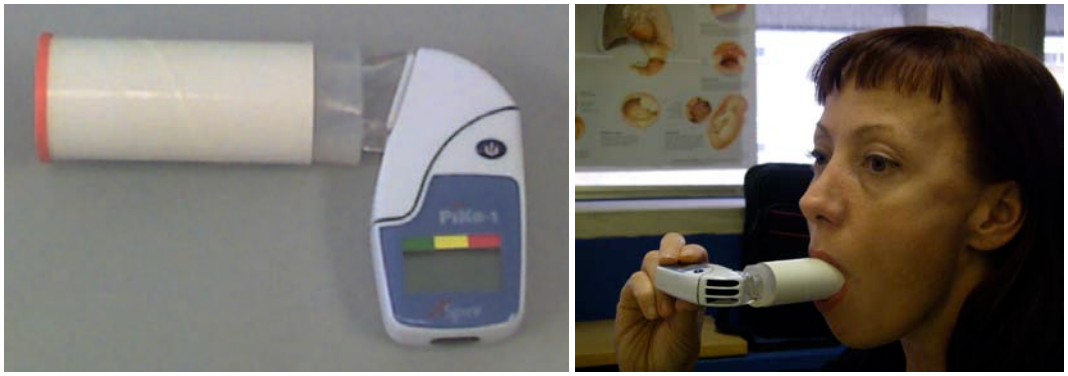
Figure 12: PiKo-1

- Adaptor for mouthpieces
- Disposable one-way mouthpieces (200 per case) single participant use
- LR44 batteries (2) for PiKo

2.15.3 Method of assessment

Initial setup:
Insert the batteries if not previously done (see maintenance)
Place the adaptor for the one-way mouthpieces on the clear PiKo mouthpiece (Figure 13).

Figure 13: PiKo assembled with mouthpiece and adaptor and held horizontally



Safety spirometry will be performed in a way similar to the FVC maneuvers except that the maneuver may be terminated after one second to prevent fatigue. PFT technicians will emphasize: 1) demonstration of the forced maneuver before participant's first attempt, 2) vigorously coaching to obtain a full inspiration followed by a "blast" at outset of maneuver 3) observation of participant throughout the maneuver and 4) enthusiastic feedback to encourage maximal efforts. A minimum of two acceptable (FEV_1) maneuvers will be obtained.
DO NOT DEMONSTRATE ON THE PARTICIPANT'S PIKO for the subsequent three minutes it will display your FEV_1 if it is larger than the participant's. If needed, you may demonstrate on an unattached mouthpiece.
For each maneuver:

- If the display is blank, press the operate button once and the last test result will be displayed.
- Place a new disposable one-way mouthpiece on the PiKo with adaptor.

- Have the participant hold the PiKo horizontally (Figure 13) and do not block the vent holes (opposite the mouthpiece). Do not hold like an MDI- the thumb may occlude the vent holes.
- Press the button once.
- At the second soft beep (about 1 sec.) inhale as deeply as possible, seal your mouth on the one-way mouthpiece and exhale as forcefully as possible for at least 1.5 seconds. Compete or prolonged exhalation (FVC) is not necessary and may produce fatigue when repeated multiple times.
- The **best** results within the prior three minutes will scroll between FEV_1 (to be recorded) and PEF
- The "!" will appear after the value if:
    - A cough detected
    - The blow was less than 1 second
    - The blow had a slow start
    - The result was unusually high or low for the set reference value
- Repeat until two acceptable maneuvers are obtained
- Dispose of paper one-way mouthpiece as medical waste. Do not throw away the adaptor
- The PiKo will shut off automatically when not in use

2.15.4 Acceptability and Repeatability:

The largest usable FEV_1 will be reported from two usable maneuvers.

2.15.5 Maintenance

Wipe clean if soiled. Do not submerge
Replace batteries when the low battery indicator appears (approximately 2190 blows)

- Rotate the battery cover from the dash to the arrow counterclockwise with a coin
- Remove the old batteries of if new, the white battery spacer which helps to eject the battery cover.

Insert two batteries in a stack with the "+" side up
Replace the battery cover aligning the dot and arrow and rotating clockwise to the dash

2.15.6 Quality assurance

Training initially and annually as needed for difficulties
No over read of the measures will be performed.

2.15.7 Derivation or calculation of variable

FEV_1 X.XX L BTPS
Altitude adjustment add 1.5% per 300m above 300m elevation
University of Utah (stadium 1419m): increase values 5.6% or decrease safety limits by 5.3%
University of Michigan (airport 253m): no adjustment

2.15.8 Normal range, protocol limits, significant change and adverse event grading

Safety limits will be set for each type of procedure
AE grade: NA

2.15.9 Data validation

NA

2.15.10 Statistical plan of analysis

Failures to qualify for procedures
Comparison with recent standard spirometry
Fall with procedure

2.15.11 Relation to specific aim/ study objective

Safety parameter

2.16 Contact Information

Area	Contact
Spirometry including filters, computer and data transfer	nSpire Health 800.915.4737 f 800.916.4737
eCO including exchange calibration	Brian Fedor 310.825.5988 bfedor@mednet.ucla.edu
6MW, back-up for spirometry	Jan Orin 310.825.3199 jorin@mednet.ucla.edu
Bronchodilators, PiKo, supplies other than spirometry filters, protocol questions	Laura Menck 310.825.3806 lmenck@mednet.ucla.edu
Emergency	Eric Kleerup, M.D. Pager 310.825.6301 ekleerup@mednet.ucla.edu

UCLA return shipping address

Pulmonary & Critical Care Medicine, UCLA
10833 Le Conte Ave, CHS 37-131
Los Angeles, CA 90095-1690

2.17 Appendices

Package insert Atrovent HFA
Package insert Ventolin HFA
Micro+Smokerlyzer User's Manual
KoKo User's Manual
PiKo User's Manual

2.18 References

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ATTENTION PHARMACIST: Detach "Patient's Instructions for Use" from package insert and dispense with the product.

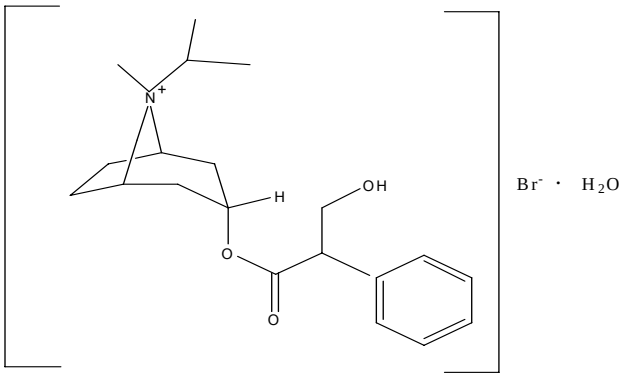
Atrovent® HFA
(ipratropium bromide HFA)
Inhalation Aerosol

For Oral Inhalation Only

Rx only

Prescribing Information

DESCRIPTION
The active ingredient in ATROVENT HFA Inhalation Aerosol is ipratropium bromide (as the monohydrate). It is an anticholinergic bronchodilator chemically described as 8-azoniabicyclo[3.2.1]octane, 3-(3-hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-,bromide monohydrate, (3-endo, 8-syn)-: a synthetic quaternary ammonium compound, chemically related to atropine. The structural formula for ipratropium bromide is:



$C_{20}H_{30}BrNO_3 \bullet H_2O$ ipratropium bromide Mol. Wt. 430.4

Ipratropium bromide is a white to off-white crystalline substance, freely soluble in water and methanol, sparingly soluble in ethanol, and insoluble in lipophilic solvents such as ether, chloroform, and fluorocarbons.

ATROVENT HFA Inhalation Aerosol is a pressurized metered-dose aerosol unit for oral inhalation that contains a solution of ipratropium bromide. The 200 inhalation unit has a net weight of 12.9 grams. After priming, each actuation of the inhaler delivers 21 mcg of ipratropium bromide from the valve in 56 mg of solution and delivers 17 mcg of ipratropium bromide from the mouthpiece. The actual amount of drug delivered to the lung may depend on patient factors, such as the coordination between the actuation of the device and inspiration through the delivery system. The excipients are HFA-134a (1,1,1,2-tetrafluoroethane) as propellant, purified water,

dehydrated alcohol, and anhydrous citric acid. This product does not contain chlorofluorocarbons (CFCs) as propellants.

Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol should be primed before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face.

CLINICAL PHARMACOLOGY

Mechanism of Action

Ipratropium bromide is an anticholinergic (parasympatholytic) agent which, based on animal studies, appears to inhibit vagally-mediated reflexes by antagonizing the action of acetylcholine, the transmitter agent released at the neuromuscular junctions in the lung. Anticholinergics prevent the increases in intracellular concentration of cyclic guanosine monophosphate (cyclic GMP) which are caused by interaction of acetylcholine with the muscarinic receptors on bronchial smooth muscle.

Pharmacodynamic Properties

Controlled clinical studies have demonstrated that Atrovent® (ipratropium bromide) Inhalation Aerosol CFC does not alter either mucociliary clearance or the volume or viscosity of respiratory secretions.

Pharmacokinetics

Most of an administered dose is swallowed as shown by fecal excretion studies. Ipratropium bromide is a quaternary amine. It is not readily absorbed into the systemic circulation either from the surface of the lung or from the gastrointestinal tract as confirmed by blood level and renal excretion studies.

Autoradiographic studies in rats have shown that ipratropium bromide does not penetrate the blood-brain barrier. The half-life of elimination is about 2 hours after inhalation or intravenous administration. Ipratropium bromide is minimally bound (0 to 9% *in vitro*) to plasma albumin and α_1-acid glycoprotein. It is partially metabolized to inactive ester hydrolysis products. Following intravenous administration, approximately one-half of the dose is excreted unchanged in the urine.

A pharmacokinetic study with 29 chronic obstructive pulmonary disease (COPD) patients (48-79 years of age) demonstrated that mean peak plasma ipratropium concentrations of 59±20 pg/mL were obtained following a single administration of 4 inhalations of ATROVENT HFA Inhalation Aerosol (84 mcg). Plasma ipratropium concentrations rapidly declined to 24±15 pg/mL by six hours. When these patients were administered 4 inhalations QID (16 inhalations/day=336 mcg) for one week, the mean peak plasma ipratropium concentration increased to 82±39 pg/mL with a trough (6 hour) concentration of 28±12 pg/mL at steady state.

Special Populations

Geriatric Patients

In the pharmacokinetic study with 29 COPD patients, a subset of 14 patients were > 65 years of age. Mean peak plasma ipratropium concentrations of 56±24 pg/mL were obtained following a

single administration of 4 inhalations (21 mcg/puff) of Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol (84 mcg). When these 14 patients were administered 4 inhalations QID (16 inhalations/day) for one week, the mean peak plasma ipratropium concentration only increased to 84±50 pg/mL indicating that the pharmacokinetic behavior of ipratropium bromide in the geriatric population is consistent with younger patients.

Renally Impaired Patients
The pharmacokinetics of ATROVENT HFA Inhalation Aerosol have not been studied in patients with renal insufficiency.

Hepatically Impaired Patients
The pharmacokinetics of ATROVENT HFA Inhalation Aerosol have not been studied in patients with hepatic insufficiency.

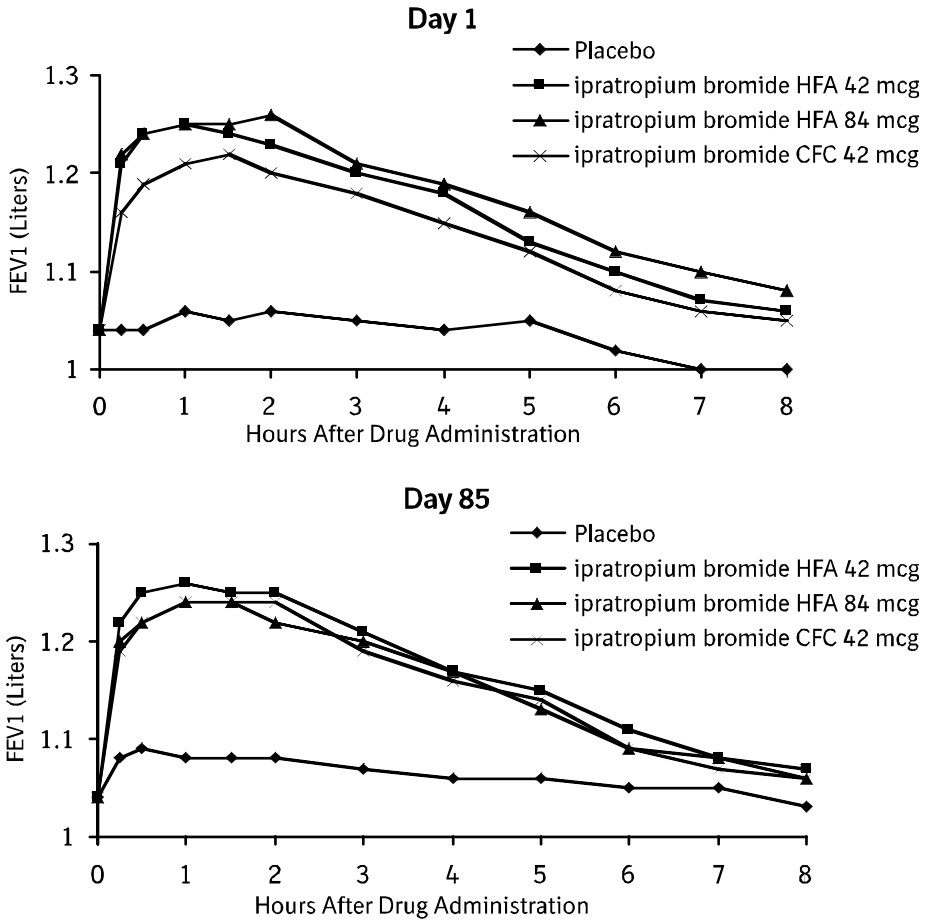
CLINICAL STUDIES
Conclusions regarding the efficacy of ATROVENT HFA Inhalation Aerosol were derived from two randomized, double-blind, controlled clinical studies. These studies enrolled males and females ages 40 years and older, with a history of COPD, a smoking history of > 10 pack- years, an $FEV_1 < 65\%$ and an $FEV_1/FVC < 70\%$.

One of the studies was a 12-week randomized, double-blind active and placebo controlled study in which 505 of the 507 randomized COPD patients were evaluated for the safety and efficacy of 42 mcg (n=124) and 84 mcg (n=126) ATROVENT HFA Inhalation Aerosol in comparison to 42 mcg (n=127) Atrovent® (ipratropium bromide) Inhalation Aerosol CFC and their respective placebos (HFA n=62, CFC n=66). Data for both placebo HFA and placebo CFC were combined in the evaluation.

Serial FEV_1 (shown in Figure 1, below, as means adjusted for center and baseline effects on test day 1 and test day 85 (primary endpoint)) demonstrated that 1 dose (2 inhalations/21 mcg each) of ATROVENT HFA Inhalation Aerosol produced significantly greater improvement in pulmonary function than placebo. During the six hours immediately post-dose on day 1, the average hourly improvement in adjusted mean FEV_1 was 0.148 liters for ATROVENT HFA Inhalation Aerosol (42 mcg) and 0.013 liters for placebo. The mean peak improvement in FEV_1, relative to baseline, was 0.295 liters, compared to 0.138 liters for placebo. During the six hours immediately post-dose on day 85, the average hourly improvement in adjusted mean FEV_1 was 0.141 liters for ATROVENT HFA Inhalation Aerosol (42 mcg) and 0.014 liters for placebo. The mean peak improvement in FEV_1, relative to baseline, was 0.295 liters, compared to 0.140 liters for placebo.

ATROVENT HFA Inhalation Aerosol (42 mcg) was shown to be clinically comparable to ATROVENT Inhalation Aerosol CFC (42 mcg).

Figure 1 Day 1 and Day 85 (Primary Endpoint) Results



In this study, both Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol and Atrovent® (ipratropium bromide) Inhalation Aerosol CFC formulations were equally effective in patients over 65 years of age and under 65 years of age.

The median time to improvement in pulmonary function (FEV_1 increase of 15% or more) was within approximately 15 minutes, reached a peak in 1-2 hours, and persisted for 2 to 4 hours in the majority of the patients. Improvements in Forced Vital Capacity (FVC) were also demonstrated.

The other study was a 12-week, randomized, double-blind, active-controlled clinical study in 174 adults with COPD, in which ATROVENT HFA Inhalation Aerosol 42 mcg (n=118) was compared to ATROVENT Inhalation Aerosol CFC 42 mcg (n=56). Safety and efficacy of HFA and CFC formulations were shown to be comparable.

The bronchodilatory efficacy and comparability of Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol vs. Atrovent® (ipratropium bromide) Inhalation Aerosol CFC were also studied in a one-year open-label safety and efficacy study in 456 COPD patients. The safety and efficacy of HFA and CFC formulations were shown to be comparable.

INDICATIONS AND USAGE

ATROVENT HFA Inhalation Aerosol is indicated as a bronchodilator for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease, including chronic bronchitis and emphysema.

CONTRAINDICATIONS

ATROVENT HFA Inhalation Aerosol is contraindicated in patients with a history of hypersensitivity to ipratropium bromide or other ATROVENT HFA Inhalation Aerosol components. ATROVENT HFA Inhalation Aerosol is also contraindicated in patients who are hypersensitive to atropine or its derivatives.

WARNINGS

ATROVENT HFA Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Immediate hypersensitivity reactions may occur after administration of ipratropium bromide, as demonstrated by rare cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema.

Inhaled medicines, including ATROVENT HFA Inhalation Aerosol, may cause paradoxical bronchospasm. If this occurs, treatment with ATROVENT HFA Inhalation Aerosol should be stopped and other treatments considered.

PRECAUTIONS

General

ATROVENT HFA Inhalation Aerosol should be used with caution in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction.

Information for Patients

Appropriate and safe use of ATROVENT HFA Inhalation Aerosol includes providing the patient with the information listed below and an understanding of the way it should be administered (see **Patient's Instructions for Use**).

Patients should be advised that ATROVENT HFA Inhalation Aerosol is a bronchodilator for the maintenance treatment of bronchospasm associated with COPD and is not indicated for the initial treatment of acute episodes of bronchospasm where rescue therapy is required for rapid response.

Patients should be cautioned to avoid spraying the aerosol into their eyes and be advised that this may result in precipitation or worsening of narrow-angle glaucoma, mydriasis, increased

intraocular pressure, acute eye pain or discomfort, temporary blurring of vision, visual halos or colored images in association with red eyes from conjunctival and corneal congestion. Patients should also be advised that should any combination of these symptoms develop, they should consult their physician immediately.

The action of Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol should last 2-4 hours. Patients should be advised not to increase the dose or frequency of ATROVENT HFA Inhalation Aerosol without patients consulting their physician. Patients should also be advised to seek immediate medical attention if treatment with ATROVENT HFA Inhalation Aerosol becomes less effective for symptomatic relief, their symptoms become worse, and/or patients need to use the product more frequently than usual.

Patients should be advised on the use of ATROVENT HFA Inhalation Aerosol in relation to other inhaled drugs.

Patients should be reminded that ATROVENT HFA Inhalation Aerosol should be used consistently as prescribed throughout the course of therapy.

Patients should be advised that although the taste and inhalation sensation of ATROVENT HFA Inhalation Aerosol may be slightly different from that of the CFC (chlorofluorocarbon) formulation of ATROVENT Inhalation Aerosol, they are comparable in terms of safety and efficacy.

Drug Interactions
ATROVENT HFA Inhalation Aerosol has been used concomitantly with other drugs, including sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, that may be used in the treatment of chronic obstructive pulmonary disease. With the exception of albuterol, there are no formal studies fully evaluating the interaction effects of ATROVENT and these drugs with respect to effectiveness.

Anticholinergic agents: Although ipratropium bromide is minimally absorbed into the systemic circulation, there is some potential for an additive interaction with concomitantly used anticholinergic medications. Caution is therefore advised in the co-administration of ATROVENT HFA Inhalation Aerosol with other anticholinergic-containing drugs.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Two-year oral carcinogenicity studies in rats and mice have revealed no carcinogenic activity at doses up to 6 mg/kg (approximately 240 and 120 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). Results of various mutagenicity studies (Ames test, mouse dominant lethal test, mouse micronucleus test and chromosome aberration of bone marrow in Chinese hamsters) were negative.

Fertility of male or female rats at oral doses up to 50 mg/kg (approximately 2000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) was unaffected by ipratropium bromide administration. At an oral dose of 500 mg/kg (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis), ipratropium bromide produced a decrease in the conception rate.

Pregnancy

Teratogenic Effects: *Pregnancy Category B.*

Oral reproduction studies were performed at doses of 10 mg/kg/day in mice, 1,000 mg/kg in rats and 125 mg/kg/day in rabbits. These doses correspond in each species, respectively, to approximately 200, 40000, and 10000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis. Inhalation reproduction studies were conducted in rats and rabbits at doses of 1.5 and 1.8 mg/kg (approximately 60 and 140 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis). These studies demonstrated no evidence of teratogenic effects as a result of ipratropium bromide. At oral doses 90 mg/kg and above in rats (approximately 3600 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis) embryotoxicity was observed as increased resorption. This effect is not considered relevant to human use due to the large doses at which it was observed and the difference in route of administration. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol should be used during pregnancy only if clearly needed.

Nursing Mothers

It is not known whether the active component, ipratropium bromide, is excreted in human milk. Although lipid-insoluble quaternary cations pass into breast milk, it is unlikely that ipratropium bromide would reach the infant to an important extent, especially when taken by aerosol. However, because many drugs are excreted in human milk, caution should be exercised when ATROVENT HFA Inhalation Aerosol is administered to a nursing mother.

Pediatric Use

Safety and effectiveness in the pediatric population have not been established.

Geriatric Use

In the pivotal 12-week study, both ATROVENT HFA Inhalation Aerosol and Atrovent® (ipratropium bromide) Inhalation Aerosol CFC formulations were equally effective in patients over 65 years of age and under 65 years of age.

Of the total number of subjects in clinical studies of ATROVENT HFA Inhalation Aerosol, 57% were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between these subjects and younger subjects.

ADVERSE REACTIONS

The adverse reaction information concerning ATROVENT HFA Inhalation Aerosol is derived from two 12-week, double-blind, parallel group studies and one open-label, parallel group study that compared ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo (in one study only) in 1,010 COPD patients. The following table lists the incidence of adverse events that occurred at a rate of greater than or equal to 3% in any ipratropium bromide group. Overall, the incidence and nature of the adverse events reported for ATROVENT HFA Inhalation Aerosol, ATROVENT Inhalation Aerosol CFC, and placebo were comparable.

TABLE 1 Adverse Experiences Reported in ≥ 3% of Patients in any Ipratropium Bromide Group

	Placebo-controlled 12 week Study 244.1405 and Active-controlled 12 week Study 244.1408			Active-controlled 1-year Study 244.2453	
	Atrovent HFA (N=243) %	**Atrovent CFC (N=183) %**	**Placebo (N=128) %**	**Atrovent HFA (N=305) %**	**Atrovent CFC (N=151) %**
Total With Any Adverse Event	**63**	**68**	**72**	**91**	**87**
BODY AS A WHOLE - GENERAL DISORDERS					
Back pain	2	3	2	7	3
Headache	6	9	8	7	5
Influenza-like symptoms	4	2	2	8	5
CENTRAL & PERIPHERAL NERVOUS SYSTEM DISORDERS					
Dizziness	3	3	2	3	1
GASTROINTESTINAL SYSTEM DISORDERS					
Dyspepsia	1	3	1	5	3
Mouth dry	4	2	2	2	3
Nausea	4	1	2	4	4
RESPIRATORY SYSTEM DISORDERS					
Bronchitis	10	11	6	23	19
COPD exacerbation	8	14	13	23	23
Coughing	3	4	6	5	5
Dyspnea	8	8	4	7	4
Rhinitis	4	2	4	6	2
Sinusitis	1	4	3	11	14
Upper respiratory tract infection	9	10	16	34	34
URINARY SYSTEM DISORDERS					
Urinary tract infection	2	3	1	10	8

In the one open label controlled study in 456 COPD patients, the overall incidence of adverse events was also similar between Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol and Atrovent® (ipratropium bromide) Inhalation Aerosol CFC formulations.

Overall, in the above mentioned studies, 9.3% of the patients taking 42 mcg ATROVENT HFA Inhalation Aerosol and 8.7% of the patients taking 42 mcg ATROVENT Inhalation Aerosol CFC reported at least one adverse event that was considered by the investigator to be related to the study drug. The most common drug-related adverse events were dry mouth (1.6% of ATROVENT HFA Inhalation Aerosol and 0.9% of ATROVENT Inhalation Aerosol CFC patients), and taste perversion (bitter taste) (0.9% of ATROVENT HFA Inhalation Aerosol and 0.3% of ATROVENT Inhalation Aerosol CFC patients).

As an anticholinergic drug, cases of precipitation or worsening of narrow-angle glaucoma, mydriasis, acute eye pain, hypotension, palpitations, urinary retention, tachycardia, constipation, bronchospasm, including paradoxical bronchospasm have been reported.

Allergic-type reactions such as skin rash, pruritus, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported (see **CONTRAINDICATIONS**).

Post-Marketing Experience
In a 5-year placebo-controlled trial, hospitalizations for supraventricular tachycardia and/or atrial fibrillation occurred with an incidence rate of 0.5% in COPD patients receiving ATROVENT Inhalation Aerosol CFC.

Allergic-type reactions such as skin rash, angioedema of tongue, lips and face, urticaria (including giant urticaria), laryngospasm and anaphylactic reactions have been reported, with positive rechallenge in some cases.

Additionally, urinary retention, mydriasis, gastrointestinal distress (diarrhea, nausea, vomiting), and bronchospasm, including paradoxical bronchospasm, have been reported during the post-marketing period with use of ATROVENT Inhalation Aerosol CFC.

OVERDOSAGE
Acute overdose by inhalation is unlikely since ipratropium bromide is not well absorbed systemically after inhalation or oral administration. Oral median lethal doses of ipratropium bromide were greater than 1001 mg/kg in mice (approximately 20,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis); 1,663 mg/kg in rats (approximately 66,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis); and 400 mg/kg in dogs (approximately 53,000 times the maximum recommended daily inhalation dose in adults on a mg/m^2 basis).

DOSAGE AND ADMINISTRATION
Patients should be instructed on the proper use of their inhaler (see **Patient's Instructions for Use**).

Patients should be advised that although Atrovent® HFA (ipratropium bromide HFA) Inhalation Aerosol may have a slightly different taste and inhalation sensation than that of an inhaler containing Atrovent® (ipratropium bromide) Inhalation Aerosol CFC, they are comparable in terms of the safety and efficacy.

ATROVENT HFA Inhalation Aerosol is a solution aerosol that does not require shaking. However, as with any other metered dose inhaler, some coordination is required between actuating the canister and inhaling the medication.

Patients should "prime" or actuate ATROVENT HFA Inhalation Aerosol before using for the first time by releasing 2 test sprays into the air away from the face. In cases where the inhaler has not been used for more than 3 days, prime the inhaler again by releasing 2 test sprays into the air away from the face. Patients should avoid spraying ATROVENT HFA Inhalation Aerosol into their eyes.

The usual starting dose of ATROVENT HFA Inhalation Aerosol is two inhalations four times a day. Patients may take additional inhalations as required; however, the total number of inhalations should not exceed 12 in 24 hours. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 17 mcg of ipratropium bromide from the mouthpiece.

HOW SUPPLIED

ATROVENT HFA Inhalation Aerosol is supplied in a 12.9 g pressurized stainless steel canister as a metered-dose inhaler with a white mouthpiece that has a clear, colorless sleeve and a green protective cap (NDC 0597-0087-17).

The ATROVENT HFA Inhalation Aerosol canister is to be used only with the accompanying ATROVENT HFA Inhalation Aerosol mouthpiece. This mouthpiece should not be used with other aerosol medications. Similarly, the canister should not be used with other mouthpieces. Each actuation of ATROVENT HFA Inhalation Aerosol delivers 21 mcg of ipratropium bromide from the valve and 17 mcg from the mouthpiece. Each 12.9 gram canister provides sufficient medication for 200 actuations. The canister should be discarded after the labeled number of actuations has been used. The amount of medication in each actuation cannot be assured after this point, even though the canister is not completely empty.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. For optimal results, the canister should be at room temperature before use.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

Patients should be reminded to read and follow the accompanying "**Patient's Instructions for Use**", which should be dispensed with the product.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the inhaler into a fire or incinerator.

Warning: Keep out of children's reach. ***Avoid spraying in eyes.***

Distributed by:
Boehringer Ingelheim Pharmaceuticals, Inc.
Ridgefield, CT 06877 USA

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Patient's Instructions for Use

Atrovent® HFA
(ipratropium bromide HFA)
Inhalation Aerosol

Read complete instructions carefully before using.

Important Points to Remember About Using ATROVENT HFA Inhalation Aerosol

Although ATROVENT HFA Inhalation Aerosol may taste and feel different when breathed in compared to your Atrovent® (ipratropium bromide) Inhalation Aerosol CFC inhaler, they contain the same medicine.

You do not have to shake the **ATROVENT HFA** Inhalation Aerosol canister before using it.

ATROVENT HFA Inhalation Aerosol should be "primed" two times before taking the first dose from a new inhaler or when the inhaler has not been used for more than three days. To prime, push the canister against the mouthpiece (see Figure 1), allowing the medicine to spray into the air. **Avoid spraying the medicine into your eyes while priming ATROVENT HFA Inhalation Aerosol.**

Ask your doctor how to use other inhaled medicines with ATROVENT HFA Inhalation Aerosol.

Use ATROVENT HFA Inhalation Aerosol exactly as prescribed by your doctor. Do not change your dose or how often you use **ATROVENT HFA** Inhalation Aerosol without talking with your doctor. Talk to your doctor if you have questions about your medical condition or your treatment.

Instructions

1. Insert the metal canister into the clear end of the mouthpiece (see Figure 1). Make sure the canister is fully and firmly inserted into the mouthpiece. The **ATROVENT HFA** Inhalation Aerosol canister is for use only with the **ATROVENT HFA** Inhalation Aerosol mouthpiece. Do not use the **ATROVENT HFA** Inhalation Aerosol canister with other mouthpieces. This mouthpiece should not be used with other inhaled medicines.

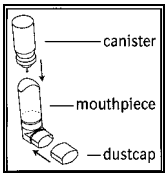

Figure 1

2. Remove the **green** protective **dust** cap. If the cap is not on the mouthpiece, make sure there is nothing in the mouthpiece before use. For best results, the canister should be at room temperature before use.

3. ***Breathe out (exhale) deeply*** through your mouth. Hold the canister upright as shown in Figure 2, between your thumb and first 2 fingers. Put the mouthpiece in your mouth and close your lips. Keep your eyes closed so that no medicine will be sprayed into your eyes. **Atrovent® HFA** (ipratropium bromide HFA) Inhalation Aerosol can cause blurry vision, narrow-angle glaucoma or worsening of this condition or eye pain if the medicine is sprayed into your eyes.

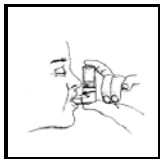

Figure 2

4. ***Breathe in (inhale) slowly*** through your mouth and at the same time firmly press once on the canister against the mouthpiece as shown in Figure 3. Keep breathing in deeply.

Figure 3

5. ***Hold your breath*** for ten seconds and then remove the mouthpiece from your mouth and breathe out slowly, as in Figure 4. **Wait at least 15 seconds and repeat steps 3 to 5 again.**

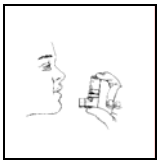

Figure 4

6. Replace the green protective dust cap after use.

7. **Keep the mouthpiece clean.** It is very important to keep the mouthpiece clean. At least once a week, wash the mouthpiece, shake it to remove excess water and let it air dry all the way (see the instructions below).

Mouthpiece Cleaning Instructions:

Step A. Remove and set aside the canister and dust cap from the mouthpiece (see Figure 1).

Step B. Wash the mouthpiece through the top and bottom with warm running water for at least 30 seconds (see Figure 5). Do not use anything other than water to wash the mouthpiece.

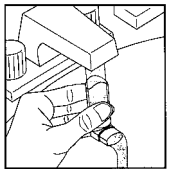

Figure 5

Step C. Dry the mouthpiece by shaking off the excess water and allow it to air-dry all the way.

Step D. When the mouthpiece is dry, replace the canister. Make sure the canister is fully and firmly inserted into the mouthpiece.

Step E. Replace the green protective dust cap.

If the mouthpiece becomes blocked, and little or no medicine comes out of the mouthpiece, wash the mouthpiece as described in Steps A to E under the **"Mouthpiece Cleaning Instructions".**

8. **Keep track of the number of sprays used. Discard the canister after 200 sprays.** Even though the canister is not empty, you cannot be sure of the amount of medicine in each spray after 200 sprays.

This product does not contain any chlorofluorocarbon (CFC) propellants.

The contents of **Atrovent® HFA** (ipratropium bromide HFA) Inhalation Aerosol are under pressure. Do not puncture the canister. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw the container into a fire or incinerator.

Keep **ATROVENT HFA** Inhalation Aerosol and all medicines out of the reach of children.

Avoid spraying into eyes.

Address medical inquiries to: http://us.boehringer-ingelheim.com, (800) 542-6257 or (800) 459-9906 TTY.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F). For best results, store the canister at room temperature before use.

Rx only

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HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use VENTOLIN HFA Inhalation Aerosol safely and effectively. See full prescribing information for VENTOLIN HFA Inhalation Aerosol.

VENTOLIN® HFA (albuterol sulfate) Inhalation Aerosol

Initial U.S. Approval: 1981

----------INDICATIONS AND USAGE----------

VENTOLIN HFA is a beta$_2$-adrenergic agonist indicated for:

- Treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease. (1.1)
- Prevention of exercise-induced bronchospasm in patients 4 years of age and older. (1.2)

---------- DOSAGE AND ADMINISTRATION ----------

FOR ORAL INHALATION ONLY.

- Treatment or prevention of bronchospasm in adults and children 4 years of age and older: 2 inhalations every 4 to 6 hours. For some patients, 1 inhalation every 4 hours may be sufficient. (2.1)
- Prevention of exercise-induced bronchospasm in adults and children 4 years of age and older: 2 inhalations 15 to 30 minutes before exercise. (2.2)
- Priming information: Prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray. (2.3)
- Cleaning information: At least once a week, wash the actuator with warm water and let it air-dry completely. (2.3)

---------- DOSAGE FORMS AND STRENGTHS ----------

Inhalation aerosol: 108 mcg albuterol sulfate (90 mcg albuterol base) from mouthpiece per actuation. Supplied in 18-g canister containing 200 actuations and 8-g canister containing 60 actuations. (3)

----------CONTRAINDICATIONS----------

Hypersensitivity to albuterol sulfate or any of the ingredients of VENTOLIN HFA. (4)

---------- WARNINGS AND PRECAUTIONS ----------

- Paradoxical bronchospasm may occur and should be treated immediately with alternative therapy. (5.1)
- Need for more doses of VENTOLIN HFA than usual may be a sign of deterioration of asthma and requires reevaluation of treatment. (5.2)
- Cardiovascular effects may occur with beta-adrenergic agonists use. Consider discontinuation of VENTOLIN HFA if these effects occur. Use with caution in patients with underlying cardiovascular disorders. (5.4)
- Immediate hypersensitivity reactions may occur. Discontinue VENTOLIN HFA if immediate hypersensitivity reactions occur. (5.6)

---------- ADVERSE REACTIONS ----------

Most common adverse reactions (incidence ≥3%) are throat irritation, viral respiratory infections, upper respiratory inflammation, cough, and musculoskeletal pain. (6)

To report SUSPECTED ADVERSE REACTIONS, contact GlaxoSmithKline at 1-888-825-5249 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- Beta-blockers: May block bronchodilatory effects of beta-agonists and produce severe bronchospasm. Patients with asthma should not normally be treated with beta-blockers. (7.1)
- Diuretics: Electrocardiographic changes and/or hypokalemia associated with diuretics may worsen with concomitant beta-agonists. Consider monitoring potassium levels. (7.2)
- Monoamine oxidase inhibitors (MAOs) or tricyclic antidepressants: May potentiate effect of albuterol on the vascular system. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants. (7.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: June 2009

VNT:6PI

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Bronchospasm

VENTOLIN HFA is indicated for the treatment or prevention of bronchospasm in patients 4 years of age and older with reversible obstructive airway disease.

1.2 Exercise-Induced Bronchospasm

VENTOLIN HFA is indicated for the prevention of exercise-induced bronchospasm in patients 4 years of age and older.

2 DOSAGE AND ADMINISTRATION

Administer VENTOLIN HFA by oral inhalation only. Shake VENTOLIN HFA well before each spray.

2.1 Bronchospasm

For treatment of acute episodes of bronchospasm or prevention of symptoms associated with bronchospasm, the usual dosage for adults and children is 2 inhalations repeated every 4 to 6 hours; in some patients, 1 inhalation every 4 hours may be sufficient. More frequent administration or a larger number of inhalations is not recommended.

2.2 Exercise-Induced Bronchospasm

The usual dosage for adults and children 4 years of age and older is 2 inhalations 15 to 30 minutes before exercise.

2.3 Administration Information

Priming: Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. Prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, release 4 sprays into the air away from the face, shaking well before each spray.

Cleaning: To ensure proper dosing and to prevent actuator orifice blockage, wash the actuator with warm water and let it air-dry completely at least once a week.

Dose Counter: VENTOLIN HFA has a dose counter attached to the canister that starts at 204 or 64 and counts down each time a spray is released *[see Dosage Forms and Strengths (3)]*. When the counter reads 020, the patient should contact the pharmacist for a refill of medication or consult the physician to determine whether a prescription refill is needed.

VENTOLIN HFA comes in a moisture-protective foil pouch, which should be removed prior to use. Discard VENTOLIN HFA when the counter reads 000 or 12 months after removal from the moisture-protective foil pouch, whichever comes first *[see Dosage Forms and Strengths (3)]*.

See 17.8 FDA-Approved Patient Labeling for instructions on how to prime and clean the inhaler to ensure proper dosing and to prevent actuator orifice blockage.

3 DOSAGE FORMS AND STRENGTHS

VENTOLIN HFA is an inhalation aerosol. Each actuation contains 108 mcg albuterol sulfate (90 mcg albuterol base) from the mouthpiece. VENTOLIN HFA is supplied as an 18-g pressurized aluminum canister with dose counter fitted with a blue plastic actuator and a blue strapcap; this canister contains 200 actuations. VENTOLIN HFA is also supplied as an 8-g pressurized aluminum canister with dose counter fitted with a blue plastic actuator and a blue strapcap; this canister contains 60 actuations.

4 CONTRAINDICATIONS

VENTOLIN HFA is contraindicated in patients with a history of hypersensitivity to albuterol or any other components of VENTOLIN HFA. Rare cases of hypersensitivity reactions, including urticaria, angioedema, and rash have been reported after the use of albuterol sulfate.

5 WARNINGS AND PRECAUTIONS

5.1 Paradoxical Bronchospasm

Inhaled albuterol sulfate can produce paradoxical bronchospasm, which may be life threatening. If paradoxical bronchospasm occurs, VENTOLIN HFA should be discontinued immediately and alternative therapy instituted. It should be recognized that paradoxical bronchospasm, when associated with inhaled formulations, frequently occurs with the first use of a new canister.

5.2 Deterioration of Asthma

Asthma may deteriorate acutely over a period of hours or chronically over several days or longer. If the patient needs more doses of VENTOLIN HFA than usual, this may be a marker of destabilization of asthma and requires reevaluation of the patient and treatment regimen, giving special consideration to the possible need for anti-inflammatory treatment, e.g., corticosteroids.

5.3 Use of Anti-Inflammatory Agents

The use of beta-adrenergic agonist bronchodilators alone may not be adequate to control asthma in many patients. Early consideration should be given to adding anti-inflammatory agents, e.g., corticosteroids, to the therapeutic regimen.

5.4 Cardiovascular Effects

VENTOLIN HFA, like all other beta$_2$-adrenergic agonists, can produce clinically significant cardiovascular effects in some patients such as changes in pulse rate or blood pressure. If such effects occur, VENTOLIN HFA may need to be discontinued. In addition, beta-agonists have been reported to produce electrocardiogram (ECG) changes, such as flattening of the T wave, prolongation of the QTc interval, and ST segment depression. The clinical relevance of these findings is unknown. Therefore, VENTOLIN HFA, like all other sympathomimetic amines, should be used with caution in patients with underlying cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

5.5 Do Not Exceed Recommended Dose

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma. The exact cause of death is unknown, but

cardiac arrest following an unexpected development of a severe acute asthmatic crisis and subsequent hypoxia is suspected.

5.6 Immediate Hypersensitivity Reactions

Immediate hypersensitivity reactions may occur after administration of albuterol sulfate inhalation aerosol, as demonstrated by cases of urticaria, angioedema, rash, bronchospasm, anaphylaxis, and oropharyngeal edema. Discontinue VENTOLIN HFA if immediate hypersensitivity reactions occur.

5.7 Coexisting Conditions

VENTOLIN HFA, like other sympathomimetic amines, should be used with caution in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus and in patients who are unusually responsive to sympathomimetic amines. Large doses of intravenous albuterol have been reported to aggravate preexisting diabetes mellitus and ketoacidosis.

5.8 Hypokalemia

As with other beta-agonists, albuterol may produce significant hypokalemia in some patients, possibly through intracellular shunting, which has the potential to produce adverse cardiovascular effects. The decrease is usually transient, not requiring supplementation.

6 ADVERSE REACTIONS

Use of VENTOLIN HFA may be associated with the following:

- Paradoxical bronchospasm *[see Warnings and Precautions (5.1)]*
- Cardiovascular effects *[see Warnings and Precautions (5.4)]*
- Immediate hypersensitivity reactions *[see Warnings and Precautions (5.6)]*
- Hypokalemia *[see Warnings and Precautions (5.8)]*

6.1 Clinical Trials Experience

The safety data described below reflects exposure to VENTOLIN HFA in 248 patients treated with VENTOLIN HFA in 3 placebo-controlled clinical trials of 2 to 12 weeks' duration. The data from adults and adolescents is based upon 2 clinical trials in which 202 patients with asthma 12 years of age and older were treated with VENTOLIN HFA 2 inhalations 4 times daily for 12 weeks' duration. The adult/adolescent population was 92 female, 110 male and 163 white, 19 black, 18 Hispanic, 2 other. The data from pediatric patients are based upon 1 clinical trial in which 46 patients with asthma 4 to 11 years of age were treated with VENTOLIN HFA 2 inhalations 4 times daily for 2 weeks' duration. The population was 21 female, 25 male and 25 white, 17 black, 3 Hispanic, 1 other.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adults and Adolescents 12 Years of Age and Older: The two 12-week, randomized, double-blind studies in 610 adolescent and adult patients with asthma that compared VENTOLIN HFA, a CFC 11/12-propelled albuterol inhaler, and an HFA-134a placebo inhaler. Overall, the incidence and nature of the adverse reactions reported for VENTOLIN HFA and a CFC 11/12-

propelled albuterol inhaler were comparable. Table 1 lists the incidence of all adverse reactions (whether considered by the investigator to be related or unrelated to drug) from these studies that occurred at a rate of 3% or greater in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group.

Table 1. Overall Adverse Reactions With ≥3% Incidence in 2 Large 12-Week Clinical Trials in Adolescents and Adults*

	Percent of Patients		
Adverse Reaction	VENTOLIN HFA (n = 202) %	CFC 11/12-Propelled Albuterol Inhaler (n = 207) %	Placebo HFA-134a (n = 201) %
Ear, nose, and throat			
Throat irritation	10	6	7
Upper respiratory inflammation	5	5	2
Lower respiratory			
Viral respiratory infections	7	4	4
Cough	5	2	2
Musculoskeletal			
Musculoskeletal pain	5	5	4

* This table includes all adverse reactions (whether considered by the investigator to be drug-related or unrelated to drug) that occurred at an incidence rate of at least 3.0% in the group treated with VENTOLIN HFA and more frequently in the group treated with VENTOLIN HFA than in the HFA-134a placebo inhaler group.

Adverse reactions reported by less than 3% of the adolescent and adult patients receiving VENTOLIN HFA and by a greater proportion of patients receiving VENTOLIN HFA than receiving HFA-134a placebo inhaler and that have the potential to be related to VENTOLIN HFA include diarrhea, laryngitis, oropharyngeal edema, cough, lung disorders, tachycardia, and extrasystoles. Palpitation and dizziness have also been observed with VENTOLIN HFA.

Pediatric Patients: Results from the 2-week pediatric clinical study in patients with asthma 4 to 11 years of age showed that this pediatric population had an adverse reaction profile similar to that of the adolescent and adult populations.

Three studies have been conducted to evaluate the safety and efficacy of VENTOLIN HFA in patients between birth and 4 years of age. The results of these studies did not establish the efficacy of VENTOLIN HFA in this age-group *[see Pediatric Use (8.4)]*. Since the efficacy of VENTOLIN HFA has not been demonstrated in children between birth and 48 months of age, the safety of VENTOLIN HFA in this age-group cannot be established. However, the safety

profile observed in the pediatric population under 4 years of age was comparable to that observed in the older pediatric patients and in adolescents and adults. Where adverse reaction incidence rates were greater in patients under 4 years of age compared with older patients, the higher incidence rates were noted in all treatment arms, including placebo. These adverse reactions included upper respiratory tract infection, nasopharyngitis, pyrexia, and tachycardia.

6.2 Postmarketing Experience

In addition to the adverse reactions listed in section 6.1, the following adverse reactions have been identified during postapproval use of VENTOLIN HFA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Cases of paradoxical bronchospasm, hoarseness, arrhythmias (including atrial fibrillation, supraventricular tachycardia), and hypersensitivity reactions (including urticaria, angioedema, rash) have been reported after the use of VENTOLIN HFA.

In addition, albuterol, like other sympathomimetic agents, can cause adverse reactions such as hypokalemia, hypertension, peripheral vasodilatation, angina, tremor, central nervous system stimulation, hyperactivity, sleeplessness, headache, muscle cramps, and drying or irritation of the oropharynx.

7 DRUG INTERACTIONS

Other short-acting sympathomimetic aerosol bronchodilators should not be used concomitantly with albuterol. If additional adrenergic drugs are to be administered by any route, they should be used with caution to avoid deleterious cardiovascular effects.

7.1 Beta-Blockers

Beta-adrenergic receptor blocking agents not only block the pulmonary effect of beta-agonists, such as VENTOLIN HFA, but may produce severe bronchospasm in patients with asthma. Therefore, patients with asthma should not normally be treated with beta-blockers. However, under certain circumstances, e.g., as prophylaxis after myocardial infarction, there may be no acceptable alternatives to the use of beta-adrenergic blocking agents in patients with asthma. In this setting, cardioselective beta-blockers should be considered, although they should be administered with caution.

7.2 Diuretics

The ECG changes and/or hypokalemia that may result from the administration of nonpotassium-sparing diuretics (such as loop or thiazide diuretics) can be acutely worsened by beta-agonists, especially when the recommended dose of the beta-agonist is exceeded. Although the clinical relevance of these effects is not known, caution is advised in the coadministration of beta-agonists with nonpotassium-sparing diuretics. Consider monitoring potassium levels.

7.3 Digoxin

Mean decreases of 16% to 22% in serum digoxin levels were demonstrated after single-dose intravenous and oral administration of albuterol, respectively, to normal volunteers who had received digoxin for 10 days. The clinical relevance of these findings for patients with

obstructive airway disease who are receiving inhaled albuterol and digoxin on a chronic basis is unclear. Nevertheless, it would be prudent to carefully evaluate the serum digoxin levels in patients who are currently receiving digoxin and albuterol.

7.4 Monoamine Oxidase Inhibitors or Tricyclic Antidepressants

VENTOLIN HFA should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of albuterol on the vascular system may be potentiated. Consider alternative therapy in patients taking MAOs or tricyclic antidepressants.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C.

There are no adequate and well-controlled studies of VENTOLIN HFA or albuterol sulfate in pregnant women. During worldwide marketing experience, various congenital anomalies, including cleft palate and limb defects, have been reported in the offspring of patients being treated with albuterol. Some of the mothers were taking multiple medications during their pregnancies. No consistent pattern of defects can be discerned, and a relationship between albuterol use and congenital anomalies has not been established. Animal reproduction studies in mice and rabbits revealed evidence of teratogenicity. VENTOLIN HFA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In a mouse reproduction study, subcutaneously administered albuterol sulfate produced cleft palate formation in 5 of 111 (4.5%) fetuses at exposures approximately equal to the maximum recommended human dose (MRHD) for adults on a mg/m^2 basis and in 10 of 108 (9.3%) fetuses at approximately 8 times the MRHD. Similar effects were not observed at approximately one eleventh of the MRHD. Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with isoproterenol (positive control).

In a rabbit reproduction study, orally administered albuterol sulfate produced cranioschisis in 7 of 19 fetuses (37%) at approximately 680 times the MRHD.

In another rabbit study, an albuterol sulfate/HFA-134a formulation administered by inhalation produced enlargement of the frontal portion of the fetal fontanelles at approximately one third of the MRHD *[see Animal Toxicology and/or Pharmacology (13.2)]*.

8.2 Labor and Delivery

Because of the potential for beta-agonist interference with uterine contractility, use of VENTOLIN HFA for relief of bronchospasm during labor should be restricted to those patients in whom the benefits clearly outweigh the risk.

8.3 Nursing Mothers

Plasma levels of albuterol sulfate and HFA-134a after inhaled therapeutic doses are very low in humans, but it is not known whether the components of VENTOLIN HFA are excreted in human milk. Because of the potential for tumorigenicity shown for albuterol in animal studies and lack of experience with the use of VENTOLIN HFA by nursing mothers, a decision should

be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Caution should be exercised when VENTOLIN HFA is administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of VENTOLIN HFA in children 4 years of age and older has been established based upon two 12-week clinical trials in patients 12 years of age and older with asthma and one 2-week clinical trial in patients 4 to 11 years of age with asthma *[see Clinical Studies (14.1), Adverse Reactions (6.1)]*. The safety and effectiveness of VENTOLIN HFA in children under 4 years of age has not been established. Three studies have been conducted to evaluate the safety and efficacy of VENTOLIN HFA in patients under 4 years of age and the findings are described below.

Two 4-week randomized, double-blind, placebo-controlled studies were conducted in 163 pediatric patients from birth to 48 months of age with symptoms of bronchospasm associated with obstructive airway disease (presenting symptoms included: wheeze, cough, dyspnea, or chest tightness). VENTOLIN HFA or placebo HFA was delivered with either an AeroChamber Plus® Valved Holding Chamber or an Optichamber® Valved Holding Chamber with mask 3 times daily. In one study, VENTOLIN HFA 90 mcg (N = 26), VENTOLIN HFA 180 mcg (N = 25), and placebo HFA (N = 26) were administered to children between 24 and 48 months of age. In the second study, VENTOLIN HFA 90 mcg (N = 29), VENTOLIN HFA 180 mcg (N = 29), and placebo HFA (N = 28) were administered to children between birth and 24 months of age. Over the 4-week treatment period, there were no treatment differences in asthma symptom scores between the groups receiving VENTOLIN HFA 90 mcg, VENTOLIN HFA 180 mcg, and placebo in either study.

In a third study, VENTOLIN HFA was evaluated in 87 pediatric patients younger than 24 months of age for the treatment of acute wheezing. VENTOLIN HFA was delivered with an AeroChamber Plus Valved Holding Chamber in this study. There were no significant differences in asthma symptom scores and mean change from baseline in an asthma symptom score between VENTOLIN HFA 180 mcg and VENTOLIN HFA 360 mcg.

In vitro dose characterization studies were performed to evaluate the delivery of VENTOLIN HFA via holding chambers with facemasks. The studies were conducted with 2 different holding chambers with facemasks (small and medium size). The in vitro study data when simulated to patients suggest that the dose of VENTOLIN HFA presented for inhalation via a valved holding chamber with facemask will be comparable to the dose delivered in adults without a spacer and facemask per kilogram of body weight (Table 2). However, clinical studies in children under 4 years of age described above suggest that either the optimal dose of VENTOLIN HFA has not been defined in this age-group or VENTOLIN HFA is not effective in this age-group. The safety and effectiveness of VENTOLIN HFA administered with or without a spacer device in children under 4 years of age has not been demonstrated.

Table 2: In Vitro Medication Delivery Through AeroChamber Plus® Valved Holding Chamber With a Facemask

Age	Facemask	Flow Rate (L/min)	Holding Time (seconds)	Mean Medication Delivery Through AeroChamber Plus (mcg/actuation)	Body Weight 50th Percentile (kg)*	Medication Delivered per Actuation (mcg/kg)†
6 to 12 Months	Small	4.9	0	18.2	7.5-9.9	1.8-2.4
			2	19.8		2.0-2.6
			5	13.8		1.4-1.8
			10	15.4		1.6-2.1
2 to 5 Years	Small	8.0	0	17.8	12.3-18.0	1.0-1.4
			2	16.0		0.9-1.3
			5	16.3		0.9-1.3
			10	18.3		1.0-1.5
2 to 5 Years	Medium	8.0	0	21.1	12.3-18.0	1.2-1.7
			2	15.3		0.8-1.2
			5	18.3		1.0-1.5
			10	18.2		1.0-1.5
>5 Years	Medium	12.0	0	26.8	18.0	1.5
			2	20.9		1.2
			5	19.6		1.1
			10	20.3		1.1

* Centers for Disease Control growth charts, developed by the National Center for Health Statistics in collaboration with the National Center for Chronic Disease Prevention and Health Promotion (2000). Ranges correspond to the average of the 50th percentile weight for boys and girls at the ages indicated.

† A single inhalation of VENTOLIN HFA in a 70-kg adult without use of a valved holding chamber and facemask delivers approximately 90 mcg, or 1.3 mcg/kg.

8.5 Geriatric Use

Clinical studies of VENTOLIN HFA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

10 OVERDOSAGE

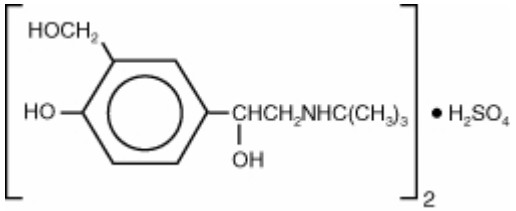
The expected symptoms with overdosage are those of excessive beta-adrenergic stimulation and/or occurrence or exaggeration of any of the symptoms listed under ADVERSE REACTIONS, e.g., seizures, angina, hypertension or hypotension, tachycardia with rates up to 200 beats/min, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, sleeplessness. Hypokalemia may also occur.

As with all sympathomimetic aerosol medications, cardiac arrest and even death may be associated with abuse of VENTOLIN HFA. Treatment consists of discontinuation of VENTOLIN HFA together with appropriate symptomatic therapy. The judicious use of a cardioselective beta-receptor blocker may be considered, bearing in mind that such medication can produce bronchospasm. There is insufficient evidence to determine if dialysis is beneficial for overdosage of VENTOLIN HFA.

The oral median lethal dose of albuterol sulfate in mice is greater than 2,000 mg/kg (approximately 6,800 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 3,200 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In mature rats, the subcutaneous median lethal dose of albuterol sulfate is approximately 450 mg/kg (approximately 3,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 1,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In young rats, the subcutaneous median lethal dose is approximately 2,000 mg/kg (approximately 14,000 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6,400 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). The inhalation median lethal dose has not been determined in animals.

11 DESCRIPTION

The active component of VENTOLIN HFA is albuterol sulfate, USP, the racemic form of albuterol and a relatively selective $beta_2$-adrenergic bronchodilator. Albuterol sulfate has the chemical name α^1-[(*tert*-butylamino)methyl]-4-hydroxy-*m*-xylene-α, α'-diol sulfate (2:1)(salt) and the following chemical structure:



Albuterol sulfate is a white crystalline powder with a molecular weight of 576.7, and the empirical formula is $(C_{13}H_{21}NO_3)_2 \bullet H_2SO_4$. It is soluble in water and slightly soluble in ethanol.

The World Health Organization recommended name for albuterol base is salbutamol.

VENTOLIN HFA is a pressurized metered-dose aerosol unit fitted with a counter. VENTOLIN HFA is intended for oral inhalation only. Each unit contains a microcrystalline

suspension of albuterol sulfate in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when it has not been used for more than 2 weeks, or when it has been dropped.

After priming, each actuation of the inhaler delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece).

Each 18-g canister provides 200 inhalations. Each 8-g canister provides 60 inhalations.

This product does not contain chlorofluorocarbons (CFCs) as the propellant.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

In vitro studies and in vivo pharmacologic studies have demonstrated that albuterol has a preferential effect on $beta_2$-adrenergic receptors compared with isoproterenol. While it is recognized that $beta_2$-adrenergic receptors are the predominant receptors in bronchial smooth muscle, data indicate that there is a population of $beta_2$-receptors in the human heart existing in a concentration between 10% and 50% of cardiac beta-adrenergic receptors. The precise function of these receptors has not been established *[see Warnings and Precautions (5.4)]*.

Activation of $beta_2$-adrenergic receptors on airway smooth muscle leads to the activation of adenylcyclase and to an increase in the intracellular concentration of cyclic-3′,5′-adenosine monophosphate (cyclic AMP). This increase of cyclic AMP leads to the activation of protein kinase A, which inhibits the phosphorylation of myosin and lowers intracellular ionic calcium concentrations, resulting in relaxation. Albuterol relaxes the smooth muscles of all airways, from the trachea to the terminal bronchioles. Albuterol acts as a functional antagonist to relax the airway irrespective of the spasmogen involved, thus protecting against all bronchoconstrictor challenges. Increased cyclic AMP concentrations are also associated with the inhibition of release of mediators from mast cells in the airway.

Albuterol has been shown in most controlled clinical trials to have more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation, than isoproterenol at comparable doses while producing fewer cardiovascular effects. Controlled clinical studies and other clinical experience have shown that inhaled albuterol, like other beta-adrenergic agonist drugs, can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or electrocardiographic changes *[see Warnings and Precautions (5.4)]*.

12.2 Pharmacokinetics

The systemic levels of albuterol are low after inhalation of recommended doses. A study conducted in 12 healthy male and female subjects using a higher dose (1,080 mcg of albuterol base) showed that mean peak plasma concentrations of approximately 3 ng/mL occurred after

dosing when albuterol was delivered using propellant HFA-134a. The mean time to peak concentrations (T_{max}) was delayed after administration of VENTOLIN HFA (T_{max} = 0.42 hours) as compared to CFC-propelled albuterol inhaler (T_{max} = 0.17 hours). Apparent terminal plasma half-life of albuterol is approximately 4.6 hours. No further pharmacokinetic studies for VENTOLIN HFA were conducted in neonates, children, or elderly subjects.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year study in Sprague-Dawley rats, albuterol sulfate caused a dose-related increase in the incidence of benign leiomyomas of the mesovarium at and above dietary doses of 2.0 mg/kg (approximately 14 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 6 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In another study this effect was blocked by the coadministration of propranolol, a non-selective beta-adrenergic antagonist. In an 18-month study in CD-1 mice, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 500 mg/kg (approximately 1,700 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 800 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis). In a 22-month study in Golden hamsters, albuterol sulfate showed no evidence of tumorigenicity at dietary doses of up to 50 mg/kg (approximately 225 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis and approximately 110 times the maximum recommended daily inhalation dose for children on a mg/m^2 basis).

Albuterol sulfate was not mutagenic in the Ames test or a mutation test in yeast. Albuterol sulfate was not clastogenic in a human peripheral lymphocyte assay or in an AH1 strain mouse micronucleus assay.

Reproduction studies in rats demonstrated no evidence of impaired fertility at oral doses of albuterol sulfate up to 50 mg/kg (approximately 340 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

13.2 Animal Toxicology and/or Pharmacology

Preclinical: Intravenous studies in rats with albuterol sulfate have demonstrated that albuterol crosses the blood-brain barrier and reaches brain concentrations amounting to approximately 5.0% of the plasma concentrations. In structures outside the blood-brain barrier (pineal and pituitary glands), albuterol concentrations were found to be 100 times those in the whole brain.

Studies in laboratory animals (minipigs, rodents, and dogs) have demonstrated the occurrence of cardiac arrhythmias and sudden death (with histologic evidence of myocardial necrosis) when beta-agonists and methylxanthines are administered concurrently. The clinical relevance of these findings is unknown.

Propellant HFA-134a is devoid of pharmacological activity except at very high doses in animals (380 to 1,300 times the maximum human exposure based on comparisons of AUC

values), primarily producing ataxia, tremors, dyspnea, or salivation. These are similar to effects produced by the structurally related CFCs, which have been used extensively in metered-dose inhalers.

In animals and humans, propellant HFA-134a was found to be rapidly absorbed and rapidly eliminated, with an elimination half-life of 3 to 27 minutes in animals and 5 to 7 minutes in humans. Time to maximum plasma concentration (T_{max}) and mean residence time are both extremely short, leading to a transient appearance of HFA-134a in the blood with no evidence of accumulation.

Reproductive Toxicology Studies: A study in CD-1 mice given albuterol sulfate subcutaneously showed cleft palate formation in 5 of 111 (4.5%) fetuses at 0.25 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis) and in 10 of 108 (9.3%) fetuses at 2.5 mg/kg (approximately 8 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). The drug did not induce cleft palate formation at a dose of 0.025 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis). Cleft palate also occurred in 22 of 72 (30.5%) fetuses from females treated subcutaneously with 2.5 mg/kg of isoproterenol (positive control).

A reproduction study in Stride Dutch rabbits revealed cranioschisis in 7 of 19 fetuses (37%) when albuterol sulfate was administered orally at a 50 mg/kg dose (approximately 680 times the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

In an inhalation reproduction study in New Zealand white rabbits, albuterol sulfate/HFA-134a formulation exhibited enlargement of the frontal portion of the fetal fontanelles at and above inhalation doses of 0.0193 mg/kg (less than the maximum recommended daily inhalation dose for adults on a mg/m^2 basis).

A study in which pregnant rats were dosed with radiolabeled albuterol sulfate demonstrated that drug-related material is transferred from the maternal circulation to the fetus.

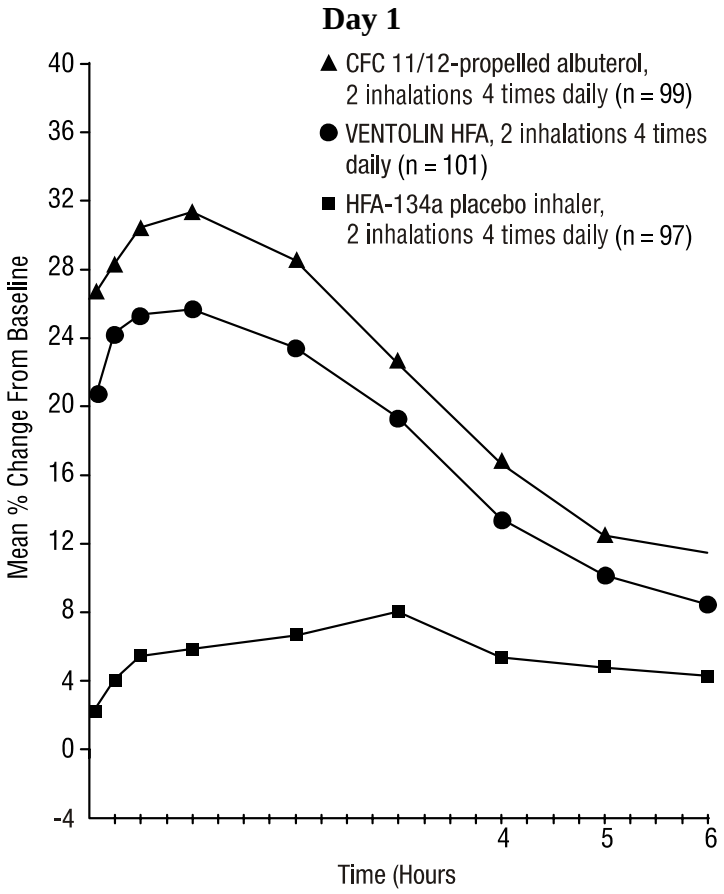
14 CLINICAL STUDIES

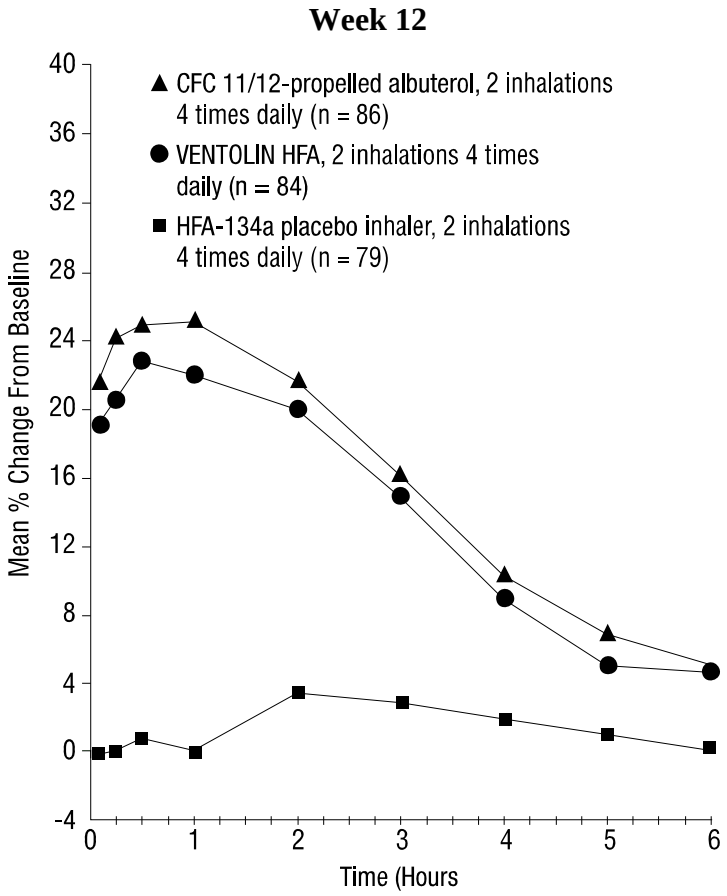
14.1 Bronchospasm Associated With Asthma

Adult and Adolescent Patients 12 Years of Age and Older: The efficacy of VENTOLIN HFA was evaluated in two 12-week, randomized, double-blind, placebo controlled trials in patients 12 years of age and older with mild to moderate asthma. These trials included a total of 610 patients (323 males, 287 females). In each trial, patients received 2 inhalations of VENTOLIN HFA, CFC 11/12-propelled albuterol, or HFA-134a placebo 4 times daily for 12 weeks' duration. Patients taking the HFA-134a placebo inhaler also took VENTOLIN HFA for asthma symptom relief on an as-needed basis. Some patients who participated in these clinical trials were using concomitant inhaled steroid therapy. Efficacy was assessed by serial forced expiratory volume in 1 second (FEV_1). In each of these trials, 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo. Results from the 2 clinical trials are described below.

In a 12-week, randomized, double-blind study, VENTOLIN HFA (101 patients) was compared to CFC 11/12-propelled albuterol (99 patients) and an HFA-134a placebo inhaler (97 patients) in adolescent and adult patients 12 to 76 years of age with mild to moderate asthma. Serial FEV_1 measurements [shown below as percent change from test-day baseline at Day 1 (n = 297) and at Week 12 (n = 249)] demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in FEV_1 over the pretreatment value than placebo.

FEV_1 as Percent Change From Predose in a Large, 12-Week Clinical Trial





In the responder population (≥15% increase in FEV_1 within 30 minutes postdose) treated with VENTOLIN HFA, the mean time to onset of a 15% increase in FEV_1 over the pretreatment value was 5.4 minutes, and the mean time to peak effect was 56 minutes. The mean duration of effect as measured by a 15% increase in FEV_1 over the pretreatment value was approximately 4 hours. In some patients, duration of effect was as long as 6 hours.

The second 12-week randomized, double-blind study was conducted to evaluate the efficacy and safety of switching patients from CFC 11/12-propelled albuterol to VENTOLIN HFA. During the 3-week run-in phase of the study, all patients received CFC 11/12-propelled albuterol. During the double-blind treatment phase, VENTOLIN HFA (91 patients) was compared to CFC 11/12-propelled albuterol (100 patients) and an HFA-134a placebo inhaler (95 patients) in adolescent and adult patients with mild to moderate asthma. Serial FEV_1 measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo. The switching from CFC 11/12-propelled albuterol inhaler to VENTOLIN HFA did not reveal any clinically significant changes in the efficacy profile.

In the 2 adult studies, the efficacy results from VENTOLIN HFA were significantly greater than placebo and were clinically comparable to those achieved with CFC 11/12-propelled albuterol, although small numerical differences in mean FEV_1 response and other measures were

observed. Physicians should recognize that individual responses to beta-adrenergic agonists administered via different propellants may vary and that equivalent responses in individual patients should not be assumed.

Pediatric Patients 4 Years of Age: The efficacy of VENTOLIN HFA was evaluated in one 2-week, randomized, double-blind, placebo-controlled trial in 135 pediatric patients 4 to 11 years of age with mild to moderate asthma. In this trial, patients received VENTOLIN HFA, CFC 11/12-propelled albuterol, or HFA-134a placebo. Serial pulmonary function measurements demonstrated that 2 inhalations of VENTOLIN HFA produced significantly greater improvement in pulmonary function than placebo and that there were no significant differences between the groups treated with VENTOLIN HFA and CFC 11/12-propelled albuterol. In the responder population treated with VENTOLIN HFA, the mean time to onset of a 15% increase in peak expiratory flow rate (PEFR) over the pretreatment value was 7.8 minutes, and the mean time to peak effect was approximately 90 minutes. The mean duration of effect as measured by a 15% increase in PEFR over the pretreatment value was greater than 3 hours. In some patients, duration of effect was as long as 6 hours.

14.2 Exercise-Induced Bronchospasm

One controlled clinical study in adult patients with asthma (N = 24) demonstrated that 2 inhalations of VENTOLIN HFA taken approximately 30 minutes prior to exercise significantly prevented exercise-induced bronchospasm (as measured by maximum percentage fall in FEV_1 following exercise) compared to an HFA-134a placebo inhaler. In addition, VENTOLIN HFA was shown to be clinically comparable to a CFC 11/12-propelled albuterol inhaler for this indication.

16 HOW SUPPLIED/STORAGE AND HANDLING

VENTOLIN HFA (albuterol sulfate) Inhalation Aerosol is supplied in the following packs as a pressurized aluminum canister fitted with a counter with a blue plastic actuator and a blue strapcap packaged within a moisture-protective foil pouch that also contains a desiccant:

NDC 0173-0682-20 18-g canister containing 200 actuations
NDC 0173-0682-21 8-g canister containing 60 actuations
NDC 0173-0682-24 8-g institutional pack canister containing 60 actuations

Before using, VENTOLIN HFA should be removed from the moisture-protective foil pouch. The pouch and dessicant should be discarded. VENTOLIN HFA should be discarded 12 months after removal from the pouch.

Priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. To prime the inhaler, release 4 sprays into the air away from the face, shaking well before each spray. The inhaler should be primed before using it for the first time, when the inhaler has not been used for more than 2 weeks, or when it has been dropped.

After priming, each actuation delivers 120 mcg of albuterol sulfate, USP in 75 mg of suspension from the valve and 108 mcg of albuterol sulfate, USP from the mouthpiece (equivalent to 90 mcg of albuterol base from the mouthpiece).

To ensure proper dosing and to prevent actuator orifice blockage, wash the actuator with warm water and let it air-dry completely at least once a week *[see FDA-Approved Patient Labeling (17.8)]*.

The blue actuator supplied with VENTOLIN HFA should not be used with any other product canisters, and actuators from other products should not be used with a VENTOLIN HFA canister.

VENTOLIN HFA has a counter attached to the canister. The counter starts at 204 or 64 and counts down each time a spray is released. The correct amount of medication in each inhalation cannot be assured after the counter reads 000, even though the canister is not completely empty and will continue to operate. VENTOLIN HFA should be discarded when the counter reads 000 or 12 months after removal from the moisture-protective foil pouch, whichever comes first. Never immerse the canister in water to determine the amount of drug remaining in the canister.

Keep out of reach of children. Avoid spraying in eyes.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw container into fire or incinerator.

Store between 15° and 25°C (59° and 77°F). Store the inhaler with the mouthpiece down. For best results, the inhaler should be at room temperature before use. SHAKE WELL BEFORE EACH SPRAY.

VENTOLIN HFA does not contain chlorofluorocarbons (CFCs) as the propellant.

17 PATIENT COUNSELING INFORMATION

See FDA-Approved Patient Labeling (17.8)

17.1 Frequency of Use

The action of VENTOLIN HFA should last up to 4 to 6 hours. VENTOLIN HFA should not be used more frequently than recommended. Do not increase the dose or frequency of doses of VENTOLIN HFA without consulting the physician. If patients find that treatment with VENTOLIN HFA becomes less effective for symptomatic relief, symptoms become worse, and/or they need to use the product more frequently than usual, they should seek medical attention immediately.

17.2 Priming and Cleaning

Priming: Patients should be instructed that priming VENTOLIN HFA is essential to ensure appropriate albuterol content in each actuation. Patients should prime VENTOLIN HFA before using for the first time, when the inhaler has not been used for more than 2 weeks, or when the inhaler has been dropped. To prime VENTOLIN HFA, patients should release 4 sprays into the air away from the face, shaking well before each spray.

Cleaning: To ensure proper dosing and to prevent actuator orifice blockage, patients should be instructed to wash the actuator and dry thoroughly at least once a week. Patients

should be informed that detailed cleaning instructions are included in the Information for the Patient leaflet.

17.3 Dose Counter

Patients should be informed that VENTOLIN HFA has a dose counter that starts at 204 or 64 and counts down each time a spray is released. Patients should be informed to discard VENTOLIN HFA when the counter reads 000 or 12 months after removal from the moisture-protective foil pouch, whichever comes first. When the counter reads 020, the patient should contact the pharmacist for a refill of medication or consult the physician to determine whether a prescription refill is needed. Patients should never try to alter the numbers or remove the counter from the metal canister. Patients should never immerse the canister in water to determine the amount of drug remaining in the canister.

17.4 Paradoxical Bronchospasm

Patients should be informed that VENTOLIN HFA can produce paradoxical bronchospasm. If paradoxical bronchospasm occurs, patients should discontinue VENTOLIN HFA.

17.5 Concomitant Drug Use

While patients are using VENTOLIN HFA, other inhaled drugs and asthma medications should be taken only as directed by the physician.

17.6 Common Adverse Effects

Common adverse effects of treatment with inhaled albuterol include palpitations, chest pain, rapid heart rate, tremor, and nervousness.

17.7 Pregnancy

Patients who are pregnant or nursing should contact their physicians about the use of VENTOLIN HFA.

17.8 FDA-Approved Patient Labeling

See tear-off leaflet below.

GlaxoSmithKline
Research Triangle Park, NC 27709

PHARMACIST—DETACH HERE AND GIVE LEAFLET TO PATIENT

Information for the Patient

VENTOLIN® HFA Inhalation Aerosol
(albuterol sulfate)

Read this leaflet carefully before you start to use VENTOLIN HFA.

Keep this leaflet because it has important summary information about VENTOLIN HFA. Your healthcare provider has more information or advice.

Read the new leaflet that comes with each refill of your prescription because there may be new information.

What is VENTOLIN HFA?

VENTOLIN HFA is a kind of medicine called a fast-acting bronchodilator. Fast-acting bronchodilators help to quickly open the airways in your lungs so that you can breathe more easily.

Each dose of VENTOLIN HFA should last up to 4 to 6 hours.

Take VENTOLIN HFA as directed by your doctor. Do not take extra doses or take more often without asking your doctor.

Get medical help right away if VENTOLIN HFA no longer helps your symptoms. Also get medical help if your symptoms get worse or if you need to use your inhaler more often.

While you are using VENTOLIN HFA, use other inhaled medicines and asthma medicines only as directed by your doctor. Tell your doctor if you are pregnant or nursing, and ask about the use of VENTOLIN HFA.

Possible side effects of taking VENTOLIN HFA include fast or irregular heartbeat, chest pain, shakiness, and nervousness. With the first use of a new canister, worsening of wheezing may occur.

The parts of your VENTOLIN HFA inhaler:

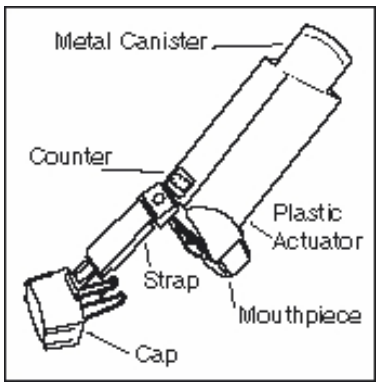


Figure 1

There are 2 main parts to your VENTOLIN HFA inhaler—the metal canister that holds the medicine and the blue plastic actuator that sprays the medicine from the canister (see Figure 1).

The inhaler also has a cap that covers the mouthpiece of the actuator. The strap on the cap will stay attached to the actuator.

Do not use the actuator with a canister of medicine from any other inhaler. And do not use a VENTOLIN HFA canister with an actuator from any other inhaler.

The canister has a counter to show how many sprays of medicine you have left. The number shows through a window in the back of the actuator.

The counter starts at either 204 or at 64, depending on which size inhaler you have. The number will count down by 1 each time you spray the inhaler. The counter will stop counting at 000.

Never try to change the numbers or take the counter off the metal canister. The counter cannot be reset, and it is permanently attached to the canister.

How to Use Your VENTOLIN HFA

Before using your VENTOLIN HFA:
Take the inhaler out of the foil pouch. Safely throw away the pouch and the drying packet that comes inside the pouch. The counter should read 204 or 64.

If a child needs help using the inhaler, an adult should help the child use the inhaler with or without a holding chamber attached to a facemask. The adult should follow the instructions that came with the holding chamber. An adult should watch a child use the inhaler to be sure it is used correctly.

The inhaler should be at room temperature before you use it.

Check each time to make sure the canister fits firmly in the plastic actuator. Also look into the mouthpiece to make sure there are no foreign objects there, especially if the strap is no longer attached to the actuator or if the cap is not being used to cover the mouthpiece.

Priming your VENTOLIN HFA:
You must prime the inhaler to get the right amount of medicine. Prime the inhaler before you use it for the first time, if you have not used it for more than 14 days, or if it has been dropped. To prime the inhaler, take the cap off the mouthpiece of the actuator. Then shake the inhaler well, and spray it into the air away from your face. Shake and spray the inhaler like this 3 more times to finish priming it. The counter should now read 200 or 60.

Instructions for taking a dose from your VENTOLIN HFA:
Read through the 6 steps below before using VENTOLIN HFA. If you have any questions, ask your doctor or pharmacist.

1. Take the cap off the mouthpiece of the actuator. **Shake the inhaler well** before each spray.
2. Hold the inhaler with the mouthpiece down (see Figure 2). **Breathe out through your mouth** and push as much air from your lungs as you can. Put the mouthpiece in your mouth and close your lips around it.
3. **Push the top of the canister all the way down while you breathe in deeply and slowly through your mouth** (see Figure 3). Right after the spray comes out, take your finger off the canister. After you have breathed in all the way, take the inhaler out of your mouth and close your mouth.

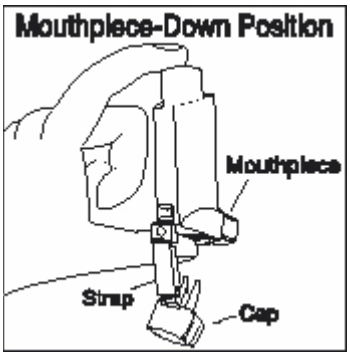


Figure 2

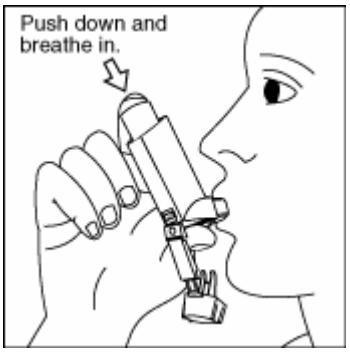


Figure 3

4. **Hold your breath as long as you can**, up to 10 seconds, then breathe normally.
5. If your doctor has prescribed more sprays, wait 1 minute and **shake** the inhaler again. Repeat steps 2 through 4.
6. Put the cap back on the mouthpiece after every time you use the inhaler, and make sure it snaps firmly into place.

When to Replace Your VENTOLIN HFA

- **When the counter reads 020**, you should refill your prescription or ask your doctor if you need another prescription for VENTOLIN HFA.
- **Throw the inhaler away** when the counter reads 000 or 12 months after you have taken the inhaler out of the foil pouch, whichever happens first. You should not keep using the inhaler when the counter reads 000 because you will not receive the right amount of medicine.
- **Do not use the inhaler** after the expiration date, which is on the packaging it comes in.

How to Clean Your VENTOLIN HFA

It is very important to keep the plastic actuator clean so the medicine will not build-up and block the spray. Do not try to clean the metal canister or let it get wet. The inhaler may stop spraying if it is not cleaned correctly.

Wash the actuator at least once a week.

Cleaning instructions:

1. Take the canister out of the actuator, and take the cap off the mouthpiece. The strap on the cap will stay attached to the actuator.
2. Wash the actuator through the top with warm running water for 30 seconds (see Figure 4). Then wash the actuator again through the mouthpiece (see Figure 5).

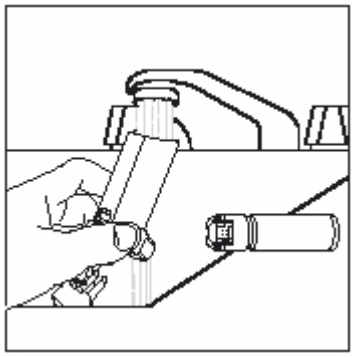


Figure 4

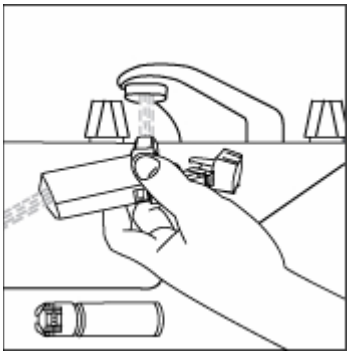


Figure 5

3. Shake off as much water from the actuator as you can. Look into the mouthpiece to make sure any medicine build-up has been completely washed away. If there is any build-up, repeat step 2.
4. Let the actuator air-dry completely, such as overnight (see Figure 6).

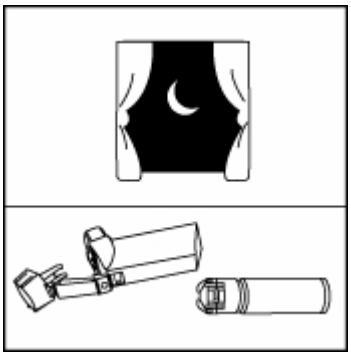


Figure 6

5. When the actuator is dry, put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. (The counter will count down by 1.) Put the cap back on the mouthpiece.

If your actuator becomes blocked:

Blockage from medicine build-up is more likely to happen if you do not let the actuator air-dry completely. If the actuator gets blocked so that little or no medicine comes out of the mouthpiece (see Figure 7), wash the actuator as described in cleaning steps 1-5.

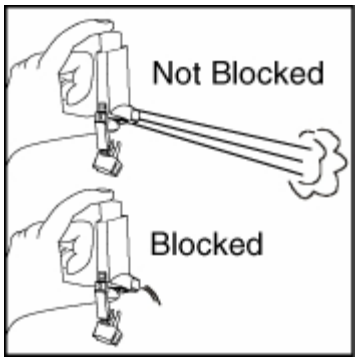


Figure 7

If you need to use your inhaler before the actuator is completely dry, shake as much water off the actuator as you can. Put the canister in the actuator and make sure it fits firmly. Shake the inhaler well and spray it once into the air away from your face. Then take your dose as prescribed. Then clean and air-dry it completely.

Storing Your VENTOLIN HFA

Store at room temperature with the mouthpiece down. Keep out of reach of children.

Contents Under Pressure: Do not puncture. Do not use or store near heat or open flame. Exposure to temperatures above 120°F may cause bursting. Never throw into fire or incinerator.

GlaxoSmithKline
Research Triangle Park, NC 27709

June 2009 VNT:6PIL

Micro+ Smokerlyzer®

bedfont

Operating Manual

s ien ific contributions to health

www.bedfont.com

Contents

Contents

Intended Use

The Micro+ Smokerlyzer® is a breath carbon monoxide monitor intended for multi-patient use by healthcare professionals in smoking cessation programmes, research and as an indicator of carbon monoxide poisoning.

Introduction

Carbon monoxide is a toxic, odourless, colourless, tasteless gas. It is formed from incomplete combustion of organic material at high temperatures with an insufficient oxygen supply.

When inhaled, CO competes successfully with oxygen in the bloodstream to form carboxyhaemoglobin (COHb). This starves the body tissues of the oxygen vital to repair, regeneration and general living. CO can remain in the blood stream for up to 24 hours, depending on a range of factors including physical activity, gender and inhalation intensity. The half-life is about 5 hours.

CO (ppm)/carboxyhaemoglobin (%COHb) correlation:

Breath carbon monoxide is measured in parts per million (ppmCO) and blood carboxyhaemoglobin in percentages (%COHb). The two are compatible and convertible, CO relating to lung/breath and COHb to blood gas – the Micro+ displays both measurements. Clinical research has demonstrated that a useful relationship between carbon monoxide and carboxyhaemoglobin is obtained by a short period of breath holding by the person. CO readings demonstrate the levels of poisonous inhaled CO while the COHb reading shows the percentage of vital oxygen that has been replaced in the bloodstream.

The Micro+ also has to capability to display %FCOHb – the equivalent carboxyhaemoglobin levels present in the foetus in correlation to a pregnant mother's expired CO levels.

The cut-off point between smoker and non-smoker has been found to be 6ppm CO. The Micro+ uses a coloured traffic light system to classify smoking status. The cut-off point for a non-smoker is shown to be 0-6ppm, a low dependence smoker to be 7-15ppm and strongly addicted smokers to be above 15ppm.

The Micro+ has been designed so that it can also be used with young smokers and pregnant women. As their smoking habits and views are generally different from other smokers, the display has been changed. 0-4ppm shows a non-smoker, 5-6ppm a light or casual smoker and 7ppm+ a more frequent smoker. The different profile settings affect only the colour classification displayed, not the smoker's CO reading.

Other cut-off points can be adopted as well as smoker classification at higher CO levels. The Micro+ has a third profile which can be set by the user with COdata+ software to achieve complete flexibility in most circumstances.

Operation is straightforward. A D-piece sampling system enables end-expired breath to be sampled easily and hygienically, using single-use disposable cardboard tube mouthpieces.

A colour touch-screen ensures ease of operation, as well as allowing the user to view patient results in a tabular or graphical format.

Micro+ readings can be downloaded from the instrument to COdata+, providing a virtual display of the instrument and an instant report of the patient's results. The report includes a specific interpretation of the patient's smoking habit and personal dependence on nicotine. This can be printed out and kept by the patient for their own records. The integrated database records patients' details and their results for subsequent sessions.

Warnings

- If an unexpectedly high CO reading is displayed, this could be due to CO poisoning. Seek further medical advice.
- Never use alcohol or cleaning agents containing alcohol or other organic solvents as these vapours will damage the CO sensor inside.
- Under no circumstances should the instrument be immersed in liquid or splashed with liquid.
- People with lung disease or chest ailments may not be able to achieve the breath-hold. In such cases, the user should inhale and hold their breath when the breath test is started, and exhale, if necessary, before the countdown has completed.
- During start-up if the  icon is displayed then the calibration is due. Please refer to page 13 for instructions. The unit may give false readings if not calibrated.
- During start-up if the  icon is displayed then the D-piece requires changing. It is recommended that the D-piece is changed every month or earlier if visibly soiled.
- The battery life is indicated by the  icon. When the  icon is displayed the batteries should be changed.
- The disposable cardboard mouthpieces are single-use only as re-use can increase the risk of cross-infection.
- See Bedfont's Infection Control and Maintenance Guidelines for further information on infection control.
- Changing profile settings does not affect the smoker's CO reading, only the traffic light colour classification displayed.

Contraindications

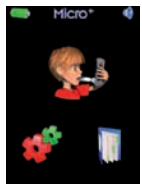
- The sensor has a cross-sensitivity to hydrogen which could affect the CO result. Hydrogen could be present on the breath due to certain gastrointestinal conditions.

Quick Start Guide

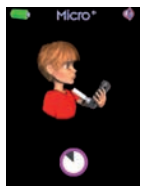
1. Press and hold the on/off button until the display becomes active. Release the button.

2. Insert the D-piece into the instrument and fit a new cardboard mouthpiece.

3. Touch the  icon to start a breath test.



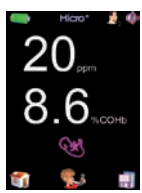
4. This starts the breath-hold countdown. The patient should inhale deeply and hold their breath while the display counts down to zero. If unable to hold their breath for the full countdown, see Warnings on page 4 or Settings on page 12.



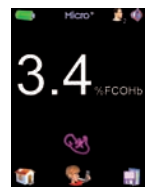
5. The audio bleep will sound during the last three seconds of the countdown.

6. At end of the countdown, the patient should blow slowly into the mouthpiece, aiming to empty their lungs completely.

7. The ppm and %COHb value will rise, and the highest level will hold.



8. To view the corresponding %FCOHb, touch the  .



9. Remove and dispose of the cardboard mouthpiece safely.

10. Remove the D-piece between tests to allow fresh air to purge sensor.

11. Touch  to perform another breath test. A new mouthpiece is required.

12. To switch off, press and hold the on/off button for 3 seconds. Unit will also auto power-off after 5 minutes of inactivity.

Pack Contents List

1. Instrument
2. Operation Instructions
3. Box of D-pieces
4. Box of disposable cardboard mouthpieces
5. 3 x AA batteries

Infection control and maintenance guidelines

Warrenty and registration card

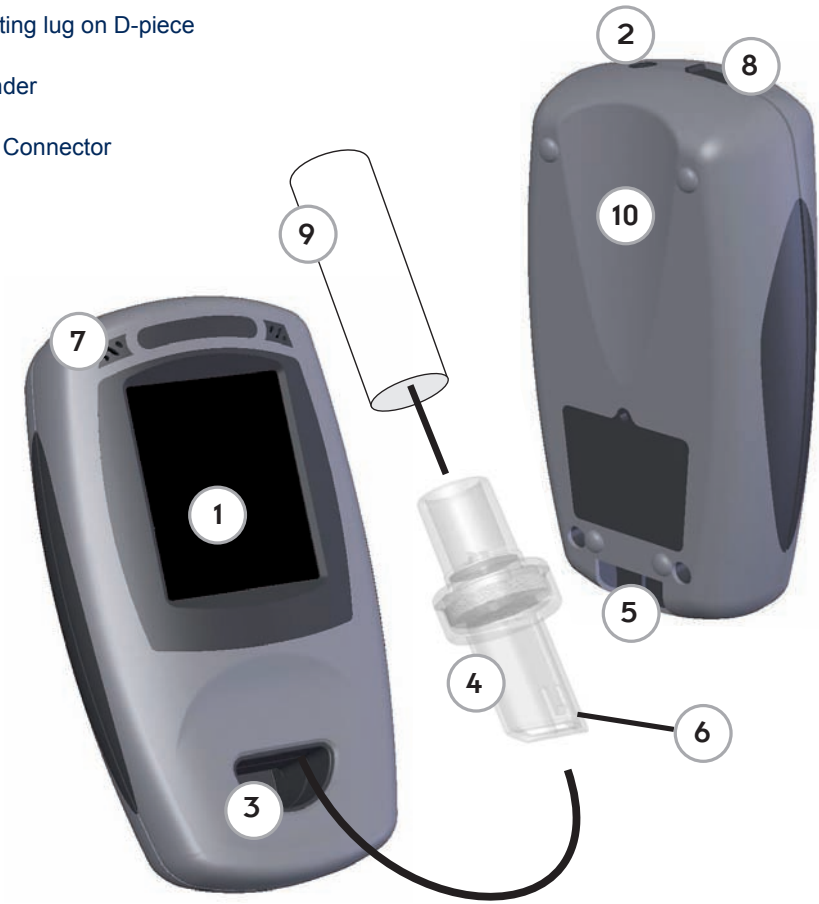
Specification

Concentration range:	0-250ppm carbon monoxide (CO)
Display:	Colour LCD with 1ppm increments
Detection principle:	Electrochemical sensor
Accuracy (repeatability of readings):	± 2%
Hydrogen cross-sensitivity:	<±5%
Batteries:	3 x AA (LR6 or equivalent) alkaline batteries
Response time:	Typically <20 seconds to 90% FSD
Operating temperature range:	0-40^{0}C (Storage 0-50^{0}C)
Operating humidity:	10-90% (Storage 0-95%) non-condensing
Sensor operating life:	2-3 years, 6 month warranty
Sensor sensitivity:	1ppm
Dimensions:	Approx. 44 x 77 x 138 mm
Weight:	Approx. 250g including batteries
Construction:	Case-Polycarbonate/ABS blend with elastomeric over-mould D-piece-Polypropylene

Instrument Layout

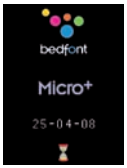
Key:

1. Display
2. On/Off switch
3. Aperture for D-piece
4. Breath sampling D-piece
5. Exhaust port for breath sample
6. Locating lug on D-piece
7. Sounder
8. USB Connector
9. Cardboard mouthpiece
10. Battery Compartment

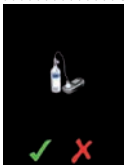


Display Symbols

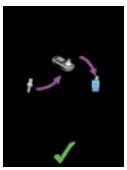
1. Start-up screen:



2. Calibration prompt start-up screen.



3. D-piece prompt start-up screen:



4. Battery condition:

5. Sounder: on

off

6. Return to main menu:

7. Return to previous menu:

8. Start breath test:

9. Settings:

10. Patient data:

11. Patient data in table format:

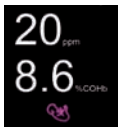
12. Patient data in chart format:

13. Inhale:

14. Breath-hold and countdown:

15. Exhale for breath test:

16. Peak reading (COppm/%COHb):



17. Display %FCOHb:

18. New breath test:

19. Save breath test:

20. Set instrument zero in fresh air:

21. Apply calibration gas at 50ppm:

22. Calibration/zero: pass

fail

23. Retry calibration/zero:

24. User profile selection:

25. Select adult user profile:

26. Select adolescent user profile:

27. Select custom user profile (if set via COdata+):

28. Breath hold timer setting:

29. Set date/time:

30. System info screen:

31. Contact Bedfont or distributor for help:

Maintenance

Calibrate in accordance with procedure on page 13.

Replace batteries when indicated.

Replace D-piece every month or if visibly soiled or contaminated. It cannot be cleaned or sterilised. The Micro+ will give a reminder during the start-up when the D-piece should be replaced, see Operation page 10.

Remove the D-piece by gently pulling out from the front of the instrument.

Batteries should be removed if the instrument is not likely to be used for some time.

Additional technical information can be made available on request; please contact Bedfont or its distributor.

Cleaning

Wipe the instrument and external D-piece surfaces with a product specifically developed for this purpose. Bedfont provides an Instrument Cleansing Wipe.

Never use alcohol or cleaning agents containing alcohol or other organic solvents as these vapours will damage the CO sensor inside.

Under no circumstances should the instrument be immersed in liquid or splashed with liquid.

Operation

- Ensure 3 AA alkaline batteries are correctly located in battery compartment.
- The touch-screen controls all functions once the instrument is switched on.
- Press and hold the on/off button for 3 seconds until the display becomes active. Release the button. After a one-minute warm-up period during which the start-up screen is displayed, the main menu is then displayed.

Note: If the Micro+ requires calibration (every 6 months) then the calibration prompt screen will appear, giving the option to calibrate or not.

If the D-piece requires changing (recommended monthly) then the D-piece change prompt screen will appear. Touch to accept. The reminder will now be reset and will prompt again in 28 days.

- The main menu displays three symbols:

1. Breath test 
2. Settings 
3. Patient select 

Note: The patient select icon will not be accessible until patient data has been downloaded from COdata+ and will remain greyed out.

- If a and ppm value is shown rather than the main menu, the instrument has failed to set a fresh air zero during start-up. Ensure that the instrument is in fresh air and then touch the screen to repeat the start-up test. If it fails again, please read Troubleshooting, page 15.

Breath test

- Attach a D-piece and a new cardboard mouthpiece to the Micro+. Check all connections are pushed firmly together.
- To start a breath test, touch the  icon.

Note: If the display shows  then the sensor has not had time to settle to zero before the test. If this happens, the display will show a  once the sensor has settled and the unit is ready for the test.

- The patient should then inhale as deeply as possible and hold their breath throughout the countdown. The display will show the countdown, and the audio beep will sound during the last three seconds of the countdown.
- Exhale slowly but gently into the mouthpiece, aiming to empty the lungs as far as possible.

Note: If the patient cannot hold their breath for the full countdown, they should commence exhalation at a comfortable point, but exhale completely. See Settings, page 12 and Warnings, page 4.

- The display will show a rising ppm and %COHb value.
- The peak reading will be shown on the display. The test is complete when the  icons are displayed.
- To view the corresponding %FCOHb value, touch the  . To go back to the ppm and %COHb reading, touch the  again.
- Remove and dispose of the cardboard mouthpiece safely.
- Removing the D-piece between tests will allow fresh air to purge the unit. It is good practice to wash hands after removing the D-piece.
- To start another breath test, fit a new cardboard mouthpiece and touch the  icon.
- To return to the main menu, touch 
- To save the result to the patient database, press  . Select the patient using the  and  arrows and press  to save or  to cancel. Either option will return to the main menu.

Note: This is only possible if patient data has been downloaded to the Micro+ via COdata+.

- If no further tests are required, press and hold the on/off button for 3 seconds until the Micro+ turns off. If left on, the Micro+ will automatically turn off after 5 minutes of inactivity.

Description	User Profile 1: Adult (ppm)	User Profile 2: Adolescent (ppm)
Non-smoker	0 – 6	0 – 4
Danger zone	7 – 10	5 – 6
Smoker	11 – 15	7 – 10
Frequent smoker	16 – 25	11 – 15
Addicted smoker	26 – 35	16 - 25
Heavily addicted smoker	36 - 50	26 - 35
Dangerously addicted smoker	51+	36+

Settings

The settings menu allows access to the following functions:

- Sounder
- User profile
- Breath-hold countdown timer
- Set date/time
- System information
- Zero/calibration

Sounder

The operation of the sounder is indicated by the small symbol on the top line of the display.

To change from sounder-on to sounder-off (or back again); touch the large  icon in the Settings menu. The large sounder symbol and the small symbol on the top line of the display will change to show whether the sounder is on or off.

Even if the sounder has been turned off, it will continue to operate during the last 3 seconds of the breath-hold countdown.

User Profiles

It is possible to change the profiles between adult and adolescent (or a custom profile if one has been set).

The profiles determine the colour of the background during a breath test. The default values for adults and adolescents are shown in the table on page 11.

To change the selected profile, touch  in the main menu, then touch  . Touch  to select the adult profile,  for the adolescent profile or  for the custom profile. The currently selected user profile is indicted by the small symbol on the top line of the display.

The custom profile will only be available if it has been previously set using COdata+.

Breath-hold Countdown Timer

It is possible to change the length of time that the patient should try to hold their breath.

Touch  in the Settings menu. Touch  or  to change the timer setting.

Press  to save or  to cancel. Return to main menu.

Date and Time

The date and time is used when saving patient data to accurately record when tests were done. To change the date and time, touch  in the Settings menu.

Touch the required field and use  or  to change.

Press  to save or  to cancel. Return to main menu.

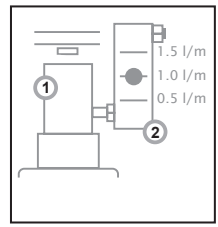
System Information

Touch  to access system information such as software version. Touch  to return to previous menu.

Zero/Calibration

- The Micro+ is calibrated before leaving Bedfont.
- The Micro+ should be calibrated at 6 monthly intervals. The Micro+ will give a reminder when calibration is due during start-up.
- The calibration gas required is 50ppm carbon monoxide in air.
- Turn the instrument on in the normal way and from the main menu select the Settings menu, then .
- Ensure that the instrument is surrounded by fresh air. Touch , to begin the zeroing. If the zeroing has been successful, a will be displayed. If the zeroing fails, an will be displayed (see Troubleshooting page 15 if this happens).
- Touch to accept the zero and return to the calibration/zero menu.
- Ensure the calibration gas valve is in the off position.
- Screw the fine control valve and flow indicator assembly to the gas can. This is best done by screwing the gas can into the valve.
- Connect calibration apparatus as illustrated.

- Touch to begin calibration.
- Immediately open the fine control valve by turning the control knob anti-clockwise and allow the gas to flow at 1 litre per minute.
- To maintain this, adjust the flow so the ball in the flow indicator remains on the middle line.
- As the 50ppm CO calibration gas is applied, the displayed ppm reading will climb.



1.Fine control valve
2.Flow indicator

- Monitoring the rate of flow, continue to apply the gas.
- If the final displayed reading is between 45 and 55ppm, the calibration value will be automatically set in the instrument as 50ppm and a will be displayed to show a successful calibration. If the displayed reading is outside these limits, the calibration fails, and a will be displayed (see Troubleshooting page 15 if this happens).
- Touch to accept the calibration and return to the calibration/zero menu.
- Turn off the gas flow, remove the D-piece and disconnect the calibration adapter.
- Unscrew the fine control valve and flow indicator from the gas can and store safely. If the valve is left attached to the can, the gas could escape.
- The Micro+ is now calibrated and ready for use.

Patient Information

Touch  on the main menu to access patient information, then touch  . This icon remains inactive until patient data has been downloaded via COdata+.

Touch  or  to highlight the required patient.

Touch  to view data in table format or  to view in graphical format.

Touch  to return to previous menu.

Troubleshooting

- If the unit fails to turn on properly, or if the low battery symbol is showing, replace the 3 x AA alkaline batteries. Ensure that the batteries are inserted the correct way round, matching the symbols moulded into the plastic.
- If the display shows  after zeroing, a second attempt can be made to zero the unit in fresh air. Check that the unit is in fresh air and touch  to restart the zero process. If, after a third zeroing attempt, the display shows  again, the unit will have to be returned to Bedfont or its distributor for investigation and repair. In this case, the display shows  . The unit can be turned off by holding the on/off button for three seconds. It is possible to re-start the unit and attempt the zeroing process again.
- If, after an attempted calibration with 50ppm CO gas, the display shows  , the gas value was not within the permitted limits. The achieved reading is displayed underneath the  .
If this value is much lower than 50ppm, there may have been a problem with the supply of gas from the cylinder during the calibration process. If the displayed value is much higher than 50ppm, it is possible that the wrong concentration of calibration gas is being used. In either case, check the cylinder, connections and flow-rate before touching  to repeat the gas calibration process.
If, after a third repeated attempt to calibrate the instrument, the display shows  again, the unit will have to be returned to Bedfont or its distributor for investigation and repair. In this case, the display shows  . The unit can be turned off by holding the on/off button for three seconds. It is possible to re-start the unit and use it with the previous calibration settings, or attempt the complete calibration process again.

Returns Procedure

Should equipment require servicing, please contact Bedfont's Customer Service Specialist before returning any goods. If equipment was not purchased direct from Bedfont, please contact the local distributor.

- When the monitor serial number and description of the fault have been supplied, the Customer Service Specialist will issue a Returns Number.
- State this number when returning the monitor, ensuring full details, including telephone and fax numbers, are clearly provided.
- Bedfont advise using a courier service when returning monitors.
- Confirmation will be sent when goods are received.
- An Engineer's Report and a quotation for the repair will be sent following investigation. This includes an Authorisation Form.
- If the monitor is still in warranty, Bedfont will repair it and return it with an Engineer's Report, free of charge. If the monitor is found to simply require calibrating, a fee will be charged.
- If outside of warranty, complete the Authorisation Form within the quotation to proceed with the repair or calibration. Ensure an Official Purchase Order Number is included, and return to Bedfont. Contact the Customer Service Specialist with any queries.
- If it is decided not to proceed with the repair, a handling fee will be charged. Ensure the completed Authorisation Form is returned with an Official Purchase Order Number.
- The equipment will be returned as soon as Bedfont have received all the relevant paperwork. A carriage fee will be charged if the monitor is no longer in warranty.

Spares & Warranty

Spares:

D-pieces

Disposable cardboard mouthpieces

Calibration gas and kits

Instrument cleansing wipes

AA alkaline batteries

The above spares are available from Bedfont Scientific Ltd, UK. For spares availability in all other countries contact your local distributor. It is recommended that only Bedfont spares are used.

Warranty:

Bedfont Scientific Limited warrants the Micro+ (batteries excepted) to be free of defects in materials and workmanship for a period of one year from the date of shipment. This warranty is extended to two years upon receipt of a completed Warranty Registration card. Bedfont's sole obligation under this warranty is limited to repairing or replacing, at its choice, any item covered under this warranty when such an item is returned intact, prepaid, to Bedfont Scientific Limited or the local representative.

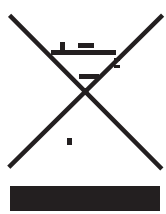
Note: Sensors are guaranteed for a period of six months from the date of shipment from Bedfont.

These warranties are automatically invalidated if the products are repaired, altered or otherwise tampered with by unauthorised personnel, or have been subject to misuse, neglect or accident.

coVita
tools for treatment professionals

U.S. Customers, please contact:
coVita
tel: 800-707-5751
fax: 800-721-2377
email: service@covita.net
www.covita.net

Bedfont Scientific Ltd
105 Laker Road,
Rochester Airport Industrial Estate,
Rochester, Kent ME1 3QX England
Tel: +44(0) 634 673 720
Fax: +44(0) 634 673 721
E-mail: ask@bedfont.com



At the end of the product's life, do not dispose of any electronic instrument in the domestic waste, but contact Bedfont or its distributor for disposal instructions.

U.S. Customers, please contact:
coVita
tel: 800-707-5751
fax: 800-721-2377
email: service@covita.net
www.covita.net

Bedfont Scientific Ltd
105 Laker Road,
Rochester Airport Industrial Estate,
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ISO 9001:2000
Cert No. FM 31664
ISO 13485:2003
Cert No. MD 502905

OPERATING INSTRUCTIONS
for the
eSP™ SPIROMETRY TESTING SYSTEM

September 7, 2010
Version 1.0

SYSTEM USER GUIDE

Part #631446

Customized for:

SPIROMICS Protocol

1.2R

1 GENERAL INFORMATION

1.1 IMPORTANT NOTICE

The intention of the System User Guide (SUG) is to provide basic operating instruction for eSP™ (electronic short path) software. This document does not serve as a protocol resource or to provide comprehensive test instructions outside of the published protocols.

Please refer to the Study Protocol and Manual of Procedures (MOP2) published by the SPIROMICS for detailed instructions on study related procedures.
This system is to be used by authorized study staff for this trial.

This User Guide and the accompanying pneumotach and syringe certification documents must be retained with the investigator's site file at the completion of this study.

Information in this SUG is specific to the SPIROMICS protocol. The software described in this document is furnished in conjunction with SPIROMICS and is only intended for use in this trial. Information is intended to assist nSpire Health customers in the use of our products; any other use of the information contained herein is prohibited.
nSpire Health reserves the right to change the content of this document at any time without prior notice. The software described in this document is furnished under a license agreement. The user is prohibited from copying, reverse engineering, disassembly, or decompilation of the software. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or storing in a retrieval system, or translated into any language in any form for any purpose without prior written permission of nSpire Health, Inc.

	This symbol indicates that the user must read and understand all instructions and warnings prior to use.
	This symbol indicates that this Class IIA equipment complies with the European Union Medical Device Directive 93/42/EEC.
	This symbol indicates a Class 2-power supply not requiring a grounded power outlet.
	This symbol indicates that this device provides a certain level of safety because the subject-applied part is floating.

Printed and Bound in the United States of America

1.2 CONTACT INFORMATION

Manufactured by
nSpire Health, Inc.
1830 Lefthand Circle
Longmont, CO 80501 USA

Authorized Representative
nSpire Health, Ltd.
Unit 10 Harforde Court
John Tate Road
Hertford, SG13 7NW U.K.

1.3 TECHNICAL SUPPORT

For subject testing and technical issues, please contact our 24-hour on-call staff using the numbers listed below and follow the prompts.

Important: If the voice mail system is reached, a message must be left with your name, protocol, principal investigator name, contact telephone number (including extension), and a brief description of your reason for calling. A phone call will be returned as soon as an agent is available.

1.3.1 SUMMARY OF PHONE AND FAX

Step 1: Dial your country's toll free access code.
Step 2: Wait for the prompt
Step 3: Dial 800 915 4737 for **Telephone** OR Dial 800 916 4737 for **Fax**

1.3.2 ORDERING SUPPLIES

Throughout the course of this clinical trial, it may be necessary to order additional supplies from nSpire Health. To order items, contact nSpire Health Technical Support personnel or use the Sales Order Request Form provided. Be sure to allow enough time for delivery to your site.

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3 CONTENTS AND SET UP

3.1 GENERAL INFORMATION

When you receive your equipment, it is important to take the time to unpack and become familiar with all components. Review the packing slip to ensure that all items have been received. Compare the parts received to the packing list making sure you have received all components and supplies and that the serial numbers match the components sent. Sign and date the packing slip and fax back to nSpire Health.

NOTE: Save *all* boxes and packaging material for return of the equipment at the completion of the study.

3.1.1 CONTENTS

Equipment includes:

- ✓ Computer, power supply block, power cable
- ✓ Modem cable (RJ11)
- ✓ Ethernet Cable (RJ45)
- ✓ Printer, power supply block, power cable
- ✓ USB Printer Cable
- ✓ KoKo Spirometer / Pneumotach
- ✓ PCMCIA adaptor OR DB9 Gender Changer
- ✓ KoKo Filters & Nose Clips
- ✓ 3 Liter Calibration Syringe
- ✓ Weather Station

NOTE: Your equipment may vary slightly.

The documents in the accompanying large white envelope include:

- ✓ System User Guide
- ✓ Investigator Statement
- ✓ Security Statement
- ✓ Technician Checklist
- ✓ Sales Order Request Form

NOTE: Please treat the last 4 documents as masters and make copies for your files.

3.2 SYSTEM SET-UP

3.2.1 PLUGGING IN THE COMPUTER

3-1, Connecting the Power Supply to the Computer

1. Connect round end of the power supply cable to the back of the computer.
2. Plug the power supply block into an electrical outlet.

3.2.2 CONNECTING PRINTER

Remove the printer and its components from the shipping box. Make sure all packing materials and tape are removed.

Figure 3-2, Connecting the Printer

1. Add paper to the paper tray.
2. Connect the printer power supply cable to the back of the printer
3. Plug the power supply block into an electrical outlet.
4. Connect the printer USB cable to the back of the printer.
5. Connect the other end of the USB printer cable to an available USB port on the computer.

6. Insert ink cartridges into the printer.

3.3 SPIROMETRY CONNECTION

The spirometer will connect to the computer using the PCMCIA card or DB9 Gender Changer.

3.3.1 PCMCIA CARD

Figure 3-3, PCMCIA Card Adaptor

1. Attach the KoKo Mouthpiece filter to the KoKo Spirometer, see Error! Reference source not found.
2. Attach the KoKo Spirometer to the PCMCIA card adapter.
3. Insert PCMCIA card into the slot on the side of the computer.
4. The yellow button will extend out as card is inserted.

NOTE: To remove card from computer push yellow button in.

Figure 3-4, Insert PCMCIA Card into Computer

3.4 INTERNET CONNECTIONS

eSP synchronization will connect your computer to the nSpire Health central server. System updates and other important information will automatically download to your study computer.
Determine which type of internet connection you will be using.

3.4.1 ETHERNET CONNECTION

Using the **Ethernet** cable (RJ45) provided, insert one end into the LAN port and the other into the computer receptacle.

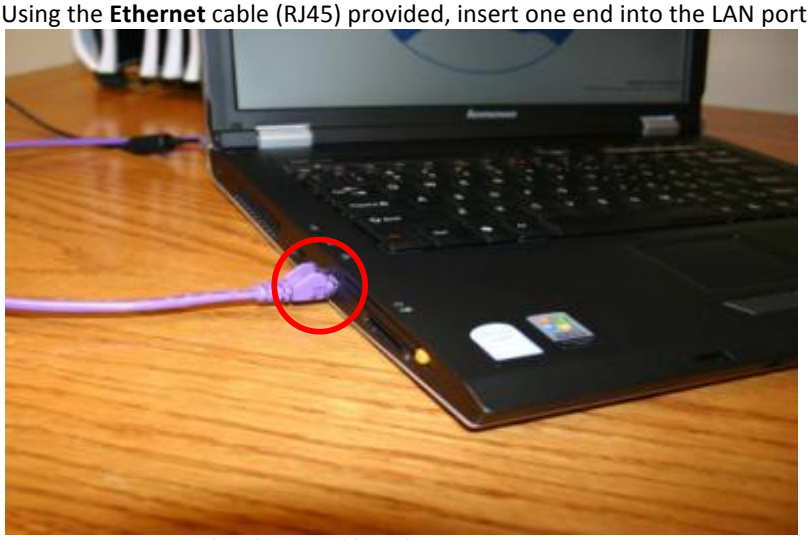


Figure 3-5, Connecting the Ethernet Cable to the Computer

If your network supports Dynamic Host Configuration Protocol (DHCP) (i.e. can acquire a network address automatically), and you have access to high speed Internet, the computer will transmit securely over this network. If you answer **YES** to the following questions, we suggest you try the LAN port for your first synchronization: (However, nSpire Health is not authorized to support or troubleshoot your network environment.)

- Do computers in your organization have high speed access to the Internet?
- Do they connect to a hub or a router?
- Is there someone in your facility that manages the access to the Internet, network equipment, or IP addressing that can answer these questions?

If you have answered **NO** to any of the above questions, use an analog phone connection.

****INFORMATION FOR YOUR NETWORK ADMINISTRATOR IN THE EVENT OF PROBLEMS WITH LAN CONNECTION EFFORTS****

IN ORDER TO FULFILL SECURITY COMPLIANCE REQUIREMENTS, OUR SYSTEM'S LAN CONFIGURATION IS STANDARD DHCP. IF YOU HAVE STATICALLY ASSIGNED IP ADDRESSES WITHIN YOUR LAN, YOU CANNOT TRANSMIT FROM OUR SYSTEM OVER LAN. NSPIRE HEALTH WILL NOT MODIFY OUR BASE WORKSTATION CONFIGURATION TO ACCOMMODATE THIS TYPE OF NETWORK.

Your site may need to open specific firewall ports. For a list of firewall ports that must remain open to support nSpire Health communications, see *Appendix 12.4* below.

3.4.2 ANALOG PHONE CONNECTION

1. Insert one end of the modem cable (RJ11) into an **analog** phone line
2. Insert the other into the modem receptacle on the back of the computer.

- The system will check to see if your modem is connected to an analog phone line.

Figure 3-6, Insert Analog Line into Computer

NOTE: The telephone line MUST be an **analog** line – such as a FAX line. Connecting the system to a digital phone line could damage the eSP System.

NOTE: The AT&T Software will update the access numbers periodically. An icon in the system tray will appear when the updates are taking place. **Do not** cancel or bypass these updates. Follow the prompts allowing updates to run while you perform testing with the eSP System.

3.4.3 WIRELESS CONNECTION

- Laptop Computers need to show green on the wireless switch located on the front edge in order for the Wi-Fi to be enabled. The Switch displays no color when the Wi-Fi is disabled. Also depending on the make and model of the laptop, the Wi-Fi key may be located differently.

3.5 TURNING ON THE COMPUTER

1. Press the **power** button on the computer.

The following compliance message will appear:

> *In compliance with the United States FDA's 21CFR Part 11 regulations, this notice informs you of your responsibilities with regard to data entered into the KoKo Spirometry System.*
> *21 CFR Part 11.10 states: "Persons, who use closed systems to create, modify, maintain, or transmit electronic records shall employ procedures and controls designed to ensure the authenticity, integrity, and, when appropriate, the confidentiality of electronic records."*

2. After reading and agreeing to this statement, click **OK.**

You will be asked to use an identification code and password for all functions that create or modify subject data. It is important that you do not share this information. Should you suspect that someone else knows your identification code and password; have the site technician reset your account and create a new password.

NOTE: This computer is not for personal use.

3.6 WINDOWS LOG-ON

1. On the *Windows Login* screen type "**esp-user**" In the user name field.
2. In the *Password* field, type "**kokolink**" in all lowercase letters. This field is case sensitive.
3. Click **OK.**

Use this login information every time you log into Windows.

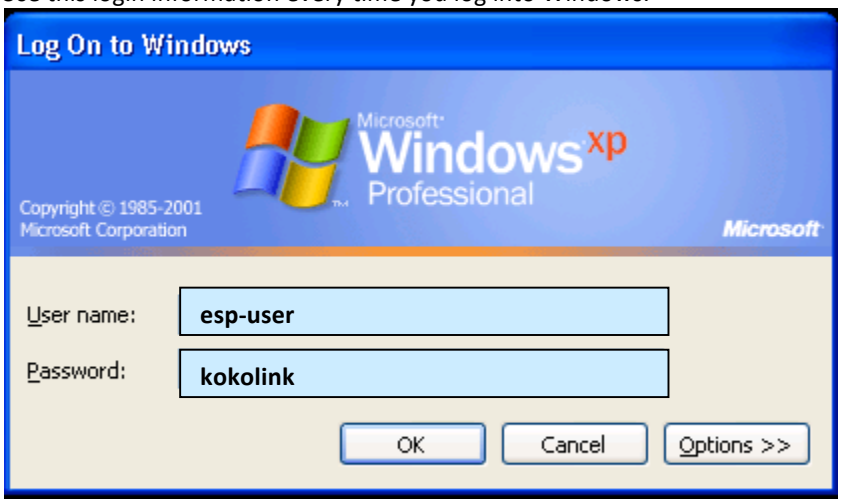


Figure 3-7, Windows Login

3.7 DATA TRANSFER (SYNCHRONIZATION)

Synchronization will connect your computer to the nSpire Health central server and automatically download system updates and other important information to your study computer.

This crucial step will enable nSpire Health to:

- Confirm the system can synchronize with the central server
- Send eSP software updates and information
- Ensure the appropriate and current system setting
- Receive, assess and back up study data
- Send and receive eQueries

Data synchronization is automatically activated after logging into Windows *and* when closing down the eSP software. Throughout the study, synchronization MUST occur at the end of each testing day. Data is assessed by nSpire Health's Clinical Analysts and securely backed up. Testing (spirometry) may be perfomed without the network connection, however the connection must be made daily to transfer the data to nSpire.

NOTE: The system clock will be automatically updated to the correct date and time upon synchronization.

- **Menu Items** display submenus when selected.
- **Progress bar** scrolls, denoting activity.
- **Progress panel** reports the action being completed.
- **Message panel** describes the state of the action.
- **Information panel** shows the date of the last data transfer.
- **Connection details** show which network is being used to connect to nSpire Health, at least one mode should be displayed.

No connection to a network could be established.

A Modem Connection exists through an analog telephone line.

An Ethernet Network cable connection has been found.

A Wireless Network has been located and connected to.

When a network is found, the system will connect to the internet, establishing a secure connection and synchronizing your site's database with the nSpire Health server. During start up, the system will automatically update the antivirus software and correct the date and time. After successful synchronization the eSP application will open.

1. Disconnect from the internet.

After you've finished testing for the day, be sure to exit out of eSP and turn the computer off but do not close your laptop until the SYNC is finished and the Computer has powered off. If the laptop is closed during this process the SYNC will not complete and the computer will go into Hibernation mode.

If synchronization is unsuccessful you will be given the option to Test only and not connect

2. Select Option **Test Only.**

3.7.1 CONFIRMING REGIONAL SETTINGS

It is important that regional settings are correct, verification instructions are contained in *Appendix 13* below.

4 SETTING UP USER ACCOUNTS

4.1 TYPES OF ACCOUNTS

There are two types of accounts in eSP:

- **Site Administrator Accounts:** The Site Administrator is designated by the Principal Investigator (PI) as the only person at the site responsible for setting up technician accounts within eSP software. Site Administrator accounts cannot test subjects. The lead study coordinator should have their own Site Administrator account.
- **Technician Accounts:** The Technician account and corresponding login allows the individual Technicians to perform subject testing. These accounts have been previously set-up by your Site Administrator.
    - If the Site Administrator is going to perform testing a separate Technician account must be created.

4.2 SETTING UP SITE ADMINISTRATOR ACCOUNTS

4.2.1 LOG IN TO ESP

- The *eSP Login* screen will automatically open after synchronization.

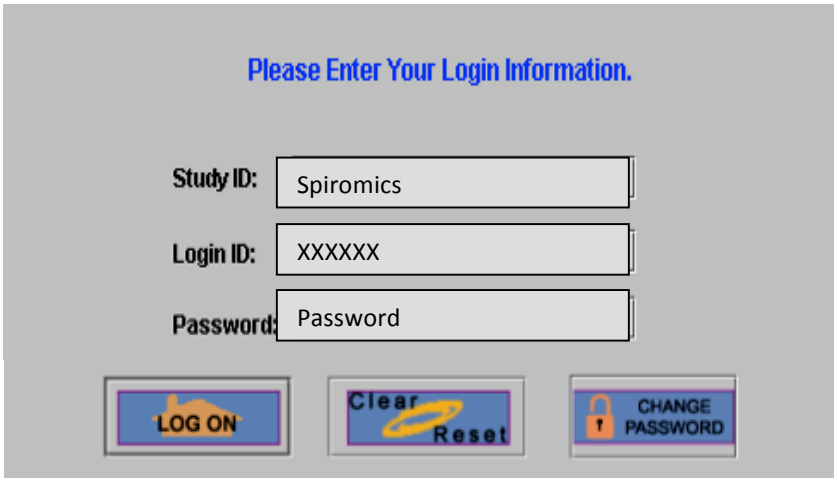


Figure 4-1, Study Log On Screen

4.2.1.1 CREATING A SITE ADMINISTRATOR ACCOUNT

1. Enter SPIROMICS in the *Study ID* field and press **Tab**.
2. Type the ***first 6 letters of the PI's last name*** in the **Login ID** field and press **Tab** to continue.

If the PI's last name contains less than 6 letters, use x's to fill in the remaining characters. (i.e. "Roy," becomes "Royxxx")

NOTE: If the PI wishes to designate someone else to function as the Site Administrator, the PI must first log on and create another Administrator account.

3. Type '**password'** in the *Password* field and click **LOG ON**.
4. eSP login fields are NOT case sensitive.

5. The system will prompt, "*Your Password is currently the Default Password. Please Change Your Password.*" Click **OK**.

4.2.2 CHANGE PASSWORD

Upon logging onto the system for the first time, you MUST change your password.

- The system will proceed to the *Password Change* Screen.
- The *Study ID, Login ID* and *Current Password* will be populated based on your entries.

1. Enter your new **password** in the *New Password* field. (Passwords must be 5 to 15 characters in length.)
2. Enter your new **password** again in the *Confirm Password* field.
3. Click **SUBMIT**.
    - Read the ICPF Acceptance terms and, if acceptable, click **I Accept**.
4. Click **SUBMIT**.
5. Enter your *Login ID* and click **OK**.
    - Your password has now been changed.

NOTE: Do NOT share your new password with anyone.

You are now logged in as an Administrator and the system will display the *eSP Home* Screen.

4.3 SETTING UP TECHNICIAN ACCOUNTS

Technician and Site Administrator **Login ID** must be different from one another.

- An Administrator must be logged in to create Technician accounts.

1. Select **Contacts** from the *Admin* menu or click **CLIENTS** on the *eSP Home* screen.

Figure 4-2, Admin Menu - Select Contacts

The title bar will display the Login ID of the Administrator who is currently logged in.

2. The system will advance to the *Site Contact Administration* Screen.

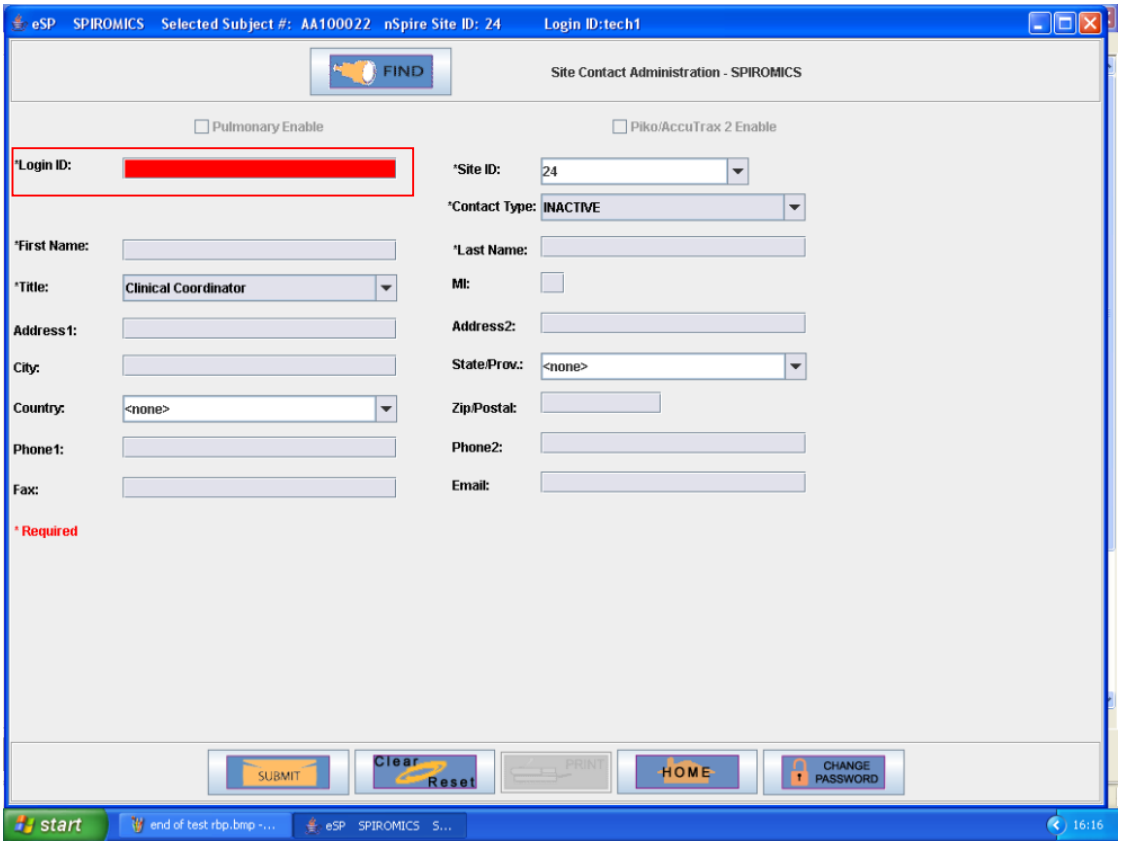


Figure 4-3, Site Contact Screen

3. Enter in a user ID for the Technician.
   - The *Site ID* field will be filled in automatically.
4. Select **Technician** at the **Contact Type** from the drop-down list.
   - The **Contact Type** selected will determine the level of access the user has to the system, if 'Technician' is not selected the account holder will not be able to perform tests.
5. Select **Country** from the drop-down list.
6. Fill in First and Last Name fields.
7. Click **SUBMIT.**
   - A message box will appear stating the information has been successfully saved in the *eSP* System.
8. Click **OK**.

4.3.1.1 ENTER ADDITIONAL TECHNICIANS,

1. Click **Clear/Reset** to empty the content fields.
2. Repeat steps outlined in Step 3 above.

4.3.2 RECALLING AND EDITING EXISTING TECHNICIAN

1. Log on as an Administrator.
2. Select **Contacts** from the *Admin* menu *or* click **Clients** from the *eSP Home* Screen**.**

The system will advance to the *Site Contact Administration* Screen.

3. Enter the **Login ID** and click **FIND**.
   - The Technician information will appear.
   - The profile will display, edit information as necessary.
4. Click **SUBMIT** when complete.

4.3.3 LOGGING IN AS A NEW TECHNICIAN

1. Open the eSP application

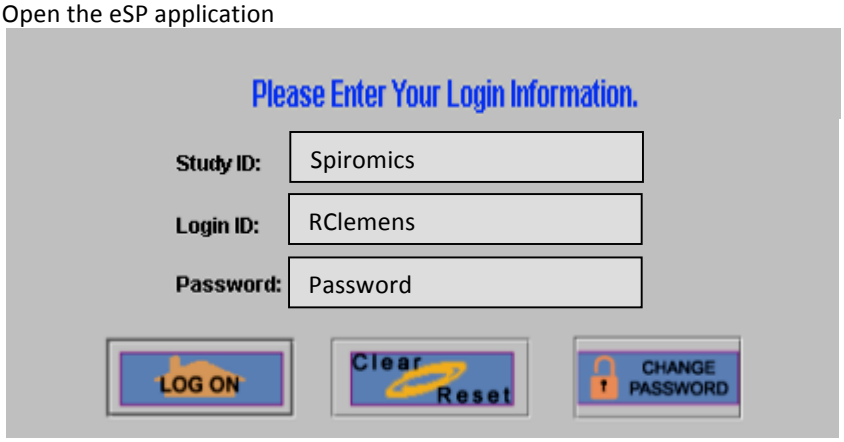


Figure 4-4, Technician Login Screen

2. Enter SPIROMICS in the *Study ID* field and press **Tab**
3. In the *Login ID* field type your **Login ID** and press **Tab**

NOTE: Your Login ID was setup by the Site Administrator.

4. Enter **password** in the *password* field, click **LOG IN**
   - The first time you login the system will prompt, "Your Password is currently the Default Password. Please change your Password."
5. Click **OK**.
   - The system will proceed to the *Password Change* Screen.
   - The *Study ID, Login ID* and *Current Password* will be populated based on your entries.
6. Enter your new **password** in the *New Password* field. (Passwords must be 5 to 15 characters in length.)
7. Enter your new **password** again in the *Confirm Password* field.
8. Click **SUBMIT**.
9. Read the ICPF Acceptance terms and, if acceptable, click **I Accept**.
10. Click **SUBMIT**.
11. Enter your *Login ID* and click **OK**.

Your password has now been changed. Do **NOT** share your new password with anyone.

You are now logged in and the system will display the *eSP Home* Screen.

Figure 4-5, eSP Home Screen

4.4 TECHNICIAN CERTIFICATION AND ENABLEMENT

Certification and enabling are required for each Technician performing spirometry testing for the SPIROMICS clinical trial. At the end of this section, the following steps must be completed for Certification and Enablement within the eSP application.

1. Review the System Users Guide because you must creat a Site Administrator account first.
2. Complete the required Site Certification Forms (SCF) to nSpire Health.
    a. Calibrate and perform a linearity check on the spirometer.
    b. Print the calibration report.
3. Perform a practice FVC test, showing three (3) or more acceptable and two (2) or more repeatable efforts.
4. Synchronize the system.
5. Print practice test results.
6. Fax all the Documents from above and from the next section (4.4.1) to nSpire Health (800)-916-4737 with supplied Cover Sheet.
7. Allow enough time for nSpire Health's Clinical Analysts to review your submission.
8. When notified, synchronize the system again to download the 'enabled' status.

4.4.1 SITE CERTIFICATION FORMS (SCF)

As part of the Certification and Enablement process each Technician is required to complete and fax (800)-916-4737 the following forms to nSpire Health:

- Investigator Statement – One per study site. Used to designate the Site Administrator
- Technician Certification Checklist – One per Technician
- Security Statement – One per Technician

These forms are part of the delivery of the system to each site.

5 CALIBRATION

5.1 HOW TO CALIBRATE THE SPIROMETER

In accordance with the study protocol, the testing system must be calibrated each testing day. Calibration can be performed at any time by following the steps below.

NOTE: Do not be alarmed by the daily "*Calibration Expired*" message. The system is only reminding you to calibrate at the start of each new testing day.

5.1.1 CONNECTING THE KOKO PNEUMOTACH

9. Connect the KoKo pneumotach to the computer.
10. Attach a KoKo filter to the KoKo pneumotach.
11. Connect the calibration syringe to the KoKo filter.

If an optional USB weather station is available, connect it at this time. Make sure not to place the weather station near a heat or cooling source, such as the computer or an air-conditioning duct.

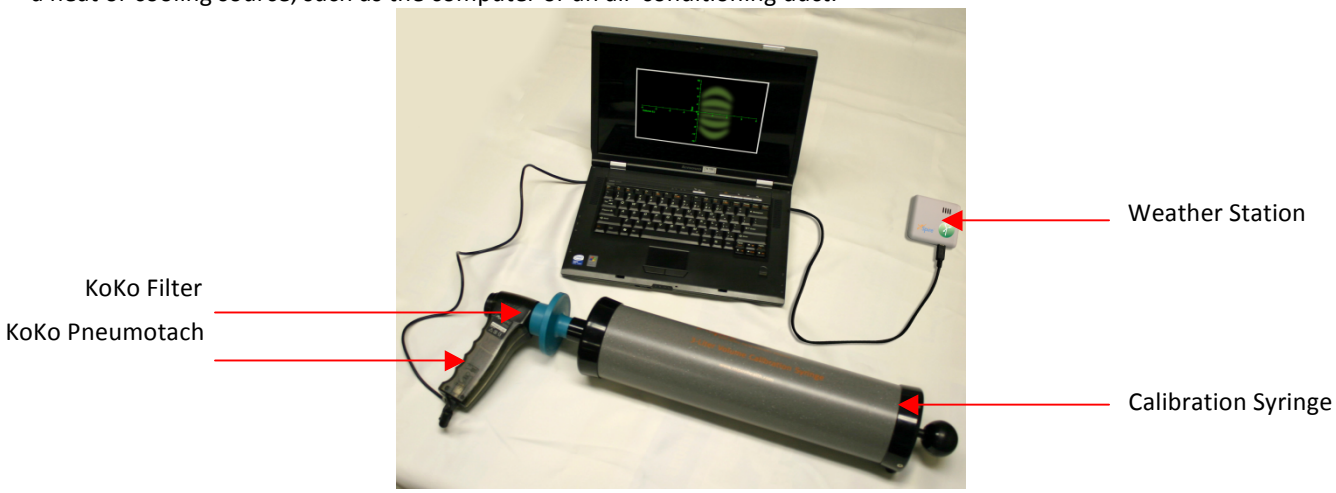


Figure 5-1, KoKo Spirometer and Components

5.1.2 ENTER ENVIRONMENTAL CONDITIONS

12. Click **Calibrate** on the *eSP Home* Screen.
    - The system will advance to the *Calibration* Screen
    - If the weather station is connected it will automatically measure and enter values for the environmental variables.
    - If you change these values for any reason, you will be prompted to enter a reason for the change.
    - If a weather station is not available or not detected:

- Warning Weather Monitor dialog will display.

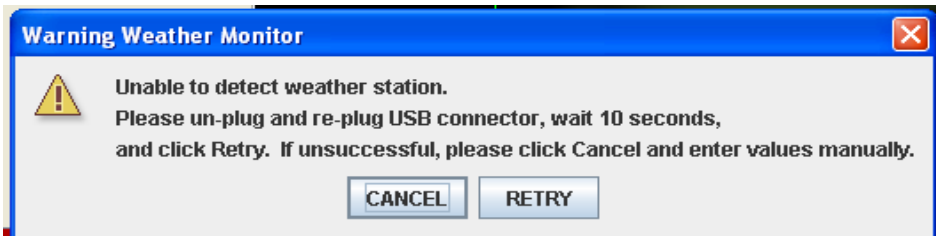


Figure 5-2, Warning Weather Monitor Dialog

13. Click **Cancel** to manually enter the conditions.

- Temperature is in Celsius
- Barometric Pressure is in millimeters of mercury
- Humidity is a percent (if unknown use 50%)

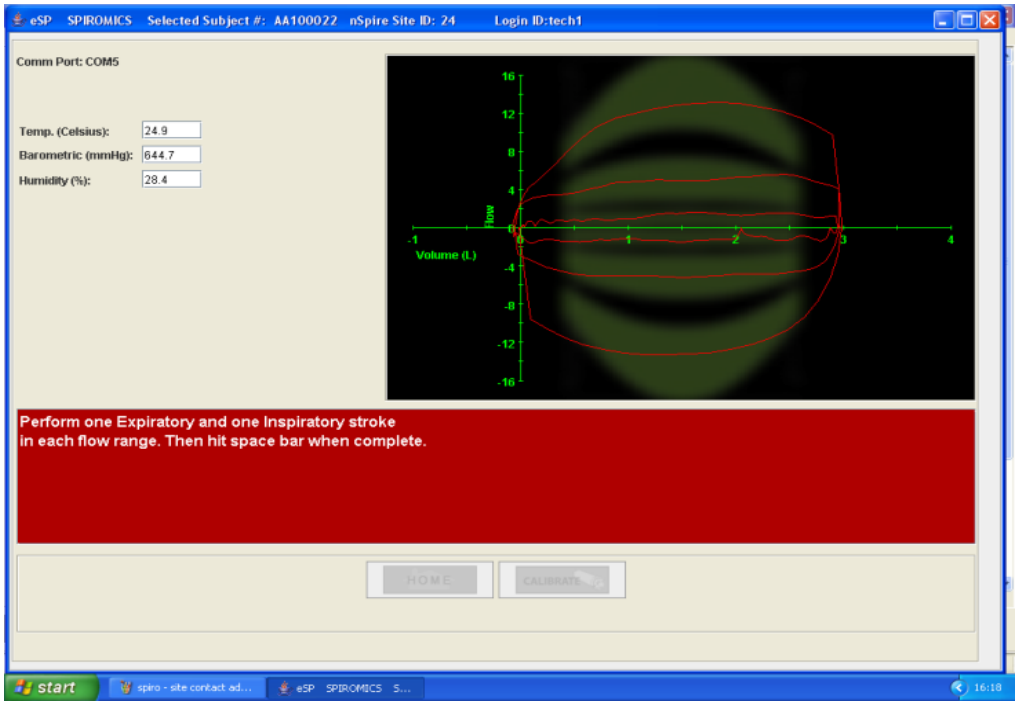
OR

- Connect the weather station, wait 10 seconds and click Retry.

Ensure that environmental variables are accurate to your ***testing room***. If they are not, click **Cancel** and manually enter the correct values.

NOTE: Room temperature is the most significant variable and must be properly monitored and entered. In the event that room temperature changes by more than ± 5º C, the system must be recalibrated.

14. Once all fields are filled in, fully extend the syringe handle.
15. Click **CALIBRATE.**
    - Wait for the pneumotach to zero, the message "*Zeroing Device*" will display in the red text area.
16. Perform calibration at Low, Mid, and High flow rates.
    - One stroke per flow rate



5.1.3 FLOW RATES

To achieve these flow rates vary the speed at which the syringe handle is pushed in and pulled out. The following is required for Certification:

- Low flow rate cycle (0-4L/sec)
- Medium flow rate (4-8L/sec
- High flow rate cycle (8-12L/sec).

Green shaded areas have been provided on the Calibration Screen to help guide your efforts.

17. Press the <**spacebar>** when complete.
    - The system automatically adjusts the calibration and displays the Calibration Report.
18. Select **Print** to print the *Calibration* Report.
    - A sample calibration report can be found in the *Reports* Section.
    - File the report

NOTE: The Calibration report with tracings can ***only*** be printed at this time. To verify calibration at any other time, select the **Calibration Log Report** from the *Report* Menu options.

19. Click **Close** to return to the *Calibration* Screen.
20. Press **HOME** to return to the *Home* Screen

TIP: TEMPERATURE AND BAROMTERIC PRESSURE VARIATION AFFECT TEST RESULTS.

All spirometers meeting ATS/ERS 2005 guidelines adjust the subject's spirometry values to normalize them for room temperature and barometric pressure conditions. Room temperature and barometric pressure are used to correct for the difference between the subject's exhaled/inhaled air volumes. The correction brings the measured volumes back to the condition of the air volume while in the subject's lungs (BTPS). A change of several degrees in room temperature can affect the accuracy of the spirometric results. A change in barometric pressure can also affect the BTPS correction of the spirometer.

Technicians are required to check current environmental conditions before performing SVC or FVC tests. If environmental conditions have changed since the last calibration, recalibrating the spirometer with the new settings is recommended. eSP allows the Technician to enter the current envoronmental conditions at the time of the calibration. The testing room should have an accurate thermometer and barometer.

6 LINEARITY CHECK

A linearity check is an additional volume calibration check performed using a 3-liter syringe to deliver three constant flows at three flow rates: low, mid, and high, for a total of 9 strokes.

Linearity checks are performed weekly per protocol guidelines. After successful calibration, a prompt will appear if a linearity check is required, advancing you to the linearity screen.

To manually open the linearity screen:

1. Click Linearity on the *eSP Home* Screen or select Linearity Check from the *Subject* Menu.

Figure 6-1, Opening the Linearity Screen

2. Follow the instructions in the colored box to perform three successful strokes at each target flow rate.
3. Click **Linearity**.

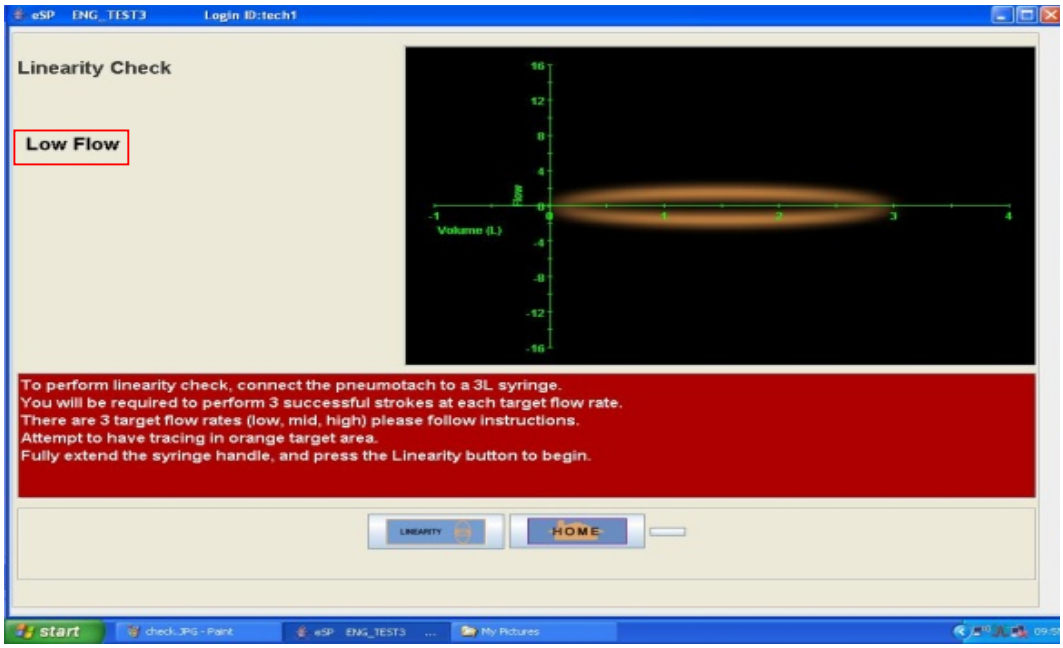


Figure 6-2, Linearity Screen

- If the system has not been calibrated a message will appear informing you to calibrate before performing a linearity check.

Figure 6-3, Calibration Required Dialog

- The system will display the message "**Zeroing Device**" in the colored text area.
- After zeroing, the system will prompt you to cycle the syringe at target flow rate until the linearity condition is met.
- Orange target areas are provided to help guide your efforts.
- Helpful hints to achieve target flow rates appear in color alongside the graph.

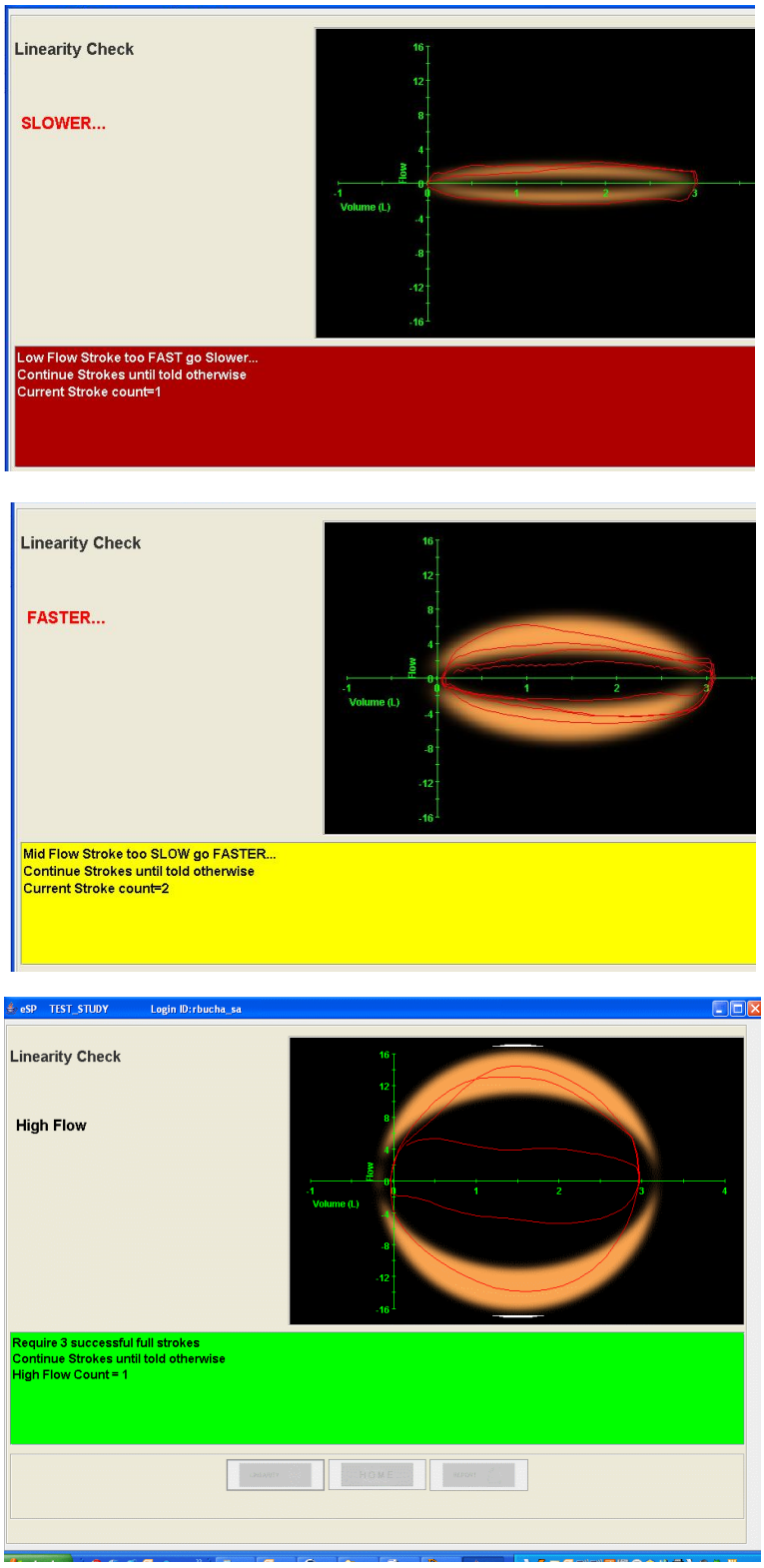


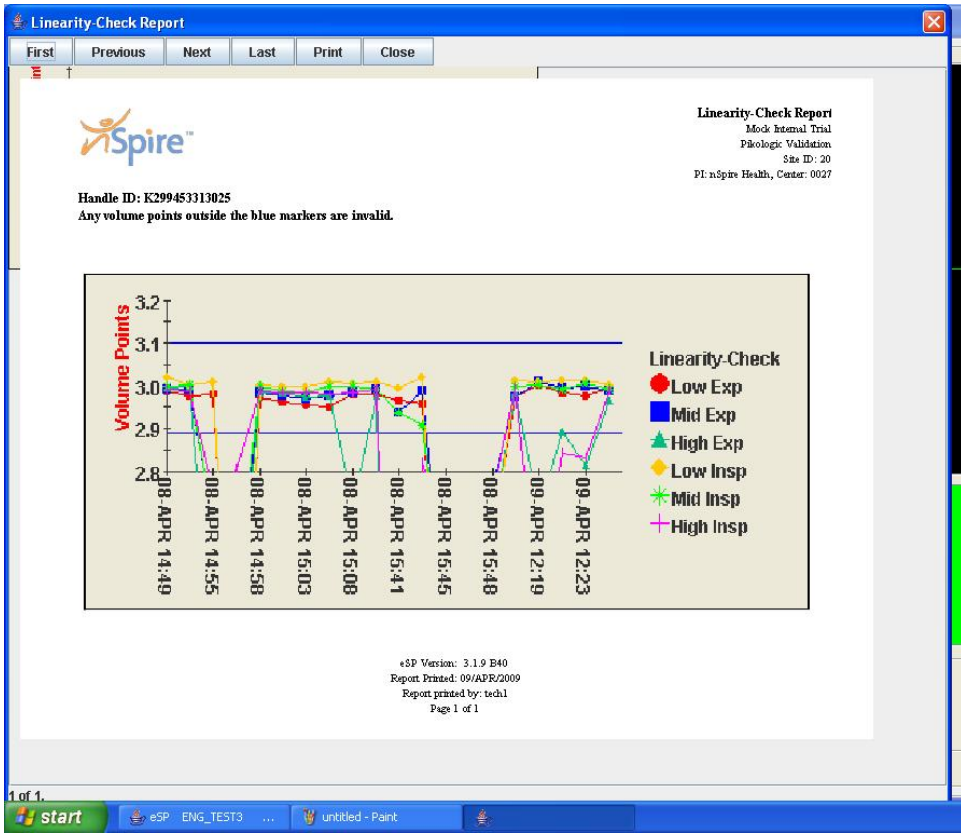
Figure 6-4, Linearity Check Screens

- Once 3 flows at the target rate have been achieved, the graph will switch to the next flow rate until all flow rates have been achieved.

- A confirmation message will appear once the check is complete.

4. Click **OK** to exit.

- The linearity report will display and can be printed.



7 SUBJECT ENTRY

7.1 CREATING A NEW SUBJECT

1. At the eSP *Home* Screen, click **Subject.**

2. Enter require subject demographic information:

- 8-digit **Subject/Participant** number. Format = AANNNNNN (range: AA000001-AA999999).
- **Age**
- **Gender** at Birth from the pull-down menu.
- **Height** in centimeters.
- **Date of Birth** as DD/MMM/YYYY (e.g., 22/JUN/1993).
- Test **Position** via the options in the drop down menu.
    - This position must remain constant throughout the trial.
- **Race/Ethnicity** using the drop down menu.

3. Click **SUBMIT**.
4. For confirmation purposes, *enter* your Technician password.
5. Click **OK**.
6. Click **TEST** to advance to the testing screen.

NOTE: **TEST** will remain inactive until all demographic information has been entered and submitted.

NOTE: **TEST** will remain inactive if the Technician logged in has not completed their certification requirements and has not been enabled to test.

7.2 RECALLING A SUBJECT

1. At the eSP *Home* Screen, click **Subject**
2. If the screen is populated with data, click **CLEAR/RESET** to clear the entries.
3. Enter the **Subject ID**
4. Click **FIND**

The subject's demographics appear along with previously performed test sets. The **TEST** option will now be active. If the subject is not in the system, a window will appear stating that the subject does not exist. Recheck your ID number, if it does not work you will need to create a new subject.

5. Click **Test** to advance to the *Visit Interval Stage* Selection screen.

You may be prompted to enter your Technician **password**.

- To view a previous test, **click on the row** containing the desired test.
- To recall a different subject, click **clear/reset** the repeat steps from above.

7.3 EDITING SUBJECT DEMOGRAPHICS

1. Recall a subject's demographics.
2. Change information directly on the *Subject Entry* screen.

For each change made, the system will prompt you to enter a reason for the change.
NOTE: Test results cannot be edited.

3. Click **SUBMIT**.
4. For confirmation purposes, enter your Technician **password**.
5. Click **OK**

8 ESP SPIROMETRY TESTING

8.1 PRACTICE SPIROMETRY TEST

Prior to subject testing, it is required to first perform acceptable practice spirometry tests using the eSP system. Each Technician must log on using their own *Login ID* to perform the following tasks.

1. Calibrate the spirometer and print the calibration report. (Refer to *Section 6* for instructions.)

NOTE: The system only allows entry of a temporary ID for the Practice Subject ID which must be in the format of "Test-*your Login ID*". (i.e., if your Login ID is "Tech1," you would enter "Test-Tech1".)

- Perform one (1) practice test of the FVC & SVC, as specified within the Technician Certification Checklist; each test consists of three (3) or more efforts for the FVC & SVC. (Refer to *Section 6* for testing instructions.)

1. Once all practice tests are complete, synchronize to transmit efforts to nSpire Health.

- Once the SCFs have been received, and the calibration and practice spirometry tests have been approved, nSpire Health will enable the Technician.

Sites will be contacted if the calibration and/or practice spirometry do not meet acceptable criteria.

NOTE: A minimum of 48 business hours from time of transmission is required for enablement.

8.2 SPIROMETRY TESTING: SLOW VITAL CAPACITY (SVC)

The SVC test must be performed before FVC.

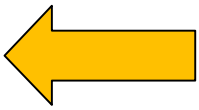
- Enter or Recall the Subject.
- Click **Test.**
- At the *Visit/Interval/Stage* Screen, confirm correct information.
- If it is not correct, make the appropriate changes from the drop down menu options.

NOTE: The eSP system is designed to calculate the next expected Visit, Interval and Stage for a selected subject. Once a test is complete, the system advances to the next expected Visit/Interval/Stage. When the system selected information is changed an exception box will appear and you must enter an explanation for the change.

- Click **SUBMIT**.
- The system will advance to the *Testing* Screen.

- Place a filter on the KoKo Spirometer.
  - The arrows on the side of the spirometer indicate the direction of expiratory flow and point away from the subject.

NOTE: Use a new filter every time you test a new subject.



Direction of expiratory flow

Figure 8-1, Attaching KoKo Filter

- Click **Begin Test** to perform each new effort.
  - The prompt "Zeroing Device-Please Stand by" will appear.
  - Make certain the KoKo Spirometer is held upright and is not moving during this period.
  - The KoKo spirometer should NOT be in or near the subject's mouth while the zero flow is measured.

CAUTION: The system must "zero" the KoKo Spirometer successfully prior to subject testing. Any airflow through the spirometer during this process may result in drift and false referencing, if this happens the zeroing process must be repeated.

After successfully Zeroing the KoKo Spirometer you will be prompted to **"***Begin Tidal Breathing Now***."**

- **Ask the participant to loosen any restrictive clothing and remove denture if they are loose.**
- When the subject is sitting upright, connect the subject to the KoKo spirometer/filter ensuring a tight seal with no leaks. Make sure the nose clips are on.
- Allow them to relax and breathe normally. When they've established a stable baseline, press the **spacebar**.
- The system will wait for five (5) more stable breaths.
- When the tracing turns red, encourage the subject to inhale maximally (inspiratroy capacity maneuver).
- When they've reached a inspiratory plateau, they may relax and slowly exhale completely.(slow expiratory vital capacity maneuver).
- Coach them to push/squeeze the last possible remaining air out of their lungs.
- Press the **spacebar** to end the test.

A maximum of 120 seconds is allowed to complete the testing maneuver.

8.2.1 SVC WARNING MESSAGES/FLAGS

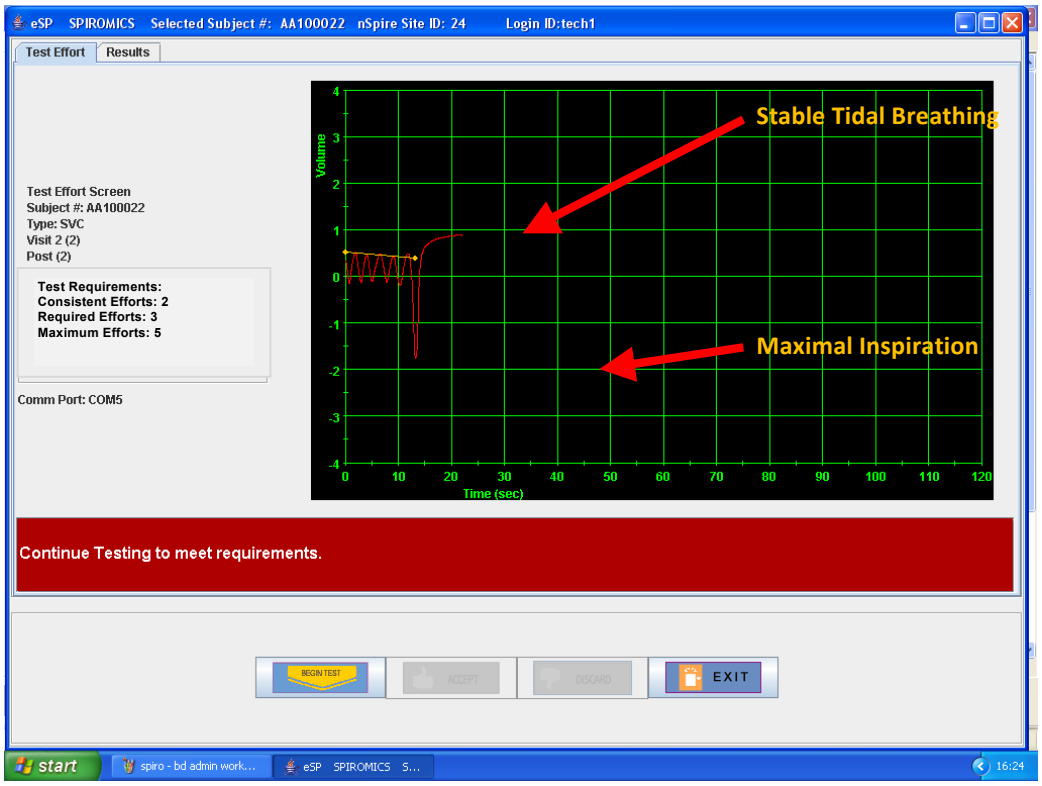
INVALID (Insufficient tidal stability to establish baseline)
Message appears when subject does not perform at least *5 stable* tidal breaths before the deep inspiration.
Resolution: Coach subject to maintain a more stable/relaxed breathing pattern.

INVALID (Insufficient tidal breaths)
Message appears when subject does not perform at least *5 stable* tidal breaths before the deep inspiration.
Resolution: Coach subject to perform more tidal breaths before they take the deep breath in.

INVALID (No SVC maneuver found)
Message appears when the subject does not perform an SVC after the IC or if the space bar is accidentally hit during IC.
Resolution: Coach subject to take a deep breath in (for IC) then exhale completely to a good plateau (for SVC)

Warning: Negative ERV (expiratory reserve volume)
Message will appear if subject does not perform a complete exhalation (after the IC) that goes past (above) the end tidal baseline.
Resolution: Coach subject to exhale completely to a good plateau

Warning: Questionable tidal stability
Message will appear when tidal stability is not reached, i.e. there more than 90 mls difference between end-tidal points. This is the top point of each tidal breath.
Resolution: Coach subject to breathe at a stable rate and volume during tidal breathing



1. Review the Results.
2. Click the **Results** Tab to view more detailed data.
    a. The test effort values will be displayed. The effort with the highest SVC value will be indicated by a ☑ in the column labeled “Best Test."
3. Accept or Discard the test effort
    a. Click **Accept** to keep the effort
    b. Click **Discard** to reject the effort.
        i. Discarded efforts are still counted as part of the maximum efforts allowed.
4. If necessary continue testing to meet protocol requirements
5. The red instruction box on the test screen provides feedback as to whether or not test requirements have been met.

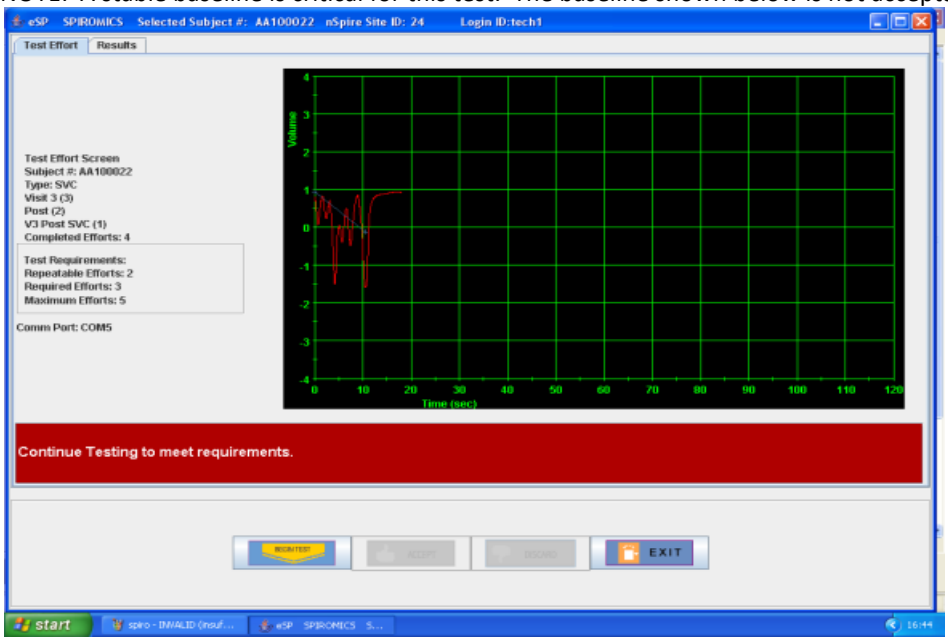
NOTE: It is important to give the subject enough rest in between efforts - allow at least one minute
NOTE: Test efforts should be both graphically and numerically consistent.

6. A minimum of three (3) acceptable IC maneuvers must be performed. The maximum of five (5) maneuvers can be performed per test session.

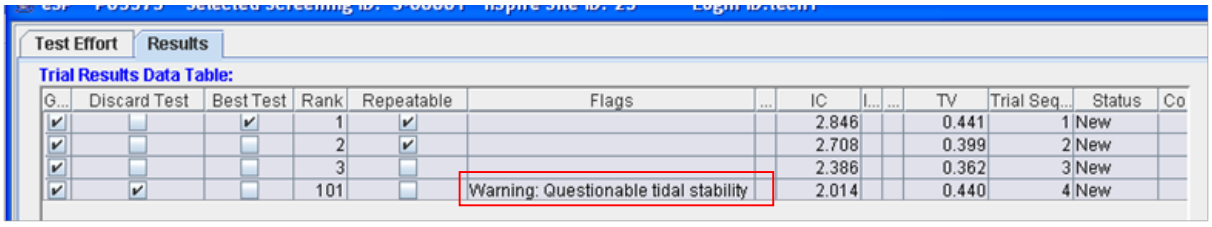
NOTE: Testing should be performed until acceptability and repeatability criteria are met or the maximum number of efforts is reached.
Repeatability: Difference between the largest and second largest SVC.

7. When all testing is complete, click **EXIT**.
8. The system will display visit specific messages. - *It is important to review all messages*.
9. Click **OK**.
10. A confirmation prompt will appear, click **OK** to return to the *Subject Entry* Screen**.**

NOTE: A stable baseline is critical for this test. The baseline shown below is not acceptable.

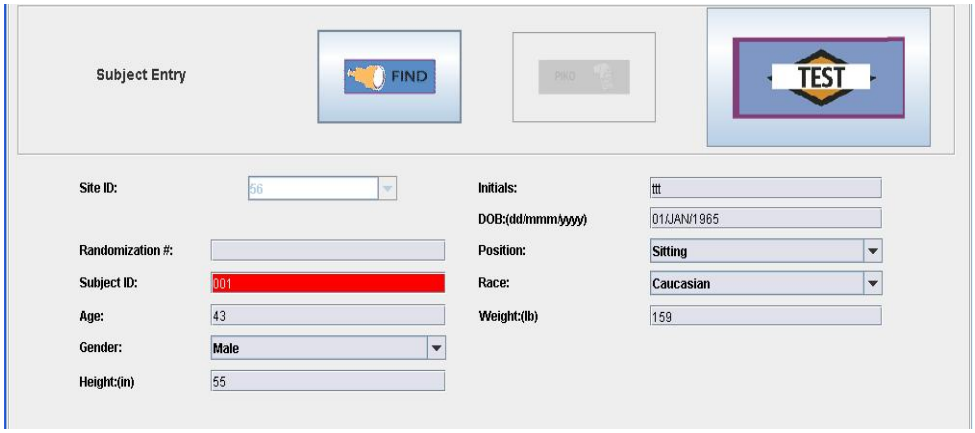


Efforts like this should be discarded.



8.3 SPIROMETRY TESTING: FVC

1. Enter or Recall the Subject.
2. Click **Test.**



3. The system will prompt for confirmation, enter your **Technician Password**.
4. Click **OK**.
5. Confirm correct information at the *Visit/Interval/Stage* Screen .

- If it i*s not correct, make t*he appropriate changes from the drop down menu options.

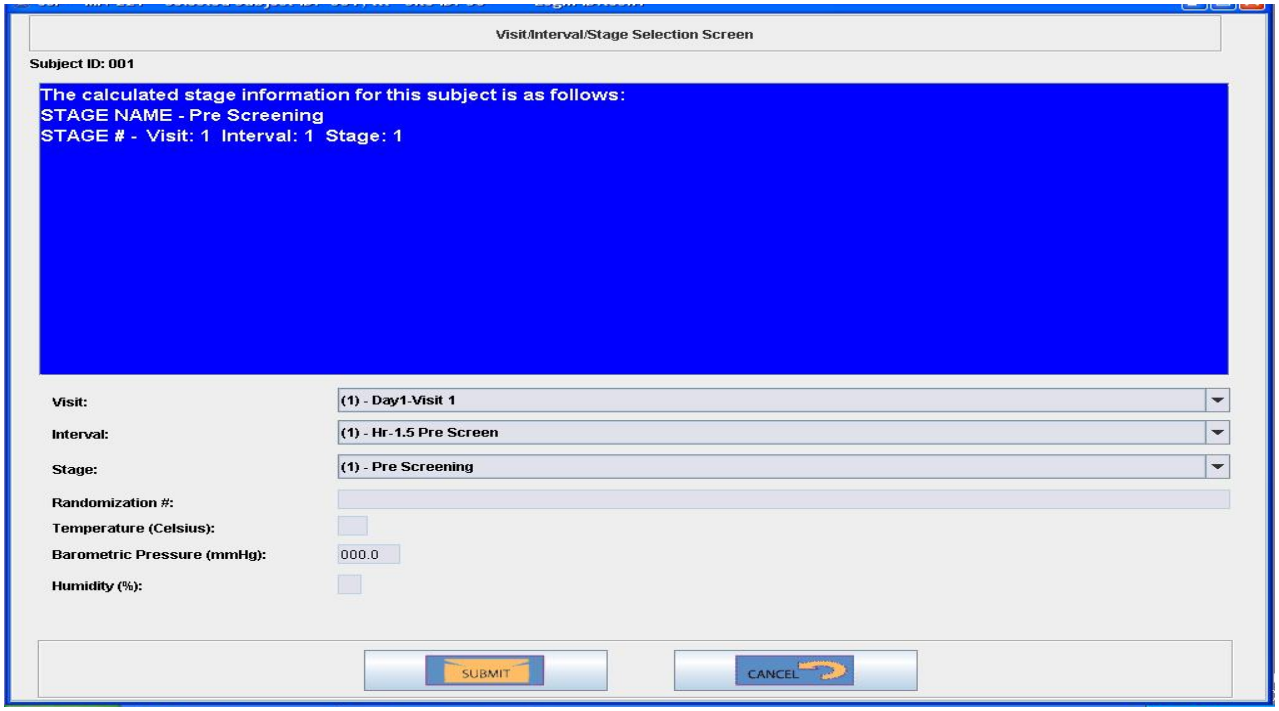


Figure 8-2, Visit/Interval/Stage Screen

NOTE: eSP calculates the next expected Visit, Interval and Stage for a selected subject. Once a test is complete, the system advances to the next expected Visit/Interval/Stage. When the system selected information is changed an exception box will appear, you must enter an explanation for the change.

6. Click **SUBMIT**.
7. The system will advance to the *Testing* Screen and prompt for confirmation of the Subject ID.
8. Enter the **Subject ID** and click **OK**.
9. Click **BEGIN TEST** to perform each new effort.

Precise and forceful coaching by the technician is required to achieve maximal results

10. Wait for the KoKo Spirometer to zero before performing the maneuver.
11. Ensure that no flow moves through the pneumotach at this time. "*Begin Tidal Breathing Now*" will appear.
12. Place the mouthpiece/filter in the subject's mouth, ensuring a tight seal with no leaks.
13. Instruct the subject to breathe comfortably on the mouthpiece for 2-3 normal (tidal) breaths
14. Observe the subject's breathing. At the end of a normal exhalation, instruct the subject to take a maximal inspiration.
15. Press the **spacebar** during this maximal inspiration to start capture the effort.

The color of the tracing will change from yellow to red, to indicate that the system is in measurement mode.

16. Coach the subject to exhale as hard and as fast as they can without hesitation.

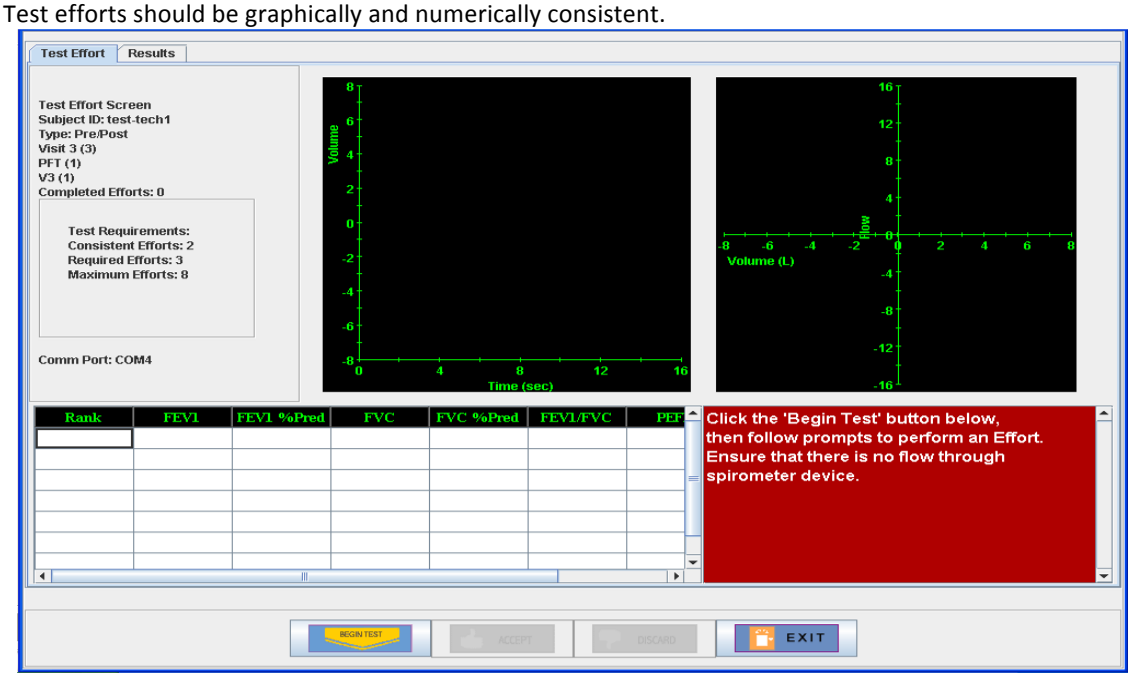
They should continue to exhale for at least 6 seconds and until a flow plateau is reached.

Once the subject blasts the air out they must continue to blow until completely empty. A prompt will let you know that they've exhaled for more than six seconds and/or have reached a one second plateau. The information box will turn green when end-of-test criteria are met.

NOTE: The subject can continue exhaling, if necessary, even though the information box turns green.

17. To complete the maneuver ask the subject to inspire quickly and fully again.
18. Press the **Spacebar** upon completion of the effort.
19. The subject can remove the mouthpiece/filter.
20. The **ACCEPT** and **DISCARD** icons will become active.
21. Messages regarding test quality will be displayed in the red Information area.

NOTE: Test efforts should be graphically and numerically consistent.



8.3.1 VIEW MORE DETAILED TEST RESULTS

1. Click the **Results** tab.
2. Predicted values and test effort values will be displayed.

- The effort with the Highest FEV1 value will be indicated by a ☑ in the column labeled "**Best Test**"

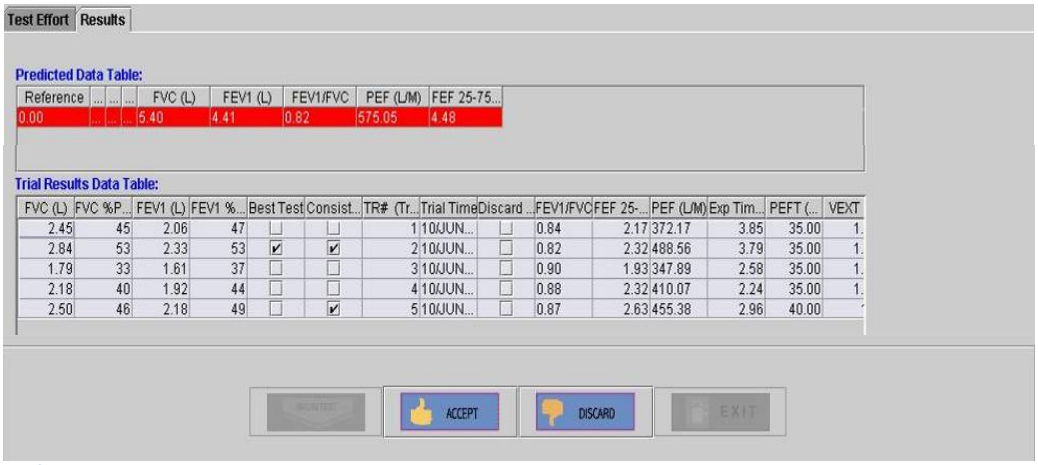


Figure 8-3, Accept / Discard Effort

3. After reviewing the information thoroughly, click **ACCEPT** or **DISCARD**.
4. Click **BEGIN TEST** to perform additional efforts.

NOTE: Testing should be performed until all test and acceptability requirements are met per protocol.

5. eSP software has an automatic discard feature, allowing the system to reject the test if predetermined protocol specific criteria are not met. If this occurs you will *not* be able to choose accept or discard and DIS will appear in the flag column on the *Results* tab screen.

- You may see several quality flags during testing.

Quality flags are described in Appendix 12.3.1

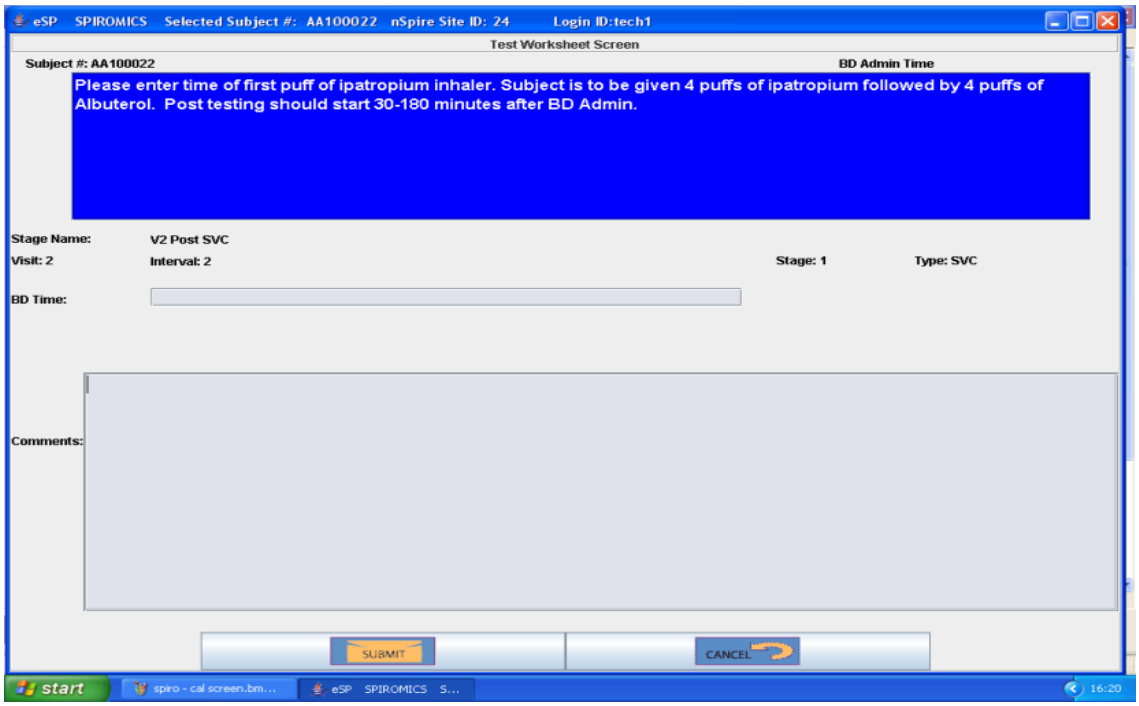
6. When testing is complete, click **EXIT**.

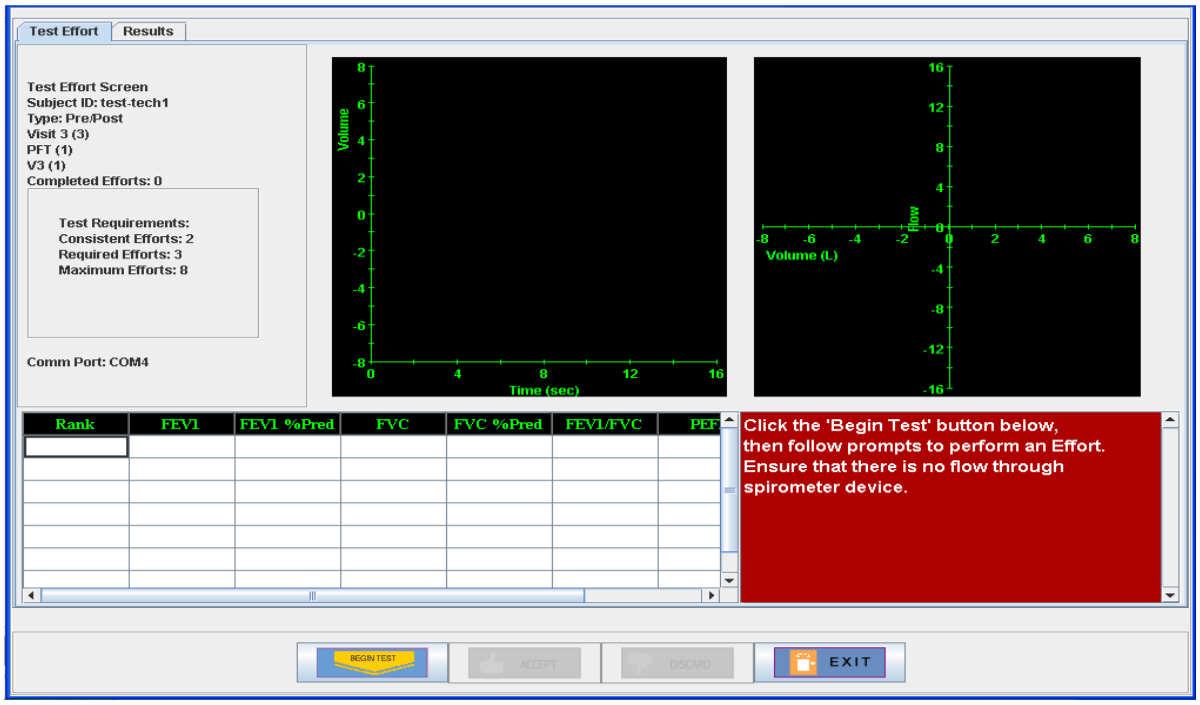
A comment box will appear displaying visit specific messages; review all messages thoroughly before advancing to the next screen.

7. Click **OK** to advance.
8. The system will prompt for confirmation of exiting.
9. Click **OK.**

8.4 WORKSHEET

A worksheet will be presented for documenting the time of the bronchodilator. The time of Bronchodilator administration is a mandatory field. Please enter a value in HH:MM (24 hour clock).





9 EQUERIES

eQueries allow communication between nSpire Health and study sites. An eQuery is an electronic data clarification form (DCF). Communication only occurs during routine data transfer or synchronization.
eQueries are bi-directional. Although they are typically generated by nSpire Health regarding data information, sites may also send eQueries to nSpire Health.
The most common eQuery topics are: new best selections, unacceptable testing, incomplete test sets, or protocol deviations.

9.1 ACCESSING AN EQUERY

Notification that an eQuery has been generated appears in the form of a mailbox on the eSP *Home* Screen.
There are two ways to access the eQuery:

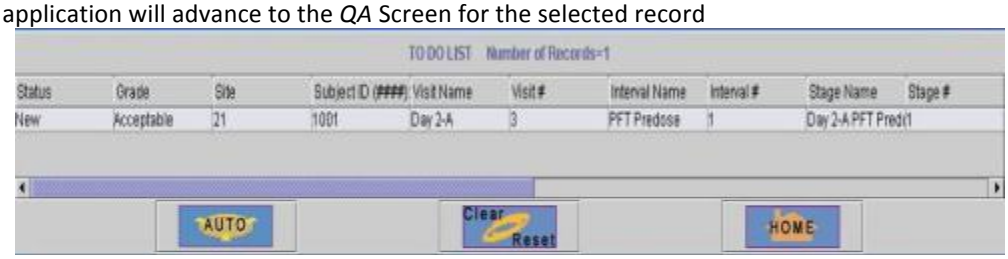
1. Click the **Mailbox** icon 

   OR

2. Click the **To Do List** tab.

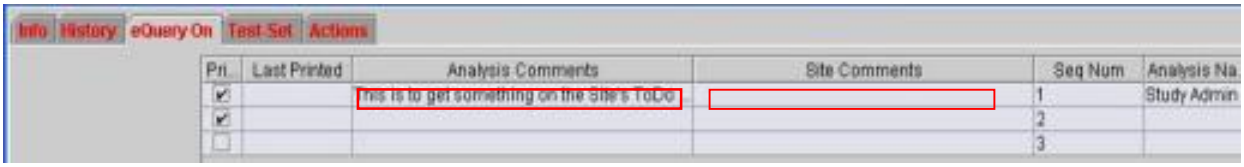
3. The system will advance to the subject records listed in the **To Do List**
4. Access an eQuery by clicking on the desired subject record listed below the header line

- The application will advance to the *QA* Screen for the selected record

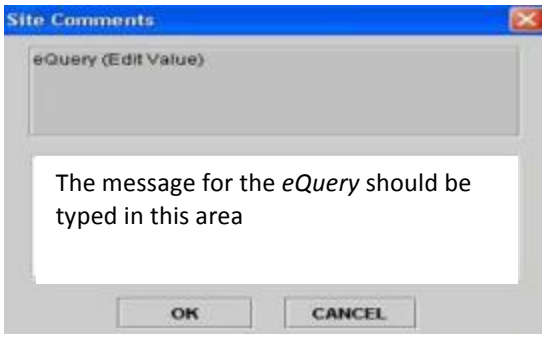


9.2 RESPONDING TO AN EQUERY

1. Click the **eQuery** tab to advance to the *eQuery* Screen
2. Click on the line within the **Analysis Comments** column to view an eQuery



3. Click **OK**
4. To respond, click on an entry within the **Site Comments** box, in the same row as the Analysis Comments.
5. In the resulting pop-up box, type your eQuery message



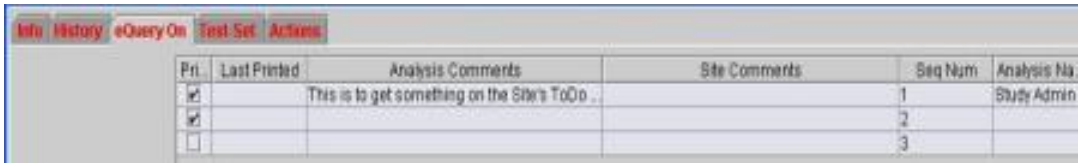
6. Click **OK** to continue
7. A pop-up box will appear
8. Type in your **password**
9. Click **OK**
10. Click **SUBMIT** to save your comment.
11. Failure to click **SUBMIT** will void your comment
12. Click **EXIT** to return to the **To Do List.**

eQueries are transmitted between nSpire Health and the study site during regular synchronization.

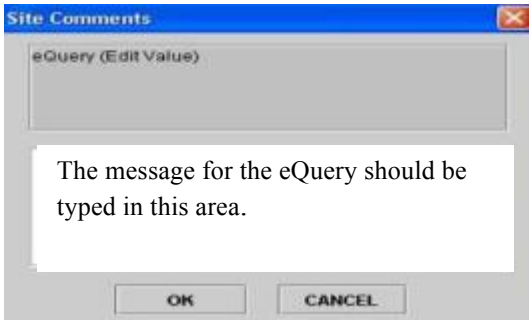
9.3 CREATING EQUERIES

Sites can create their own eQuery by following the instructions below:

1. Recall a subject (see section 7.2 for details)
2. Previously performed tests are be displayed in the lower portion of the *Subject Entry* Screen
3. Click on the row containing the desired test. The system will advance to the *QA* Screen
4. Click the **eQuery** tab
5. Click an new line in the **Site Comments** column.



6. In the resulting pop-up box, type your eQuery message



7. Click **OK** when finished typing the eQuery message
8. Enter your **password** in the pop-up box

9. Click **SUBMIT** to save your comment

Failure to click **SUBMIT** will void your comment

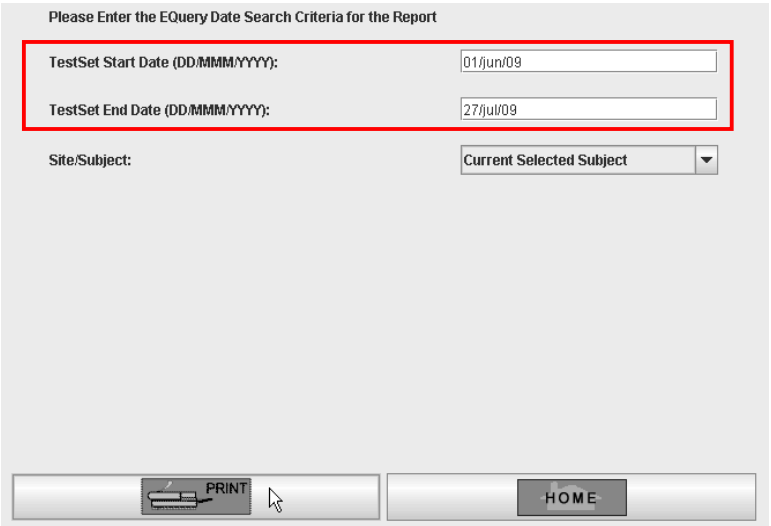
10. Click **EXIT** to return to the *Subject Entry* Screen

Your eQuery message will be transmitted at the next synchronization.

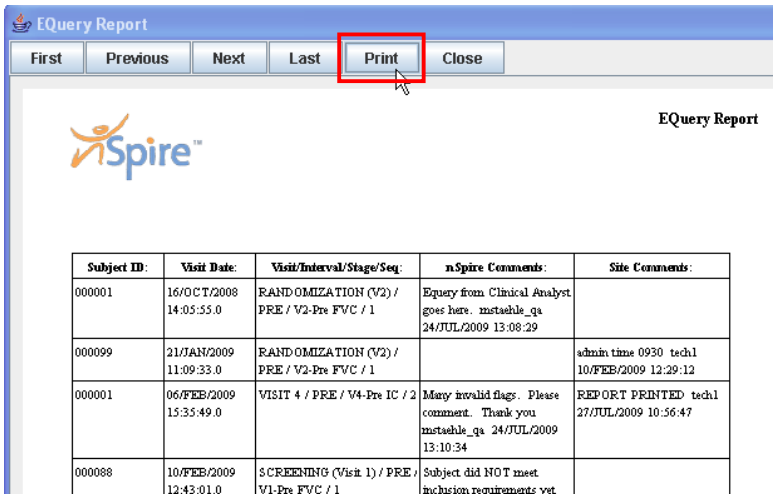
9.4 PRINTING EQUERY SUMMARY REPORT

To view a report:

1. Select **eQuery Summary Report** from the Report menu located on the *eSP Home* Screen.
2. Enter the desired date range for the report criteria you want to see.
3. Click **Print** to generate a preview.



NOTE: nSpire Health recommends that you review these reports weekly to ensure valuable feedback that could impact your study is not overlooked. Never assume an eQuery is closed. It is common to have a follow up eQuery. On the *report preview* screen you can print a copy of the report for your records.



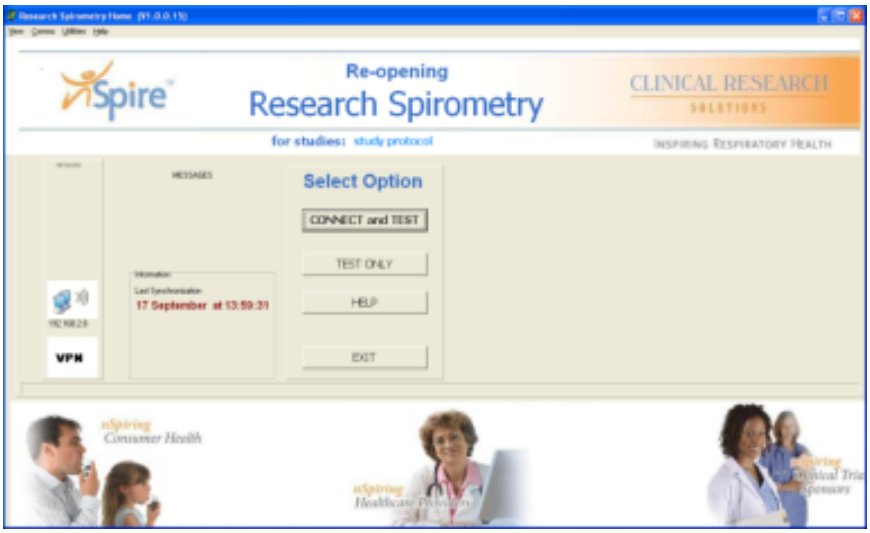
4. Select **Print**.

10 EXITING THE ESP SYSTEM

1. Click **Exit** in the menu bar to "log off" but not closing the eSP application.
2. Click the close window (**X)** box in the upper right corner of the window to close out of the eSP application.

- eSP will close and the following screen will display.

3. Upon successful synchronization the screen will show *Research Spirometry 'Re-Opening'*.
4. At this point the test session is usually finished and 'EXIT' would be used to close the computer, but other options are presented via '**Select Option'**.



5. Choose **CONNECT and TEST**, if another session is required.
6. **HELP** shows user instruction for the study or the program.
7. **TEST ONLY** is used when no network is available**.**

Synchronization should always be done within hours of testing.

11 SAMPLE REPORTS

11.1 CALIBRATION REPORT

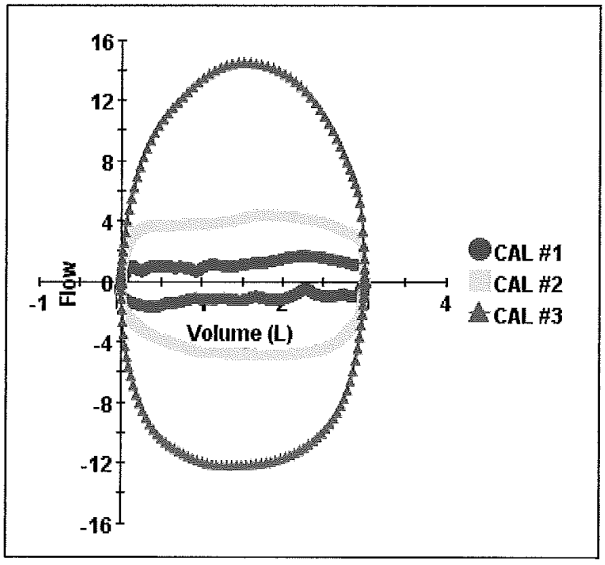
Calibration Report

nSpire Site ID: 22
PI: No Primary Investigator

Calibration Performed: 04/DEC/2009 16:12:49
Calibration Successful on Device #K299A38313025

Measured Value	Expected	Measured	% Expected	Measured	% Expected	Measured	% Expected
FVC	3.000	2.997	99.89	2.999	99.97	3.006	100.19
PEF (L/S)		1.674		4.367		14.495	

Temperature (Celsius): 22 Barometric Pressure (mmHg): 630 Humidity (%): 50
Calibration Performed by: tech1



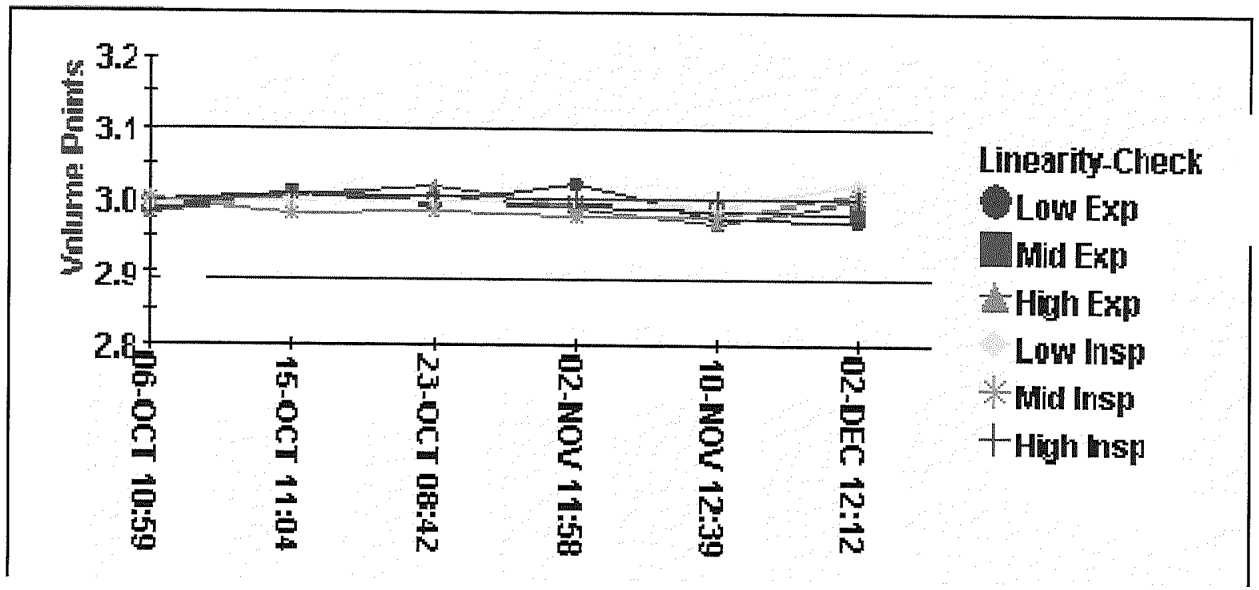
Authorized Signature:_____ **Date:**_____

eSP Version: 3.1.9 B95 SPXXX
Report Printed: 04/DEC/2009 16:12:49
Report printed by: tech1
Page 1 of 1

Linearity-Check Report

nSpire Site ID: 22
PI: No Primary Investigator

Handle ID: K299A38313025
Any volume points outside the blue markers are invalid.



eSP Version:
Report Printed: 04/DEC/2009 16:09:47
Report printed by: tech1

11.3 SPIROMETRY FVC REPORT

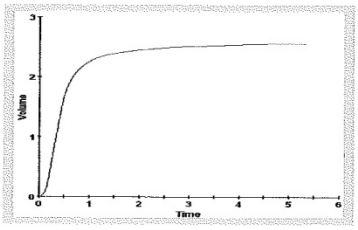
Spirometry Report

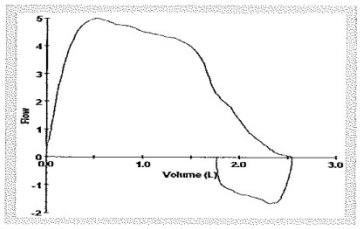
nSpire Site ID: 23
PI: No Primary Investigator

Screening ID: S-00005 | Initials: | Race: Non-Black
Gender: F | Age: 46 | Date of Birth: 12/OCT/1963
Position: Sitting | Height: 160.0 | Weight: 66.0
Visit: Visit 1 Screening (1) | Interval: Pre FVC (2) | Stage: V1 Pre FVC (1)
Randomization #: 1001 | Enrollment Code: | Tech: tech1
Predicteds: nHANESIII_P05575
First Test: 09/DEC/2009 08:46:55 | Best Test: 09/DEC/2009 08:46:55 | Last Test: 09/DEC/2009 08:46:55
Report Comments:
Repeatability Check NOT Reached.(FVC & FEV1)

Function	Pred	B-Meas	%Prd	Meas	Meas	Meas	Meas	Meas	Meas	Meas	Meas	Comp
FVC (L)	3.489	2.554	73.20%									2.554
FEV1(L)	2.8	2.309	82.46%									2.309
FEV1/FVC (%)	0.81	0.90	111.11 %									0.90
PEF(L/M)	402	299	74.38%									299
FEF25-75% (L/S)	2.855	3.597	125.99 %									3.597
VEXT L		0.100										
VEXT (%)		3.91										
FLAGS		BST										
EXP TIME		5.340										

Attempts for this Stage: 1. Ranking order: 1 Graphs in Rank Order





Authorized Signature:_____ Date:_____

eSP Version: 3.1.9 B108
Report Printed: 16/DEC/2009 14:48:09
Report printed by: tech1
Page 1 of 1

11.4 SPIROMETRY SVC REPORT

SVC Report

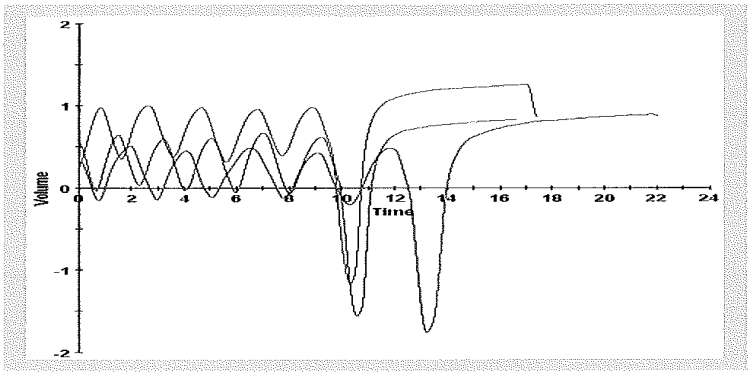
SPIROMICS-SubPopulations and
Intermediate Outcome Measures In COPD Study
nSpire Site ID: 24
Center: 0024, PI: nSpire Health

Subject #: AA100022	Initials:	Race/Ethnicity: Native Hawaiian or Other Pacific Islander
Gender: F	Age: 40	DOB (DD/MMM/YYYY): 12/MAY/1970
Position: Sitting	Height: 160.0	
Visit: Visit 2 (2)	Interval: Post (2)	Stage: V2 Post SVC (1)
Randomization #:	Enrollment Code:	Tech: tech1
First Test: 30/AUG/2010 16:24:42	Best Test: 30/AUG/2010 16:24:42	Last Test: 30/AUG/2010 16:26:31

Report Comments: Repeatability Check NOT Reached.(SVC)

Function	Meas	Meas	Meas	Meas	Meas	Meas	Pred	%Pred	Comp
SVC	2.65	2.42	2.38				3.57	74.2	2.65
IC	2.15	2.11	2.22						2.22
IRV	1.54	1.49	1.56						1.56
ERV	0.50	0.31	0.17						0.50
TV	0.61	0.62	0.66						0.66
Flags	BST								
EFF TIME	16:24:42	16:25:43	16:26:31						

Attempts for this Stage: 3. Ranking order: 1,2,3 Graphs in Rank Order



Authorized Signature:_____ Date:_____

eSP Version: 3.1.0.3
Report Printed: 30/AUG/2010 16:26:51
Report printed by: tech1
Page 1 of 1

Please note: Percentage figures are rounded to the nearest whole number for convenience.

12 APPENDIX

12.1 KOKO SPIROMETER SPECIFICATIONS

The KoKo Spirometer is manufactured by nSpire Health, Inc. as a pulmonary function testing device.

Pneumotach:	Brass Fleisch-type
Dimensions:	18 x 10 x 6 cm
Weight:	0.3 kg
Data Sampling Rate:	128/sec
Volume Scaling:	10 mm/L, user variable
Volume Range:	0-19.9 L
Flow Scaling:	5 mm/L/sec, user variable
Flow Range:	±16 L/sec
Accuracy:	±2%
Power source:	Serial port; battery; or AC power pack; 110, 220, 240 VAC, depending on model
Computer Requirements:	DOS 6.22 or higher Pentium or higher, minimum 100MHZ, minimum 32MB RAM, minimum 60MB available space on hard drive, available Com port
Operating Environment:	20°-35°C
Safety:	EN 60601-1 Class I (grounded typed for both specified power supply and personal computer) Type BF subject applied part. Ordinary equipment (not protected against harmful ingress of moisture). Not suitable for use with flammable anesthetics. Suitable for continuous operation.
EMC:	EN 60601-2 IEC 801-2 / EN 61000-4-2: 3 kV CD, 8 kV AD IEC 801-3 / EN 61000-4-3: 3 V/m IEC 801-4 / EN 61000-4-4: .5 kV I/O, 1 kV AC mains IEC 801-5 / EN 61000-4-5: 1 kV DM, 2 kV CM

12.1.1 CONFORMANCE TO STANDARDS

Industry Recommendations:	ATS 1999, NIOSH, SSD, OSHA, ECCS
Quality System Regulations:	FDA QSR, ISO 9002, EN 46002
Product Testing Regulations:	IEC 601 series, 601-1-1, 601-1-2
European Union Standard:	MDD 93/42/EEC

12.2 ESSENTIAL PRESCRIBING INFORMATION

12.2.1 INTENDED USE AND INDICATIONS

The nSpire Health KoKo Spirometer is indicated for use in pulmonary function diagnostic testing and monitoring of allergies, asthma, and respiratory diseases.

The spirometry software is contained on a computer supplied by nSpire Health. The spirometer connects via its signal input/output port to the serial port of the computer.

During testing, the KoKo pneumotach must be connected to a single subject use, viral/bacterial KoKo Filter and operated by trained medical personnel. The operator must maintain a subject area of 1.5m horizontally and 2.5m vertically and at no time bridge the subject and the computer/printer specified power supply system. The subject holds the pneumotach, but it does not in any way interact with or influence the subject when used as specified.

12.2.2 WARNINGS AND PRECAUTIONS

NOTE: Federal Law restricts this device to sale by or use on the order of a physician.
The computer and specified power supply used with the KoKo Spirometer must be located outside of the subject environment.

Always use the power pack that accompanied your system. Using a different power pack can cause permanent damage to your system. Plug the power supply and all associated computer equipment into grounded outlets.
Always use the KoKo Filter with the KoKo Spirometer. Failure to use the filter could affect accuracy due to expectorated matter in the pneumotach.

The KoKo Filter is designed for single subject use only. Do not attempt to clean or sterilize.
Do not attempt to wash or submerge the KoKo Spirometer in water or cleaning fluid, as there are electronic components inside the handle that will be permanently damaged.

Do not use anti-static or electrically conductive hoses or tubing with this device.

This device complies with the minimum electromagnetic compatibility requirements of the MDD. However, electromagnetic interference may still be encountered. If the device is behaving erratically due to electromagnetic interference, contact Technical Support.

If the power supply included with this device is Class 1 (grounding type), please ensure that it is plugged into a properly grounded receptacle.

Do not attempt to wash or submerge the PiKoLogic in water, there are electronic components inside the device that will be permanently damaged.

12.2.3 QA FLAGS / ABBREVIATIONS

BST - Best Effort

AE- Abrupt End

CG - Cough

6 SEC - Expiration Time < 6 seconds

DIS - Discarded

PEFT – Peak Expiratory Flow Time

BE – Back Extrapolation (VEXT)

RB –Rebreathing - extra breath occurred at end of FVC

NOPLT – No plateau reached during FVC exhalation

12.3 FIREWALL PORTS

IP ADDRESSES AND PORT REQUIREMENTS REQUIRED FOR ESP COMMUNICATIONS			
216.183.118.190	VPN Concentrator		
216.183.118.184	Internet Ping Test		If you are behind a hardware firewall that supports IPSEC pass thru, please enable this option. If your router does not support IPSEC Pass thru you need to open UDP Port 500, protocols 50 and 51 outbound for the Cisco VPN Client to work.
129.6.15.28	Time Server	Gaithersburg, MD	The NIST servers listen for a NTP request on port 123
129.6.15.29	Time Server	Gaithersburg, MD	The NIST servers listen for a NTP request on port 123
132.163.4.101	Time Server	Boulder, CO	The NIST servers listen for a NTP request on port 123
132.163.4.102	Time Server	Boulder, CO	The NIST servers listen for a NTP request on port 123
132.163.4.103	Time Server	Boulder, CO	The NIST servers listen for a NTP request on port 123
128.138.140.44	Time Server	Boulder, CO	The NIST servers listen for a NTP request on port 123
192.43.244.18	Time Server	Boulder, CO	The NIST servers listen for a NTP request on port 123
131.107.1.10	Time Server	Redmond, WA	The NIST servers listen for a NTP request on port 123
66.243.43.21	Time Server	San Jose, CA	The NIST servers listen for a NTP request on port 123
216.200.93.8	Time Server	(Abovenet) VA	The NIST servers listen for a NTP request on port 123
208.184.49.9	Time Server	San Jose, CA	The NIST servers listen for a NTP request on port 123
207.126.98.204	Time Server	Sunnyvale, CA	The NIST servers listen for a NTP request on port 123
205.188.185.33	Time Server	(AOL) VA	The NIST servers listen for a NTP request on port 123
64.156.240.50	liveupdate.symanteclive update.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
204.10.30.16	liveupdate.symanteclive update.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
204.10.30.15	liveupdate.symanteclive update.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
204.10.30.5	liveupdate.symanteclive update.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
209.133.111.3	update.symantec.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).

64.124.186.85	update.symantec.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
216.200.68.150	update.symantec.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
208.254.75.146	update.symantec.com		RTVScan makes a request to Winsock for port 2967/UDP for IP and port 33345 for IPX - Live Update requires access to ports 80 (HTTP), 21 (FTP) and 443 (HTTPS).
	MobiLink		
	Manage Anywhere		
	Sybase		

13 REGIONAL SETTINGS

Upon installation at nSpire Health, the *eSP* Testing System is set as closely as possible to your regional date and time settings. It is important that these settings are verified and adjusted, if necessary.

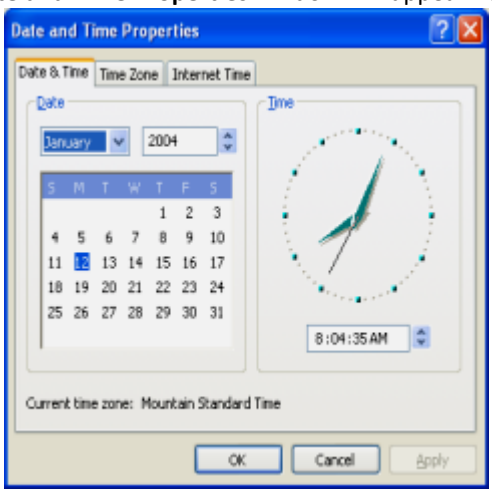
NOTE: Your clock will automatically update to the correct date and time during synchronization. Once you have confirmed your regional settings, you should never have to adjust the time.

To confirm your regional settings, please follow the steps listed below.

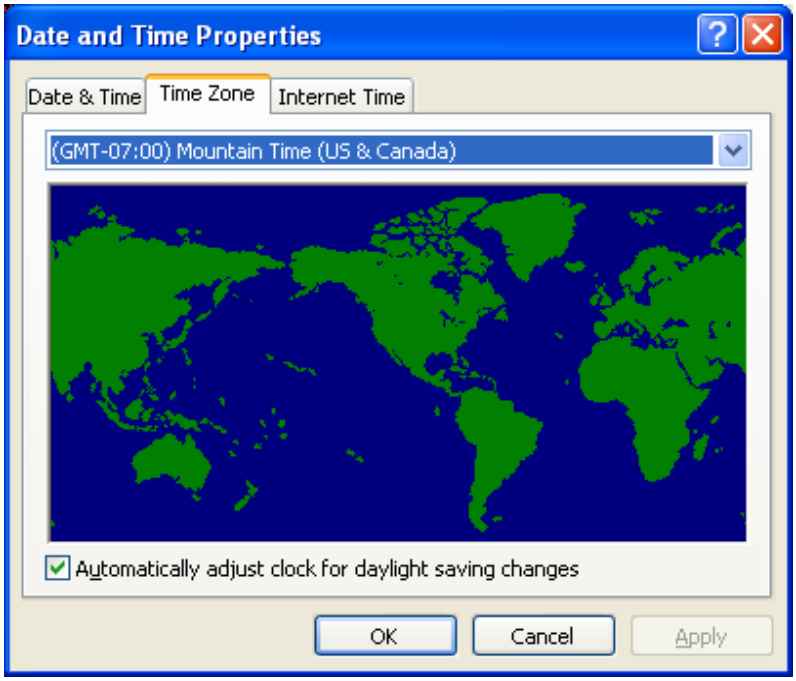
1. On the Windows Desktop, the bar across the bottom of the screen is called the Taskbar.

- The *System Clock* is displayed in the lower right corner on the Taskbar.

2. Double-click the *System Clock*.
3. The **Date and Time Properties** window will appear. Click the **Time Zone** tab.



4. The currently selected Time Zone will appear highlighted at the top of the screen. If the displayed Time Zone is correct for your area, click **OK**. If the Time Zone is incorrect, click the drop-down arrow.



5. A list of Time Zones will appear. Using the cursor or the scroll bar. Go through the list and select the correct Time Zone for your area.

Some areas follow the "Daylight Saving Time" system. If your location does, be sure that the checkbox labeled "*Automatically adjust clock for daylight saving changes*" is checked. If your location does not use daylight saving time, be sure that this checkbox is not checked.

6. Click **OK** when complete

14 FAQ

Q: How are demographic changes made?

A: On the subject entry screen make the changes. You will be required to note a reason for the change.

Q: What if the site administrator leaves?

A: Ask them to create an account for the new administrator before they leave, or

A: Contact nSpire technical support to reset the PI Admin account (First six letters of PI's last name.)

Q: What if a new technician is hired?

A: Site Administrator creates a user account for the new technician, then the technician follows the certification process

Q: After Synchronization, must the system stay connected to the analog phone line or internet during testing?

A: No, the system can be disconnected during testing

Q: Must calibration be performed every day?

A: No, just on days you will be testing

Q: Can the computer be left on overnight?

A: No. Please shutdown at the end of the day

Q: How are passwords reset?

A: Your site administrator can reset your password. nSpire Health's Technical Support can also reset the password

Q: Can we close the laptop lid when the system is idle or being moved?

A: No it is not recommended. However, if you do so, you will need to reboot the laptop before you can resume testing.

15 NOTES: