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SPIROMETRY IN ULTRA2 STUDY

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KTL Kuopio				
University of Wageningen				
GSF Oberschleissheim				
ECN Petten				
University of Kuopio				
University of Helsinki				

SPIROMETRY IN ULTRA2 STUDY

1.0 Purpose and Applicability

The purpose of this SOP is to ensure that all spirometric measurements within the ULTRA-II study are done in the same way by the different fieldworkers at the participating centers. It is the objective of quality control to achieve maximal accuracy and precision. Biological variability is minimized by careful attention to the time and circumstances of the test (e.g. with respect to environmental conditions). Variability in the measurement is minimized by frequent checks of instrument performance, instrument maintenance, proper instrument use, adequate instruction of the person being tested and well-trained personnel who can administer the test professionally and according to this standard operating procedure.

2.0 Definitions

Spirometric terms are derived from the Official Statement of the European Respiratory Society, 1993.

BTPS ***B****ody* ***T****emperature, ambient* ***P****ressure,* ***S****aturated with water vapor*.

FEV_t The timed ***F****orced* ***E****xpiratory* ***V****olume* is the maximal volume of gas exhaled in a specified time from the start of the forced vital capacity maneuver; conventionally, the time used is 1 second, symbolized $FEV_{1.0}$, expressed in liters (BTPS).

FVC The ***F****orced* ***V****ital* ***C****apacity* is the volume of gas delivered during an expiration made as forcefully and complete as possible starting from full inspiration, expressed in liters (BTPS).

MMEF The ***M****aximal* ***M****id-****E****xpiratory* ***F****low*, also called forced mid-expiratory flow ($FEF_{25-75\%}$), is the mean forced expiratory flow during the middle half of the FVC, expressed in liters/second (BTPS).

PEF The ***P****eak* ***E****xpiratory* ***F****low* is the maximal flow during a forced expiratory vital capacity maneuver starting from a position of full inspiration, expressed in liters/second (BTPS).

3.0 References

1. ATS Board of Directors. Standardization of Spirometry. Am J Respir Crit Care Med 1995;152:1107-1136.
2. ATS Joint Committee on Pulmonary Nomenclature. Pulmonary terms and symbols: a report of the ACCP-ATS Joint Committee on Pulmonary Nomenclature. Chest 1975;67:583-593.
3. Denolin H, Arhirii M. Nomenclature and definitions in respiratory physiology and clinical aspects of chronic lung diseases. Bull Physiopath Respir 1975;11:937-959.
4. Enright PL, Johnson LJ, Connett JE, Voelker H, Buist AS. Spirometry in the Lung Health Study: methods and quality control. Am Rev Respir Dis 1991;143:1215-1223.
5. Gardner RM, Claussen JL, Crapo RO, Epler GR, Hankinson JL, Johnson RL (Jr.), Plummer AL. Quality assurance in pulmonary function laboratories. Am Rev Respir Dis 1986;134:626-627.
6. Quanjer PH, Tammeling GJ, Cotes JE, Pederson OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. Eur Respir J Suppl 1993;16:5-40.

4.0 Discussion

This SOP follows the protocol of the European Respiratory Society (6), with the exception of the number of required acceptable attempts (two instead of three).

5.0 Responsibilities

University of Wageningen is responsible for developing the contents of the SOP for spirometry. All centers are responsible for spirometric measurements in their study. Quality control will be monitored by the University of Wageningen.

6.0 Equipment and Materials

The spirometer or pneumotachograph and software for data acquisition should fulfill the technical requirements of the ECCS (Quanjer, 1993). Each center will use available equipment.

In Finland a portable computerized spirometer with a heated pneumotachograph (Medikro 909, Medikro Oy, Kuopio, Finland), with disposable breathing tubes is used.
In the Netherlands a computerized spirometer with a heated pneumotachograph (Jaeger Benelux, Masterscope pneumotachograph; with disposable breathing tubes is used.
In Germany a computerized spirometer with a heated pneumotachograph (Jaeger Benelux, Masterscope pneumotachograph, with disposable breathing tubes is used.

List of necessary equipment:
- spirometer/pneumotachograph
- spare parts spirometer/pneumotachograph
- personal computer
- equipment to adjust height of mouth piece to each person
- mouthpieces
- alcohol
- tissues
- 3 l syringe
- data sheets for recording spirometer checks (Figure 1)
- pens
- diskettes for backups
- weighing scale
- height meter
- thermometer
- manufacturers manual
- this SOP
- list of subject names and numbers

7.0 Procedure

7.1 Overview
Before measurements of subjects take place, the following procedures have to be followed by the technician:
- Installation of the spirometer and other equipment such as weighing scale in the research room
- Calibration and checking of the spirometer

With each subject the following procedures have to be followed:

1. Recording of the descriptive data:
Unique technician number
Unique spirometer number
Date and time of the measurement
Temperature of the room
Unique subject number
Height and weight (only the first time)
Medication use
Presence of a cold or attack of shortness of breath with wheezing

2. Adjusting equipment to personal height of subject.
Instruction and demonstration of the maneuver
Performance of at least two acceptable forced expiratory maneuvers

In the next sections these procedures are presented in more detail. Actions that are very specific for the equipment used (such as how to put together the measuring head of a pneumotachograph) are not discussed in this manual. The manufacturer's manual should be followed for these issues.

7.2 Preparation

7.2.1 Appointments
Several factors need to be taken into account when appointments with the subjects are made. Because of diurnal variations serial measurements of subjects should take place at the same moment of the day, preferably within a 2 hours range. When an appointment is made for lung function testing, technicians should determine beforehand whether the subject is taking medications. If the subject is taking any of the below mentioned medicines an appointment time should be agreed upon that causes the least disruption to the normal dosing schedule of the subject.
The subject should not:
- take any inhalator in the last one hour before the test
- smoke within one hour before the test
- eat 15 minutes prior to testing.
The subject should *ideally not:*
- take a beta-2 stimulating or anticholinergic inhalator within the last 4 hours before the test
- take oral beta-2-agonist, oral theophylline or oral anticholinergicum within the last 8 hours before the test.

7.2.2 Installation

Before installation of spirometric equipment the investigation room has to be chosen carefully in order to prevent excessive temperature fluctuations. Spirometric equipment should not be located in direct sunlight. Spirometric performances should not be conducted with temperatures less than 17 EC or more than 25 EC. The reason for this is that the correction for ambient temperature is not without problems.

Spirometric equipment should be rinsed thoroughly before use according to the manufacturer's manual. Reusable mouthpieces, breathing tubes, valves and manifolds should be disinfected after each subject. Disposable mouthpieces should be discarded after each subject.

The equipment should be calibrated according to specifications of the manufacturer. Record the descriptive information from the calibration to document the quality of the calibration. Checks on volume measurement have to be performed daily prior to testing and then every 4 hours during use, with a calibrated syringe with a volume of at least 3 liters (accurate within 25 ml). Type of syringe should be recorded. Before checking heated pneumotachometers have to warm up for the time specified by the manufacturers manual. Discard first stroke whereas a residual volume in the syringe would distort the check. At least 3 different strokes should be obtained. These checks should be recorded (11.0; table 1). This frequent checking is in excess of recommendations from most manufacturers and the ECCS protocol (Quanjer, 1993). An error of up to 3.5% or 70 ml, whichever is greater, is acceptable. It is not necessary to actually change calibration factors of the equipment after each check. Every day (non-asthmatic) all field technicians should make two spirometric attempts prior to testing in order to detect potential differences in expiratory flows. FVC and FEV1 should be within 6% of the mean value; PEF and MMEF should be within 15% of the mean value of the technician. These measurements should only be conducted when the technician does not an airway infection or airway problems.

Subjects should only be tested if all specified conditions are satisfied.

7.3 Recording of descriptive data for each test

Recording of the following items is necessary before each test. Height and weight are measured only during the first test day.

- Every technician has his/her own unique number to allow adjustment for possible variation introduced by differences between pulmonary function technicians per center.
- If more than one spirometer is being used, each spirometer should be recorded by its own unique number.
- Time (hh:mm) and date (ddmmyy) of the measurement.
- The temperature of the room has to be noted to make correction possible to BTPS. Temperature has to be recorded before each individual test, since temperature changes in the investigation room can occur. The thermometer may not be exposed to direct sunlight or laid down on a table. The thermometer should not be hung along a cold wall. The temperature in the investigation room has to be kept as stable as possible, because gases in the volume type spirometers have finite cooling times. This means that the exhaled gases may not have cooled down to ambient temperature assumed in the BTPS correction (ATS, 1987).
- Ambient barometric pressure has to be collected from the nearest weather station or measured from a calibrated barometer in the research room. Daily average pressure is sufficient. The weather station should be located at the same height as the research room.
- Subject numbers are unique numbers to be given to each subject participating in the study.

Identification code is similar to that of the Holter-recording. Beginning with Ultra2-Spiro, and after this a three digit number indicates the study center and subject: 100 - 299 = Amsterdam, 300 - 499 = Erfurt, and 500 - 699 = Helsinki, and finally, a 6-number set indicates the date of the recording. Example: Ultra2-Spiro-134-010399 indicates that the spirometric recording has been done in Ultra2 study in Amsterdam to subject with an identification number 134 on the first of March, 1999.
- Height of each subject, without shoes (∀ 1 cm). The subjects' heels should be placed against the wall and the head should be kept upright.
- Weight of the subject (∀ 1 kilo). The measurement is performed without shoes but with clothes. Remove heavy objects from the pockets. Place the balance on a hard, flat surface.
- The subject is asked if she/he had an airway infection, shortness of breath or wheeze. This has to be reported by the subject, not diagnosed by the technician. The exact questions are listed in the clinical visit questionnaire.
- Medication use. The exact questions are listed in the clinical visit questionnaire.
- Smoking in the past hour.

If subjects report smoking or the use of any inhalator within one hour before the test was planned, the test should be postponed. If one of the other conditions mentioned in 7.2.1 is not fulfilled, the measurement continues and the response to the question is recorded.

7.4 Performance of forced expiratory maneuvers
The subject should have been at rest 15 minutes before measurement is performed. Rinsing of the mouth with water is recommended when left-behind food particles are present.

Forced expiratory maneuvers are performed:
- Sitting
- With noseclip
- Using a plastic or cardboard mouthpiece without teethgrips
- Thorax must move freely so tight clothing has to be loosened.
- Dentures should not be removed.

Adjust equipment to personal height of subject. The subject is asked to sit upright. The mouthpiece must be placed slightly higher than the mouth in order to prevent the larynx to block the exhalation. The subject should not lean forward during expiration since it will compress the trachea.

Instruct the subject how to perform the maneuver. Technicians must explain to the subject that the aim of the test is to measure how much air can be blown out of the lungs and how forcefully it can be blown out. This is done by asking the subject to follow these steps:

Place mouthpiece in the mouth.
- Close lips tightly around the mouthpiece.
- Take in as deep a breath as possible and when full;
- Exhale through the mouthpiece into the equipment, blowing out air as fast, smoothly and completely as possible. The subject should continue to push out air actively for as long as possible. During this time it is extremely important that the technician offers positive encouragement to push or squeeze out more air. The technician will tell the subject when to stop.

If closed circuit measuring equipment is used subjects should in- and exhale normally a few times before forced exhalation to get use to the equipment.

At the first visit the maneuver has to be demonstrated, using a detached mouthpiece, to each subject at least once (more often if he/she appears uncertain). Two practice attempts are allowed; if performed they should be recorded. If the subject fails to produce acceptable maneuvers, the technician must show the subject again how to conduct the maneuver.
Have the subject perform at least 2 acceptable (defined below) forced expiratory maneuvers. The technician should carefully observe the subject for correct conduct of the test; he/she should not only watch the computer screen or paper recorder. Flow-volume and/or volume time curves should be checked as well.

The highest FVC and $FEV_{1.0}$ may not exceed the second highest FVC and $FEV_{1.0}$ with more than 5% or 100 ml, whichever is greater. This criterion is used to determine whether more than 2 acceptable maneuvers are needed.
Technicians are always free to demand additional maneuvers in case there=s doubt about the maximal exhalation of the subject. However this should occur in a limited number of the subjects since the goal is to obtain two acceptable maneuvers.

If subjects are unable to produce 2 acceptable maneuvers after 5 attempts it is generally not useful to perform more tests. However if the subject has just learned the procedure more attempts can be performed.

Record if the obtained data is in compliance with the instructions. Record on the clinic visit logbook (backside) also which attempts are suitable for data-analysis and why other attempts should not be used (e.g. person didn't exhale completely).

Acceptability criteria maneuvers
All maneuvers should comply with the general acceptability criteria of the ERS. Maneuvers, which do not comply, to these criteria should not be used in the analysis. The criteria are:
- no unsatisfactory start of expiration characterized by excessive hesitation or slow start,
- not greater than 5% FVC or 100 ml back extrapolated volume,
- no coughing that interferes with the accurate measurement of the variables,
- no Valsalva Maneuver (glottis closure),
- no leak in the system around the mouthpiece or elsewhere
- no obstructed mouthpiece e.g. tongue in front of the mouthpiece,

The criterion that the highest FVC ($FEV_{1.0}$) may not exceed the second highest FVC ($FEV_{1.0}$) with more than 5% or 100 ml is not used for excluding complete tests from data analysis (Quanjer, 1993). Tests that did not meet this criterion should be marked, in order to be able to analyze these data separately.

7.5 Calculations
7.5.1 BTPS correction
Spirometric recordings made at temperatures and water vapor pressures that differ from those in the lung should be corrected to BTPS conditions as follows:

$$V_{BTPS} = V_{ATP} * 310.2 * (P_B - P_{H20}) / [273.2 + t) * (P_B - 6.3)]$$

V_{BTPS} = Volume at Body Temperature, ambient Pressure, Saturated with water vapor (l or l/s)
V_{ATP} = Volume at ambient temperature and pressure (l or l/s)
P_B = barometric pressure (kPa)

P_{H20} = water vapor pressure (kPa) =1.63 - 0.071 t + 0.0053t^2 (=6.3 at 37EC)
t = ambient temperature (EC)

Note that “ambient” relates to the temperature and saturation attained by the air when it is exhaled into an instrument. For the purpose of this study it is assumed that it can be approximated by that of room air.
7.5.2 Selection of best lung function values
For each test we will have a different number of maneuvers available. From these maneuvers, the best FVC, FEV1, PEF and MMEF have to be selected.
First, all recordings in the database which don’t comply with the general acceptability criteria of the ERS should be eliminated from the database. This is done by identifying all attempts, which are recorded as not suitable for data-analyses. The data from subjects who where unable to perform 2 acceptable attempts are not used.

Second, multiple recordings from the remaining subjects should be reduced to 2 *best* attempts. Determination of which attempts are best should be done in the following order. Note: this is not dealt with in the ERS protocol.
Attempts should be within 10% of the highest PEF. Submaximal efforts may lead to FVC and FEV1 values that are too high.
If the number of attempts still exceeds 2, attempts with a $FEV_{1.0}$/FVC-ratio that is at least 5% higher than the ratio found for other maneuvers should be eliminated, since it=s likely that exhalation was terminated early (resulting in too high MMEF values).
If the remaining amount of attempts still exceeds 2, the 2 attempts with the highest FVC should be selected for analyses.

Third, selection of the best values from the two remaining (*best*) maneuvers has to be done according to the >maximum value= method described in the ERS protocol. The highest value of the FVC, $FEV_{1.0}$ and PEF has to be selected from the two curves. The highest MMEF and other flow variables ($MEF_{x\%}$) has to be determined from the two curves, but the curve being used may not have a FVC differing more than 5% from the highest FVC. Thus, it is possible to select different lung function variables from different curves.

7.6 Quality Control
Technicians have to be instructed thoroughly how to perform the measurement on the subjects. It has been proven useful to provide the technicians with examples of flow-volume and volume-time curves in which errors or disturbances are indicated. Curves collected by ATS have therefore been attached (11.0; Figure 2).

Spirometers are checked frequently by a 3 liter syringe and by technicians performing a spirometric test every day.

Checks have to be performed on data entry errors such as observations with unusually high or low pulmonary function variables and impossible combinations of pulmonary function variables, e.g. FVC less than $FEV_{1.0}$. During analysis comparisons have to be made between the different spirometers and/or technicians at each center.

To test for potential differences between centers, the results of the first measurement day of all subjects will be sent to the University of Wageningen where they will be checked. Feedback will be given to all technicians in order to increase comparability between the centers. Transferred data should include the flow-volume, volume-time curves and the quantitative values for FVC, FEV1, PEF and MMEF. Only the final results, that is the best

values defined above, from each test should be sent. In addition, a 5% random selection of data from all test days will be checked at the University of Wageningen after all measurements have been done.

During a site visit of the coordinating center a comparison will be made of the local equipment operated by the local technician with a standard spirometer operated by a technician from the coordinating center. At least ten subjects (probably laboratory staff) will be tested in random order.

8.0 Data Records

Recording of the FVC, $FEV_{1.0}$, MMEF and Peak Expiratory Flow and temperature is necessary. Syringe checks should at least be done before measurements and every 4 hours. Also a spirometric performance of the field technician should be recorded every day prior to the measurements. For every subject weight, height, medication use, having a cold, shortness of breath and wheezing have to be recorded in the clinical visit questionnaire. Back-ups should be made at least every day after measurements. Data has to be stored on separate diskettes for each spirometer. Label each diskette with dates, location and number of spirometer.
Checks on the spirometric equipment have to be recorded on a data-sheet (11.0; tables 1 and 2).

9.0 Sample Archiving

Data sheets and files have to be stored (password-protected) for at least 5 years at the respective institutes.

10.0 Implementation and Application

This SOP will be distributed by KTL ULTRA center to other ULTRA centers by mail or telefax. Reception of a new SOP or revision should always be confirmed to KTL ULTRA center.

11.0 Attachments

Figure 1. Data sheet for recording of quality checks of spirometric equipment.
Figure 2. Examples of flow-volume and volume-time curves.
Figure 3. Local and temporal deviation from or local change of a SOP.
Figure 4. SOP confirmation sheet.

Figure 1. Data sheet for recording of quality checks of spirometric equipment.

Center :_____

Record calibration information as appropriate for your spirometer. Next checks should be performed daily each four hours. Perform three maneuvers with the syringe and record the three readings of the FVC. Next the technicians should perform at least two expiratory maneuvers to check especially the expiratory flows.

Table 1. Syringe checks of spirometer.

Date (dd/mm/yy)	Time (HH:MM)	Spirometer ID	Technician ID	Temperature (EC)	FVC (l) Results of 3 strokes

Table 2. Technician checks of spirometer (expiratory maneuvers before start of a measurement day only).

Date (dd/mm/yy)	Time (HH:MM)	Spirometer ID	Technician ID	Temperature (EC)	FVC (l)	FEV1 (l)	PEF (l/s)	MMEF (l/s)

Figure 2. Examples of flow-volume and volume-time curves.

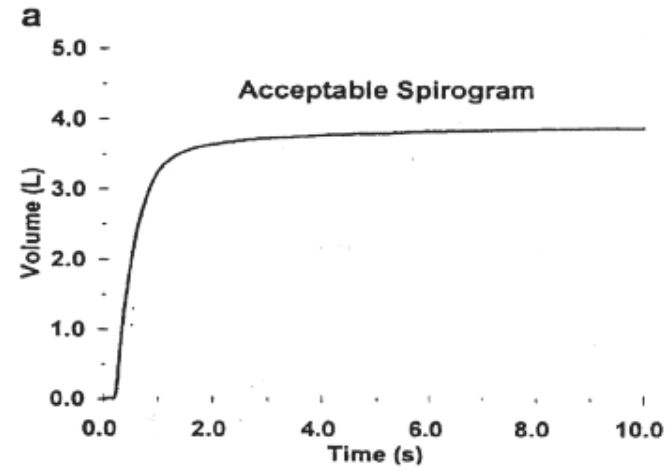

Figure A1a. Acceptable volume–time spirogram.

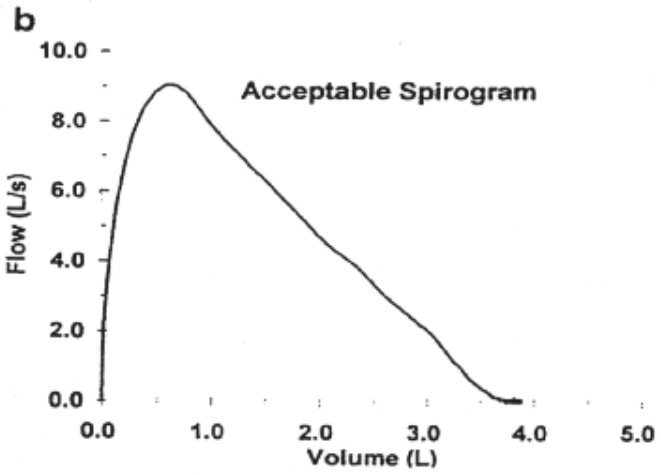

Figure A1b. Acceptable flow–volume spirogram.

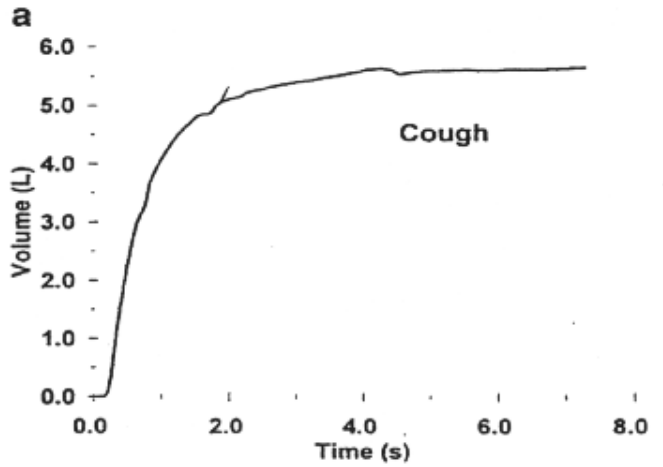

Figure A2a. Volume–time spirogram with a cough during the first second of exhalation.

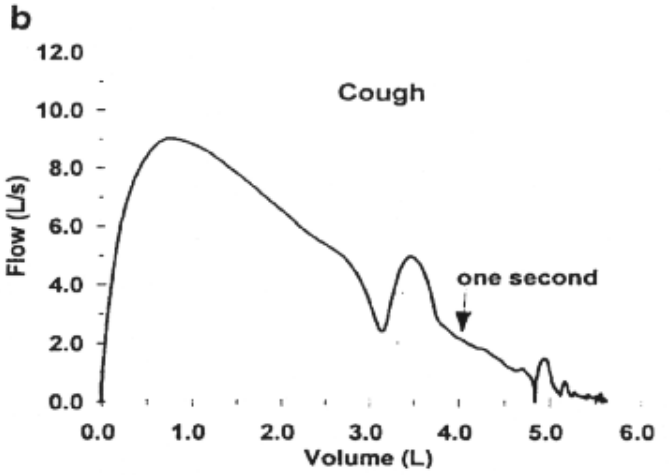

Figure A2b. Flow–volume spirogram with a cough during the first second of exhalation.

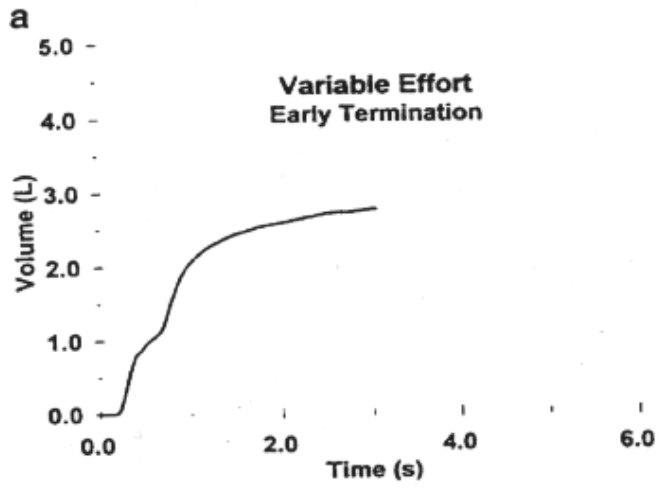

Figure A3a. Unacceptable volume–time spirogram due to variable effort and early termination.

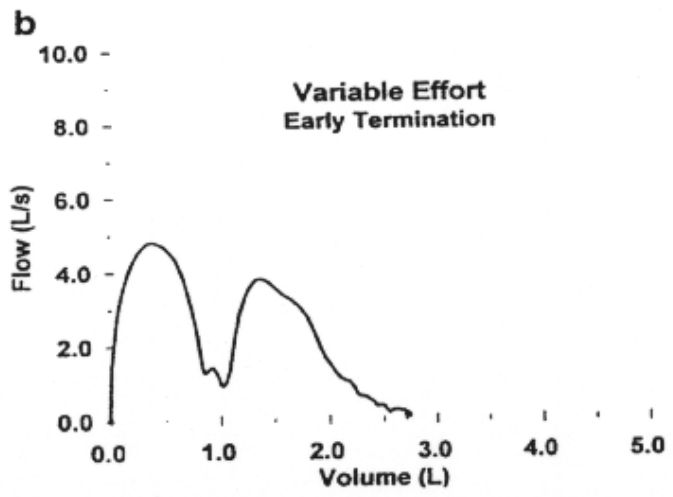

Figure A3b. Unacceptable flow–volume spirogram due to variable effort and early termination.

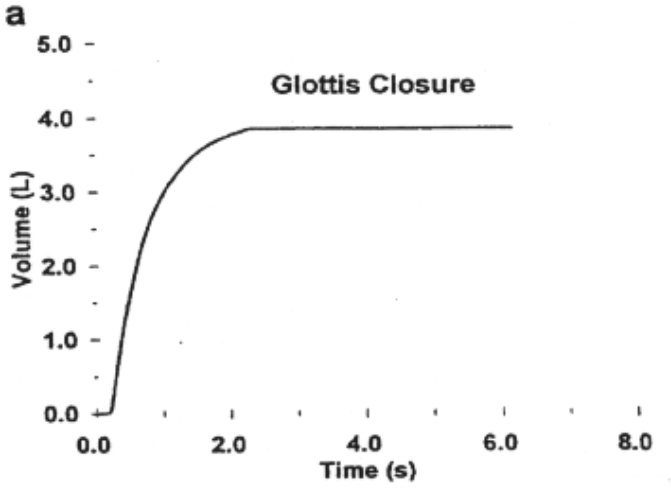

Figure A4a. Unacceptable volume–time spirogram due to possible glottis closure.

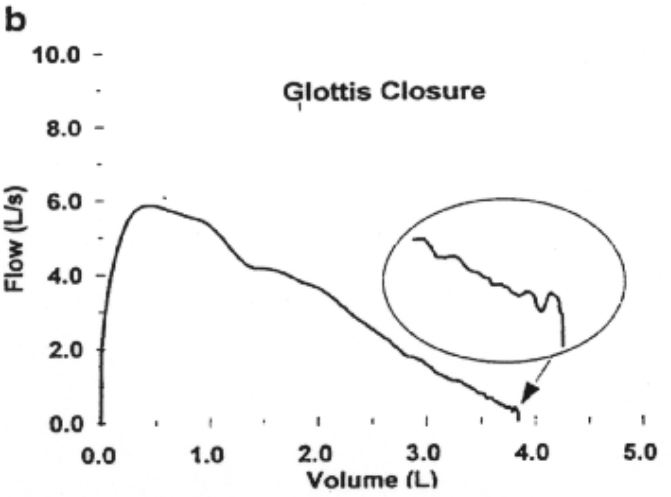

Figure A4b. Unacceptable flow–volume spirogram due to possible glottis closure.

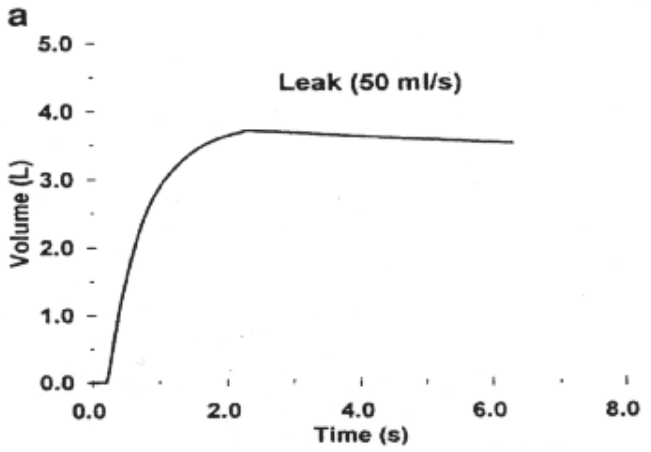

Figure A5a. Unacceptable volume–time spirogram due to a leak.

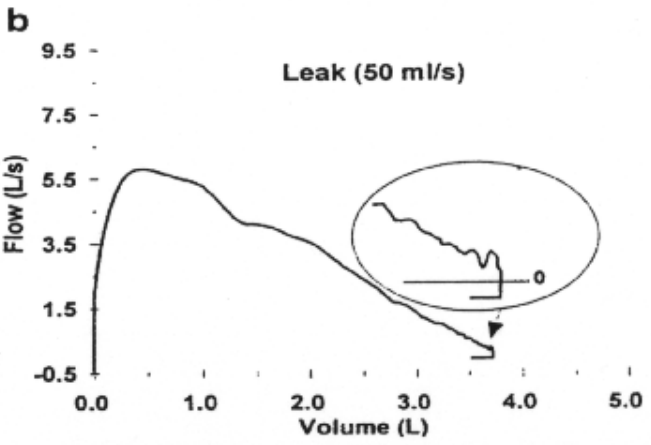

Figure A5b. Unacceptable flow–volume spirogram due to a leak.

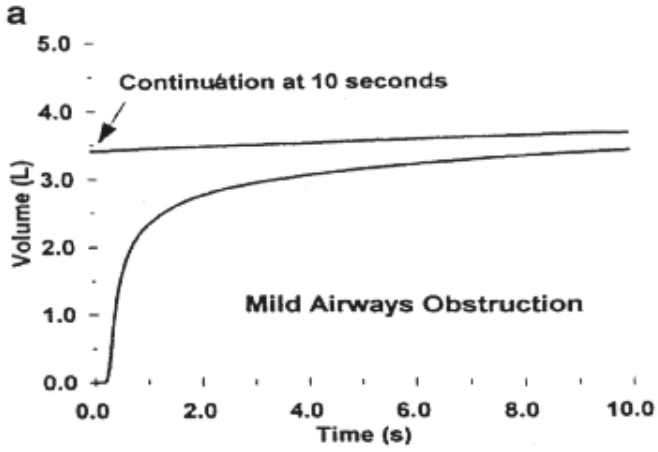

Figure A6a. Acceptable volume–time spirogram for an individual with mild airways obstruction.

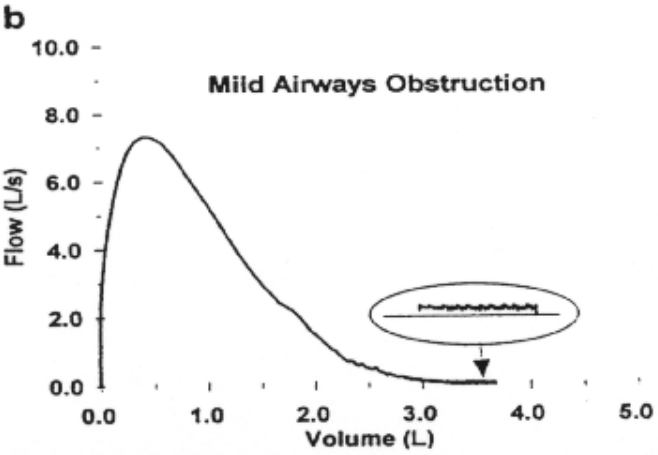

Figure A6b. Acceptable flow–volume spirogram for an individual with mild airways obstruction.

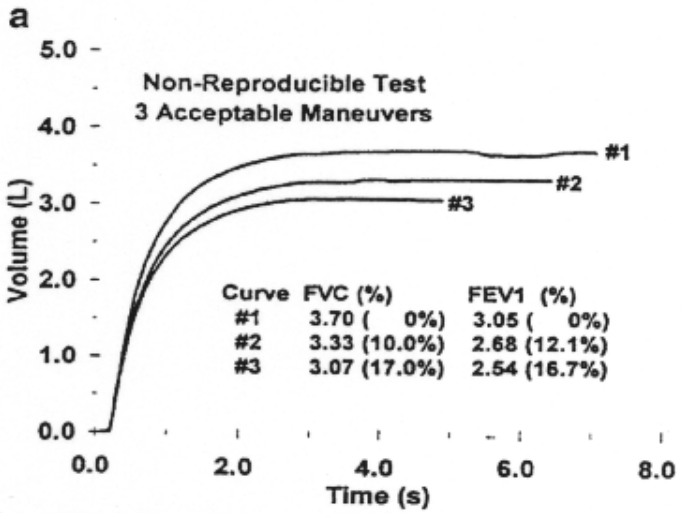

Figure A7a. Nonreproducible test with three acceptable volume–time curves. Percents are difference from largest value.

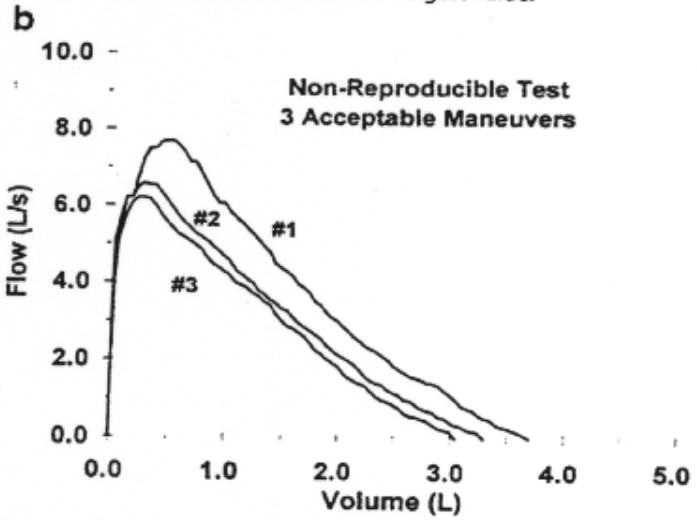

Figure A7b. Nonreproducible test with three acceptable flow–volume curves.

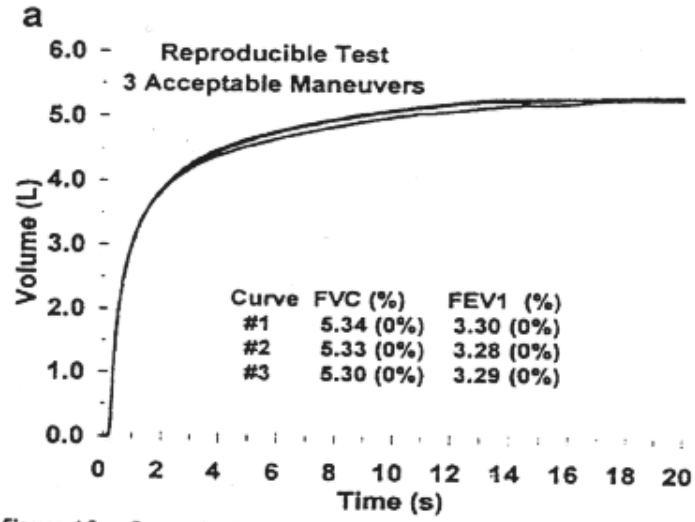

Figure A8a. Reproducible test with three acceptable volume–time curves. Percents are difference from largest value.

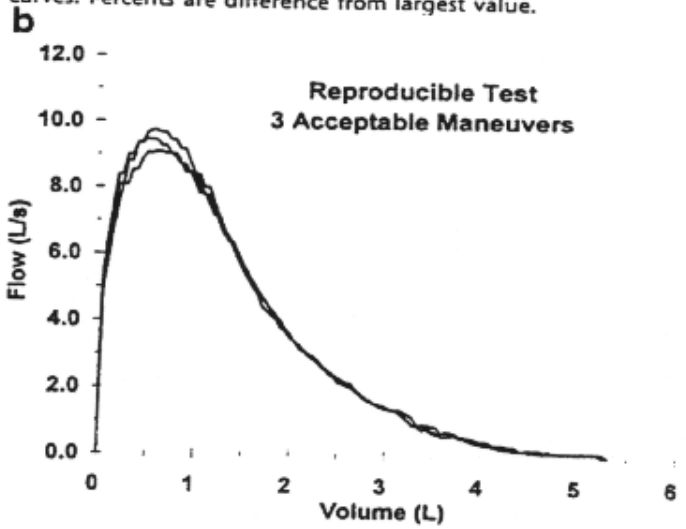

Figure A8b. Reproducible test with three acceptable flow–volume curves.

Figure 3. Local and temporal deviation from or local change of a SOP.

Identification code:	Center: _____
Deviation Change No:___ pages___	Approval by Principal Investigator
Begin date: __/__/__ End date:__/__/__	Date and Signature:__/__/__ _____
Original text(s); full paragraph, page No:	Changed text(s), full paragraph:

Figure 4.

SOP CONFIRMATION SHEET
Spirometry

This SOP has been received by Principal Investigator of

Research center _____ Date ___ / ___ / _____

Signature of PI: _____

INSTRUCTIONS :

0) **Keep this sheet attached to the original copy of the corresponding SOP**
1) When copying the SOP, mark the date of copying for each copy, number each copy
2) When delivering the SOP copy, take the signature and mark the date
3) When delivering a new revision to this SOP, collect previous SOP copies away and confirm with signature and mark the date
4) After each change fax this sheet to coordinator

Copy	Date of the copy	Delivered to Signature	Date of delivery	Received back PI signature	Received back Date
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					

Coordinator fax : + 358 - 17 – 201 265