SPIROLA

Spirometry Longitudinal Data Analysis

Version 1.0
(Updated: June, 2008)

User Manual

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Contents

1. Background

Monitoring of lung function in at-risk populations enables the identification of individuals with excessive decline of lung function. The spirometry test of forced expiratory volume in one second (FEV_1) is the measure best suited for monitoring changes in lung function over time. The method of longitudinal FEV_1 evaluation should identify those with an excessive FEV_1 decline as early and accurately as possible. An excessive decline in lung function over several years can indicate development of lung disease and has been shown to be associated with increased respiratory morbidity, loss of productivity at an earlier age, and increased mortality.[1-3]

To ensure that individuals with excessive decline in lung function can be identified early and accurately, it is important to maintain precision of the longitudinal spirometry data. Statistical monitoring of longitudinal data precision, in addition to good quality control for individual spirometry tests, helps to maintain data precision at an acceptable level and provides the basis on which to determine an appropriate limit of longitudinal decline.[4-6]

The *Spirometry Longitudinal Data Analysis* software (SPIROLA) is an integrated visual and quantitative tool for the detection of excessive lung function decline in individuals participating in spirometry monitoring. SPIROLA may help to preserve lung function through early identification of excessive decline followed by appropriate intervention. SPIROLA provides the following functions:

For an individual:
- It monitors the level of FEV_1 and FVC in relation to criteria for assessment of cross-sectional data: the lower limit of normal (LLN) and 60% of predicted.
- It monitors FEV_1 change over time in relation to criteria for assessment of longitudinal data: the limits of longitudinal decline (LLD).
- It provides interpretation of the rate of FEV_1 decline and its variability in an individual's summary report and suggests actions to prevent further excessive loss.

For a group of individuals:
- It monitors longitudinal data precision using the pair-wise estimate of within person standard deviations s_p (absolute) or s_r (relative) (Section 5);[4-6]
- It monitors spirometry quality control grades as provided by a spirometry system. These are expressed as a percentage of tests that do not meet the 2005 ATS/ERS criteria for acceptability and repeatability. The evaluation can be done by a technician code to determine whether additional training is needed for a technician.
- It monitors means for observed, predicted, and percent predicted FEV_1 and FVC to enable the user to identify systematic changes taking place at a group level.
- It screens for individuals whose most recent lung function tests fall below the LLN and whose rate of lung function decline is excessive.

2. SPIROLA Installation

SPIROLA runs on PC with Microsoft Windows system. For detailed software requirements see **Appendix**.

1. Open NIOSH SPIROLA webpage http://www.cdc.gov/niosh/topics/spirometry/spirola.html.
2. Click **Software Download** to download SPIROLA.
3. Click **Run** button on the **File Download** window to start setup procedure. (If a warning "Publisher could not be verified" appears, click **Run** button to continue the installation.) If **Run** does not work, click **Save** on the **File Download** and follow the instructions to save the setup file on the local C: drive (for example: C:\SpirolaSetup) and then run on the local drive.
4. Follow instructions specified by the installation procedure. User needs to read and agree with a *DISCLAIMER* to install and use the software.
5. The *Select Installation Folder* window will appear, as shown below. By default, SPIROLA is installed into **C:\SPIROLA** folder. The user can override this default setting by designating an alternative location. Click **Next>** to proceed.
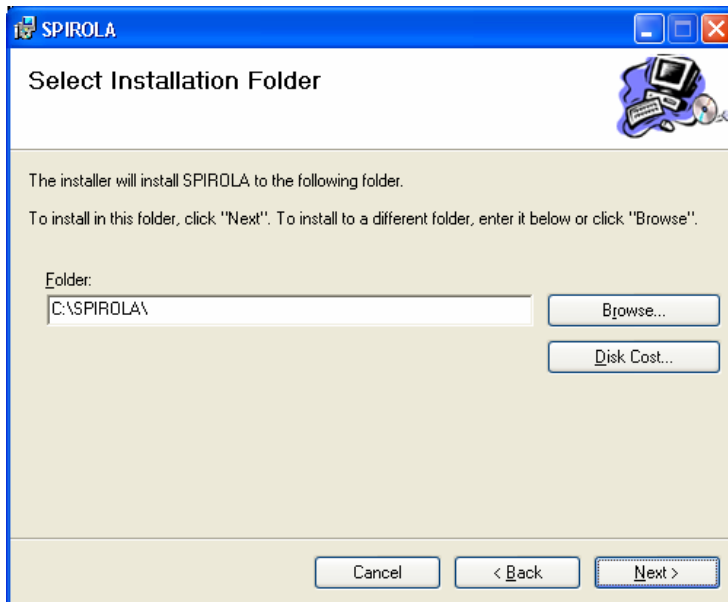
6. Follow the setup wizard instructions to complete the installation. On completion, an *Installation Complete* window will display message "SPIROLA has been successfully installed." Click **Close** to exit.
7. SPIROLA item will be added to the All Programs menu on the Windows Start menu, and a SPIROLA icon will be created on the Desktop.

3. Operating Instructions

3.1 Start and Close SPIROLA

To run SPIROLA, double click the **SPIROLA** icon from the Desktop**,** or click the **SPIROLA** program via **Start** > **All Programs** > **SPIROLA**.

A SPIROLA start screen will appear, as shown below. To close SPIROLA, on the **File** menu click **Exit**, or just click the **close** button in the right upper corner of the window.
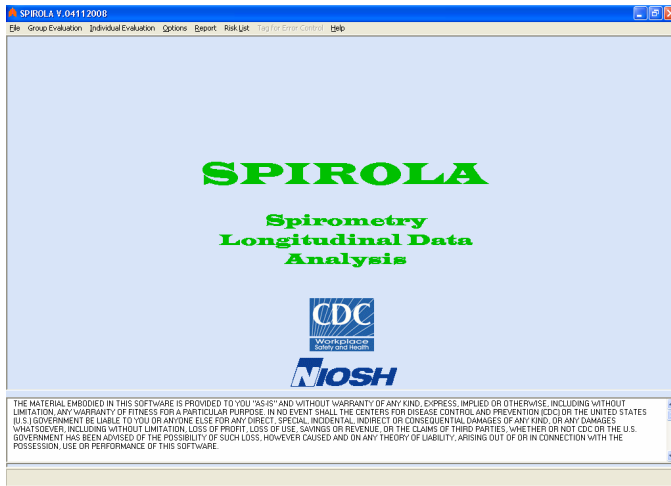
3.2 Open Dataset

The first step is to open a SPIROLA dataset which is to be processed. For demonstration purposes the SPIROLA package includes a dataset (**C:/SPIROLA/DemoDataSet.mdb**). See **Appendix** on how to create user's own database in a correct format.

1. On the **File** menu click **Open.** A window will appear, as shown below.
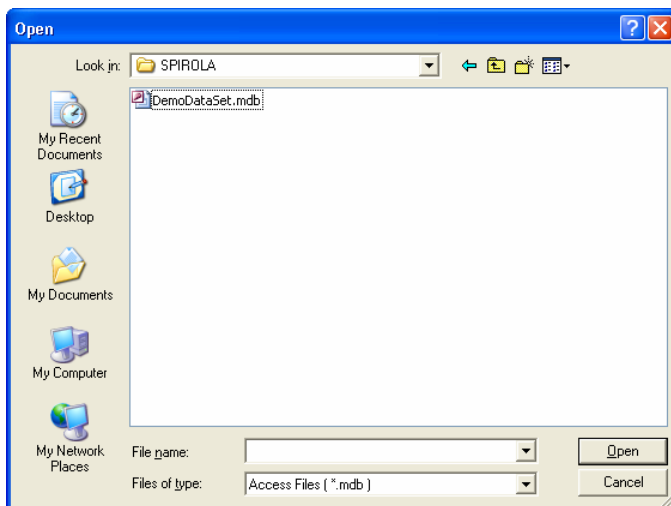
2. Click on the desired .mdb file (for example, SPIROLA.mdb). If the dataset file is not in the current folder, click on the **Look in** list, and then double click the drive and folder that contains the .mdb database file. Click **Open** to proceed. For back-up, it is recommended that users keep copies of all SPIROLA .mdb files in a different folder (e.g., C:\SPIROLADATA).
3. Click on a desired data table listed under **Select a Table from Current Database** as shown below and then click **OK** to load the whole dataset into SPIROLA.

Note:

To select a sub-dataset that contains only individuals whose last test is within a specified period, click on **Last Test** and select the appropriate period. SPIROLA will process the sub-dataset only during the current session.

To automatically load the whole dataset next time, check the **Load this Database and Table automatically next time**.
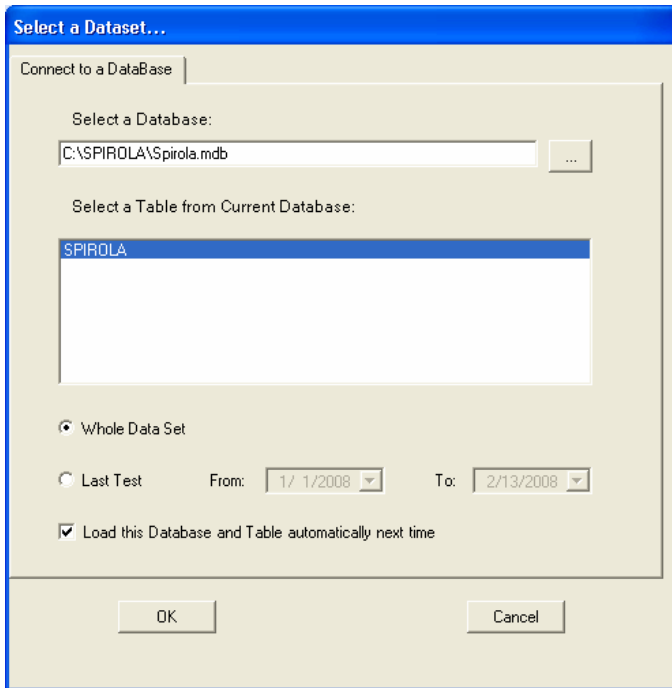
3.3 Individual Evaluation Menu

The **Individual Evaluation** menu lists functions for evaluation of individual FEV_1 and FVC values, and percent predicted values (FEV_1, FVC) and the FEV_1/FVC ratio. Dual window feature shows the FEV_1, and percent predicted values and the ratio on one chart. The summary report provides results of the analysis. Individual identity specification helps to identify an individual by name.
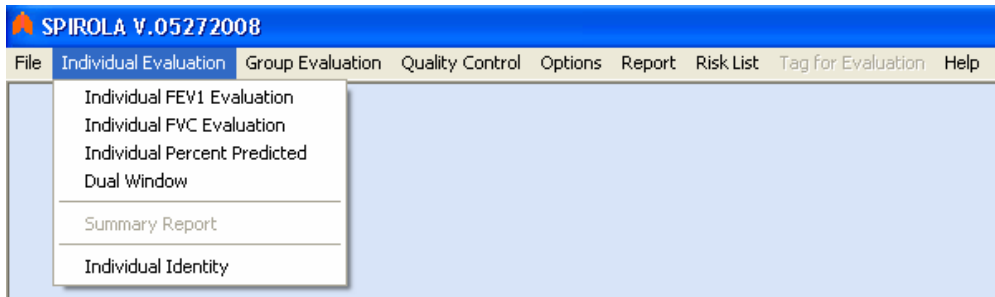
Monitor FEV_1 in an individual

1. On the **Individual Evaluation** menu click **Individual FEV₁ Evaluation** to show a chart for the first individual.
2. Click the arrow next to combo box (ID box) on the left bottom corner and a part of the ID list will be shown (see below).
3. Click up or down arrows or drag the scrollbar next to the ID list and click on an individual's ID. Alternatively, click on a starting ID and use the up and down arrows on the keyboard to display individual IDs or type the ID into the ID box.

The individual FEV$_1$ chart shows: the observed FEV$_1$ values (green dots) plotted against age; the linear regression (green) line fitted to the observed FEV$_1$ data (when at least 4 years of follow-up data are available); cross-sectional lower limit of normal (LLN) (purple) and 60% predicted (red) based on Hankinson *et al*. equations.[7] (see **Section 5**). The blue solid line represents the limit of longitudinal decline (LLD$_r$) calculated from the baseline observation(s) based on the default relative within-person variation of 4% and reference slope of 40 mL/yr (see **Section 5**-theory and **Section 3.7**-changing default). This LLD$_r$ is used to identify excessive declines up to 8 years of follow-up. Observations that fall below LLD should be evaluated as to whether the decline represents data quality issue or true decline. The turquoise (greenish-blue) dashed line represents the American College of Occupational and Environmental Medicine (ACOEM) longitudinal limit of decline calculated as LLD=Baseline FEV$_1$×0.85- years×30 mL/yr.[8]

Beginning with 4 years of follow-up, SPIROLA also tracks changes in the rate of FEV$_1$ decline and displays this against the scale on the right axis of the figure, as shown below. The brown dots show the running change in the rate of decline up to each data point and enable the user to discern the change in rate due to the last data point. The yellow dots show the running change in the slope for the previous 8 years and enable the user to discern changes in the rate of decline in the last 8 years. The three parallel lines represent 30, 60, and 90 mL/yr rates of decline.[3] The bottom margin displays the linear *Regression Slope and within-person variation Sw* for the individual who has 4 or more years of follow-up and *Group Slope and Group Sw* calculated as the mean of regression slopes and within-person variations for all individuals in the group.

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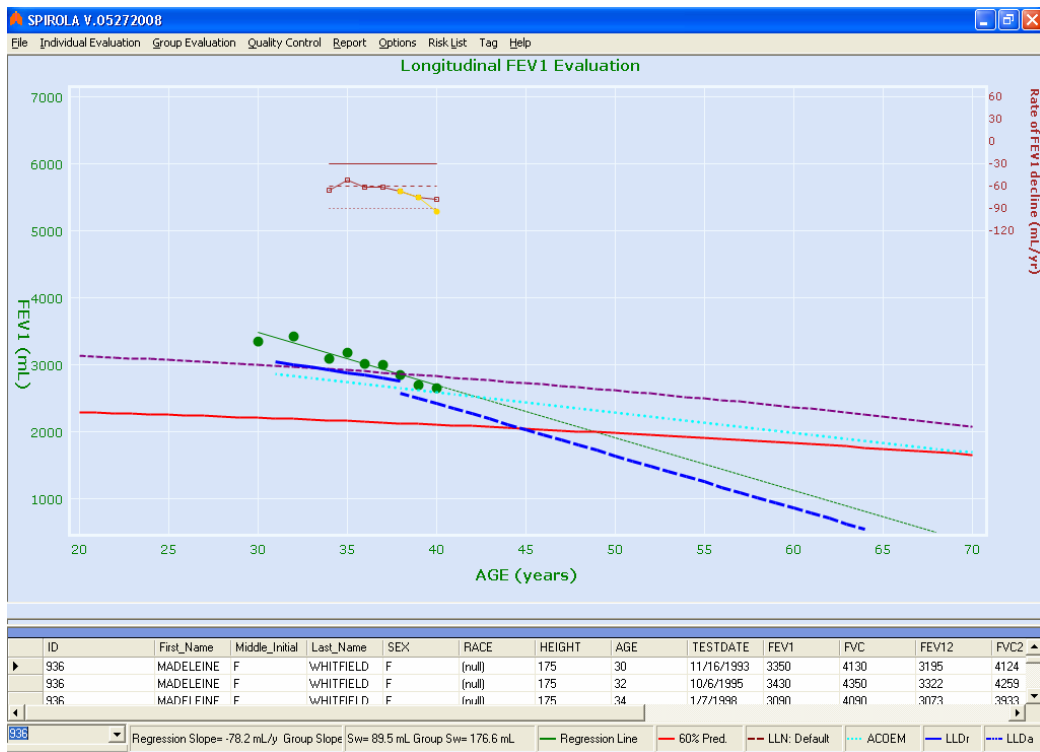
Beginning with 8 years of follow-up, SPIROLA's decision-making is based on the estimated regression slope and the projected age when the regression (dashed green) line crosses the 60% predicted line (solid red line). The blue dashed line shows the longitudinal lower 95% confidence limit for the fitted regression line, estimated from 8 years of follow-up data. This limit can be used to test whether the last observation deviates significantly from the regression line predicted using all observations (see **Sections 4 and 5**).

The table below the chart shows the individual's demographic and lung function data and calculated rates of decline (Rate) at each test date. Other data, for example name, weight, smoking status, cigarettes per day, quality control data, and a technician's code will be shown also if included in the database. The bottom margin shows the individual and the group mean linear regression slopes and the absolute within-person FEV_1 variation for the individual. If desired, one or more outliers can be removed from the analysis by right clicking on it (see "**Remove outliers from a longitudinal analysis**" below).

4. On the **Evaluation** menu, click **Summary Report** to view summary results of an individual's lung function evaluation and a suggested course of action (see **Section 4**) as shown below. Click **OK** to close the window. Click **Print** to print the chart and evaluation in one report. (See **Section 3.6**: **Report Menu** for details.)

Results of Evaluation

ID:	936
SEX:	Female
RACE:	White
DATE OF LAST TEST:	4/28/2004
YEARS OF FOLLOW-UP:	10 years 5 months
REGRESSION SLOPE:	-78 mL/year. 95% CI (-96. -60)
WITHIN-PERSON VARIATION:	90 mL
PROGRAM VARIATION:	195 mL

INTERPRETATION:
LAST OBSERVATION: FEV1 below LLN

RATE OF FEV1 DECLINE: Overall: 78 mL/year. 95% CI (60. 96)
Last 8 years: 94 mL/year. 95% CI (76. 112)
Rate of decline is increasing.
WITHIN-PERSON VARIATION: Within the normal range of 200 mL
PROGRAM VARIATION: Excessive (> 180 mL)

SUGGESTED ACTIONS:
• The rate of FEV1 decline is 78 mL/year. 95% CI (60. 96) overall and increased to 94 mL/year. 95% CI (76. 112) over the last 8 years: consider annual testing and intervention.

• Examine spirometry quality and re-test. Because this individual is at risk of developing moderate-severe respiratory impairment around 49 years of age: consider annual testing and intervention.

OK   Help   Print

Monitor FVC in an individual

1. On the **Individual Evaluation** menu click **Individual FVC Evaluation** to show a FVC chart.
2. Click the arrow next to combo box (ID box) on the left bottom corner to select the ID. See **Monitor FEV$_1$ in an individual** for details on ID selection**.**

The individual FVC chart shows: the observed FVC values (green dots) plotted against age; the linear regression (green) line fitted to the observed FVC data (when at least 4 years of follow-up data are available); cross-sectional lower limit of normal (LLN) (purple, if specified to display) or 70% predicted (purple) and 60% predicted (red) based on Hankinson *et al*. equations.[7] Observations that fall below the cross-sectional limits should be evaluated as to whether the decline represents data quality issue or true decline.

Monitor percent predicted values in an individual

1. On the **Individual Evaluation** menu click **Individual Percent Predicted** to obtain a chart with percent predicted values for an individual person, as shown below.
2. Click the arrow next to combo box (ID box) on the left bottom corner to select the ID. See **Monitor FEV$_1$ in an individual** for details on ID selection**.**
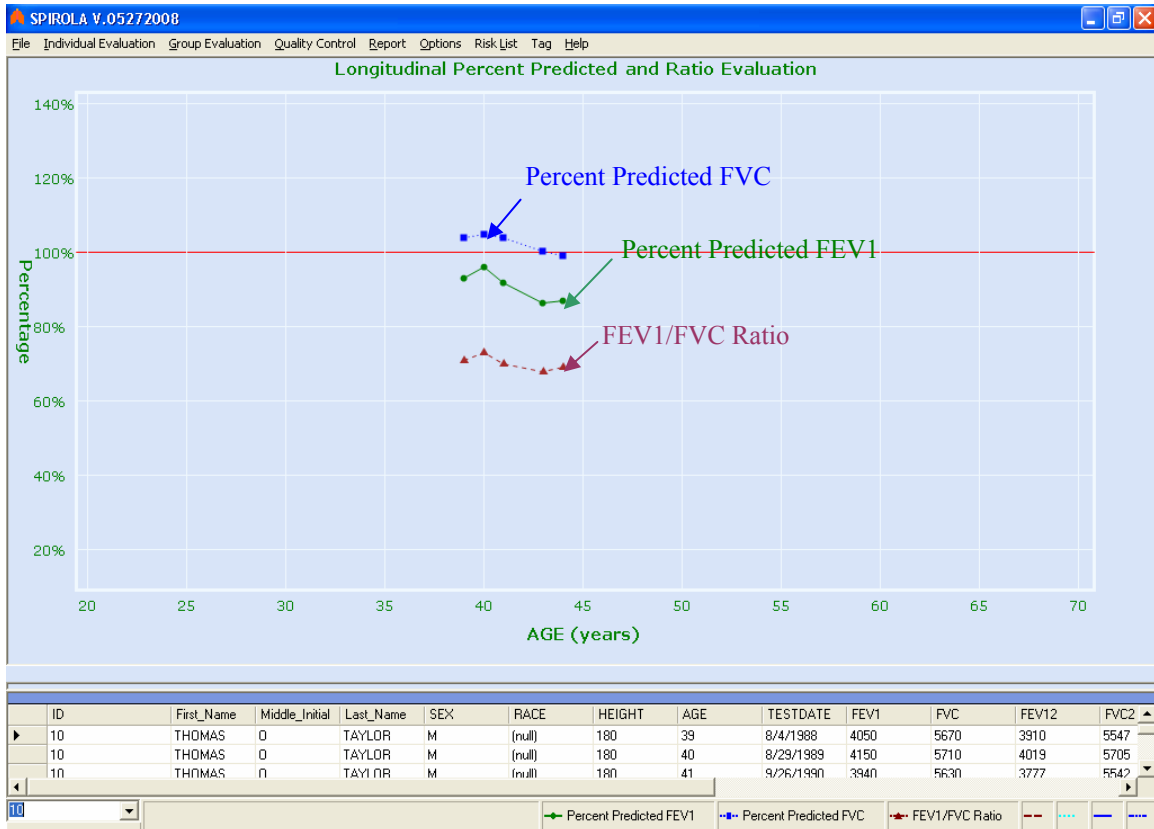
Monitor an individual in a dual window

1. On the **Individual Evaluation** menu click **Dual Window** to obtain a chart which shows both observed FEV_1 evaluation and percent predicted evaluation on the same screen, as shown below.
2. Click the arrow next to combo box (ID box) in the left bottom corner to select the ID. See **Monitor FEV_1 in an individual** for details on ID selection.

Individual identity specification

1. This option enables the user to select an individual by his name. The option will function only if individuals' names (Last_Name, First_Name, Middle_Initial) are included in the SPIROLA database.
2. On the **Individual Evaluation** menu click **Individual Identity** to display an *Individual Identity* window, as shown below.
3. Type the person's name into the *Individual Identity* window and click **Find…**
4. Select the desired name from the list and click **OK**.

Individual Identity …

Type Name:

| Last Name | First Name | Middle Initial | Find... |

	Last_Name	Middle_Initial	First_Name	ID	SEX	Race
▶	Jackson	L	Michael	0985	M	W
	Rather	L	Dan	0995	M	W
	Smith	L	John	9876	M	W
	WALTER	L	WILLIAM	1811	M	W
	WALTERS	W	RANDOLPH	2637	M	W
✳						

OK   Cancel

3.4 Group Evaluation Menu

The **Group Evaluation** menu lists functions for evaluation of: pair-wise within-person variation; means for FEV_1 and FVC; and the mean slope and within-person variation.
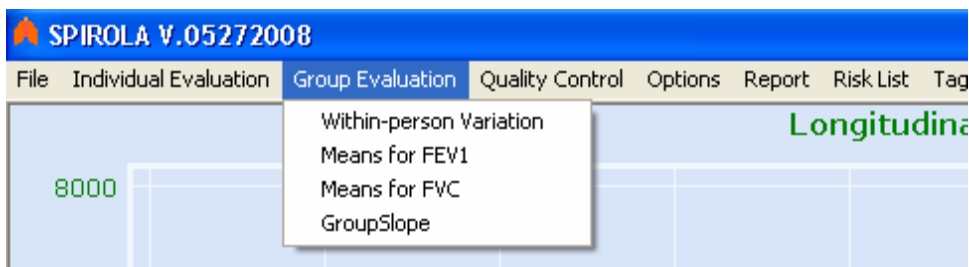
Monitor longitudinal data precision in a group

1. Double click on **Within-person Variation** on the **Group Evaluations** menu to show the yearly values of the pair-wise within-person variation s_p (absolute) and s_r (relative), as shown below. The annual pair-wise within-person variation s_p and s_r are calculated using FEV_1 measurements repeated within 18 months. A sample of at least 50 individuals with repeated measurements is needed to obtain a reliable estimate of the within-person variation. If the number of repeated measurements (the number shown in orange on the screen) is less than 50 in any one year, the s_p and s_r values for that year are not displayed. The legend at the bottom of the screen shows the mean s_p and s_r values for the monitoring program (**Section 5**).
2. To print the figure or preview the printout click **Report Print** or **Report Preview** on the **Report** menu. **Close** the report preview to proceed.
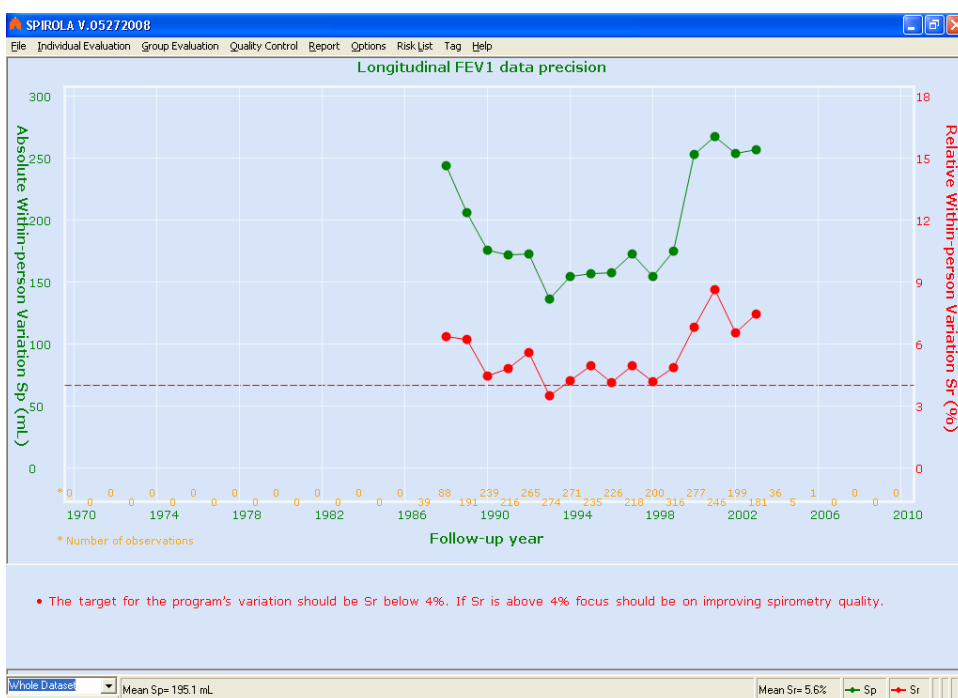
Monitor mean FEV_1 and FVC values in a group

1. On the **Group Evaluations** click **Means for FEV_1** (or **FVC**) to display yearly means for observed, predicted, and percent predicted values as shown below for FEV_1.
2. To print the figure or preview the printout click **Report Print** or **Report Preview** on the **Report** menu.
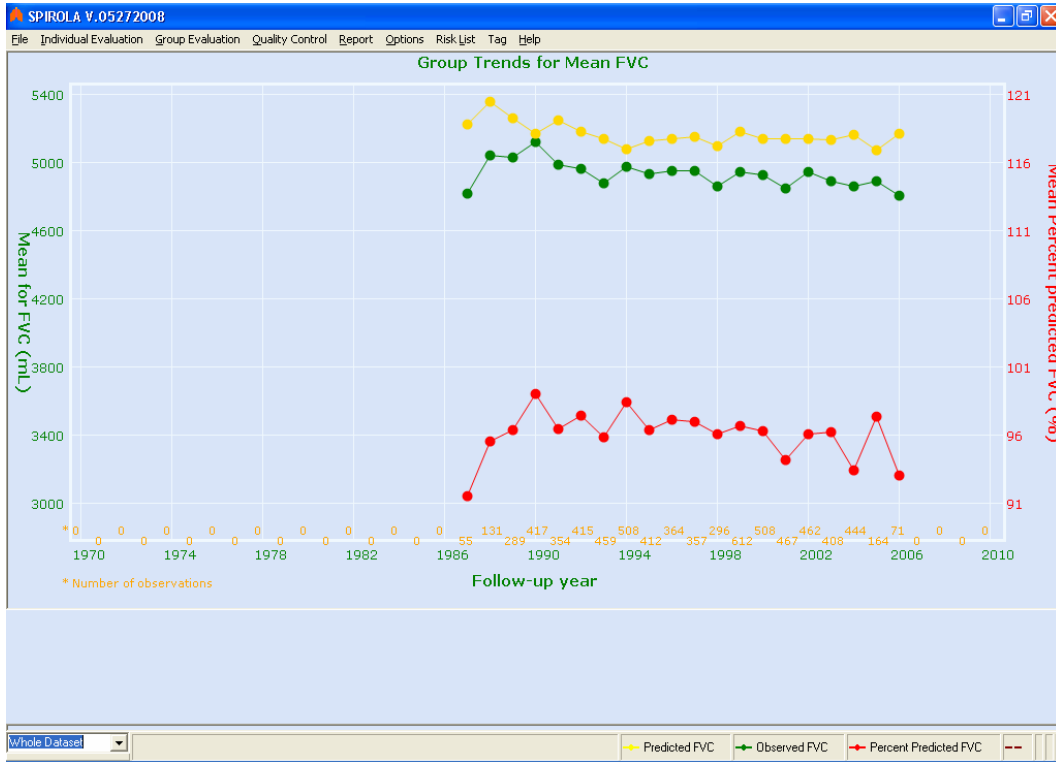
The mean FEV_1 chart shows group means for predicted (yellow), observed (green), and percent predicted (red) FEV_1 values. Same applies for FVC chart. The predicted values are derived from prediction equations that take into account age, height, sex, and race/ethnic background, and are based on nationally representative healthy never-smokers.[7] Irregular deviations of observed mean values from predicted values may be due to changes in measurement procedures, or due to effects of occupational exposure or interventions. Monitoring mean FEV_1 and FVC values can help to identify systematic effects taking place at a group level.

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3.5 Quality Control Menu

Monitoring quality control indices

1. Double click on **Quality Control** menu to show the quarterly quality indices and relative pair-wise within-person variation s_r, as shown below. The quality indices are expressed as: (a) the percentage of tests that do not meet the 2005 ATS/ERS criteria for acceptability and repeatability (i.e., grades C, D, or F), and (ii) the percentage of tests that do not meet the 2005 ATS/ERS criteria for repeatability (>150 ml between best and second best tests). This function is available only if the quality control variables are included in the user's SPIROLA database (**Appendix,** data format).
2. To view charts for individual technicians, click the arrow next to the combo box (ID box) on the left bottom corner and select a technician's code.
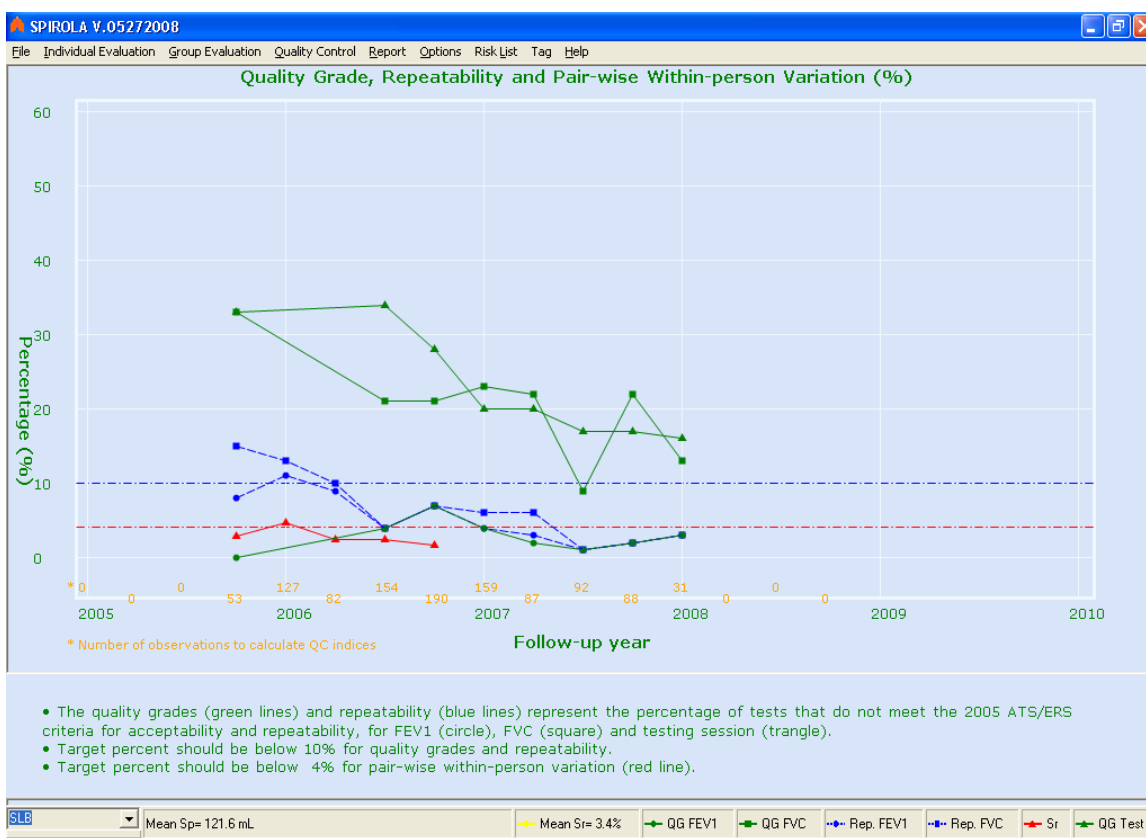
The chart shows spirometry quality grades (green lines) and repeatability scores (blue lines) for FEV_1 (circle), FVC (square) and for test session (triangle). The relative pair-wise within-person variation is also plotted on the chart (red line). Calculation of the quality grades requires data for variables Q FEV_1, QFVC, or QTEST, and repeatability scores require best and second best FEV_1 and FVC values (see **Appendix**).

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3.6 Report Menu

1. To print a current chart, click **Report Print** on the **Report** menu (see below).
2. Results in an individual report can be printed together with the FEV$_1$ or FVC chart.
3. To preview the report, click **Report Preview** on the **Report** menu and a printable report will appear. **Close** the report to proceed.

An example of a printed report:

Report on Longitudinal FEV1 Evaluation

Legend: ——— Regression Line ·········· ACOEM ----- LLN
——— LLDr ········ LLDa ——— 60% Pred.

ID: 936 **DATE OF LAST TEST:** 4/28/2004
YEARS OF FOLLOW-UP: 10 years 5 months
REGRESSION SLOPE: -78 mL/year, 95% CI (-96, -60)
WITHIN-PERSON VARIATION: 90 mL individual 194 mL program
INTERPRETATION:
 LAST OBSERVATION: FEV1 below LLN
 RATE OF FEV1 DECLINE: Overall: 78 mL/year, 95% CI (60, 96)
  Last 8 years: 94 mL/year, 95% CI (76, 112)
  Rate of decline is increasing.
 INDIVIDUAL VARIATION: Within the normal range of 200 mL
SUGGESTED ACTIONS:
• The rate of FEV1 decline is 78 mL/year, 95% CI (60, 96) overall and increased to 94 mL/year, 95% CI (76, 112) over the last 8 years; consider annual testing and intervention.
• Examine spirometry quality and re-test. this individual is at risk of developing significant respiratory impairment around 49 years of age; consider annual testing and intervention.
• The program's FEV1 variation is excessive (>180 mL), focus on the spirometry quality control.

3.7 Options Menu

SPIROLA provides options to change default values or adjust parameters; these changes take effect during the current SPIROLA session only. (To save and automatically load the changes on the next run, see **Save Options** later in this chapter.) The user may:

- select a referential rate of decline for the calculation of LLD based on the actual data;
- select within-person variation for the calculation of LLD based on the actual data;
- customize data display on charts;
- temporarily remove outliers from the individual data analysis;
- customize reference equations used for LLN and 60% predicted FEV_1 values.

The **Option** menu allows implementation of some of the options.
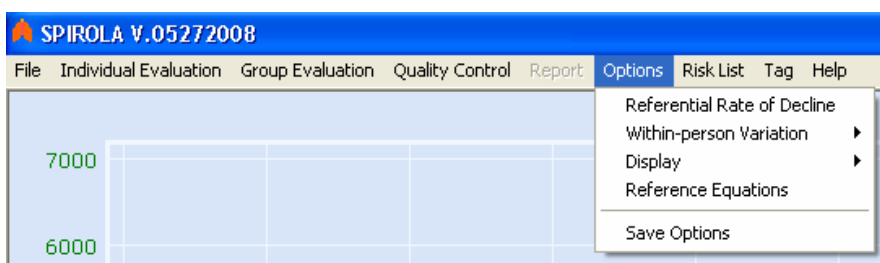
Referential rate of decline

SPIROLA uses a default of 40 mL/yr for the referential rate of FEV_1 decline. The **Referential Rate of Decline** option enables changing the default value. Studies indicate that the mean rate of FEV_1 decline in healthy never-smokers is about 30 mL/yr. To achieve greater predictive values of the limit of longitudinal decline (LLD) for moderate impairment of lung function, a referential rate of decline based on all healthy individuals regardless of smoking status, should be used. In preliminary analyses, we determined this to ranges from 40 to 45 mL/yr. SPIROLA calculates the mean rate of decline for the group using all individuals with four or more years of follow-up and shows the result on the **Group Evaluation** menu. Using the mean rate of decline as the referential rate of decline together with the average within-person variation will result in identifying about 5% of declines as excessive.[5]

1. On the **Options** menu, click **Referential Rate of Decline** and a dialog window will appear, as shown below. Select a desired value from the list box, click **OK**.
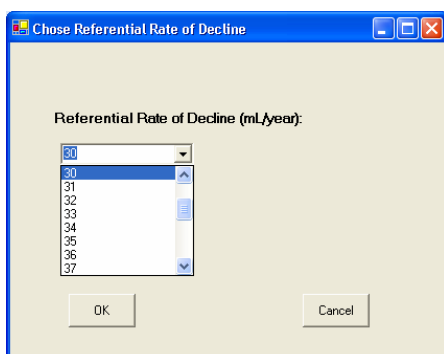
Within-person standard deviation

SPIROLA uses as the relative within-person standard deviation s_r of 4% and the corresponding LLD$_r$ of 10% as defaults (see **Section 5)**. When ATS/ERS recommendations on quality control are followed, workplace monitoring programs can achieve comparable data precision. These limits are goals that can help to achieve a satisfactory level of data precision.

However, if the relative within-person standard deviation $\bar{s}_r$, shown at the bottom of the **Group Within-person Variation** chart, is significantly higher/lower than the default value of 4%, SPIROLA provides an option for changing the default value to the observed $\bar{s}_r$ value. If the $\bar{s}_r$ value is greater than 6%, then the LLD$_r$ of 15%, which corresponds to the ACOEM limit, should be used and effort be made to improve spirometry quality.

1. On the **Options** menu, click **Within-person Variation,** and then click **Absolute Value** or **Relative Value**, and a new dialog window will appear, as shown below.
2. To select an existing value from the list box, click the arrow button of **Within-person standard deviation** or **Longitudinal limit,** and click a desired value. If a desired value is not in the list box, enter the value, and click the **Add** button to add it.
3. Click the **OK** button to confirm the selection or **Cancel** button to cancel the selection.
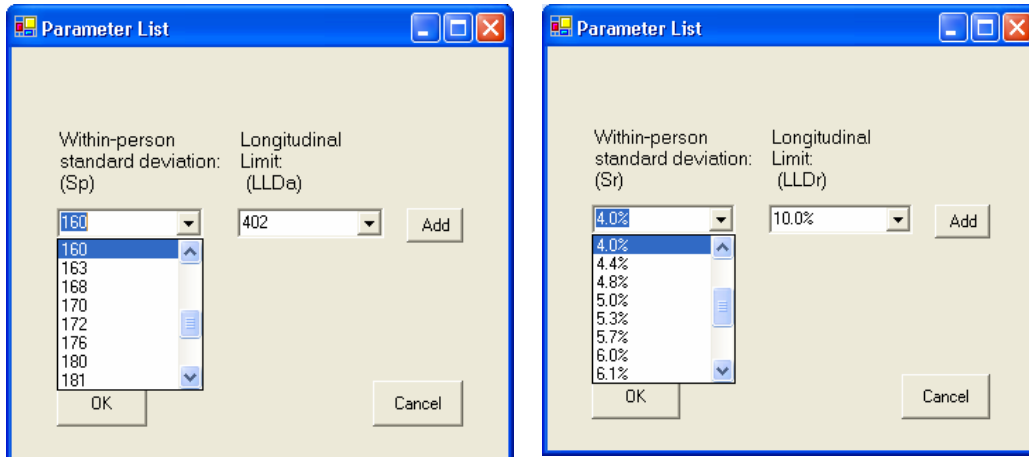
Critical limit curves

1. On the **Options** menu, click **Display**, and then click **Curves.** A new dialog window will appear, as shown below.
2. To enable or disable display of a critical limit curve, click the check box next to the name of each critical limit curve to check or uncheck that box. By default, all curves are checked except the absolute LLD for FEV$_1$ and the LLN for FVC.
3. Click the **OK** button to confirm the selections and close this window, or click the **Cancel** button to cancel any current selections and close this window.

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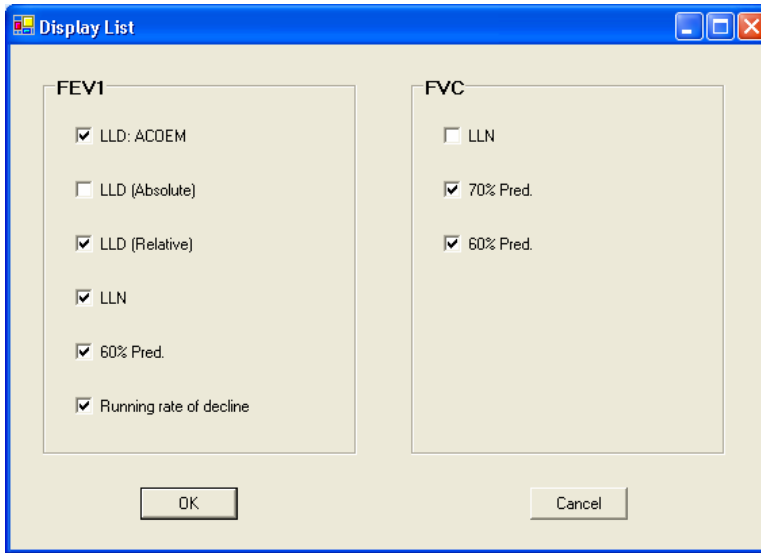
Show height in inches or centimeters

1. By default, each individual's height is shown in centimeters in the data table. To display height in inches, click **Display** on the **Options** menu, and then click **Show Height in cm** to remove the "check" mark.
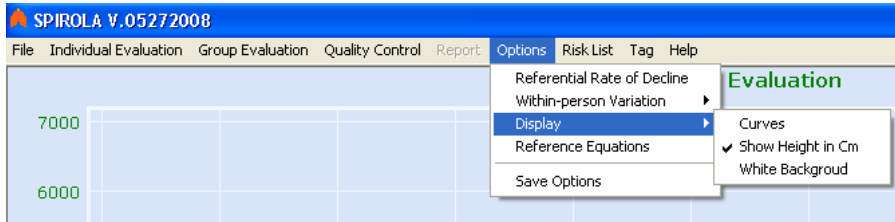
Display charts using a white background

1. By default, the background color for all charts in blue. To change to a white background, click **Display** on the **Options** menu, and then click **White Background.**

Display values of an observation

1. Place the cursor on any data point on the longitudinal FEV_1 evaluation chart, and then left click. A small yellow tooltip label will popup.
2. After a second, this tooltip label will disappear automatically.

Remove outliers from a longitudinal analysis

1. On the chart, place the cursor on any data point(s) which you want to temporarily remove, and then right click. The data point(s) will disappear from the chart, and the regression line and other curves will be recalculated and redrawn (see two charts below). The last data point can not be deleted.

Note: The deleted data points are not deleted from the dataset, but only from the current report. When the user reloads the individual's ID, all points will be shown again. If the user wishes to correct a data value, this needs to be done directly in the .mdb database.

Customize the reference equation for LLN and predicted values

1. On the **Options** menu, click **Reference Equations** to display a *Select Reference Equations* window, as shown below. By default, we use reference equations based on NHANES III data to calculate lower limit of normal (LLN) and predicted values.[7]

Select Reference Equations ...

Select Data Format:

      ⊙ Hankinson's Reference   ○ Custom Reference

Hankinson Equation | Custom Equation |

Lung function parameter=b0+b1*age+b2*age^2+b3*height^2

Parameter	Sex	Race	b0 (PRD/LLN)	b1	b2	b3PRD	b3LLN	
FEV1	Male	White	0.5536	-0.01303	-0.000172	0.00014098	0.00011607	
FEV1	Male	Black	0.3411	-0.02309	0	0.00013194	0.00010561	
FEV1	Male	Mexican	0.6306	-0.02928	0	0.00015104	0.00012670	
FEV1	Female	White	0.4333	-0.00361	-0.000194	0.00011496	0.00009283	
FEV1	Female	Black	0.3433	-0.01283	-0.000097	0.00010846	0.00008546	
FEV1	Female	Mexican	0.4529	-0.01178	-0.000113	0.00012154	0.00009890	
FVC	Male	White	-0.1933	0.00064	-0.000269	0.00018642	0.00015695	
FVC	Male	Black	-0.1517	-0.01821	0.0	0.00016643	0.00013670	
FVC	Male	Mexican	0.2376	-0.00891	-0.000182	0.00017823	0.00014947	
FVC	Female	White	-0.3560	0.01870	-0.000382	0.00014815	0.00012198	
FVC	Female	Black	-0.3039	0.00536	-0.000265	0.00013606	0.00010916	
FVC	Female	Mexican	0.1210	0.00307	-0.000237	0.00014246	0.00011570	
FEV1/FVC	Male	White	(88.066/78.388)	-0.2066				
FEV1/FVC	Male	Black	(89.239/78.822)	-0.1828				
FEV1/FVC	Male	Mexican	(90.024/80.925)	-0.2186				
FEV1/FVC	Female	White	(90.809/81.015)	-0.2125				
FEV1/FVC	Female	Black	(91.655/80.978)	-0.2039				
FEV1/FVC	Female	Mexican	(92.360/83.044)	-0.2248				

[OK]   [Cancel]

2. To customize the LLN reference equations, select **Custom Reference** and a tab page will appear, as shown below.

Select Reference Equations ...

Select Data Format:

      ○ John L. Hankinson's Reference   ⊙ Custom Reference

John Hankinson | **Custom Equation** |

FEV1 = b0 + b1 * age + b2 * age ^2 + b3 * height + b4 * hight^2

No	Sex	Race	b0	b1	b2	b3	b4	SEE	
0	Male	White	0.5536	-0.01303	-0.000172	0.00014098	0.00011607	0	
1	Male	Black	0.3411	-0.02309	0	0.00013194	0.00010561	0	
2	Male	Mexican	0.6306	-0.02928	0	0.00015104	0.00012670	0	
3	Male	Other	-3.8375	-0.021	0	0.0499	0	0.44	
4	Female	White	0.4333	-0.00361	-0.000194	0.00011496	0.00009283	0	
5	Female	Black	0.3433	-0.01283	-0.000097	0.00010846	0.00008546	0	
6	Female	Mexican	0.4529	-0.01178	-0.000113	0.00012154	0.00009890	0	
7	Female	Ohter	-1.43	-0.025	0	0.0317	0	0.31	

New Values

| No	Sex	Race	b0	b1	b2	b3	b4	SEE
0 ▾	Male	White	0.5536	-0.01303	-0.000172	0.00014098	0.00011607	0

[Save]

[OK]   [Cancel]

3. Enter custom parameters in the *New Values* area, and then click **Save**. The new values will be saved and show as a row in the equation table.

4. Repeat step 3 until all custom parameters are shown in the table.
5. Click **OK.** All relative curves will then be redrawn based on the new custom reference equations.

Save Options

To save user selected options and automatically load these options on the next startup of SPIROLA on the **Options** menu click **Save Options** and the options selected by the user will be saved into an .xml file named *app.xml* stored in the C:/SPIROLA folder and applied on the next run.
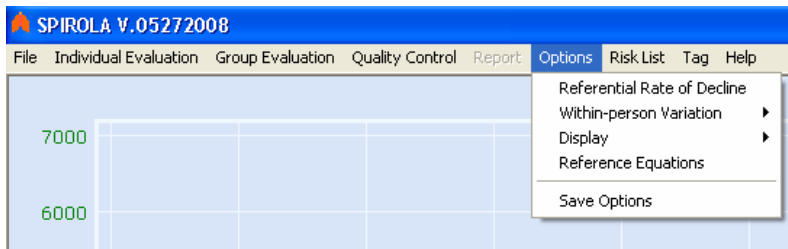
3.8 Risk List Menu

Screen for individuals at risk for respiratory impairment

1. On the **Risk List** menu, click **Risk List** to create a list of individuals whose rate of decline is excessive or whose last lung function tests (FEV_1, FVC, or the FEV_1/FVC ratio) are below LLN. The final list is marked by orange background. See **Section 4** for the selection criteria.
2. Risk List processing time depends on the size of the dataset and the performance of the computer. SPIROLA shows processing progress as shown below.
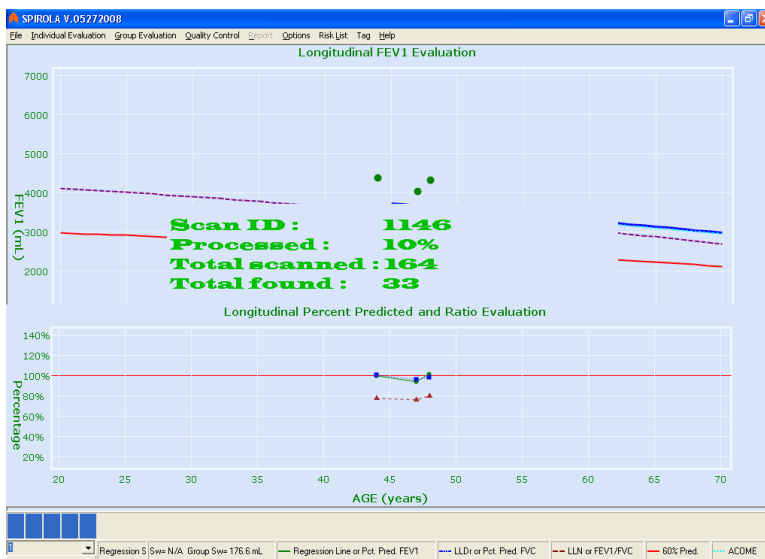
3. When completed, the results are displayed on the **Risk List Query** window, see below. These results will be shown each time the user clicks on the **Risk List**. The Risk List will be permanently saved until another **Update Risk List** is executed.
4. The information provided on the **Risk List Query** summary table enable the user to determine when was the risk list created or updated, and the database information. If the risk list is not for the current dataset or is outdated, the user needs to update the risk list by clicking on **Update the Risk List** on the **Risk List Query**.
5. To print only the summary statistics click on **Print Summary**.
6. To select a subset of individuals with excessive decline only or individuals whose last spirometry values are below the LLN only, click on **Excessive Decline** or **Below LLN**, respectively.
7. To evaluate the selected group of individuals click on **Evaluate** button and proceed to select a method of analysis from the **Individual Evaluation** or **Group Evaluation** menus, or click on **Print List** to print the selected list.
8. To identify a particular individual from the selected subset, place a pointer next to a desired ID and click on **Current ID**.
9. To exit from the Risk List click on **Exit**.

Tag individuals for further evaluation

The user may search through either whole data set or the risk list and tag individuals for further data evaluation by clicking on the **Tag** menu and then on a selected item, see below. For example, an individual whose spirometry value is below LLD can be tagged for Quality Control or Re-testing at the initial stage of evaluation.
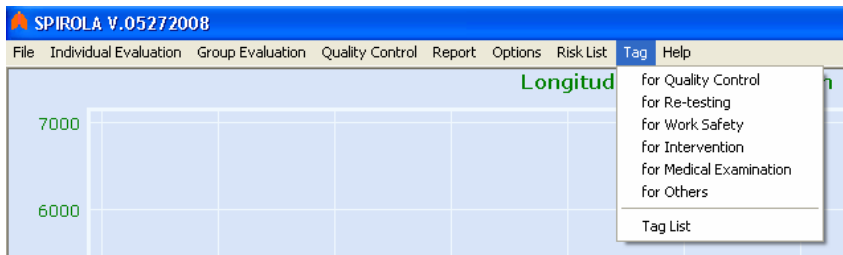
On completion of tagging, click **Tag List** (see above) to display the list (see below).
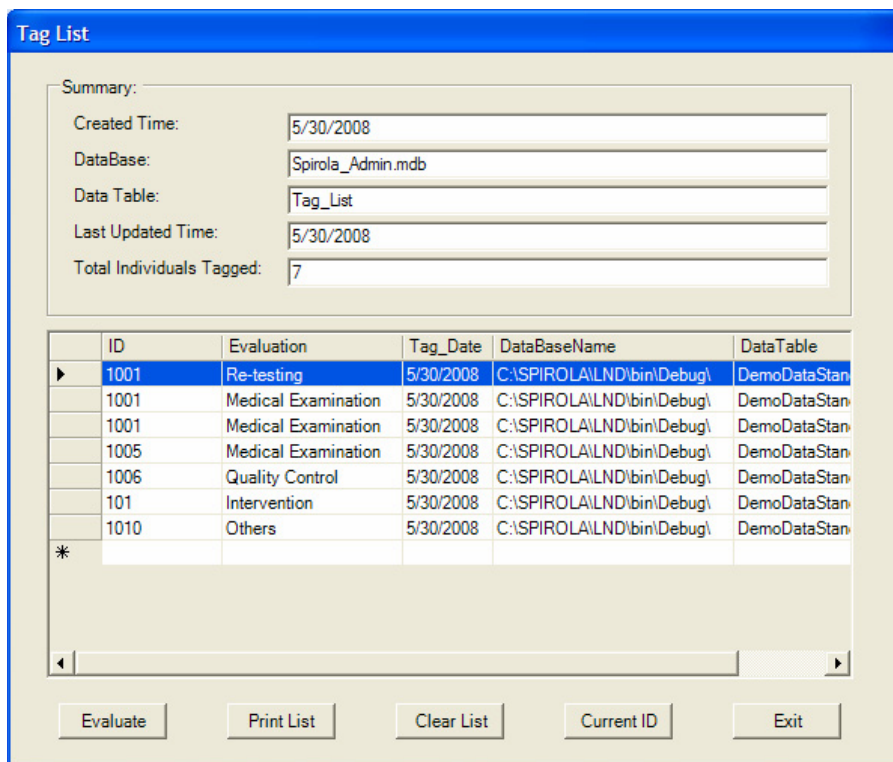
4. Evaluation and Interpretation of Results

Interpretation and suggested actions

The table below summaries "Interpretations" and "Suggested actions" provided in the
Summary Report, according to the duration of follow-up. Individuals whose lung
function is categorized as shown in the table are selected into **Risk List** (see below).

Interpretation	Suggested action(s)
Less than 8 years of follow-up	
$FEV_1 < LLDr$	Examine spirometry quality and re-test. If confirmed that $FEV_1 < LLDr$, consider annual testing and intervention.
$FEV_1 < LLN$	Examine spirometry quality and re-test. If confirmed that $FEV_1 < LLN$, consider annual testing and intervention.
$FEV_1/FVC < LLN$	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC < LLN$, the individual has airflow obstruction; consider annual testing and intervention.
$FEV_1/FVC \geq LLN$ and $FVC < LLN$†	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC \geq LLN$ and $FVC < LLN$, the individual may have restriction; consider annual testing and intervention.
$FEV_1/FVC \geq LLN$ and $FEV_1 < LLN$ and $FVC < LLN$†	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC \geq LLN$, $FEV_1 < LLN$, and $FVC < LLN$, the individual may have mixed obstructive and restrictive impairment; consider annual testing and intervention.
$FEV_1 < 60\%$ predicted	Examine spirometry quality and re-test. If confirmed that $FEV_1 < 60\%$ predicted, the individual has substantial impairment of lung function; consider annual testing, intervention, and referral for clinical evaluation.
Rate of FEV_1 decline and within-person variation are provided.	Prior to 8 years of follow-up, excessive decline is evaluated using the LLD limit. The rate of decline is provided as additional information.
8 or more years of follow-up	
$FEV_1 < LLDr$ (derived from the regression line)	Examine spirometry quality and re-test. If confirmed that $FEV_1 < LLDr$, consider annual testing.
Rate of FEV_1 decline >90 mL/yr.[5]	Examine spirometry quality and re-test. If confirmed that the rate of FEV_1 decline is > 90 mL/yr, consider annual testing and intervention.
Projected FEV_1 declines to 60% predicted before 70 years of age	Examine spirometry quality and re-test. Because the individual is at risk of developing moderate-severe respiratory impairment around [AGE] years of age, consider annual testing and intervention.
$FEV_1/FVC < LLN$	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC < LLN$, the individual has airflow obstruction.
$FEV_1/FVC \geq LLN$ and $FVC < LLN$†	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC \geq LLN$ and $FVC < LLN$, the individual may have restriction; consider annual testing and intervention.
$FEV_1/FVC \geq LLN$ and $FEV_1 < LLN$ and $FVC < LLN$†	Examine spirometry quality and re-test. If confirmed that $FEV_1/FVC \geq LLN$, $FEV_1 < LLN$, and $FVC < LLN$, the individual may have mixed obstructive and restrictive impairment; consider annual testing and intervention.
$FEV_1 < 60\%$ predicted	Examine spirometry quality and re-test. If confirmed that $FEV_1 < 60\%$ predicted, the individual has substantial impairment of lung function; consider annual testing, intervention, and referral for clinical investigation.

† For FVC, SPIROLA uses 70% predicted criteria when NHANES[3] reference values are used.

Risk List evaluation procedure

The **Risk List** identifies individuals who fulfill any of the criteria listed in the above table. In evaluating an individual identified to be at risk of impairment the following procedure should be considered.

1. **Examination of the individual's existing data**
   (i)   Examine the longitudinal demographic, FVC, and FEV_1 data shown in the table below the FEV_1 chart, to make sure that the data are reasonable.
   (ii)   If a data point appears to be an outlier, temporarily exclude the point by right clicking on it and then evaluate the new results on the chart and in the report.
   (iii)   If a single data point appears to be an outlier and causes the individual's selection into the risk list, check for possible data errors. The first (baseline) observation may sometimes be lower due to the learning effect. When this happens, exclusion of the baseline value may improve precision of the interpretation.
   (iv)   If a data error is found, correct the data in the .mdb database using Microsoft Access software, re-run SPIROLA, and review the new **Summary Report**.

2. **Examination of the individual's spirometry data quality**
   (i)   If quality grades are provided in the SPIROLA data, examine these and the technician report for the percentages of test meeting the ERS/ATS criteria.
   (ii)   Examine the original spirometry tracings using the ATS standardization criteria of: (a) acceptability (extrapolated volume, cough in first second, end of test criteria, obstructed mouthpiece, extra breath, cessation of airflow); and (b) repeatability ($\leq$ 150 mL).[9]
   (iii)   If an acceptability error is found, consider removing data for that test from the dataset, correct the SPIROLA .mdb file using Microsoft Access, and then re-run SPIROLA to produce a new **Summary Report** for the individual.
   (iv)   Provide feedback to the spirometry technician(s) on the spirometry errors found.

3. **Re-test the individual**
   After the first two steps have been completed and SPIROLA still identifies the person as being at risk, consider re-testing the person within six months from the most recent test. If the re-tested spirometry values confirm the original interpretation, consider the suggested actions in the new **Summary Report**.

Suggested intervention measures

When spirometry quality issues are satisfied and re-testing confirms that a person has impairment or is at increased risk of developing respiratory disease, implementation of annual testing and intervention measures should be considered. The severity of existing impairment and the projected age at which substantial impairment is likely to occur should be considered when deciding on the type of intervention(s).

Interventions on an individual level:
Discussing lung function results with a worker can motivate the individual and can help to determine what course of action is acceptable to the individual to prevent further

excessive lung function loss. Decreasing inhalation of noxious particulates and gases is usually the most important intervention. The most important risk factor for excessive decline in lung function in smokers is often tobacco smoking, for which nicotine replacement therapy may provide best results for smoking cessation.[10] Complete smoking cessation may be needed to halt excessive lung function decline.[11] Occupational exposures to respiratory hazards also represent an important risk.[12] Evaluation of individual occupational exposures should be done. Where possible, hazardous exposures should be reduced or eliminated through engineering controls (e.g., substitution of less hazardous materials, process enclosure, workplace ventilation). Administrative controls (e.g., revised work practices) may also help limit hazardous occupational exposures. Finally, use of effective personal protective equipment (e.g., respirators) should be recommended when other measures are infeasible or insufficient by themselves. The potential synergistic effect of smoking and occupational exposure on increased risk of excessive decline in lung function should be explained to individuals who smoke and are exposed to occupational respiratory hazards. Weight gain can also contribute to lung function decline due to loss of fitness and difficulty in performing the spirometry test at full lung capacity. Body mass index (BMI) greater than 25 kg/m^2 can be associated with lower lung function when other factors such as gender, height, race, smoking, and respiratory symptoms, are controlled for. Increasing change in BMI/year can be also associated with an additional FEV_1 decline.

Interventions at a company level:
Management commitment to an integrated worksite health and safety program provides a key foundation for success in maintaining a healthy workforce. Programs are likely to be more effective when they are based on management's understanding of workers' concerns about health risks on the job. By identifying workers' priorities, smoking (for example) can be addressed in the broader context of worksite safety. Intervention at the individual level is then more likely to be successful.

Evaluation of the effect of intervention(s):
To determine the effect of individual intervention on the rate of FEV_1 decline using SPIROLA, use the small rate of decline chart on the individual FEV_1 evaluation. To determine the effect of an integrated worksite health and safety program using SPIROLA, assess trends on the FEV_1 and FVC means for the whole group and for the at-risk subgroup. An expansion of this feature is planned for a future version of SPIROLA.

5. Theoretical Background

The use of SPIROLA may help preserve lung function by:
(i)   evaluating longitudinal data precision and quality control indices,[13] and promptly identifying when intervention on spirometry quality is warranted to maintain data precision at an acceptable level;
(ii)   identifying individuals with excessive decline in lung function using limits of longitudinal decline (LLD) based on the program's actual data precision, or if data precision can not be determined, based on the default criteria (i.e., s_r=4% or LLDr=10%) or the ACOEM longitudinal limit criteria (i.e., s_r=6% or LLDr=15%);
(iii)   identifying individuals who already have lung function impairment using ATS/ERS criteria based on cross-sectional data evaluation;
(iv)   identifying when an individual's lung function warrants individualized intervention measures;
(v)   evaluating the effects of intervention at the individual level and the group level.

Evaluation of FEV$_1$ precision in a group

Monitoring a program's data precision on an annual basis can help to identify and address data quality problems soon after these occur and this way achieve and maintain high data precision. To monitor data precision, SPIROLA calculates and charts yearly values of the *absolute within-person standard deviation s_p* and the *relative within-person standard deviation s_r*.[4-6] These statistics are calculated on a yearly basis as the difference between $FEV1_{1i}$ and $FEV1_{2i}$ measured within 18 months of each other and summed over $i =$ 1,..,n individuals. The year of the first measurement determines the assigned year. A sample of at least 50 individuals with repeated measurements is needed to obtain a reliable estimate of yearly FEV$_1$ variation.

The absolute within-person standard deviation s_p for a specific year is defined as:

$$s_p = \sqrt{\frac{1}{2n} \sum_{i=1}^{n} (FEV1_{1i} - FEV1_{2i})^2}$$

The relative within person standard deviation s_r adjusts for each individual's FEV$_1$ size and for a specific year is defined as:

$$s_r = \sqrt{\frac{1}{2n} \sum_{i=1}^{n} \left(\frac{FEV1_{1i} - FEV1_{2i}}{(FEV1_{1i} + FEV1_{2i})/2} \right)^2}$$

The average values $\bar{s}_p = (1/kN)\sum(s_{pi}n_i)$ and $\bar{s}_r = (1/kN)\sum(s_{ri}n_i)$ are calculated by summing the yearly weighted s_p and s_r values over all years of follow-up and then dividing by the total number of repeated observations N. These values represent the average program-specific absolute and relative pair-wise within-person variation, respectively. The $\bar{s}_p$ and $\bar{s}_r$ values are shown at the bottom of SPIROLA's Group Within-person Variation chart as 'Mean s_p' and 'Mean s_r'. The mean within-person standard deviations $\bar{s}_p$ and $\bar{s}_r$ can be used also to derive the program-specific *limits of longitudinal decline* (LLD) by substituting these for the default values on the **Options** menu under **Within-person Variation** option.

Note: If the sample of measurements repeated within 18 months is less than 50, the s_p and s_r values are considered unreliable and are not displayed. If $\bar{s}_p$ and $\bar{s}_r$ values are not displayed or are based on a sparse sample, the user could use the default LLD_r value of 10% or change the default to LLD_r of 15% as based on the ACOEM limit. Alternatively, the user can use the group mean within-person variation, shown as RMSE on the Group Evaluation menu or as Group s_w under each FEV_1 chart, estimated as the mean of individuals' within person variations estimated by the linear regression analyses. The validity of this estimate will depend on the number of individuals who have four or more longitudinal measurements.

Estimation of limits of longitudinal decline for an individual

Because of inherent FEV_1 variability, it takes approximately 5-8 years of follow-up to obtain a reliable estimate of the rate of FEV_1 decline in an individual.[4-6] To identify individuals with an excessive FEV_1 decline within the first 8 years of follow-up, SPIROLA uses by default the relative limit of longitudinal decline (LLD_r),[6] but the absolute limit (LLD_a) or the ACOEM limit based on 15% can also be displayed. The LLD_r limit is applied to determine whether the lung function decline between the baseline FEV_1 value (or a mean of the first two observations, if the first FEV_1 value is lower than the second one) and each follow-up FEV_1 value is excessive. Observations that fall below the LLD warrant concern. The absolute or relative longitudinal limits are calculated based on the average within-person FEV_1 variability for the group or using the default values.

The <u>absolute limit of longitudinal decline LLD_a</u> (mL/yr) is defined as a one-sided 95% confidence limit:

$$LLD_a = t \times (b + 1.645 \times SE(b))$$

where t is the duration of follow-up in years and b is either the referent slope of decline (up to 8 years of follow-up) or the individual's estimated regression slope (beginning with 8 years of follow-up). SPIROLA uses a default referent slope of decline of 40 mL/yr based on an analysis evaluating performance characteristics of the limit with

respect to sensitivity and specificity for long-term excessive decline in FEV_1 of ≥ 90 mL/yr and $FEV_1 \leq 60\%$ predicted. The standard error of the slope b is defined as

$$SE(b) = \sigma_w \sqrt{12(P-1)}/t\sqrt{P(P+1)} \qquad (1)$$

where t is the duration of follow-up in years, $P=2$ represents two repeated measurements done during the follow-up time t (the baseline and last observation), and σ_w is the within-person standard deviation. By substituting the program-specific pair-wise estimate of the within-person standard deviation $\bar{s}_p$ for the within-person variation σ_w in equation (1), one can estimate program-specific absolute LLD_a.

The <u>relative limit of longitudinal decline LLD_r</u> (%) standardizes for the magnitude of FEV_1 and is defined as:

$$LLD_r = t \times (b/\overline{FEV}_{1b} + 1.645 \times SE_r(b)) \qquad (2)$$

where $\overline{FEV}_{1b}$ is the program-specific mean baseline FEV_1, and $SE_r(b)$ is the approximate standard error of $b/\overline{FEV}_{1b}$ calculated by substituting the program-specific relative within-person standard deviation $\bar{s}_r$ for σ_w in equation (1).

The limit for the actual value of FEV_1 (mL) below which an individual's FEV_1 should not decline after t years of follow-up without raising concern can be calculated in terms of the individual's baseline FEV_{1b} value and LLD_a or LLD_r, as follows:

$$FEV_1 = FEV_{1b} - LLD_a$$

or

$$FEV_1 = FEV_{1b} - FEV_{1b} \times LLD_r$$

SPIROLA's default value for the relative within-person variation $\bar{s}_r$ is 4%, which corresponds to LLD_r of 10% for $t=1$ (i.e., annual follow-up). The LLD_r of 15% for $t=1$, which corresponds to the ACOEM limit, is based on $\bar{s}_r$ of 6%. To change this default value, on the **Options** menu use the **Within-person Variation** option. Beginning with 8 years of follow-up, the interpretation of excessive decline is based on an individual's regression slope and the lower 95% confidence limit around the regression line calculated as above. Here b represents the estimated regression slope and the individual's baseline measurement FEV_{1b} is replaced by the individual's predicted FEV_1 value.

Cross-sectional evaluation to identify respiratory impairment

SPIROLA evaluates and reports for the most recent spirometry test whether the FEV_1, FVC, or FEV_1/FVC ratio values are below the respective "cross-sectional" lower limit of normal (LLN) values or whether the FEV_1 value is below 60% predicted. By default, the LLN values and the predicted values are calculated using the Hankinson et al. reference equations estimated separately for Caucasians, African-Americans, and Mexican-Americans on US population data.[7] In addition, user-defined reference equations for FEV_1, FVC, and the FEV_1/FVC ratio can be specified. For FVC SPIROLA uses 70%

predicted value for decision making, when NHANES[7] based reference values are used, but LLN for user-specified reference values. The **Options > Display >Curves** menu enables users to select for display either LLN or 70% predicted or both.

6. References

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Appendix

Data source and format

SPIROLA requires demographic and spirometry data stored in or transported to a Microsoft Access database as a data table. The table needs to be sorted by ID and TestDate. Each record contains information on a single spirometry test with the following fields and a specified type. Fields can be in any order and variable names are not case sensitive.

The following variables are essential (must be included) for the SPIROLA analysis:

- **ID –** A text field (alpha numerical) to identify a tested individual
- **Sex –** A text field to store "M" for male or "F" for female gender
- **Race –** A text field to store "M" for Mexican-Americans, "B" for African-Americans, or "W" for Caucasians and other groups. This variable is used for selecting the appropriate set of reference equations.
- **Age –** A numerical field for age in years at a test (optional if date of birth provided)
- **BirthDate –** A date field (format: mm/dd/yyyy) to store date of birth (optional, allow more accurate calculation of age, eg. 45.5 vs. 45)
- **Height –** A numerical field to store height (cm) measurements of a tested individual
- **FEV1 –** A numerical field to store best FEV_1 (mL) value of a tested individual
- **FVC –** A numerical field to store best FVC (mL) value of a tested individual
- **TestDate –** A date field (format: mm/dd/yyyy) to store test dates

The following variables are optional for spirometry quality analysis:

- **FEV12 –** A numerical field to store second best FEV_1 (mL) value
- **FVC12 –** A numerical field to store second best FVC (mL) value
- **QFEV1** – A character variable for FEV_1 quality grades (if available)
- **QFVC** – A character variable for FVC quality grades (if available)
- **QTest** – A character variable for session quality grades (if available)
- **Oper** – A character variable for operator (spirometer technician) code or name
- **Provider –** A character variable for a provider (e.g., a van service)

The following name variables are optional and are need for a search by name:

- **Last_Name** – A text field (Surname/family name)
- **Middle_Initial** – A text field (leave blank if not available)
- **First_Name** – A text field

Inclusion of names in the database enables the user to identify an individual by name using 'Individual Identity' function in the 'Evaluation menu'. To use 'Identity Function' all three name variables must be provided.

Additional fields containing, for example, weight, smoking status, cigarettes/day, asthma status, quality control code, technician code, or respiratory symptoms data can be added. These data will be shown at the bottom of individual's FEV$_1$ chart, but will not be used in the analysis.

Importing data into SPIROLA

Data stored in other standard databases can be imported into a Microsoft Access database using the "Import" facility. To create the required variable format (e.g., "M" for male), the original variables can be converted by designing a *Make-Table* Q*uery* object in Access or by *Macro programming*. To avoid data loss, all .mdb files should be backed up in C:\SPIROLADATA.

ATS/ERS guidelines on Standardization of Lung Spirometry, recommend a standard format for databases generated by spirometers (Eur Respir J 2005; 26:319-338). All the variables specified by SPIROLA are defined by the ATS/ERS guidelines to be included in the standard database. At this stage the user needs to convert the spirometer-generated database into an Access database. Future SPIROLA revisions will enable automatic access to the ATS/ERS standardized data files.

Incorrect records or missing values

If a record has missing or incorrect values for variables such as ID, Age or BirthDate (one needs to be present), Height, FEV$_1$, FVC, or TestDate, the record is excluded from the analysis, but it is stored in a data file DeletedRecords.xml on the folder C:\Spirola.

Software requirements to run SPIROLA

- Microsoft Windows XP or Windows 2000/2003
- Microsoft .NET Framework and Database engine. In most cases these software packages are already installed in the user's computer.
- Microsoft Access is optional and enables viewing or editing data in Microsoft Access format.

SPIROLA installation package downloaded from webpage or from CD. Some support programs are required to run SPIROLA. In most cases, these programs are already installed with Microsoft Windows XP. SPIROLA may alert the user to install the .NET Framework or other components from Microsoft web sites.

- Microsoft .NET Framework version 1.1 redistributable package. This package includes everything needed to run applications developed using the .NET Framework. To install this framework, run program **DOTNETFX.EXE** provided in the SPIROLA software package or obtained as a free download from following link: http://www.microsoft.com/downloads/details.aspx?FamilyID=262d25e3-f589-4842-8157-034d1e7cf3a3&displaylang=en

- Microsoft Data Access Components (MDAC). This is for applications that use data access. To install this framework, run program **MDAC_TYP.EXE** provided in the SPIROLA software package or obtained as a free download from following link: http://www.microsoft.com/downloads/details.aspx?familyid=78cac895-efc2-4f8e-a9e0-3a1afbd5922e&displaylang=en