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Introduction

Program installation

System requirements

To run the MedCalc program you need a PC with Windows XP, Windows Vista, Windows 7, 8, 8.1 or 10; or Windows Server 2003, 2008 and 2012 (all 32-bit and 64-bit versions supported), with at least 1024 MB RAM and about 60 Megabyte free space on the hard disk.

MedCalc installation

You can download the software from www.medcalc.org/download. Select the 32-bits or 64-bits corresponding to your Windows version. If in doubt: the 32-bits MedCalc installer will work on both 32-bits and 64-bits Windows versions.

After you have downloaded the software, you locate the setup file medcalcsetup[32/64].msi on your hard disk and execute (double-click) it.

When installation is complete, you start MedCalc by clicking the Start button and point to Programs, next click MedCalc.

You can freely use the software, without any feature limitations, during 15 days without registration.

Note: To install MedCalc you must be logged on to your computer with administrator privileges.

Sample data

At first run, MedCalc creates a folder named "MedCalc" with a subfolder "Sample files" in the "(My) Documents" map. The "Sample files" folder contains the following MedCalc sample files:

- Bland and Altman plot.mc1
- Bland Altman multiple observations.mc1
- Clustered graphs.mc1
- Control chart.mc1
- Cox regression - Gallstones.mc1
- Dates.mc1
- Logistic regression.mc1
- Meta-analysis - Continuous measure.mc1
- Meta-analysis - Correlation.mc1
- Meta-analysis - Odds ratio.mc1
- Meta-analysis - Proportions.mc1
- Meta-analysis – Risk ratio & difference.mc1
- Nonlinear regression – 4PL.mc1
- Patients - sample data.mc1
- ROC curve analysis.mc1
- Serial measurements.mc1
- Survival curves.mc1
- Youden.mc1

Registration

When you start MedCalc for the first time a dialog box appears with the following options:

- **Buy now**: click to connect to the MedCalc web site and order a product key.
- **Enter product key**: click to enter your user name and product key. You only have to enter your user name and product key once. The next time you start MedCalc, the program will not ask you this information again. If you do not have a product key, you can purchase one from the MedCalc web site (https://www.medcalc.org/). If you are a registered user and you have lost your product key, use the Recover product key form https://www.medcalc.org/productkey/. Alternatively, you can contact MedCalc Software (mailto:info@medcalc.org), and we will email you your user name and product key.
- **Free trial**: you can run the software, without any feature limitations, during 15 days without registration.
Auto-update

Important: the auto-update feature is only available if you have a legal, non-network MedCalc license.

Step 1
When you start MedCalc, the program will check whether a new version of the software is available from the MedCalc website. When the program can successfully connect to the MedCalc website, and an update is available, the following dialog box is displayed:

MedCalc updates are free of charge and updating to the latest version is always recommended. If you don't want to install the update, click Cancel and MedCalc will remind you of the update after a user-defined number of days (see Options, p. 68). If you do not want MedCalc to automatically check for updates in the future, select the option Do not check for MedCalc updates in the future. You can always re-enable this option in MedCalc's Options dialog box (p. 68).

Step 2
If you click Update, the update will be downloaded from the MedCalc website:

You can interrupt and cancel the download by clicking the Cancel button.

Step 3
When the update could successfully be downloaded, the update software is launched automatically.

Privacy
When MedCalc checks for updates, no personal information (name, product key) is being sent to the MedCalc web server. The software will only retrieve the most recent version number from the website and compare it with the version number of your MedCalc copy.

What's new
If you are already familiar with MedCalc, you can read about the latest changes and additions in MedCalc by selecting What's new in the MedCalc Help menu.
It is possible that new features are available in the software, which are not described in this manual. You can find information on these new features in the MedCalc Help file (see Online help, p. 3), or on the MedCalc web site (see MedCalc on the Web, p. 307). Updated versions of the manual in PDF format can be downloaded from the MedCalc web site https://www.medcalc.org.

Regional settings support

MedCalc supports regional differences as entered in the Regional settings dialog box in the Windows Control panel. The following are taken from the Windows settings:

- **Decimal symbol**: the character used to separate the decimal digits from whole numbers.
- **List separator**: the symbol used to separate elements in a list, e.g. arguments in spreadsheet functions, or fields when exporting data as a text file.
  
  E.g. when the list separator is a comma, the arguments in the RANDNORM function are separated by a comma: RANDNORM(m,s). If the list separator is a semicolon, the arguments are separated by a semicolon: RANDNORM(m;s).
  
  The list separator is also used to separate the fields or variables when you export spreadsheet data.
  
  The list separator cannot be equal to the decimal separator!
  
  If MedCalc finds the list separator to be equal to the decimal separator in the Windows settings, then it will use a semicolon as the list separator when the decimal separator is a comma.
- **Date format**: MM.DD.YYYY, DD.MM.YYYY or YYYY.MM.DD (see Date functions, p. 322).

You can use different characters for the Decimal symbol and List separator, or use a different date format in the Options panel, see Options, Regional settings, p. 68.

To select a different display language for user-interface and reports, see the Options panel (p. 68)

The MedCalc menu bar

After starting the program, the MedCalc program window appears, with a menu bar at the top of the screen containing the following headings:

- **File**: Disk input and output of spreadsheet data files, printing, quit MedCalc
- **Edit**: Cut, copy, paste, find, insert…
- **View**: Open Contents bar, spreadsheet, notes editor, set view characteristics…
- **Format**: Character formatting, spreadsheet & column format, graph formatting…
- **Tools**: Sort data, edit variables list, options…
- **Statistics**: Statistical analysis of spreadsheet data, t-tests, Wilcoxon tests, comparison of groups, regression, survival analysis, meta-analysis, reference intervals, method comparison, ROC curve analysis, etc.
- **Graphs**: Statistical graphs, control chart
- **Tests**: Statistical tests on tabulated or summarized data (useful when you do not have the raw data available in the spreadsheet): difference between means, standard deviations, percentages, correlation coefficients, relative risk, odds ratio
- **Sample size**: Calculation of sample sizes
- **Window**: Rearrange windows or activate a specific window
- **Help**: Get help and information.

On line help

At any moment during working with MedCalc on line help is available, e.g. information on a menu item, explanations on a dialog box, etc. After you press function key F1 the program displays a context-sensitive help text.

You can also call the help function by selecting Contents and Index in the Help menu.

Help in dialog boxes

To get comprehensive help on the dialog box, click the Help button.
To get help on any item in the dialog box: click the question mark \( \mathbb{Q} \) in the title bar of the dialog box, and then click an item in the dialog box.

- You can print or copy the information in a pop-up window by right clicking inside the pop-up window, and next clicking **Print Topic** or **Copy**.
- To close the pop-up window, click inside it.
- You can also get help on an item by right-clicking it, and then clicking **What's This?**

**Screentips & quick help**

When the mouse is moved over one of the buttons in a toolbar, a short explanation appears in a small pop-up window.

While you are making a selection in the menu, a description of the highlighted command is displayed in the status bar at the bottom of the window.

## The spreadsheet data window

In MedCalc, data are entered in a spreadsheet. You open the spreadsheet window by selecting **Spreadsheet** in the **View** menu, or selecting **Data** in the **Contents bar**.

![Spreadsheet Window](image)

One cell (rectangle) of the spreadsheet is highlighted. This rectangle is called the *cell pointer*.

The first character(s) of this cell address (A) is the column indicator and the next number is the row number (row 1 is the first row number). Above row 1, there is an additional fixed row where you can enter a column heading, i.e. a name for the variable for which data will be entered in this column.

The column and row of the cell pointer are also called the current column and row.

The cell pointer can be moved with the arrow and/or cursor keys, or by means of the mouse. When you click on a cell, the cell pointer jumps to this cell. You can browse in the spreadsheet window by clicking on the right and bottom border of the spreadsheet window, or by using the **Page Up** and **Page Down** and other cursor or arrow keys.

By pressing the **Ctrl+Home** key you move the cell pointer to the first data cell in the spreadsheet: cell A1, and with **Ctrl+End** to the last cell used in the spreadsheet.

You can fix a number of columns in the spreadsheet by using the **Split window** command (see p. 305):

![Split Window](image)

**Total number of columns and rows in the spreadsheet**

The MedCalc spreadsheet can contain up to 16384 columns and 1048576 rows.
How to enter data

Data for the different variables are entered in different columns of the spreadsheet. All data for a single subject or case are entered in one row in the spreadsheet. In the top row of the columns you can enter the names of the variables.

A variable name should not include any spaces. If necessary, you can use the underscore character _ to separate words, e.g. GRADE_A. Also the following characters cannot be used in a variable’s name:

- + / * = < > ^ ( ) $ " ' : , .

In addition, the variable name must not start with a number and must be different from reserved words such as TRUE, FALSE, ROW and COLUMN. The variable name should also not be equal to the address of a spreadsheet cell such as A1, S1, AB35, IL6, etc.

In order to enter the variable name LENGTH in the top row of column A, you first position the mouse pointer on this cell, and click the left mouse button. The cell pointer is now located in this cell, and you can type the variable’s name on the keyboard. Next, you press the → key to store the name in the computer’s memory and move the cell pointer to cell A1. You can now enter the first value 171 for the variable LENGTH in this cell, followed by pressing the → key to go to the next cell.

The data are not stored in the computer’s memory until you have pressed the Enter key, or have moved the cell pointer to another cell.

When you want to change or edit the content of a cell, place the cell pointer on this cell and press function key F2. You can now move the cursor in the cell’s text by means of the arrow keys ← and → and make the necessary changes. After you have made the changes, press the Enter key or move the cell pointer to another cell to store the new cell content in memory.

While you are entering data you must, from time to time, save your data on the disk. When you save the file for the first time then select the command Save as in the File menu, and next enter the file name in the file selector box described on page 9. After you have given a name to your data file, you can select the Save command in the File menu to save your data under the same file name.

The program automatically formats the numbers that you enter according to the number of decimals selected in the Format spreadsheet box (see p. 49).

If you want a different number of decimals for a column, then select Column in the Format menu and enter the new number of decimals. In this dialog box you can also specify a different width for the column. You can also specify that a format for the data in the column.

For example, when column A contains dates, select the “Date” format:
A variable may either be **categorical** or **numerical**. Categorical variables may either consist of numeric or alphanumeric (string) data. A numerical variable always consists of numerical data.

**Categorical or qualitative variable**

Categorical or qualitative data may either be entered as numbers or as text **strings**. A text string consists of one or more alphanumeric characters, placed in quotation marks. The program will consider every expression that cannot be interpreted as a number to be a string, even if it is not placed between quotation marks, e.g. "Green", yellow, "10". Distinction can be made between **Nominal** and **Ordinal** data:

Nominal data: a classification without obvious order, e.g. blood group, male/female.

Ordinal data: ordered categorical data, e.g. endometriosis stage, varicocele grade.

A variable that can only have 2 values is also called a dichotomous variable, for example pregnant/not pregnant, male/female.

In MedCalc, it is often useful to code categorical data with numerical values: 0 and 1, or 1 2 3 4, etc.

**Numerical or quantitative variable**

A numerical variable consists of numbers, for example 0, 25 or 3.258, or expressions that can be interpreted as a number, e.g. LOG(25) or SQRT(VAR1) where VAR1 is a variable’s name containing numerical data.

Numerical data may either be **continuous** or **discrete**.

Continuous data: numbers that can theoretically assume any value between two given values; usually **measurements**, for example: the height of a person.

Discrete data: data that are not continuous (and may have a limited number of values), usually **counts**, for example: the number of children in a family.

You can easily convert a numerical variable into a categorical variable using the Create groups tools (see p. 56-58) or the CATEGORISE function (see p. 324) or IF function (see p. 325).

**How to enter dates**

First open the spreadsheet (select the Spreadsheet command in the View menu or click the button) and enter a heading in the column that will contain the dates:
Next, select the Format spreadsheet command in the Format menu or click the button.

On the Column tab, select the "Date" option for "Format" and increase the column width to e.g. 12 so there is enough space to enter dates. If you do not specify "Date" for "Format", MedCalc will display the number 0.0127551 when you enter a date as 5/7/56 (5 divided by 7 divided by 56).

Now you can start entering the dates. MedCalc allows entering dates using a slash or dot or any non-numerical character as a separator: e.g. 10.12.88.

How MedCalc handles date and time data

MedCalc stores a date and time as a number $ddddd.tttttt$ with the integer portion $ddddd$ representing the number of days since 1801-Jan-1, plus a fractional portion of a 24 hour day $ttttt$. The number $ddddd.tttttt$ is called a serial date, or serial date-time number.

The date format, i.e. the way the serial date number is converted to a string, can be chosen in the Regional settings dialog box of the Control box window that is part of the Windows operating system (see your Windows documentation).

Serial date numbers can be used for comparison, sorting, arithmetic operations and statistical analysis.

For example:
Both columns A and B have been formatted as Date, see above.

When you enter a date in the spreadsheet with a year less than 100, MedCalc will interpret this year as a year in the 20th century: 20.12.88 = 20.12.1988. When you enter 0 as the year number, MedCalc will interpret this as the year 1900: 20.12.00 = 20.12.1900. So when you want to enter a date situated in the 19th or 21st century, enter the year using 4 digits.

### Dates

The integer portion of the serial date-time number, *ddddd*, represents the number of days since 1801-Jan-1, with 1801-Jan-1 begin the first day. For example, the date 5-Jul-2011 is stored as 76887.

- Date strings, for example "5.12.72" or "5.7.1956" can be converted to serial date numbers using the DATEVALUE function (see Date and time functions, p. 322).
- A serial date number can be back-transformed to a date string using the DATE function.

### Times

The fractional portion of the serial date-time number, *tttttt*, represents the fractional portion of a 24-hour day. For example, 6:00 AM is stored as 0.25, or 25% of a 24-hour day. Similarly, 6PM is stored at 0.75, or 75% percent of a 24-hour day.

- Time strings, for example "14:30" can be converted to serial time numbers using the TIMEVALUE function.
- A serial time number can be back-transformed to a time string using the TIME function.

### Missing values

The data for all variables of one case (patient, sample) are entered on one row in the spreadsheet. When for one variable you do not know the value (or entry) for the case, you leave the corresponding cell blank and do not enter any data in this cell.

As a rule, the program will ignore an entry for a numeric variable when it is unable to interpret this entry as a number.

When text is entered in a cell for a numeric variable, the program will not take this case into account for calculations (it will not substitute the text value by a zero).

The following are recognized as numbers:

- 5.4
- \( \log(36.5) \)
- \( \text{HEIGHT/WEIGHT} \) (when 'Height' and 'Weight' are correctly defined variables)
- \( \text{HEIGHT/100} \)

The following are not recognized as numbers and are ignored for calculations:

- 5,8
- '4.6
- \( \log(\text{CONC}) \) (when 'CONC' is not a correctly defined variable or in case the variable 'CONC' has a zero, negative or missing value)
- \( \text{SQRT}(-9) \) (error!)
- 1/ \( \text{HEIGHT} \) (when 'HEIGHT' is not a correctly defined variable or in case 'HEIGHT equals zero')
Data checking

After having entered the data, you should carefully check the data to ensure that they have been entered correctly. Sometimes erroneous data input will become apparent when looking at the data range in the summary statistics report (e.g. maximum value of 78 for pH), or when plotting box-and-whisker plots, dot plots or scatter diagrams for the different variables. You should check clear outliers since they may indicate incorrect data entry, or they may result from a technical failure in measurement or from a study protocol violation. Only for such plausible reason you may exclude a value from further analysis, and not simply because a value is the smallest or largest. If there is no evidence of such a mistake, then the value must remain unaltered.

You can locate any value in the spreadsheet using the Find procedure (p. 41).
You can exclude outliers from further calculations by using the Exclude command (p. 51).

How to save data

When you want to save the data, select the command Save as in the File menu. The program will display the following dialog box:

- **Save in:** select the directory where you want to save the data file.
- **File Name:** select or type the name of the file for the data. This box lists files with the file name extension selected in the Save as type box. You can select a file by clicking on a file name.
- **Save as type:** select the type of file you want to see in the file name list box.

When the correct file name is entered, click the Save button.

Variables

1. The basic variable: column heading

These variables refer directly to columns in the spreadsheet. The name of the variable is the heading you enter for the column in the spreadsheet.
If you have the following data in the spreadsheet:

![Spreadsheet data](image)

then ID_NR, TREATMENT, AGE, HEIGHT and WEIGHT are valid variables. Remember that a variable name should not include spaces, nor the following characters: - + / = < > ^ ( ) { } | ? & $ " ' :. In addition, the variable name should not start with a number and it must be different from reserved words such as TRUE, FALSE, ROW and COLUMN. Finally, it should not be equal to the address of a spreadsheet cell such as A1, S1, AB35, IL6, etc.

2. Combination of variables

When performing statistical analyses or creating graphs, you can enter a combination of variables as a variable in the dialog panels:

![Combination of variables](image)

In this example, the variables WEIGHT and HEIGHT are combined into a new variable (the Body Mass Index) with the formula WEIGHT/(HEIGHT*HEIGHT). Any of the following operators can be used to combine variables (in order of precedence):

- ^ Exponentiation
- - Negation
- * / Multiplication, Division
- + - Addition, subtraction

As shown in the example, brackets can be used to change the operator’s precedence.

3. Transformation of a variable

When a variable needs transformation, you can use one of the many MedCalc spreadsheet functions. For example, if a variable needs square root transformation you use the SQRT(variable) function as new variable:
Note:
The formula $\text{WEIGHT}/(\text{HEIGHT}^2)$ can also be written using the \texttt{POWER} function as: $\text{WEIGHT}/\text{POWER}(\text{HEIGHT},2)$

when a function requires more than one argument, these arguments are separated by the list separator that is selected in the Windows settings (Control panel - Regional settings - Number). Usually this is a comma (as in the examples in this help file), but in European countries the list separator commonly is a semicolon ";". In the latter case, the above example should be written as: $\text{WEIGHT}/\text{POWER}(\text{HEIGHT};2)$.

Filters

A filter is a logical expression which evaluates to 1 (\texttt{=TRUE}) or 0 (\texttt{=FALSE}). For every case in the spreadsheet, this expression is evaluated and if the result is \texttt{TRUE}, the case is included in the analysis or graph but if the result is \texttt{not TRUE}, then the case is excluded from the statistical analysis or graph.

1. Simple filter

A basic filter exists of a variable, a logical operator and a constant value. The relational operators, in order of precedence, are:

- = Equality
- <> Inequality
- < Less than
- > Greater than
- <= Less than or equal to
- >= Greater than or equal to

For example, if you have the following data in the spreadsheet:

![Spreadsheet Data](image)

then the expression \texttt{AGE}>40 can be used as a filter:
When MedCalc calculates the summary statistics for the variable WEIGHT, it will evaluate the expression AGE>40 for every case. MedCalc will only include the cases for which the expression evaluates to the logical value TRUE.

Other examples of filters:

- TREATMENT="A" : Treatment must be equal to "A" - notice the use of quotation marks for text constant in formula.
- AGE<=60 : Age must be less than or equal to 60
- ROW<21 : Only the first 20 cases in the spreadsheet will be selected (see ROW)

2. Combined filter

Different filters can be combined into one single filter using the logical functions AND, OR and NOT, e.g.

- AND(AGE>40,AGE<60) : only cases with age more than 40 and less than 60 will be selected.
- AND(AGE>40,TREATMENT="A") : only cases with age more than 40 and treatment "A".
- OR(AGE>40,TREATMENT="A") : cases with age more than 40 or treatment "A" will be selected.
- AND(AGE>40,OR(TREATMENT="A",TREATMENT="B")) : cases with age more than 40 and treatments "A" or "B" will be selected.

When you have used a filter, you should check the resulting sample size and verify that the cases you intended to be selected have indeed been selected, and that you did not make a logical error in composing the filter formula.

Statistics

After you have entered data in the spreadsheet, it is advised to save the data on disk. This is done by selecting the command Save as in the File menu. You will have to enter a name for your data file in the File selector box (see p. 9).

To load a data file from disk, select the command Open in the File menu. Next, select the name of the file in the File selector box. For example, you can select the data file Patients - sample data.mc1. This file contains data on length and weight for a number of persons.

When you want to obtain summary statistics for the variable Weight, select the command Summary statistics in the Statistics menu. The following dialog box appears on the screen.
Click the button to obtain a list of variables.

From this list you can select a variable by clicking on the variable's name.

If the variable requires a logarithmic, square root, or any other mathematical transformation, then you can enter a formula in the variable field:

- SQRT(WEIGHT)
- LOG(LENGTH)

or you can enter a formula combining different variables, e.g.

WEIGHT/LENGTH

By doing so, new variables will be added to the variables list: SQRT(WEIGHT), WEIGHT/LENGTH, etc...

For an overview of mathematical operators and functions available in MedCalc, refer to pages 309 and 312.

Optionally, you may also enter a data filter in the Filter field of the dialog box, in order to include only a selected subgroup of cases in the statistical analysis.

The Select field may contain a combination of different criteria, using the AND and OR functions (see also p. 324):

AND(LENGTH>160,LENGTH<170)

These expressions may make use of all mathematical and other spreadsheet functions as described in a next part of this manual (p. 309).
After you have entered a data filter in a dialog box (in order to include only a selected subgroup of cases in the statistical analysis), this data filter will be ‘remembered’ by the program and will be selectable in the Filter list.

After you have clicked OK, the following statistics are calculated and displayed in the results window:

<table>
<thead>
<tr>
<th>Variable</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter</td>
<td>Treatment: 'A'</td>
</tr>
<tr>
<td>Sample size</td>
<td>50</td>
</tr>
<tr>
<td>Lowest value</td>
<td>40.0000</td>
</tr>
<tr>
<td>Highest value</td>
<td>105.0000</td>
</tr>
<tr>
<td>Arithmetic mean</td>
<td>77.6800</td>
</tr>
<tr>
<td>95% CI for the mean</td>
<td>74.6536 to 80.7965</td>
</tr>
<tr>
<td>Median</td>
<td>76.0000</td>
</tr>
<tr>
<td>95% CI for the median</td>
<td>71.6034 to 81.3966</td>
</tr>
<tr>
<td>Variance</td>
<td>113.4057</td>
</tr>
<tr>
<td>Standard deviation</td>
<td>10.6492</td>
</tr>
<tr>
<td>Relative standard deviation</td>
<td>0.1371 (13.71%)</td>
</tr>
<tr>
<td>Standard error of the mean</td>
<td>1.5060</td>
</tr>
<tr>
<td>Coefficient of Skewness</td>
<td>0.3216 (P=0.3231)</td>
</tr>
<tr>
<td>Coefficient of Kurtosis</td>
<td>-0.2553 (P=0.8116)</td>
</tr>
<tr>
<td>Shapiro-Wilk test</td>
<td>W=0.9792</td>
</tr>
<tr>
<td>for Normal distribution</td>
<td>accept Normally (P=0.5200)</td>
</tr>
</tbody>
</table>

For more details about the displayed statistics, see p. 70.

Note that when you change the data in the spreadsheet, this will not automatically cause a recalculation of the displayed statistics, but you have to repeat the statistical analysis for the new data.

To facilitate this, use the Saved tests and graphs feature (p. 26): by clicking the button you can save the analysis so you can recall the analysis later, possibly with new data. After you have clicked this button the graph is added to the Saved tests and graphs list in the Contents bar, with a default name, which you can edit in the Contents bar (see p. 47).

**Graphs**

When you want to create a graph, proceed in a way similar as for any other statistical procedure. As an example, you will create a histogram for the variable Weight of the data file you have loaded in the previous section.

To obtain the histogram, you select the command Histogram in the Statistics menu.
A dialog box is displayed similar to the one for *Summary statistics*. Again, enter the name of a variable and optionally a data filter. If you have previously entered this data filter in e.g. the dialog box for summary statistics, then this will be selectable in the *Filter* list (click the ![button](image)).

When you have identified the variable in the dialog box, click the OK button to proceed. The program will display the following box:

After you have clicked OK the histogram is displayed in a new window:

To get statistical information on the data represented in the graph (sample size, etc.):
- click the right mouse button in the graph window:
• select the Info command in the shortcut menu.

By clicking the button you can save the graph, so you can recreate the graph later, possibly with new data. After you have clicked this button the graph is added to the Saved tests and graphs list in the Contents bar, with a default name, which you can edit in the Contents bar (see p. 47).

Graph formatting

Click the button in the Formatting toolbar to format the graph. The effects of the changes in the left panels (displayed below) of the dialog box can be previewed in the right panel:

Scheme

In the graph colors box you can select a color for every object used in the graph.

Schemes

In this box you can select a predefined or user-defined color scheme.

• Save scheme: “Save scheme...” can be used to save the currently defined color selections as a named scheme for later use.
• **Set as default:** When you click “Set as default”, the current color scheme will be saved and used as the default color scheme for new graphs. The color schemes also include the Fills, Lines and Marker style and color selections.

• **Delete scheme:** Click this button to delete the currently selected color scheme.

• **Restore predefined schemes:** Click this button to restore the different predefined color schemes.

### Options

- **Display grid:** displays gridlines in the graph.
- **Plot area border: XY only:** when this option is selected, lines for the X and Y axes are drawn. If this option is not selected, the plot area is enclosed in a rectangle.
- **Outside tickmarks:** select this option to have the tickmarks drawn on the outside of the graph frame.

![Inside tickmarks](Image1)

![Outside tickmarks](Image2)

- **Side margins:** this option lets you set a margin between the chart’s plot area and lines for X and Y axis. This option is only available when the option Outside tickmarks is selected.

![No side margins](Image3)

- **Use digit grouping symbol in numbers:** option to use the digit grouping symbol (thousands separator) in formatting numbers in the graph. E.g. when the digit grouping symbol is a comma, the number 10000 will be displayed as 10,000. The digit grouping symbol is taken from Windows’ regional settings, or is a user-defined character specified in MedCalc options (p. 68).

- **Allow exponential notation:** when this option is selected, the program will display small or large numbers in exponential notation, e.g. 2000000 will be displayed as $2 \times 10^6$.

### Titles

In this box you can edit the main text sections (title and axes) of the graph.

![Title TextArea](Image4)

### Axis

In this box you define the scaling of the X and/or Y-axis by entering the following information:

- **Minimum:** this is the lowest value that appears on the utmost left of the X-axis or bottom of the Y-axis;

- **Maximum:** this is the highest value that appears on the utmost right of the X-axis or top of the Y-axis;
- **Increment**: the increment value between two major grid lines;
- **Minor tickmarks**: the number of minor tickmarks between two major increments.

In MedCalc, the default increments are 1, 2 or 5 times a power of ten, yielding about 6 to 10 major tickmarks. If you are preparing a graph for publication, you are advised (Tukey, 1977) to limit the number of major tickmarks to about 2 or 3, so you will have to increase the value for increment, preferably also steps of 1, 2 or 5 times a power of 10.

If a logarithmic transformation of the data was selected in the graph's dialog box, then the information for the lowest value (**Minimum**) and **Increment** must be logarithmic values as well (e.g. for **Minimum** enter -2 for the value 0.01, or 0 for the value 1, 3 for the value 1000, etc.). **Increment** is then the exponent increment and should preferentially remain equal to 1.

**Scale reversal**: if you want to reverse the scale of the axis, you enter the higher value in the **Minimum** field and the lower value in the **Maximum** field. Scale reversal is possible for both X- and Y-axis in most MedCalc graphs.

After clicking OK, the graph will be replotted using the new axis scaling. However, the program will ignore a new axis scaling if this new scaling would cause data to fall outside the full axis range.

**Font**

In this box you can select the font, font style and font size used in the graph. The font **Sample** box (in which you can enter text freely) ignores the selected font size. The effect of font size can be seen in the **Preview** box.

**Format graph components**

To format different graph components, you right-click on the component and next select "Format..." in the pop-up menu.

**Example**

In a box-and-whisker plot, right-click on a marker.
Select "Format marker..."
Select the desired marker attributes in the dialog box.

**Add graphical objects**

In all MedCalc graphs, you can add additional text boxes, lines, rectangles, ellipses and connectors.

**Text box**

Example:  

P<0.05

To add a text box in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Add text box": 
Next click in the graph to set the new text box position. To edit the text box characteristics, double click on the text box or right-click on the text box and select "Format Text box...":

**Line**

Example:

To add a line in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Draw line". Next click in the graph and drag the mouse to create the line. To edit the line characteristics, double click on the line object or right-click on the line object and select "Format line object...".

**Rectangle**

Example:

To add a rectangular frame in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Draw rectangle". Next click in the graph and drag the mouse to create the rectangle. To edit the rectangle characteristics, double click on the rectangle or right-click on the rectangle and select "Format rectangle...".

**Ellipse and Circle**

Example:
To add an ellipse in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Draw ellipse". Next click in the graph and drag the mouse to create the ellipse. To draw a circle: press the Shift key while dragging the mouse. To edit the ellipse characteristics, double click on the ellipse or right-click on the ellipse and select "Format ellipse...".

**Error bar**

Example:

To draw an error bar in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Draw error bar". Next click in the graph and drag the mouse to create the error bar. To rotate the error bar or to edit line color and style, double click on the error bar or right-click on the error bar and select "Format error bar...".

**Connector**

A connector is commonly used to indicate statistical significance of differences between groups.

Example:

To add a connector in the graph: right-click in the graph and in the pop-up menu select "Add graph object" and "Draw connector". Next click in the graph and drag the mouse to create the connector. To edit the (optional) text attached to the connector, to rotate the connector or to edit its characteristics, double click on the connector object or right-click on the connector object and select "Format connector...".

**Selecting graphical objects**

To select a graphical object:
- place the mouse pointer over the object and click the left mouse button
- small circles at the corners of the object (grab handles) indicate that the object is selected
- to add other objects to the selection, press the Ctrl key while clicking on the other objects.

**Moving, resizing and deleting graphical objects**

Graphical objects can be moved from their original location or can be changed in size or shape.
- select one or more objects
- click on one of the objects and move the mouse to move the selected objects, or use the arrow keys on the keyboard
- click on one of the graph grab handles (the small circles at the corners of the object) and move the mouse to resize the selected objects
- press the Delete key to delete the selected objects.

**Reference lines**

Reference lines are vertical or horizontal lines in a graph, corresponding with user-defined values on the x-axis and y-axis respectively. Each graph can contain up to 16 vertical and horizontal reference lines.

**Add reference line**

**Method 1**

Right click in the graph and select "Add graph object" and "Horizontal reference line" or "Vertical reference line".
Method 2
Click in the margin of the graph to create a reference line and drag it into the graph plot area.

While you are dragging the reference line in the plot area, the corresponding value is displayed next to the reference line.

Format reference line
To format a reference line, you right-click on the reference line and select "Format reference line" in the pop-up menu.
In the dialog box you can select line color, style and width, and enter an exact value for the reference line:

Note: all reference lines in one graph have the same color style and width.

**Remove reference line**

**Method 1**
You right-click on the reference line and select "Remove reference line" in the pop-up menu.

**Method 2**
You drag the reference line into the graph's margins.

**Export metafile**

When a graph window is active, you can select the *Export* command in the *File* menu to save the picture in Windows metafile format. Windows metafiles can be imported in almost every Windows word processor, drawing or presentation program (Microsoft Word, PowerPoint, etc.).

You can also transfer a graph from MedCalc to another Windows application without saving the file intermediately by selecting the *Copy* command in the *File* menu, activate the other application and there select the *Paste* command.
Export results and graphs to Microsoft Word

Save as a Word file
- Right-click on the results window title bar.
- In the pop-up menu select "Export results".
- In the Export results file selector box, for "Save as type:" select "Word document".
- Enter a file name.
- Click "Save".
This method works for all results reports as well as results displayed in dialog boxes such as in the Tests (p. 267) or Sample size (p. 285) menus.

Save to or append to Word file (docx files only)
- Click the Save to Word button or press Ctrl+W.
- A dialog appears in which you can enter the name of the Word document.
- Click the Browse button to call the common file selector dialog.
- You can save the report or graph to a new word document or append it to an existing document.
- Use the option "Include a heading with file name, date and time" to insert a separator/header above the report or graph with the name of the datafile, and the current date and time.
This method works for all results reports as well as for graphs and the spreadsheet table.
The keyboard shortcut Ctrl+W also works for results displayed in dialog boxes such as in the Tests (p. 267) or Sample size (p. 285) menus.
This feature requires Microsoft .NET 4 framework, which is already available on most Windows PCs, or can be downloaded freely from the Microsoft website.

Copy-Paste to Microsoft Word
- Open your document in Microsoft Word.
- Activate the MedCalc results window.
- Select "Select all" in the Edit menu, or press Ctrl+A.
- Select "Copy" in the Edit menu, or press Ctrl+C.
- Activate Microsoft Word and place the cursor where you want to insert the table.
- Select "Paste" in Word's Edit menu, or press Ctrl+V.

Recall dialog

Recall most recent dialog (F7)
After you have completed a dialog box or statistical procedure in the Tools, Statistics, Graphs, Tests or Sample size menu, you can immediately recall the dialog by pressing function key F7.
When you recall a dialog box, the dialog box will be redisplayed with all fields containing the same entries. For example, after you have completed the dialog box for Regression, you may want to repeat the same analysis with a minor change in the dialog box, e.g. a different equation. You just need to press F7 and the selections of the first analysis are displayed in the dialog box.

List recent dialogs (Ctrl-F7)
Press function key Ctrl-F7 or click to obtain a pop-up menu with recent dialogs.
Recall dialog of a results or graph window

Right-click in the title bar of a results or graph window. Next select Recall dialog in the pop-up menu. This will recall the dialog box for the corresponding analysis or graph.

Recall dialog box of a saved procedure

When you have saved a statistical procedure or graph (see p. 26) you can recall the dialog box by right-clicking on the item:

Recall selections from a previous and different dialog box

Function key F7 can also be used to enter the data from a previous dialog box in a new dialog box. For example, after you have created a scatter diagram, you want to calculate the correlation statistics for the same variables. In order to obtain this, select Correlation coefficient in the Statistics menu. When the dialog box is displayed, you press function key F7 to enter the same variables as in the previous dialog box for the scatter diagram. This functionality is available to exchange information among similar dialog boxes, such as

- Summary statistics, Histogram, Cumulative distribution, Box-and-whisker plot, Normal plot, Reference interval
• Correlation, Rank correlation, Regression, Scatter diagrams
• Multiple regression, Logistic regression, Multiple variables graphs, Clustered multiple variables graphs
• T-tests, Wilcoxon tests, Data comparison graphs.
• One-way analysis of variance, Kruskal-Wallis test, Multiple comparison graphs, Clustered multiple comparison graphs.
• Bland-Altman plot, Passing & Bablok regression, Mountain plot.
• Frequency table, Frequency charts, Inter-rater agreement (Kappa), Fisher's exact test, McNemar test
• ROC curve and Comparison of ROC curves

Save and recall graphs and statistics

Create a graph and, if necessary, click the Format graph button in the Formatting toolbar to format the graph (font, colors, etc.).

Next click the Save report or graph button to save the graph into the Saved tests and graphs list in the Contents window, with a default name (which you can edit by pressing function key F2).

The graph is added to the “Saved tests and graphs” section of the Contents window:
Save the MedCalc file, and next clear all data or exit the program. After opening the file again, you double click the graph item in the Contents window to recreate the graph.

The graph is recreated:
To delete an item from the Saved tests and graphs list you right-click on it and select Delete in the pop-up menu.

Notes editor

Notes editor

The MedCalc Notes editor is an editor that you can use to edit short texts. These texts are associated with the spreadsheet data, and when you load or save the MedCalc data file, the notes are loaded or saved with it. When you want to save the text in a separate file, you have to use the Export text command.

The MedCalc notes offer for example the possibility to add explanations about codes used in the spreadsheet.

To create a new Notes document, right click Notes in the Contents bar (see p. 47) and select New notes in the shortcut menu:

A new notes document is listed in the Contents bar with a default name "New notes". Right-click the New notes item to obtain the following shortcut menu:
You can now open the notes document and start editing notes.

**Text block functions**
Deleting, moving and copying text blocks is possible by means of the commands in the *Edit* menu, or the corresponding buttons in the toolbar.

**Export text**
The text entered in the text window is always saved in the MedCalc data file. Therefore, after you have entered some text, select *Save* or *Save as* in the *File* menu to save the text, together with the data.

The *Export text* command can be used to save the text as a separate text file, which can be imported in a word processor.
File menu

New

Select New if you want to close the data file, clear all data in the spreadsheet, freeing up the memory for new data. If you have already entered some data and the latest additions or changes have not been saved, then the program will display an appropriate warning. In this case you will have the option to save the data (Yes), or clear the data without saving the data (No), or cancel the New command, keeping the existing data in memory (Cancel).

After having cleared all data in memory, the program will display a blank spreadsheet window so you can start entering new data.

Open

Button:  
Shortcut:   Ctrl+O

If you want to retrieve a data file that you previously have saved on disk, select the Open command in the menu. In the file selector box (described on p. 9) you select the name of the file to be read into memory. Together with the spreadsheet data the associated notes are loaded (see p. 28) and the options that are also included in the MedCalc data file.

If you want to read a MedCalc data file without erasing existing data in memory, e.g. to combine two files into one, then select the Add file command (see p. 34).

Supported data file types

MedCalc support the following file formats:
- MedCalc files (*.mc1)
- Excel files (*.xls, *.xlsx, *.xlsm)
- SPSS files (*.sav)
- Stata files (*.dta)
- DBase files (*.dbf)
- Lotus files (*.wk1)
- SYLK (*.slk) and DIF (*.dif) files
- Text files (*.txt, *.csv, *.prn)

MedCalc files (*.mc1)

When you open a MedCalc data file (which have file extension MC1) MedCalc will lock the open file, preventing other programs and users access to the file. To close and unlock the file, you select the New command.
From time to time the MedCalc file format is revised. MedCalc will automatically convert old files as you open and save them. However, previous MedCalc versions may not be able to read the data files written by some newer versions of the software. It is advised that you always download and install the latest version of MedCalc (visit https://www.medcalc.org).

**Excel files (*.xls, *.xlsx, *.xlsm)**

To import an Excel worksheet file, select the file type *Excel Worksheet*. If the Excel file contains more than 1 worksheet, then the program will display a dialog box in which you can select the worksheet you want to import.

- MedCalc will convert all formulas in the Excel spreadsheet into their calculated values.
- The import procedure will import data files from Microsoft Excel version 2.1 and higher.
- On Windows versions prior to Windows 8 or Windows Server 2012, support for Excel (*.xlsx) files requires Microsoft .NET Framework 4.0 (a free download from Microsoft).

**SPSS files (*.sav)**

When you open an SPSS data file (with file extension *sav*), MedCalc will present a *Select variables* dialog box in which you select the names of the variables to be imported in MedCalc.

The available variables in the file are listed in the box at the left side of the dialog box. If you want to import all variables, i.e. all data in the file, then click the All button. If you do not want to import all variables, then select the names of the variables you require by clicking the variables’ names. The names of the selected variables are displayed in reverse. To unselect a selected variable, click it again. By clicking the None button, you can cancel the selections.

When you have finished selecting the variables, click OK.

**DBase files (*.dbf)**

The file type *DBase file* must be used when you want to import a database file (with file name extension DBF) created by DBase III+ and compatible programs.

After you have selected the file name in the *File selector box*, select the names of the fields to be imported in MedCalc using the *Select variables* dialog box (see *Import SPSS file*).

After you have finished selecting the variables, click OK.

In DBase files *missing values* are often coded by the maximum value possible in the corresponding field (column). E.g. in a field with a maximum number of characters (field width) of 3, the number 999 will indicate a missing value. The number 9999 will be used to code missing values in a field with width of 4 characters, etc. After you have imported the DBase file, you must check whether this is the case. If it is, you can use the *Find & Replace procedure* (see p. 42) to clear the cells containing these missing values.

E.g. after you have imported the DBase file, you can open the spreadsheet window and inspect the data. When you see any values 999 in a column with a width of 3 characters, then this almost certainly means that missing values for this variable are indeed coded as 999. You can place the cell pointer in the top row of this column, select the *Find & replace* option in the *Edit* menu, and enter the following in the dialog box:
The Replace with field is left blank because in MedCalc missing values are indicated by an empty, blank, cell. After clicking OK, all 999 codes will be erased in the column.

If missing values in the DBase file were coded with a different number, for example 0, you can take a similar approach, but you will have to be careful not to confuse the genuine 0 values with the missing value code 0.

Lotus files (*.wk1)

Lotus files (*.wk1) are data files created by Lotus123 (version 2) and Symphony.

If the Lotus spreadsheet contains formulas that are not supported by MedCalc, it is recommended that you use the Lotus commands Range Value (/RV) to convert the formulas into values, before you import the file in MedCalc.

SYLK (*.slk) and DIF (*.dif) files

MedCalc can import both SYLK (Symbolic Link Format) and DIF (Data Interchange format) files.

Text files (*.txt, *.csv, *.prn)

In a text file, one text line contains data on one case, and every text line ends with a carriage return character (ASCII code 13).

In a formatted text file, the different fields (variables) are separated by spaces so that, when the file is opened with a text editor (such as Notepad), the variables appear as distinct columns, e.g.

<table>
<thead>
<tr>
<th>LENGTH</th>
<th>WEIGHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>171</td>
<td>66</td>
</tr>
<tr>
<td>174</td>
<td>61.5</td>
</tr>
<tr>
<td>182</td>
<td>82</td>
</tr>
<tr>
<td>172</td>
<td>80</td>
</tr>
<tr>
<td>179</td>
<td>72.0</td>
</tr>
<tr>
<td>177</td>
<td>78.50</td>
</tr>
</tbody>
</table>

In a delimited text file, the data are separated by commas, and text is placed between single or double quotation marks, e.g.

"LENGTH","WEIGHT"
171,66
174,61.5
182,82
172,80
179,72.0
177,78.50

To read such a file select the Text file type in the dialog box and next you select the file name. The program will first check the text file to determine whether it is a formatted or delimited text file. The result is displayed in a new dialog box.
You must confirm the file type by clicking the OK button. If the program would have selected the wrong file format, you can choose the correct file format by selecting the corresponding button. Next click OK to proceed.

Finally, you will have to select the fields or variables to be imported in the Select variables dialog box (see Import SPSS file). If no name is available for a particular variable in the text file, then MedCalc will give the name FIELD.xx to the variables, where xx is the number of the field (or variable) in the file.

Save

Button:   
Shortcut: Ctrl+S or F12

The Save command is used to save the data on disk.

If the data have not been saved in the native MedCalc file format (files with extension MC1) before, then MedCalc will present the File selector box and suggest the MedCalc data file format. It is recommended to save in this format.

A MedCalc data file contains the following information:
- spreadsheet data
- variables list
- filters list
- named graphs and tests
- column width, precision, fill column specifications
- text entered in the notes window
- spreadsheet window position and size
- date of creation of file
- original Excel, Lotus, DBase or Text file name, if the current data have been imported from such data files
- other settings

MedCalc file format revisions

From time to time the MedCalc file format is revised. MedCalc will automatically convert old files as you open and save them. However, previous MedCalc versions may not be able to read the data files written by some newer versions of the software. It is advised that you always download and install the latest version of MedCalc (visit www.medcalc.org).
Save as

When you want to save the data as a new file, or save a file with a new file name, select the command Save as. Next, you enter a new name for the spreadsheet data in the file selector box (see p. 9). MedCalc also allows saving the data in different file formats: Excel, OpenDocument, SPSS, Lotus, SYLK (Symbolic Link), DIF (Data Interchange Format) or Delimited text file (CSV).

On Windows versions prior to Windows 8 or Windows Server 2012, support for Excel *.xlsx files requires Microsoft .NET Framework 4.0 (a free download from Microsoft).

Add file

If you want to read a MedCalc data file without first erasing the data in memory, then use one of the Add file commands.

- **Merge cells**: the cells in the file will replace existing cells in memory.
- **Append rows**: the data in the file will be placed in the open rows located under the rows already used in the spreadsheet. This option is useful to combine two files containing data on the same variables and with the same column headings.
- **Add columns**: the data will be placed in the columns at the right side of the columns already used in the spreadsheet. This option can be used to add the variables in the file to the variables already present in memory.

Export

*Shortcut: F10*

The Export command is used to export the contents of the top window. The top window can either be the spreadsheet data window and then the data can be exported as a plain text file.

If the top window is a statistics results window, these results can be exported as a text file. Finally, when the top window is a graph window, the graph can be exported as a Windows metafile.

**Export data**

When you want to export the data to another program, first open the spreadsheet window, or activate it and bring it on top of possible other open windows. When the spreadsheet window is on top, you can select Export data to save the spreadsheet data into one of the following file formats: MedCalc, Excel, OpenDocument, SPSS, Lotus, SYLK (Symbolic Link), DIF (Data Interchange Format) or Delimited text file (CSV). See Save as (p. 34).

When you export the spreadsheet data using Export data in the file menu, you can define a filter to select a subset of cases to be saved in the new file.

**Export results**

When the top window is a statistical text results window, then the Export results command can be used to save the text of the results window as a separate Word document or HTML file.

**Export graph**

When the top window is a graph window, you can select Export graph in order to save the graph as a Windows metafile format, as a Device Independent Bitmap (BMP), GIF (Graphics Interchange Format), TIF, PNG or JPG file, or as a PowerPoint slide (*.pptx).

On Windows versions prior to Windows 8 or Windows Server 2012, support for PowerPoint (*.pptx) files requires Microsoft .NET Framework 4.0 (a free download from Microsoft).

To control the height and width of the saved image, click the "Options" button in the "Export graph as" dialog box.
Export graph options

- **Aspect ratio**: select the aspect ratio of the image.
- **Use window aspect ratio**: the height:width ratio of the image will be the same as the height:width ratio of the graph window as displayed on the screen.
- **Height:width ratio 3:4**: the height:width ratio of the image will be 3:4
- **Free**: you can select the height and width independently.
- **Size (pixels)**: select the height and width, in pixels, of the image saved to disk.
- **Resolution (TIF files only)**: here you can set the resolution in dots per inch.

**Export notes**

When the top window is the notes editor window, then the *Export notes* command can be used to save the notes as a separate text file. This text file can be imported in any word processor program.

**Page setup**

Select *Page setup* to select the page orientation (portrait, landscape), and print margins for the active document (spreadsheet, text results or notes).
Print

Button: ☐
Shortcut: Ctrl+P
F9

The Print command is used to print the contents of the top window: the spreadsheet, a statistical text results window, graph window, or the notes window.

After you have selected the Print data, Print Notes or Print results command, the program will display the following (or similar) dialog box:

In this dialog box, you can select the printer by clicking the Select button.
Select the Black & white option in case you want to print in black and white only. When you select the Print to file option, the output will be redirected to a file and not to the printer.
You can select the page orientation (portrait, landscape), and print margins.

Print data

When you want to print the data, you open the spreadsheet window, or activate it and bring it on top of possible other open windows. Next, select Print data in the File menu or alternatively, press Ctrl+P.

The program will automatically split the columns and rows in order to fit the printed output on the paper. The numbering of the printed pages is indicated in the following diagram (the outer rectangle represents the complete spreadsheet):
Print results
Results of statistical calculations, summary statistics, correlation and regression are displayed in the results text window. When you want to obtain a printed copy of these results, select the Print results command, or press Ctrl+P.

Print graph
When the top window is a graph window, then you can select Print graph to print the graph. In the Preview area of the Print graph dialog box, you can size and position the graph on the paper.

Print notes
When you want to obtain a printed copy of the text entered in the Notes editor window, select the Print notes command, or press Ctrl+P.
Properties

The Properties box displays the following information about the data and file present in memory:

- **File name**: the name of the file loaded from disk, or NONAME.MC1 when no file has been loaded;
- **Imported from**: if the file was created by importing an Excel, Lotus, DBase or Text file, then the name of this original file is displayed;
- **Title**: the title you want to use when searching for this file. The title can be different from the file name;
- **Subject**: the subject of the file. Use this property to group similar files together, so you can search for all files that have the same subject;
- **Keywords**: list of keywords describing the file’s content, and you want to use when you search for this file.
- **Created**: the date the MedCalc file was created, or today’s date if no MedCalc file has been loaded from disk;
- **Last saved**: the date when the file was saved;
- **Columns**: the number of columns used in the MedCalc spreadsheet (minimal 1);
- **Rows**: the number of rows used in the spreadsheet.
- **Comments**: comments associated with this file. Can be used when you search for this file.

Exit

Shortcut:  

The Exit command must be selected to stop the program. Be sure to have saved all data before selecting this command and returning to the operating system.

However, if the latest changes have not been saved, then the program will display an appropriate warning. In this case you will have the option to save the data (Yes), or exit the program without saving the data (No), or cancel the Exit command and stay in the program (Cancel).
Double-clicking the MedCalc application window’s Control-menu box is the same as choosing the Exit command from the File menu.
Edit menu

Undo

Button: [Undo]
Shortcut: Ctrl+Z

With the Undo command you can undo the last edit operation in the spreadsheet or notes editor window.

Cut

Button: [Cut]
Shortcut: Ctrl+X

With this command you can remove the selection from the window and place it on the clipboard. The selection can be a text, a text in a cell, a cell or a range of cells.
The clipboard is a temporary area in memory for data that you cut or copy. From the clipboard, you can paste the cut or copied data to another location or to another document.
To completely remove a row or column in the spreadsheet, and shift other rows and columns to fill the space, use the Remove command in the Edit menu (p. 44).

Copy

Button: [Copy]
Shortcut: Ctrl+C

With this command you can copy the selection from the window and place it on the clipboard. The selection can then be pasted at a new location. In the spreadsheet window, the selection can be a text, a text in a cell, a cell or a range of cells.
Spreadsheet data can be transferred to other programs by selecting the range of cells you want to copy, followed by selecting the Copy command. Next activate the other program and select Paste in the Edit menu.
You can also copy the MedCalc graphs to the clipboard. Next you can open a drawing or presentation program (PowerPoint) and paste the graph into it. By default, the graph is copied onto the clipboard with a height/width ratio of 2/3. If you want to use the height/width ratio of the graph window, you must select the option “Use window aspect ratio” in the Options box (see p. 69).
Paste

Button: 
Shortcut: Ctrl+V

The Paste command is used to paste the contents of the clipboard onto the active window. If the Cut-Copy-Paste commands are used to move or copy a range of spreadsheet cells, then choosing this command pastes the contents of copied or cut cells into the area indicated by the cell pointer where the cell pointer is the upper-left corner of the paste area.

The Paste command can also be used to transfer data from Excel to MedCalc. First activate Excel and select the range of cells you want to transfer, followed by selecting the Copy command. Next activate MedCalc, open the spreadsheet window, position the cell pointer on the target location and select Paste in the Edit menu.

Delete

Shortcut: Del

With the Delete command you can clear the contents of a cell or a selected range of cells, a selected row or column. The Delete command does not affect the clipboard.

To completely remove a row or column in the spreadsheet, and shift other rows and columns to fill the space, use the Remove command in the Edit menu (p. 44).

Select all

Shortcut: Ctrl+A

This command is used to select the entire contents of the current window (does not affect the clipboard).

Find

Shortcut: Ctrl+F

The Find command is used to search for a specific string or data entry, starting from the current cell pointer position. First the current column is searched through, starting at the current cell pointer position, from top to bottom. If no match is found, you are offered the choice to continue the search in the next columns.

The search specification can contain the ? and * wildcards. The ? wildcard indicates that the character on this position can be ignored and, * indicates that the rest of the cell can be ignored. For example: Jones matches Jon* and Jo?es.
If the option *Show formulas* is selected and checked (see p. 50), then the search string is compared with the literal or raw contents of the cell, otherwise it is compared with the cells’ calculated values. E.g. if cell B10 contains SIN(90), resulting in 1.00, and the search string is ‘SIN\*’, then cell B10 will be ignored when *Show formulas* is OFF.

FIND does not distinguish uppercase from lowercase characters.

**Options**
- *Match entire cell contents*: Searches for an exact and complete match of characters that are specified in the Find what box.

**Find & replace**

**Shortcut:** Ctrl+H

The *Find & replace* procedure can be used to replace certain values in the spreadsheet with another value, or clear the cells containing these values. The value to be located and to be replaced is entered in the *Find* field of the dialog box. The new value is entered in the *Replace with* field:

**Options**
- *Match entire cell contents*: Searches for an exact and complete match of characters that are specified in the Find what box.
- *Automatic*: replacements will be performed automatically. If this option is not selected, then the program will display a dialog box before the old cell content is replaced with the new text.
- *All columns*: all columns will be searched through. If this option is not selected, then the find & replace procedure will be limited to the current column (the column containing the cell pointer).

You do not have to enter any text in the *Replace with* input field. In this case, the cells containing the *find text*, will be cleared.

Refer to the *Find command* for some explanation concerning the search wildcards * and ?, and the way MedCalc performs text comparison and treats the search specification.

Remember that searching always starts from the current cell pointer position. So when you want to search an entire column, you must put the cell pointer in the top cell of this column.
Go to cell

Shortcut: Ctrl+G

This command allows to quickly move the spreadsheet cellpointer to any cell in the spreadsheet. This dialog also appears when you double-click on the cell address in the MedCalc spreadsheet formula bar.

Required input
- Column: select a spreadsheet column.
- Row: enter a spreadsheet row.

Fill

Fill down

Shortcut: Ctrl+D

Use this command to copy the contents of the topmost cells of a selected range into the cells below.

Example:
Before:  
After:

Fill right

Shortcut: Ctrl+R

Use this command to copy the contents of the leftmost cells of a selected range into the cells to the right.
Example:
Before: 

<table>
<thead>
<tr>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

After: 

<table>
<thead>
<tr>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fill series**

Shortcut: Ctrl+L

Use this command to fill the selected range of cells with a series of numbers, characters, or dates. The content of the first cell in the selected range is used as the starting value for the series. Fill details can be given in the subsequent Fill series dialog box.

In this dialog box you enter:

- **Start value**: Enter the start value for the series. The start value must be a number, character or properly formatted date.
- **Step value**: Enter a positive or negative number to indicate the amount by which you want a series to increase or decrease.
- **Step unit (dates)**: Specify whether the series of dates will increase by days, weeks, months, or years. Available only when creating a date series.

**Insert - Remove**

To insert or remove the spreadsheet row or column where the cell pointer is located, select the corresponding command in the Edit menu.

Examples:

- When the cell pointer is located in row 20 and you select the command Insert row in the menu, then all rows starting with row 20 will be moved down and a new row will be inserted at this position. So row 20 will be moved to row 21, row 21 to 22, etc., and row 20 will be empty.
- When the cell pointer is located in column B and you select the command Remove column in the menu, then column B will be removed and all columns starting with column C will be moved to the left. So the data in column B will be lost, and column C will be moved to column B, column D to C, etc.
**Transpose**

With this command you can switch the orientation of data, either in a selected area, or in the complete spreadsheet. Data from the top row of the area to transpose will appear in the left column of the transposed area, and data from the left column will appear in the top row.

When you want to transpose only a particular area of the spreadsheet, you first select this area with the mouse. In this case, the number of rows and the number of columns of the selected area must be equal (while selecting, this can be checked in the status bar).
View menu

Spreadsheet

This command is used to open a spreadsheet window so you can enter new data, or examine the data already entered in the spreadsheet.

The active cell in the spreadsheet is indicated by the cell pointer. The cell pointer can be moved to another cell by pressing the arrow or cursor keys (see Appendix A for an overview of control keys and special key functions).

When you want to put new data in a cell, move the cell pointer to the cell and enter the data on the keyboard.

To change the content of a cell, move the cell pointer to this cell and press function key F2. The cell content will be displayed at the top of the window. You can now change the cell, and edit the data. The ← and → arrow keys can be used to move the cursor in the cell (just like editing a text in a word processor). The Backspace key is used to delete the character at the left side of the cursor, and the Delete key deletes the character at the right side. If desired, you can erase the entire cell by pressing the Backspace key repeatedly. You can use the Insert key to toggle between Overwrite and Insert editing mode.

The new content of the cell is stored in memory by moving the cell pointer up or down. By pressing the Enter key you can store the new or edited contents of a cell without moving the cell pointer.

To copy the contents of one cell to another cell, place the cell pointer on the first cell (the source cell), and select Copy in the Edit menu (you can obtain a shortcut menu by clicking the right side mouse button). By doing so, the content of this cell is copied into a buffer in memory. Now you move the cell pointer to the second cell (the target cell) and select Paste in the Edit menu. As a result, the content of the buffer is copied into this second cell.

If you want to copy a range of cells, you first select the cells with the mouse, and proceed as described above.

Show formulas

When the option Show formulas is checked then the spreadsheet will display the formulas that you have entered, otherwise the results of the formulas are displayed.

If you have to enter a lot of data (on a slow computer), or when you want to see the possible relationship between cells, then it is convenient to select this option.

Show gridlines

Select this option if you want gridlines to be displayed in the spreadsheet window. When the command has a check mark next to it, the Show gridlines option is on.
Contents bar

The contents bar displays the contents of the MedCalc data file in a treeview structure.

Select **Data** to open the MedCalc spreadsheet if you want to enter or edit data.
Select **Notes** if you want to write comments or notes to be saved in the MedCalc data file.
Select **Variables** to edit the Variables list. You can delete variables, create derived variables, and give descriptive labels to the variables.
Select **Filters** to edit the Filters list. You can create and delete selection criteria, and give descriptive labels.
In the **Saved test and graphs** section you can select a named graph, which you can restore, rename or delete (right-click an item to obtain a shortcut menu).

Saved tests and graphs

You can save a statistical analysis or graph in the MedCalc data file by clicking the button in the toolbar. By doing so, the graph is added to the **Saved tests and graphs list** in the Contents bar. A default name is given to the graph, which you can edit in the Contents bar.
This feature is very useful if you would want to recreate the graph later, possibly with new data.

Toolbars

Select the corresponding command when you want to show or hide the following toolbars:
- Standard toolbar
- Formatting toolbar

Toolbar options

- Merged toolbars: merge the two toolbars into one (all buttons will be displayed on one single row)
Check marks are displayed in the menu when the corresponding toolbar/option is selected.

Status bar

This command displays or hides the status bar at the bottom of the MedCalc main window, which shows information about the current state of the program.
A check mark is displayed in the menu when the Status bar is displayed.
Full screen

In full screen view, the MedCalc application window is maximized and status bar as well as toolbars are removed. You can restore these by using the appropriate commands in the menu (see above).

MedCalc keeps a separate set of toolbar options for Full screen and Normal view mode.

A check mark is displayed in the menu when the program operates in Full screen view mode. Click **Full screen** again to return to normal view mode.
Format menu

Font

Use this command to select a font for the top spreadsheet, notes, results or graph window. Alternatively, you can use the font and font size selectors in the formatting toolbar:

Arial 10

Increase font size

Button: 

Select this command to increase the font size for the top spreadsheet, notes, results or graph window.

Decrease font size

Button: 

Select this command to decrease the font size for the top spreadsheet, notes, results or graph window.

Format spreadsheet

Button: 

In the Format spreadsheet dialog box, you can select the following formatting options:

Sheet tab

In the Format spreadsheet box, you can select the following options:

- **Default column width and decimals**: The default column width and global number of decimals affect those columns for which a specific width and number of decimals has not been specified.
Column tab

- **Format**: Select the type and format of the data in this column:
  - **General**: use this for numbers
  - **Text**: all cells in this column will be treated as text, even when a number or formula is entered. The text will be displayed exactly as entered.
  - **Date**: use this for dates. Dates will be displayed using the settings from the Regional settings options in the Windows control panel. E.g. 05/09/2011
  - **Time**: use this for time data.
  - **Date Time**: use this for data and time date. E.g. 05/09/2011 14:00
- **Width, decimals**: You can define the column’s width and number of decimals. After you have specified a specific width or number of decimals for a column, then changing the global width or global number of decimals (in the Format spreadsheet dialog box, p. 49) will have no effect on the cells of this column. To reset the width and/or number of decimals of a column to the global width and/or global number of decimals, you must blank the corresponding input field and click OK.
- **Alignment**: You can select whether cell content should be centered or left or right justified in the column (default is right justified).
- **Default value**: The default value or formula for every cell in this column (this value or formula is only applied to empty cells or cells for which no value has been entered). Default values are displayed in a different color in the spreadsheet, see Options dialog box (p. 68)

**Format graph**

Button: ![Format graph button](image)

Use this command to select different formatting options for the top graph window. Graph formatting is described on page 16.

**Reset graph titles and options**

Use this command to undo all user edits and reset the graph titles and options to default values and apply the default color scheme.
Tools menu

Sort

The Sort command is used when you want to sort a range of rows of the spreadsheet according to the contents of a specific column.

If the option Show formulas is not selected (see p. 50) then the spreadsheet is sorted according to the calculated values of the cells. If on the other hand the option Show formulas is selected then the literal content of the cell is used for sorting.

Note:
- Sorting the data in the spreadsheet is not required for any of the MedCalc statistical tests or procedures.
- The Sort command is only available when the MedCalc spreadsheet is open and active.

Exclude - Include

If you need to exclude data from statistical analysis, then you:
- Select the data to exclude in the spreadsheet; the selection may either be a range of cells, or one or more complete rows (cases).
- Select the Exclude command in the Tools menu.

To include data that have been excluded, you:
- Select the data to include in the spreadsheet; the selection may either be a range of cells, or one or more complete rows (cases).
- Select the Include command in the Tools menu.

Data that have been marked as excluded in the spreadsheet will be displayed in red, but you can select a different color in the Format Spreadsheet box (p. 49).

The Exclude and Include commands are also available in the spreadsheet shortcut menu (after right-clicking).

Note: these commands are only available when the MedCalc spreadsheet is open and active.
**Fill column**

With the *Fill column* command you can fill an entire column, or a range of rows in a column, with a formula.

![Fill column dialog box](image)

You can select two options:

- *Convert formulas to values*: to convert the formulas to their calculated values.
- *Fill empty cells only*: to fill only empty cells with the new formula, and so saving the contents of the non-empty cells in the column.

Click the button to call the *Formula editor* dialog box (see Variable editor on p. 64).

In the example, rows 1 to 100 of column A will be filled with the result of the RANDNORM(0,1) function. This function generates random numbers drawn from a Normal distribution with mean 0 and standard deviation 1.

When you save the data then the formulas that you have entered in this dialog box will also be saved in the MedCalc data file, so you can easily re-use them at a later stage.

The *Fill column* command can also be used to clear a range of cells in a column, by letting the *Fill with field* blank.

Some examples of useful formulas are given in the following table.

<table>
<thead>
<tr>
<th>Fill with</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>SQRT(LENGTH)</td>
<td>fill with the square root of variable LENGTH</td>
</tr>
<tr>
<td>ROW</td>
<td>the cells will be filled with the row number</td>
</tr>
<tr>
<td>IF(var&lt;20,&quot;A&quot;,&quot;B&quot;)</td>
<td>recoding of variable var into two classes A and B</td>
</tr>
<tr>
<td>RAND(2)</td>
<td>the cells will be filled with 1 or 2 at random</td>
</tr>
<tr>
<td>RANDNORM(0,1)</td>
<td>fill with random numbers from a Normal distribution with mean 0 and standard deviation 1</td>
</tr>
<tr>
<td>VAR1+VAR2</td>
<td>fill with the sum of the variables VAR1 and VAR2</td>
</tr>
<tr>
<td></td>
<td>the cells will be cleared (empty Fill with field)</td>
</tr>
</tbody>
</table>

Note: the *Fill column* command is only available when the MedCalc spreadsheet is open and active.

**Stack columns**

With the *Stack columns* tool you can perform a multivariate to univariate conversion by stacking several spreadsheet columns into a new column.

The procedure creates 3 new columns for data, variables and cases.
Example

Original data:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NP</td>
<td>3.87</td>
<td>3.1</td>
</tr>
<tr>
<td>2</td>
<td>AM</td>
<td>4.65</td>
<td>3.26</td>
</tr>
<tr>
<td>3</td>
<td>FS</td>
<td>2.34</td>
<td>3.18</td>
</tr>
<tr>
<td>4</td>
<td>CV</td>
<td>2.45</td>
<td>2.72</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Variables **Hour12** and **Hour24** stacked with variable **Patient** as variable with case identification:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NP</td>
<td>3.87</td>
<td>3.1</td>
<td>NP</td>
<td>Hour12</td>
<td>3.87</td>
</tr>
<tr>
<td>2</td>
<td>AM</td>
<td>4.65</td>
<td>3.26</td>
<td>AM</td>
<td>Hour12</td>
<td>4.65</td>
</tr>
<tr>
<td>3</td>
<td>FS</td>
<td>2.34</td>
<td>3.18</td>
<td>FS</td>
<td>Hour12</td>
<td>2.34</td>
</tr>
<tr>
<td>4</td>
<td>CV</td>
<td>2.45</td>
<td>2.72</td>
<td>CV</td>
<td>Hour12</td>
<td>2.45</td>
</tr>
<tr>
<td>5</td>
<td>NP</td>
<td>3.1</td>
<td></td>
<td>NP</td>
<td>Hour24</td>
<td>3.1</td>
</tr>
<tr>
<td>6</td>
<td>AM</td>
<td>3.26</td>
<td></td>
<td>AM</td>
<td>Hour24</td>
<td>3.26</td>
</tr>
<tr>
<td>7</td>
<td>FS</td>
<td>3.18</td>
<td></td>
<td>FS</td>
<td>Hour24</td>
<td>3.18</td>
</tr>
<tr>
<td>8</td>
<td>CV</td>
<td>2.72</td>
<td></td>
<td>CV</td>
<td>Hour24</td>
<td>2.72</td>
</tr>
</tbody>
</table>

This function may be useful when you have to rearrange your data for procedures such as Serial measurements analysis (p. 180), or Bland-Altman plot with multiple measurements per subject (p. 199).

Required input

- **Source**: Variables to stack
  - **Variables**: select the variables of interest in the top left box and next click the right arrow button to move the selection to the list of selected variables.
  - **Variable with case identification**: a variable that will be replicated in one column for each stacked variable. If left blank, the row number will be used for case identification.
- **Target**: Spreadsheet columns for new data and identifier variables.
- **Option List empty columns only**: if this option is selected, only those columns that are empty will be listed in the following selection boxes.

- **Stacked case identification column**: a new spreadsheet column that will be filled with a case identification, replicated for each stacked variable (column Case in the example above)

- **Source variables identifier column**: a spreadsheet column that will be filled with the variables names (column Hour in the example above)

- **Stacked data column**: a spreadsheet column that will be filled with the stacked data (column Data in the example above)

- **Option Extract numbers from variable names**: if the variable names contain numbers, like in the example Hour12 and Hour24, the numbers 12 and 24 will be extracted from the variables names and placed in the Source variables identifier column (see example below)

- **Option Clear columns**: the selected columns will be cleared prior to storing the stacked data.

Click OK to proceed.

**More examples**

Example with the option "Extract numbers from variable names" selected:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient</td>
<td>NP</td>
<td>3.87</td>
<td>3.1</td>
<td>NP</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>AM</td>
<td>4.65</td>
<td>3.26</td>
<td>AM</td>
<td>12</td>
<td>4.65</td>
</tr>
<tr>
<td>3</td>
<td>FS</td>
<td>2.34</td>
<td>3.18</td>
<td>FS</td>
<td>12</td>
<td>2.34</td>
</tr>
<tr>
<td>4</td>
<td>CV</td>
<td>2.45</td>
<td>2.72</td>
<td>CV</td>
<td>12</td>
<td>2.45</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>NP</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>AM</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>FS</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>CV</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

The numbers 12 and 24 are extracted from the variables names, making the variable Hour suitable for numerical analysis or inclusion in numerical procedures.

Example with the selection "Variable with case identification" left blank:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient</td>
<td>NP</td>
<td>3.87</td>
<td>3.1</td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>AM</td>
<td>4.65</td>
<td>3.26</td>
<td></td>
<td>12</td>
<td>4.65</td>
</tr>
<tr>
<td>3</td>
<td>FS</td>
<td>2.34</td>
<td>3.18</td>
<td></td>
<td>12</td>
<td>2.34</td>
</tr>
<tr>
<td>4</td>
<td>CV</td>
<td>2.45</td>
<td>2.72</td>
<td></td>
<td>12</td>
<td>2.45</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

The row number is used as case identifier.
Generate random sample

Using this command you can generate a series of uniform or normal distributed random numbers.

Required input

- **Column**: the column in which you want to place the random numbers.
  - Option List empty columns only: if this option is selected, only empty columns are listed in the column selection box.
- **Header**: the header (top cell) for the selected column.

You can select a random sample with Normal distribution or Uniform distribution.

- For **Normal distribution** enter the desired mean and standard deviation, and the required sample size.
- For **Uniform distribution** enter the minimum and maximum values and the required sample size. If minimum and maximum values both are whole numbers, the program will generate whole random numbers only.

Click OK to proceed. The selected column in the spreadsheet is filled with the requested number of random values (all other cells in the column are cleared).
Create groups from quantiles

This tool allows categorizing a continuous variable by generating a new categorical variable with group numbers based on the quantiles of the continuous variable.

Required input

- **Column**: the column in which you want to place the group number.
- **Options**
  - **List empty columns only**: if this option is selected, only empty columns are listed in the column selection box.
  - **Clear column**: the selected column will be cleared prior to generating and storing the group numbers.
- **Header**: the header (top cell) for the selected column.
- **Data**: select the continuous variable and a possible data filter.
- **Number of groups**: the required number of groups, e.g. enter 4 to create groups based on the quartiles of the selected continuous variable.

Click OK to proceed. The selected column in the spreadsheet is filled with the group numbers (e.g. 1, 2, 3 and 4) corresponding with the quantiles of the continuous variable.
Create random groups

This tool allows assigning cases to random groups.

Required input

- **Column**: the column in which you want to place the group number.
- **Options**:
  - **List empty columns only**: if this option is selected, only empty columns are listed in the column selection box.
  - **Clear column**: the selected column will be cleared prior to generating and storing the group numbers.
- **Header**: the header (top cell) for the selected column.
- **Data**: select a variable that contains a case identification, and a possible data filter.
- **Number of groups**: the required number of groups, e.g. enter 2 to create 2 random groups.

Click OK to proceed. The selected column in the spreadsheet is filled with a random group number.
Create user-defined groups

This command allows assigning cases to groups based on a combination of user-defined criteria.

Required input

- **Column**: the column in which you want to place the group number.
- **Options**:
  - **List empty columns only**: if this option is selected, only those columns that are empty will be listed in the previous selection box.
- **Header**: the header (top cell) for the selected column.
- **Criteria and categories**: enter up to 7 conditions and group identifiers and a default group identifier.

Click OK to proceed. The selected column in the spreadsheet is filled with group/category identifiers according to the different criteria. The default group identifier is used for a case when none of the selected conditions is true for that case.

Rank cases

Description

This procedure allows creating a new variable that contains the rank numbers of the data in a numeric variable.

Required input

- **Column**: the column in which you want to place the rank numbers.
- **Options**
  - List empty columns only: if this option is selected, only empty columns are listed in the column selection box.
  - Clear column: the selected column will be cleared prior to generating and storing the rank numbers.
- **Header**: the header (top cell) for the selected column.
- **Data**: select the numeric variable and a possible data filter.

Click OK to proceed. The selected column in the spreadsheet is filled with the rank numbers of the selected data.
Percentile ranks

Description
This allows creating a new variable containing the Percentile ranks of the data in a numeric variable.

Required input
- **Column**: the column in which you want to place the Percentile ranks.
- **Options**
  - List empty columns only: if this option is selected, only empty columns are listed in the column selection box.
  - Clear column: the selected column will be cleared prior to generating and storing the Percentile ranks.
- **Header**: the header (top cell) for the selected column.
- **Data**: select the numeric variable and a possible data filter.

Click OK to proceed. The selected column in the spreadsheet is filled with the Percentile ranks of the selected data.

Z-scores

Description
With this command you can create a new variable containing the z-scores of the data in a numeric variable.

Required input
- **Column**: the column in which you want to place the z-scores numbers.
- **Options**
  - List empty columns only: if this option is selected, only empty columns are listed in the column selection box.
  - Clear column: the selected column will be cleared prior to generating and storing the z-scores.
- **Header**: the header (top cell) for the selected column.
- **Data**: select the numeric variable and a possible data filter.
- **Reference value and Standard Deviation**
  - Use mean and SD of sample: calculate the mean and Standard Deviation of the data in the sample and use these in the calculations for the z-scores.
  - User-defined values: use pre-specified values for reference value and Standard Deviation.
    - Reference value: the pre-specified reference value.
    - Standard Deviation: the pre-specified Standard Deviation.

Click OK to proceed. The selected column in the spreadsheet is filled with the z-scores of the selected data.

The z-score of every observation \( x \) is calculated as \((x - \text{reference value}) / \text{SD}\)

Power transformation

Allows to create a new variable containing a power transformation of a numeric variable. The transformation is defined by a power parameter \( \lambda \) (Lambda):

\[
\begin{align*}
  x(\lambda) &= x^{\lambda} & \text{when } \lambda \neq 0 \\
  x(\lambda) &= \log(x) & \text{when } \lambda = 0
\end{align*}
\]

Optionally, you can select the Box-Cox transformation. The Box-Cox power transformation is defined as:

\[
\begin{align*}
  x(\lambda) &= (x^{\lambda} - 1) / \lambda & \text{when } \lambda \neq 0 \\
  x(\lambda) &= \log(x) & \text{when } \lambda = 0
\end{align*}
\]
When some of the data are negative, a shift parameter $c$ needs to be added to all observations (in the formulae above $x$ is replaced with $x+c$).

**Required input**

![Power transformation dialog box](image)

- **Column**: the column in which you want to place the transformed variable.
- **Options**
  - List empty columns only: if this option is selected, only empty columns are listed in the column selection box.
  - Clear column: the selected column will be cleared prior to generating and storing the transformed data.
- **Header**: the header (top cell) for the selected column.
- **Data**: select the numeric variable and a possible data filter.
- **Transformation parameters**
  - **Lambda**: the power parameter $\lambda$
  - **Shift parameter**: the shift parameter is a constant $c$ that needs to be added to the data when some of the data are negative.
  - Button **Get from data**: click this button to estimate the optimal value for Lambda, and suggest a value for the shift parameter $c$ when some of the observations are negative. The program will suggest a value for Lambda with 2 to 3 significant digits. It may be advantageous to manually round this value to values such as -3, -2, -1, -0.5, 0, 0.5, 1, 2 and 3 (see below).
  - Option **Box-Cox transformation**: select this option to use the Box-Cox power transformation as described above.

Click OK to proceed. The selected column in the spreadsheet is filled with the power-transformed data.

**Interpretation of the power transformation**

When you do not select Box-Cox transformation and the shift parameter $c$ is zero then the power transformation is easy to interpret for certain values of lambda, for example:

- $\lambda = 0$ logarithmic transformation
- $\lambda = 0.5$ square root transformation
- $\lambda = -1$ inverse transformation
- $\lambda = 1$ **no transformation**!
Case-control matching

The case-control matching procedure is used to randomly match cases and controls based on specific criteria. MedCalc can match on up to 4 different variables. In the example we will use the following data:

The treated cases are coded 1, the controls are coded 0. For each treated case, MedCalc will try to find a control case with matching age and gender.

**Required input**

- Classification variable: select or enter a dichotomous variable indicating group membership (0=control, 1=case). If your data are coded differently, you can use the Define status tool to recode your data.
- Variable with case identification: select a variable that contains a unique identification code for each subject in the spreadsheet. If you do not select a variable here (not recommended), MedCalc will use row numbers as case identification.
- Match on: select up to 4 variables and for each variable the maximum allowable difference (caliper). Smaller calipers will result in reduced bias and closer matches, but may also result in a smaller number of matches. Select the option "Exact match" to match on a variable that is not numerical (for example, a variable "Gender" that is coded 'Male' and 'Female').
- Filter: (optionally) a filter in order to include only a selected subgroup of cases (e.g. SEX="Male").
- Advanced: click the Advanced button to enter the number of iterations and the random number seed.

For the example data, we complete the dialog box as follows:
Results

The results are displayed in a dialog box.

The program gives the total number of subjects, number of cases, number of controls and the number of matched cases, i.e. the number of cases for which a matching control has been found.

Next, the mean difference between the matched subjects are given, with mean difference, SD, 95% CI of the difference and associated P-value (paired samples t-test). The 95% confidence intervals should be small and neglectable. P-values should be non-significant. If for one or more variables the confidence interval is large, or the P-value is significant, the “maximum allowable difference” entered in the input dialog box (see above) was probably too large.

Save match IDs in spreadsheet column

Click the "Save match IDs..." button to create a new column in the spreadsheet with for each case the identification of the matched control (and vice-versa).
A column is added in the spreadsheet:

In subsequent statistical analyses this new column can be used in a filter in order to include only cases and controls for which a match was found.
E.g. if the new column has MatchID as a heading, the filter could be MatchID>0 or MatchID<> (<> means Not Equal To).

Save as new file with paired data
Click the “Save new file...” button to create a new MedCalc data file in which the data are rearranged as follows:
• The file includes the data of cases with matching controls only.
• A first set of columns contains the data of the cases. The heading of these columns is the original heading with "_T" appended. A second set of columns contains the data of the controls. The heading of these columns is the original heading with "_C" appended.
• On each row, the data of a case and its matching control is given.

This new datafile will allow to perform statistical tests on paired data.
Edit variables list

MedCalc automatically keeps track of variables that you add in the spreadsheet, while you enter data, or when you import Excel, SPSS, Lotus or text files. When you save the data, the variables list is included in the file. However, from time to time an error may occur in the list (e.g. double occurrence of a variable, or non-existing or deleted variables), and with the command *Edit variables list* you can edit the list. The variables list is displayed in the left side box in the dialog box.

When you click the Create list button, a new list will be created based on the column headers in the spreadsheet. Click New when you want to create a new derived variable. In the Variable properties dialog box you can enter the formula for the derived variable, and optionally enter a descriptive label for the variable and assign labels to data values. When a variable is selected in the left box, you can click the Properties button to edit the variable properties (see below). You can select one or more variables in the list and next click the Remove button to remove the selected variables from the list. This will just remove the variable name from the list; the corresponding columns in the spreadsheet will not be deleted. When you click the Clear list button, the entire list will be cleared.

Variable properties

In this dialog box you can define the variable properties (formula, variable label and value labels).

Variable

First the variable is displayed, or the formula in case of a derived variable. E.g. if you have a variable named LENGTH containing the height of patients in cm, and you have another variable WEIGHT containing the weight of patients in kilograms, then you can complete the dialog box as follows to obtain a new variable containing the Body Mass Index.
WEIGHT/POWER(LENGTH/100,2)

Click the button to call the Variable formula editor (see below) for easy editing of the formula.

Label

Next you can give a descriptive label to the variable. This label will be displayed in reports and graphs.

For example:

Body Mass Index

Value labels

You can assign labels to particular values of the variable. These labels will be used for example to identify subgroups in graphs.

Click in the cells in the columns "Value" and "Label" to start to enter data and labels.

Click the Up and Down arrow buttons to move selected rows up or down.

Click Scan data to scan the data and to populate the list with existing values.

You can also delete selected rows from the list by clicking the Delete button.

Variable formula editor

In this dialog box you can edit the formula for the variable. E.g. when you have a variable named LENGTH containing the height of patients in cm, and you have another variable WEIGHT containing the weight of patients in kilograms, then you can complete the dialog box as follows to obtain a new variable containing the Body Mass Index:

WEIGHT/POWER(LENGTH/100,2)

When entering the formula, you can select variables and functions from the respective lists shown in the dialog box.

Edit filter list

After you have entered a data filter in a dialog box, in order to include only a selected subgroup of cases in the statistical analysis, this data filter will be 'remembered' by the program and added to the filters list.

When you want to edit this list, select the Edit filters list, and you obtain the following dialog box:
At the left side of the dialog box, the filters list is displayed.
Click New when you want to create a new Filter. In the Filter properties dialog box (see below), you can enter the formula for the new filter, and/or you can enter a descriptive label for it.
When a filter is selected in the left box, you can click the Properties button to edit the filter’s properties such as formula and label.
You can select one or more filters in the list and next click the Remove button to remove the selected items from the list.
When you click the Clear list button, the entire list will be cleared.

**Filter properties**
In this dialog box you can define filter and give it a descriptive label.

**Filter**
In the top input box you can enter the formula for the data filter.
E.g. if you have a variable named TREATMENT containing codes (0, 1) for the treatment given to patients, you can enter a filter as follows:

   TREATMENT=0

You can combine different criteria into one filter using the AND() and OR() functions (see Logical functions p. 324). Click the button to call the Filter formula editor (see below) for easy editing of the formula.

**Label**
Next you can enter a descriptive label for the filter. This label will be displayed in reports and graphs.
For example:

   Placebo

**Filter formula editor**
In this dialog box you can edit the formula for the filter.
E.g. if you have a variable named TREATMENT containing codes (0, 1) for the treatment given to patients, you can define a filter as follows:

**Formula:**

```
TREATMENT=0
```

You can combine different criteria into one filter using the AND() and OR() functions (see Logical functions p. 324).

When entering the formula, you can select variables and functions from the respective lists shown in the dialog box.

### Select variable for case identification

In this dialog box you can select a variable that can be used by the program to identify cases, e.g. when you click on a marker in a graph.

Note that you can enter a combination of variables in the dialog box, using spreadsheet functions. E.g. if the spreadsheet contains a column with header "NAME" and a column with header "FIRST_NAME", you can enter the following formula for case identification:

```
CONCAT(FIRST_NAME," ",NAME)
```

The **Formula editor** (see Variable editor on p. 64) is a useful tool to compose such a formula (click the button).

If no variable for case identification is selected, the program will use the spreadsheet row numbers to identify cases.

### Enter key moves cell pointer…

With these commands you control the movement of the cell pointer in the spreadsheet:

- **Down:** After you press the Enter key, the cell pointer will move to the next row in the spreadsheet.
• **Right**: After you press the Enter key, the mouse will move to the next column in the spreadsheet.

## Options

In the *Options* dialog box you can select several options such as the maximum number of rows and columns in the spreadsheet, default file locations, etc.

### General

- **Recently used file list: number of entries**: the number of recently used files displayed at the bottom of the File menu, so you can open the files quickly. Enter the number of files you want to display in the entries box.
- **Recently used file list - number of entries**: the number of recently used files displayed at the bottom of the File menu, so you can open the files quickly. Enter the number of files you want to display in the entries box.
- **Background image**: an image used as background in the MedCalc application window. Click the Browse button to locate an image on your PC.

### Language

- **User Interface**: the language that is used in menus, dialogs, and other user interface elements.
- **Output**: the language that is used in the output.

The available languages for user-interface and output are: English, Chinese (simplified and traditional), French, German, Italian, Japanese, Korean, Polish, Portuguese (Brazilian), Russian and Spanish.

In case you inadvertently selected a wrong language for the user-interface and you cannot find the language settings, you can press Ctrl-Shift-E to quickly switch to the English user interface.

Note: the help file and software documentation are available in English only.

### Auto-update

- **Enable auto-update**: select this option to enable the auto-update feature.

  Check for updates every *n* days: the update frequency. If you set at 3 days, the program will check for updates every 3 days. If you set at 0 days, MedCalc will check for updates every time it is launched.

- **Check for updates now**: check if an update is available immediately.

### Regional settings

- **Use Windows settings**: select this option if you want to use the Windows settings (see Regional settings support, p. 3).
- **Use the following alternative settings**: select this option if you want to use your own settings:
  - **Decimal symbol**: enter the character to be used as decimal symbol. In the number 3.14 the character ‘,’ is used as the decimal character; in Germany a comma is used as decimal character and Pi is written as 3,14.
  - **List separator**: enter the character to be used as the list separator. In the formula Power(2,8) the character ‘,’ is used as the list separator. In Germany a ‘;’ is used as list separator and the formula is written as Power(2;8).
  - **Date format**: MM.DD.YYYY, DD.MM.YYYY or YYYY.MM.DD (see *Date functions*, p. 322).

### Spreadsheet

- **Spreadsheet dimensions** (informational): shows the maximum number of the spreadsheet rows (1048576) and spreadsheet columns (16384).

  When you load a data file with more cases (rows) or variables than the number of rows and columns available in the spreadsheet, the program will display an appropriate warning.

- **Open spreadsheet window after loading/importing file**: option to automatically open the spreadsheet window after a data file is read, or after data have been imported.

- **Enable AutoComplete for cell values**: when this option is selected, MedCalc completes text entries you start to type in a column of data. If the first few letters you type match an existing entry in that column, the program fills in the remaining text for you.
• **Show Formula bar**: select this option to show the formula bar in the spreadsheet window.

**Spreadsheet colors**

• **Numbers and text**: the text color for numeric and text entries in the spreadsheet.
• **Dates & times**: the text color for date and time entries in the spreadsheet.
• **Default values**: the color for default values as defined in Format column (p. 49).
• **Excluded**: the color for cases or values that are excluded from calculations and statistical analysis.
• **Grid color**: the color of the gridlines in the spreadsheet.

**Variables**

• **List variables alphabetically**: when this option is selected then the variables are listed alphabetically in the different selector boxes for variables. When this option is not selected, the variables are listed in the order they are entered in the spreadsheet.
  This option does not influence the order of the variables in the spreadsheet.

**Save**

• **Default file locations**: the default file location for data files, graphs, text and other items you create or use in MedCalc. Click the item you want to change, and then click Modify to set a new default location.
• **AutoRecover**: AutoRecover attempts to recover files automatically in the event of data loss, such as from a power outage. You can set how frequently the AutoRecover information for your data is saved. For example, if you set AutoRecover to save every 5 minutes, you may recover more information in the event of data loss than if it's set to save every 10 or 15 minutes. By default, AutoRecover information is saved every 10 minutes.
  AutoRecover does not replace the Save command (p. 33). You should use the Save command to save your document at regular intervals and when you finish working on it.

**Text results**

• **Colors**: Select colors used in statistical text results windows: normal text color, color used for highlighting results, color for warnings and error messages, color used for background shading and line/border color.
• **Display small P-values in Exponential Notation**: select this option to represent small P-value using exponential notation, e.g. $P=0.121\times10^{-6}$ ($P=0.000000121$). This option is useful in for example the field of genomics where massive multiple testing requires very small significance levels.

**Graphs**

• **Copy graph**: the Image aspect ratio option allows to select the width/height aspect ratio of the copied image. With the Landscape option the height/width ratio is 2/3 and with the Portrait option the height/width ratio is 3/2. With the Graph window aspect ratio option, the height and width of the copied image corresponds to the aspect ratio of the graph window.
• **Color palette**: all possible colors that can be used in a graph. Click a color rectangle to modify that entry in the MedCalc color table.
• **Use placeable file header in metafiles (*.wmf)**: select this option to use the Aldus Placeable Metafile (APM) format for metafiles (*.wmf).
Statistics menu

Summary statistics

After you have selected Summary statistics in the menu, the Select variable dialog box appears on the screen, and in this dialog box you can identify the variable to be analyzed in the statistical procedure. You can also enter a data filter in the Select field, in order to include only a selected subgroup of data in the statistical procedure, as described in the Introduction part of this manual.

Options

- Logarithmic transformation
- MedCalc offers the following tests for Normal distribution:
  - The **Shapiro-Wilk test** (Shapiro & Wilk, 1965; Royston, 1995) and the **Shapiro-Francia test** (Shapiro & Francia, 1972; Royston, 1993) calculate a W and W’ statistic, respectively, that tests whether a random sample comes from a Normal distribution. Small values of W or W’ are evidence of departure from normality. The Shapiro-Wilk W statistic can only be computed when sample size is between 3 and 5000 (inclusive) (Royston, 1995), the Shapiro-Francia W’ statistic can be computed when sample size ranges from 5 to 5000 (Royston, 1993a & 1993b).
  - The **D’Agostino-Pearson test** (Sheskin, 2011) computes a single P-value for the combination of the coefficients of Skewness and Kurtosis.
  - The **Kolmogorov-Smirnov test** (Neter et al., 1988) with Lilliefors significance correction (Dallal & Wilkinson, 1986) is based on the greatest discrepancy between the sample cumulative distribution and the Normal cumulative distribution.
  - The **Chi-squared goodness-of-fit test** is applied to binned data (the data are put into classes) (Snedecor & Cochran, 1989) and requires a larger sample size than the other two tests.
- Click the More options button for additional options:
▪ Percentiles: allows to select the percentiles of interest.
▪ Other averages:
  ▪ Trimmed mean: option to calculate a trimmed mean. You select the percentage of observations that will be trimmed away. For example, when you select 10% then the lowest 5% and highest 5% of observations will be dropped for the calculation of the trimmed mean.
  ▪ Geometric mean. The geometric mean is given by:
    \[
    \left( \prod_{i=1}^{n} x_i \right)^{\frac{1}{n}} = \sqrt[n]{x_1 x_2 \cdots x_n} = \exp \left[ \frac{1}{n} \sum_{i=1}^{n} \ln x_i \right]
    \]
    This option is not available when Logarithmic transformation is selected (when Logarithmic transformation is selected, the reported mean already is the Geometric mean).
  ▪ Harmonic mean. The harmonic mean is given by:
    \[
    \frac{1}{x_1} + \frac{1}{x_2} + \cdots + \frac{1}{x_n} = \frac{n}{\sum_{i=1}^{n} \frac{1}{x_i}}
    \]
    This option is not available when Logarithmic transformation is selected.
▪ Subgroups: (optionally) select a categorical variable to break-up the data in several (max. 8) subgroups. Summary statistics will be given for all data and for all subgroups.
Results

Sample size: the number of cases \( n \) is the number of numeric entries for the variable that fulfill the data filter. The lowest value and highest value of all observations (range).

Arithmetic mean: the arithmetic mean \( \bar{X} \) is the sum of all observations divided by the number of observations \( n \):

\[
\bar{X} = \frac{X_1 + X_2 + \ldots + X_n}{n} = \frac{1}{n} \sum_{i=1}^{n} X_i = \frac{1}{n} \sum X
\]

95% confidence interval (CI) for the mean: this is a range of values, calculated using the method described later (see Standard Error of the Mean), which contains the population mean with a 95% probability.

Median: when you have \( n \) observations, and these are sorted from smaller to larger, then the median is equal to the value with order number \((n+1)/2\). The median is equal to the 50th percentile. If the distribution of the data is Normal, then the median is equal to the arithmetic mean. The median is not sensitive to extreme values or outliers, and therefore it may be a better measure of central tendency than the arithmetic mean.

95% confidence interval (CI) for the median: this is a range of values that contains the population median with a 95% probability (Campbell & Gardner, 1988). This 95% confidence interval can only be calculated when the sample size is not too small.

Variance: the variance is the mean of the square of the differences of all values with the arithmetic mean. The variance \( s^2 \) is calculated using the formula:

\[
s^2 = \frac{\sum (X - \bar{X})^2}{n - 1}
\]

Standard deviation: the standard deviation \( (s \text{ or } SD) \) is the square root of the variance, and is a measure of the spread of the data:
When the distribution of the observations is Normal, then it can be assumed that 95% of all observations are located in the interval mean - 1.96 SD to mean + 1.96 SD (for other values see table p. 329).

This interval should not be confused with the smaller 95% confidence interval for the mean. The interval mean - 1.96 SD to mean + 1.96 SD represents a descriptive 95% confidence range for the individual observations, whereas the 95% CI for the mean represents a statistical uncertainty of the arithmetic mean.

Relative standard deviation (RSD): this is the standard deviation divided by the mean. If appropriate, this number can be expressed as a percentage by multiplying it by 100 to obtain the coefficient of variation.

Standard error of the mean (SEM): is calculated by dividing the standard deviation by the square root of the sample size.

\[ S.E.M. = \frac{s}{\sqrt{n}} \]

The SEM is used to calculate confidence intervals for the mean. When the distribution of the observations is Normal, or approximately Normal, then there is 95% confidence that the population mean is located in the interval \( \bar{X} \pm t \text{SEM} \), with \( t \) taken from the \( t \)-distribution with \( n-1 \) degrees of freedom and a confidence of 95% (table on p. 330). For large sample sizes, \( t \) is close to 1.96.

Skewness

The coefficient of Skewness is a measure for the degree of symmetry in the variable distribution. If the corresponding P-value is low (P<0.05) then the variable symmetry is significantly different from that of a Normal distribution, which has a coefficient of Skewness equal to 0 (Sheskin, 2011).
Kurtosis

The coefficient of Kurtosis is a measure for the degree of tailedness in the variable distribution (Westfall, 2014). If the corresponding P-value is low (P<0.05) then the variable tailedness is significantly different from that of a Normal distribution, which has a coefficient of Kurtosis equal to 0.

![Platykurtic distribution](image1)  
**Thinner tails**  
Kurtosis <0

![Mesokurtic distribution](image2)  
**Normal distribution**  
Kurtosis = 0

![Leptokurtic distribution](image3)  
**Fatter tails**  
Kurtosis >0

Test for Normal distribution

The result of the test for Normal distribution is expressed as 'accept Normality' or 'reject Normality', with P value. If P is higher than 0.05, it may be assumed that the data have a Normal distribution and the conclusion 'accept Normality' is displayed.

If the P value is less than 0.05, then the hypothesis that the distribution of the observations in the sample is Normal, should be rejected, and the conclusion 'reject Normality' is displayed. In the latter case, the sample cannot accurately be described by arithmetic mean and standard deviation, and such samples should not be submitted to any parametrical statistical test or procedure, such as e.g. a t-test. To test the possible difference between not Normally distributed samples, the Wilcoxon test can be used, and correlation can be estimated by means of rank correlation.

When the sample size is small, it may not be possible to perform the selected test and an appropriate message will appear.

Percentiles (or "centiles"): when you have \( n \) observations, and these are sorted from smaller to larger, then the \( p \)-th percentile is equal to the observation with rank number (Lentner, 1982; Schoonjans et al., 2011):

\[
R(p) = 0.5 + \frac{p \times n}{100}
\]

When the rank number \( R(p) \) is a whole number, then the percentile coincides with the sample value; if \( R(p) \) is a fraction, then the percentile lies between the values with ranks adjacent to \( R(p) \) and in this case MedCalc uses interpolation to calculate the percentile.

The formula for \( R(p) \) is only valid when

\[
\frac{1}{n} \leq \frac{p}{100} \leq \frac{n-1}{n}
\]

E.g. the 5th and 95th percentiles can only be estimated when \( n \geq 20 \), since

\[
\frac{1}{20} \leq \frac{5}{100} \text{ and } \frac{95}{100} < \frac{20 - 1}{20}
\]

Therefore, it makes no sense to quote the 5th and 95th percentiles when the sample size is less than 20. In this case it is advised to quote the 10th and 90th percentiles, at least if the sample size is not less than 10.

The percentiles can be interpreted as follows: \( p \) % of the observations lie below the \( p \)-th percentile, e.g. 10% of the observations lie below the 10th percentile.

The 25th percentile is called the 1st quartile, the 50th percentile is the 2nd quartile (and equals the Median), and the 75th percentile is the 3rd quartile.

The numerical difference between the 25th and 75th percentile is the interquartile range. Within the 2.5th and 97.5th percentiles lie 95% of the values and this range is called the 95% central range. The 90% central range is defined by the 5th and 95th percentiles, and the 10th and 90th percentiles define the 80% central range.

Logarithmic transformation

If the option Logarithmic transformation was selected, the program will display the back-transformed results. The back-transformed mean is named the Geometric mean. Variance, Standard deviation and Standard error of the mean cannot be back-transformed meaningfully and are not reported.
Presentation of results

The description of the data in a publication will include the sample size and arithmetic mean. The standard deviation can be given as an indicator of the variability of the data: the mean was 25.6 mm (SD 3.2 mm). The standard error of the mean can be given to show the precision of the mean: the mean was 25.6 mm (SE 1.6 mm).

When you want to make an inference about the population mean, you can give the mean and the 95% confidence interval of the mean: the mean was 25.6 (95% CI 22.4 to 28.8).

If the distribution of the variable is positively skewed, then a mathematical transformation of the data may be applied to obtain a Normal distribution, e.g. a logarithmic or square root transformation. After calculations you can convert the results back to the original scale. It is then useless to report the back-transformed standard deviation or standard error of the mean. Instead, you can antilog the confidence interval in case a logarithmic transformation was applied, or square the confidence interval if you have applied a square root transformation (Altman et al., 1983). The resulting confidence interval will then not be symmetrical, reflecting the shape of the distribution. If, for example, after logarithmic transformation of the data, the mean is 1.408 and the 95% confidence interval is 1.334 to 1.482, then you will antilog these statistics and report: the mean was 25.6 mm (95% CI 21.6 to 30.3).

If the distribution of the variable is not normal even after logarithmic or other transformation, then it is better to report the median and a percentiles range, e.g. the interquartile range, or the 90% or 95% central range: the median was 25.6 mm (95% central range 19.6 to 33.5 mm). The sample size will be taken into consideration when you decide whether to use the interquartile range or the 90% or 95% central range (see p. 74) (Altman, 1980).

The precision of the reported statistics should correspond to the precision of the original data. The mean and 95% CI can be given to one decimal place more than the raw data, the standard deviation and standard error can be given with one extra decimal (Altman et al., 1983).

Finally, the summary statistics in the text or table may be complemented by a graph (see p. 84).

Outlier detection

Outlier detection is used to detect anomalous observations in sample data.

Required input

![Outlier detection dialog box](image)

**Data**
- **Variable**: the name of the variable containing the data to be analyzed.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases in the statistical analysis.

**Methods of outlier detection**
- **Grubbs - left-sided**: check only the smallest value(*) (Grubbs, 1969).
• Grubbs - right-sided: check only the largest value (*) (Grubbs, 1969).
• Grubbs - double-sided: check the most extreme value at either side (*) (Grubbs, 1969).
• Generalized ESD test: the Generalized Extreme Studentized Deviate (ESD) procedure can detect multiple outliers in one step (Rosner, 1983).
  ▪ test for maximum number of outliers: enter the maximum number of outliers to detect.
• Tukey: check for multiple outliers at either side, categorized as 'outside' or 'far out' values (Tukey, 1977).
  ▪ An outside value is defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (the 'inner fences').
  ▪ A far-out value is defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range (the 'outer fences').
(*) The single-sided Grubbs' tests are more sensitive than the double-sided test.

Options
• Alpha level for Grubbs' and ESD test: select the alpha-level (ranging from 0.10 to 0.001), applicable only in Grubbs's test and the Generalized ESD test. With a bigger alpha-level the test will be more sensitive, and outliers will more rapidly be detected; however, this may result in false-positive results.
• Logarithmic transformation: the outlier detection methods assume that the data follow an approximately normal distribution (see next option). Sometimes data should be logarithmically transformed before analysis.
  The example uses the data from Rosner (1983) on their original scale. Therefore, Logarithmic transformation is performed like in the Rosner paper.
• Test for Normal distribution.

Results

Summary statistics
• Summary statistics for the selected data are displayed (see p. 70).
• If the test for Normal distribution reports 'reject Normality' the outlier detection methods may be invalid since they assume that the data follow an approximately normal distribution. Perhaps data should have been logarithmically transformed before analysis.
  In the example, data are logarithmically transformed.

Suspected outliers
The program lists the outliers identified by the different procedures.
Grubbs’ test can only be used to detect one single outlier; if you suspect there is more than one outlier you should not repeat the procedure but use the Generalized ESD test.

**What to do when you have identified an outlier**

Do not remove outliers automatically.

- Remove outliers only when a cause can be found for the spurious result, such as a pre-, post-, or analytical error.
- When you conclude that a pre-, post-, or analytical error is the cause of the spurious result, be aware that the same errors may exist in the other data values.
- Check the distribution of the data. Logarithmically transformed sample data may more closely follow a Normal distribution. Graph the data with and without logarithmic transformation, for example using a Box-and-Whisker plot.
- You may consider replacing the outlier value with the next highest/lowest (non-outlier) number.
- Keep the outlier but use robust or nonparametric statistical methods that do not assume that data are Normally distributed.
- Do the statistical analysis and report conclusions both with and without the suspected outlier.

In all cases, report the outliers and how you have dealt with them.

**Distribution plots**

**Histogram**

After selecting *Histogram*, a similar dialog box is displayed as for *Summary statistics*. Enter the name of a variable and optionally a data filter. If you have previously entered this variable and data filter in the box for summary statistics, then this new variable will be selectable in the Variable list (click the ▼ button).

![Histogram dialog box](image)

**Options**

- **Show Normal distribution**: option to have a Normal distribution curve (with Mean and Standard Deviation of the data represented in the histogram) superimposed over the histogram.
- **Relative frequency (%)**: option to express frequencies as percentages.

After a moment (the program first collects the data and performs some calculations) the following dialog box is displayed on the screen:
This dialog box displays:

- the mean, standard deviation, minimum and maximum value for the selected variable
- the default lower and upper limits, and the default number of classes in the histogram are displayed.

If you prefer other values than these default values, you can make the necessary changes. For **Lower** and **Upper limit**, the program will not accept values greater or less than the minimum and maximum of the variable. When you click the **OK** button, the program will continue with the new settings, but when you click **Cancel**, the program will display the histogram with the initial default settings.

This is the histogram for the variable Weight:

![Histogram](image)

The first bar in this histogram represents the number of cases (frequency) with weight \( \geq 55 \) and \( < 60 \). The second bar represents the number of cases with weight \( \geq 60 \) and \( < 65 \), etc.

In the **Histogram** dialog box, you have the option to superimpose a **Normal distribution** plot on the histogram.

![Histogram dialog box](image)

When this option is selected, a Normal distribution plot (with Mean and Standard Deviation of the data represented in the histogram) is superimposed over the histogram.
Using the histogram it can be evaluated visually whether the data are distributed symmetrically, Normally or Gaussian or whether the distribution is asymmetrical or skewed.

When the distribution is not Normal, it cannot accurately be described by mean and standard deviation, but instead the median, mode, quartiles and percentiles should be used. The latter statistics are reported in the **Summary statistics** window.

To change the titles, colors or axis scaling used in the graph, refer to page 16.

By selecting the **Export** command in the **File** menu you can export the displayed graph as a picture file (see p. 34). When you want to print the graph, press **Ctrl+P**.

### Cumulative frequency distribution

To obtain a cumulative frequency distribution, select **Cumulative frequency distribution** in the menu and proceed as for **Histogram**.

**Required input**

![Cumulative frequency distribution dialog box](image)

In the dialog box for **Cumulative frequency distribution**, you can either select a **Cumulative frequency polygon** or **Cumulative dot plot**, or both.

Finally you have the option to superimpose a **Normal distribution** curve on the diagram. The mean and standard deviation of this Normal distribution curve are those of the variable represented in the graph. When this option is selected the cumulative frequency distribution is plotted using a different algorithm, allowing comparison of the observed frequency distribution with the theoretical Normal distribution.

- **Variable**: the variable of interest.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases in the graph.
- **Options**
  - Select a Cumulative frequency polygon or a Cumulative dot plot, or both.
  - You also have the option to have a cumulative Normal distribution curve displayed together with the cumulative distribution of the data. The cumulative Normal distribution (with Mean and Standard Deviation of the data represented in the graph)
curve is displayed as a smooth line. When this option is selected the cumulative frequency distribution (Cumulative frequency polygon and/or Cumulative dot plot) is plotted using a different algorithm, allowing better visual comparison of the observed frequency distribution with the theoretical Normal distribution.

- **Subgroups**: click the Subgroups button if you want to identify subgroups in the graph. A new dialog box is displayed in which you can select a categorical variable.

When you have completed the dialog box, click OK, or press the Enter key to obtain the graph.

**Graphs**

![Cumulative frequency distribution](image)

In the next figures, some combinations of the possible selections are displayed:

- **Polygon and Normal distribution**
- **Dots and Normal distribution**

**Normal plot**

The *Normal plot* is a graphical tool to judge the Normality of the distribution of the sample data.
Select or enter the variable's name in the variable input field. You may enter a data filter in order to include only a selected subgroup of cases in the graph.

**Options**

- Select the Q-Q plot option to create a Q-Q (Quantile-Quantile) plot, see below.
- Test for Normal distribution (see p. 70).

When you have completed the dialog box, click the OK button to proceed.

The horizontal axis of the Normal plot shows the observed values, and the vertical axis shows the corresponding expected number of standard deviations from the mean (z-score), based on the ranks of the observed values.

When the option Q-Q plot is selected, the horizontal axis shows the z-scores of the observed values, $z = (x - \text{mean}) / SD$.

A straight reference line represents the Normal distribution. If the sample data are near a Normal distribution, the data points will be near this straight line.

**Test for Normal distribution**

- To see the results of the test for Normal distribution, use the Graph info command (which is available in the pop-up menu after you right-click in the graph).
- To show the results of the test in the graph's legend, you
  - right-click in the graph
  - select "Format legend"
  - in the legend's dialog box the results of the test for Normal distribution are prefilled
  - select the options "Show legend" and "Use free text".
Dot plot

Description
Creates a dot plot for a single variable with different graph options such as the inclusion of a Bar, Line or Marker for mean or median, with choice of different error bars for mean (95% CI, 1 SEM, 1 SD, 2 SD, 3 SD, range) or median (95% CI, 25-75 percentiles, 10-90 percentiles, 5-95 percentiles, 2.5-97.5 percentiles, 1-99 percentiles, range), and/or Box-and-whisker plot (Tukey, 1977).

Required input

Select the variable of interest, and optionally a data filter to include only particular cases in the graph. Several elements can be selected to add onto the dot plot, and some of these can be combined:

- **Bar, Horizontal Line and/or Marker for mean or median**
  
  The following error bars are available if Bars, Horizontal Line and/or Markers is selected:
  
  - If mean is selected: (none), or 95% CI for the mean, 1 SD, 2 SD, 3 SD, 1 SEM, range
    
    Note that 2 SEM is not in this list: when the number of cases is large, mean ± 2 SEM corresponds to the 95% confidence interval (CI) for the mean. When the number of cases is small, then the 95% CI interval is calculated as mean ± t * SEM, where t is taken from a t-table (with DF=n-1 and area A=95%).
    
    Although 1 SEM gives the narrower error bar, this option is not recommended since the resulting error bar may be highly misleading, especially when the number of cases in the groups is different. Preferably the 95% CI for the mean is used for providing a valid graphical comparison of means (Pocock, 1983), or use 2 SD as an indication for the variability of the data.
    
    - If median is selected: (none), or 95% CI for the median, 25-75 percentile, 10-90 percentile, 5-95 percentile, 2.5-97.5 percentiles, 1-99 percentile, range
      
      When the number of cases is small, it is possible that the 95% CI for the median is not defined and that it will not be displayed in the graph.
      
      When you use percentile ranges, consider the number of observations: you need at least 100 observations for 1-99 percentiles, at least 20 for 5-95 percentiles, at least 10 for 10-90 percentile and at least 4 for 25-75th percentiles.
  
- **Box-and-Whisker plot**: see below for details.

- **Option**: logarithmic transformation of the data.
Example

When you click an individual observation in the graph, the corresponding case is identified in a pop-up window (see also Select variable for case identification command, p. 66). If you double-click an observation, the spreadsheet window will open with the corresponding case highlighted.

Select the **Info** command in the shortcut menu that appears after right-clicking in the graph window to get detailed information on the data represented in the graph (sample size, etc.).

**Box-and-whisker plot**

The box-and-whisker plot (Tukey, 1977) displays a statistical summary of a variable: median, quartiles, range and, possibly, extreme values.

The **Define variable** dialog box for **Box-and-whisker plot** is similar to the one for **Summary statistics**: the name of the variable has to be entered as described on page 12:

If you require a logarithmic transformation of the data (e.g. to Normalize the data), then click the **Logarithmic transformation** option.

You can choose between vertical and horizontal orientation of the box-and-whisker plot.

This is the box-and-whisker plot for the variable **Weight**:
In the Box-and-whisker plot, the central box represents the values from the lower to upper quartile (25 to 75 percentile). The middle line represents the median. The horizontal line extends from the minimum to the maximum value, excluding outside and far out values, which are displayed as separate points.

- **An outside value** is defined as a value that is smaller than the lower quartile minus 1.5 times the interquartile range, or larger than the upper quartile plus 1.5 times the interquartile range (**inner fences**).
- A **far out value** is defined as a value that is smaller than the lower quartile minus 3 times the interquartile range, or larger than the upper quartile plus 3 times the interquartile range (**outer fences**). These values are plotted using a different marker, drawn in the “warning” color.

As an option, you may select to plot all individual data points. This enables you to obtain a diagram representing a statistical summary of the data without the disadvantage of concealing the real data.

When you click an individual observation in the graph, the corresponding case is identified in a pop-up window (see also Select variable for case identification command, p. 66). If you double-click an observation, the spreadsheet window will open with the corresponding case highlighted. If the value is an outlier, you can exclude the value or the entire case from further statistical analysis by selecting the Exclude command in the Tools menu (see p. 51).

**Presentation of results**

The description of the data in the text or table may be complemented by a graphical representation of the data: a histogram, cumulative distribution or box-and-whisker plot. The **histogram** is not very effective to display location and spread. The **cumulative distribution** has the advantage that it makes it easy to estimate the median (or other percentile) by reading off the horizontal value at which the curve attains 50% (or other percentage) (Moses, 1987). Secondly, the plot can contain the individual observations (cumulative dot plot). Finally, the **box-and-whisker plot** may be preferable because it can combine a display of all the data together with a statistical summary.
Correlation procedures

Correlation

Correlation analysis is used to see if the values of two variables are associated. The two variables should be random samples, and should have a Normal distribution (possibly after transformation).

When you select Correlation in the menu, the following dialog box appears on the screen:

![](image)

This dialog box has to be completed in a way similar to the box for summary statistics (see also p. 12), but now 2 variables must be selected. If you want to select the variables from the variables list, click the button, and select the variable in the list that is displayed. Next, you move the cursor to the Variable X field, and again click the button to select the variable in the list.

Finally, you can select a logarithmic transformation for one or both variable(s) in order to obtain Normal distributions.

After you click the OK button, or press the Enter key, you obtain the requested statistics in the results window:

![](image)

Results

**Sample size**: the number of data pairs \(n\)

**Correlation coefficient** with P-value: the correlation coefficient is a number between -1 and 1. In general, the correlation expresses the degree that, on an average, two variables change correspondingly.

If one variable increases when the second one increases, then there is a positive correlation. In this case the correlation coefficient will be closer to 1. For instance, the height and age of children are positively correlated.

If one variable decreases when the other variable increases, then there is a negative correlation and the correlation coefficient will be closer to -1.

The P-value is the probability that you would have found the current result if the correlation coefficient were in fact zero (null hypothesis). If this probability is lower than the conventional 5% (\(P<0.05\)) the correlation coefficient is called statistically significant.

It is, however, important not to confuse correlation with causation. When two variables are correlated, there may or may not be a causative connection, and this connection may moreover be indirect. Correlation can only be interpreted in terms of causation if the variables under investigation provide a logical (biological) basis for such interpretation.
95% confidence interval (CI) for the correlation coefficient: this is the range of values that contains with a 95% confidence the ‘true’ correlation coefficient.

Presentation of results
The number of data pairs (sample size) should be reported, the correlation coefficient (two decimal places), together with the P-value and the 95% confidence interval: the correlation coefficient was 0.45 ($P<0.001$, 95% CI 0.27 to 0.59).
The relationship between two variables can be represented graphically by a scatter diagram.

Partial correlation

Use Partial correlation when you suspect the relationship between 2 variables to be influenced by other variables. The partial correlation coefficient is said to be adjusted or corrected for the influence by the different covariates.

Required input

- Variable Y - Variable X: Select the 2 variables of interest.
- Covariates: The variables that you suspect to influence the relationship between the X and Y variables.
- Filter: (Optionally) enter a data filter in order to include only a selected subgroup of cases in the statistical analysis.
- Options: You can select a Logarithmic transformation for one or both variables.
Results

The results window for Partial correlation displays:
- Sample size: the number of (selected) data pairs
- Correlation coefficient: Partial correlation coefficient, with P-value

Rank correlation

When the distribution of variables is not Normal, the degree of relationship between the variables can be calculated using *Rank correlation*. Instead of using the precise values of the variables, the data are ranked in order of size, and calculations are based on the differences between the ranks of corresponding values X and Y.

**Required input**
- **Variable Y - Variable X**: Select the 2 variables of interest.
- **Select**: (Optionally) enter a data filter in order to include only a selected subgroup of cases in the statistical analysis.
- **Correlation coefficients**: Select Spearman’s *rho* and/or Kendall’s *tau*.
  The confidence interval for Kendall’s *tau* is estimated using the bias-corrected and accelerated (BCa) bootstrap (Efron, 1987; Efron & Tibshirani, 1993). Click the Advanced... button for bootstrapping settings such as number of replications and random-number seed.

Click OK, or press the *Enter* key to obtain the following statistics in the results window.
Results

In this example, the Spearman's coefficient of rank correlation \( \rho \) is 0.114. The 95% confidence interval ranges from -0.084 to 0.304. The associated P-value is 0.255 and the conclusion therefore is that there is not a significant relationship between the two variables.

Scatter diagram

In a scatter diagram, the relation between two numerical variables is presented graphically. One variable (the variable X) defines the horizontal axis and the other (variable Y) defines the vertical axis. The values of the two variables on the same row in the data spreadsheet, give the points in the diagram.

You can click the button to obtain a list of variables. In this list you can select a variable by clicking the variable’s name. Optionally, you may also enter a data filter in order to include only a selected subgroup of cases in the graph.

You can select a logarithmic transformation for one or both variables (in this case the program will use a logarithmic scale for the corresponding axis in the graph).

Use the Subgroups button if you want to identify subgroups in the scatter diagram. A new dialog box is displayed in which you can select a categorical variable. The graph will display different markers for the different categories in this variable.

After you click the OK button, or press the Enter key you obtain the following graph:
This is the same scatter diagram, but the categorical variable “Treatment” has been used to identify different subgroups in the graph.

Regression procedures

Regression

Regression is a statistical method used to describe the relationship between two variables and to predict one variable from another (if you know one variable, then how well can you predict a second variable?). Whereas for correlation (see p. 85) the two variables need to have a Normal distribution, this is not a requirement for regression analysis. The variable X does not need to be a random sample with a Normal distribution (the values for X can be chosen by the experimenter). However, the variability of Y should be the same at each level of X.
When you select *Regression* in the menu, the following box appears on the screen:

**Variables**
- **Variable Y** and **Variable X**: select the dependent and independent variables Y and X.
- **Weights**: optionally select a variable containing relative weights that should be given to each observation (for weighted least-squares regression). Select the dummy variable "***AutoWeight 1/SD^2***" for an automatic weighted regression procedure to correct for heteroscedasticity (see p. 95) (Neter et al., 1996). This dummy variable appears as the first item in the drop-down list for Weights.
- **Filter**: you may also enter a data filter in order to include only a selected subgroup of cases in the statistical analysis.

**Regression equation**
By default the option *Include constant in equation* is selected. This is the recommended option that will result in ordinary least-squares regression. When you need regression through the origin (no constant \(a\) in the equation), you can uncheck this option (an example of when this is appropriate is given in Eisenhauer, 2003).

MedCalc offers a choice of 5 different regression equations:

\[
\begin{align*}
y &= a + b \quad \text{straight line} \\
y &= a + b \log(x) & \quad \text{logarithmic curve} \\
\log(y) &= a + b \quad \text{exponential curve} \\
\log(y) &= a + b \log(x) & \quad \text{geometric curve} \\
y &= a + b x + c x^2 & \quad \text{quadratic regression (parabola)}
\end{align*}
\]

where \(x\) represents the independent variable and \(y\) the dependent variable. The coefficients \(a\), \(b\) and \(c\) are calculated by the program using the method of least squares.

**Options**
- **Subgroups**: allows to select a categorical variable containing codes to identify distinct subgroups. Regression analysis will be performed for all cases and for each subgroup.
Results

Sample size: the number of data pairs \( n \)

Coefficient of determination: this is the proportion of the variation in the dependent variable explained by the regression model, and is a measure of the goodness of fit of the model. It can range from 0 to 1, and is calculated as follows:

\[
R^2 = \frac{\text{explained variation}}{\text{total variation}} = \frac{\sum (Y_{\text{est}} - \bar{Y})^2}{\sum (Y - \bar{Y})^2}
\]

where \( Y \) are the observed values for the dependent variable, \( \bar{Y} \) is the average of the observed values and \( Y_{\text{est}} \) are predicted values for the dependent variable (the predicted values are calculated using the regression equation).

Note: MedCalc does not report the coefficient of determination in case of regression through the origin, because it does not offer a good interpretation of the regression through the origin model (see Eisenhauer, 2003).

Residual standard deviation: the standard deviation of the residuals (residuals = differences between observed and predicted values). It is calculated as follows:

\[
s_{\text{res}} = \sqrt{\frac{\sum (Y - Y_{\text{est}})^2}{n - 2}}
\]

The residual standard deviation is sometimes called the Standard error of estimate (Spiegel, 1961).

The equation of the regression curve: the selected equation with the calculated values for \( a \) and \( b \) (and for a parabola a third coefficient \( c \)), e.g. \( Y = a + b \times X \)

Next, the standard errors are given for the intercept (\( a \)) and the slope (\( b \)), followed by the t-value and the P-value for the hypothesis that these coefficients are equal to 0. If the P-values are low (e.g. less than 0.05), then you can conclude that the coefficients are different from 0.

Note that when you use the regression equation for prediction, you may only apply it to values in the range of the actual observations. E.g. when you have calculated the regression equation for height and weight for school children, this equation cannot be applied to adults.

Analysis of variance: the analysis of variance table divides the total variation in the dependent variable into two components, one which can be attributed to the regression model (labeled Regression) and one which cannot (labeled Residual). If the significance level for the F-test is small (less than 0.05), then the hypothesis that there is no (linear) relationship can be rejected.

Comparison of regression lines

When you have selected a subgroup in the regression dialog box MedCalc will automatically compare the slopes and intercepts of the regression equation obtained in the different subgroups.

This comparison is performed when
• there are 2 subgroups
• there is no weight variable
• a constant is included in the equation

The results window then includes the following table:

<table>
<thead>
<tr>
<th>Comparison of slopes and intercepts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Comparison of slopes</strong></td>
</tr>
<tr>
<td>Difference</td>
</tr>
<tr>
<td>Standard error</td>
</tr>
<tr>
<td>t</td>
</tr>
<tr>
<td>DF</td>
</tr>
<tr>
<td>P</td>
</tr>
<tr>
<td><strong>Common slope</strong></td>
</tr>
<tr>
<td>Slope</td>
</tr>
<tr>
<td>Standard error</td>
</tr>
<tr>
<td><strong>Comparison of intercepts</strong></td>
</tr>
<tr>
<td>Adjusted difference</td>
</tr>
<tr>
<td>Standard error</td>
</tr>
<tr>
<td>t</td>
</tr>
<tr>
<td>DF</td>
</tr>
<tr>
<td>P</td>
</tr>
</tbody>
</table>

The calculations are performed according to Armitage et al., 2002.

First the difference between the slopes is reported with its standard error, t-statistic, degrees of freedom and associated P-value. If P is not less than 0.05 the slopes do not differ significantly and the regression lines are parallel. If P is less than 0.05 then the regression lines are not parallel and the comparison of intercepts below is not valid.

Next a common slope is calculated, which is used to calculate the adjusted difference between the intercepts. This adjusted difference between the intercepts is reported with its standard error, t-statistic, degrees of freedom and associated P-value. If P is less than 0.05 there is a significant difference between the 2 intercepts. If P is not less than 0.05 then the two regression lines are indistinguishable.

**Comparing regression lines using ANCOVA**

When there are more than 2 subgroups, ANCOVA (p. 127) can be used to compare slopes and intercepts.

In the ANCOVA model you first select the dependent variable and next the independent variable is selected as a covariate. For Factors you select the grouping variable.

In the results for ANCOVA, below "Homogeneity of regression slopes" you will find a P-value which is the significance level for the comparison of the regression slopes. If this P-value is not less than 0.05 then the regression lines are parallel.

Next, below "Pairwise comparisons", you find the P-values for the differences between the intercepts.

**Analysis of residuals**

Linear regression analysis assumes that the residuals (the differences between the observations and the estimated values) follow a Normal distribution. This assumption can be evaluated with a formal test, or by means of graphical methods. The different formal Tests for Normal distribution may not have enough power to detect deviation from the Normal distribution when sample size is small. On the other hand, when sample size is large, the requirement of a Normal distribution is less stringent because of the central limit theorem.

Therefore, it is often preferred to visually evaluate the symmetry and peakedness of the distribution of the residuals using the Histogram (p. 77), Box-and-whisker plot (p. 83), or Normal plot (p. 80).

To do so, you click the hyperlink "Save residuals" in the results window. This will save the residual values as a new variable in the spreadsheet. You can then use this new variable in the different distribution plots.

**Presentation of results**

If the analysis shows that the relationship between the two variables is too weak to be of practical help, then there is little point in quoting the equation of the fitted line or curve. If you give the equation, you also report the standard error of the slope, together with the corresponding P-value. The residual standard deviation should also be reported (Altman, 1980). The number of decimal places of the regression coefficients should correspond to the precision of the raw data.

The accompanying scatter diagram should include the fitted regression line when this is appropriate. This figure can also include the 95% confidence interval, or the 95% prediction interval, which can be more informative, or both. The legend of the figure must clearly identify the interval that is represented.
Scatter diagram & Regression line

In a scatter diagram, the relation between two numerical variables is presented graphically. One variable (the independent variable X) defines the horizontal axis and the other (dependent variable Y) defines the vertical axis. The values of the two variables on the same row in the data spreadsheet, give the points in the diagram.

The dialog box for the scatter diagram is similar to the one for Regression (see p. 89):

Variables

- **Variable Y** and **Variable X**: select the dependent and independent variables Y and X.
- **Weights**: optionally select a variable containing relative weights that should be given to each observation (for weighted least-squares regression). Select the dummy variable "*** AutoWeight 1/SD^2 ***" for an automatic weighted regression procedure to correct for heteroscedasticity (see p. 95) (Neter et al., 1996). This dummy variable appears as the first item in the drop-down list for Weights.
- **Filter**: you may also enter a data filter in order to include only a selected subgroup of cases in the graph.

Regression equation

By default, the option **Include constant in equation** is selected. This is the recommended option that will result in ordinary least-squares regression. When you need regression through the origin (no constant a in the equation), you can uncheck this option (an example of when this is appropriate is given in Eisenhauer, 2003).

MedCalc offers a choice of 5 different regression equations (X represents the independent variable and Y the dependent variable):

\[
\begin{align*}
    y &= a + b \quad x & \text{straight line} \\
    y &= a + b \quad \log(x) & \text{logarithmic curve} \\
    \log(y) &= a + b \quad x & \text{exponential curve} \\
    \log(y) &= a + b \quad \log(x) & \text{geometric curve} \\
    y &= a + b \quad x + c \quad x^2 & \text{quadratic regression (parabola)}
\end{align*}
\]

When you select an equation that contains a Logarithmic transformation for one of the variables, the program will use a logarithmic scale for the corresponding variable.

Options

- **95% Confidence**: two curves will be drawn next to the regression line. These curves represent a 95% confidence interval for the regression line. This interval includes the true regression line with 95% probability.
- 95% Prediction: two curves will be drawn next to the regression line. These curves represent the 95% prediction interval for the regression curve. The 95% prediction interval is much wider than the 95% confidence interval. For any given value of the independent variable, this interval represents the 95% probability for the values of the dependent variable.

- Line of equality: option to draw a line of equality (y=x) line in the graph.

Residuals
In regression analysis, residuals are the differences between the predicted values and the observed values for the dependent variable. The residual plot allows the visual evaluation of the goodness of fit of the selected model.

To obtain a residuals plot, select this option in the dialog box. This graph will be displayed in a second window.

Subgroups
Click the Subgroups button if you want to identify subgroups in the scatter diagram. A new dialog box is displayed in which you can select a categorical variable. The graph will use different markers for the different categories in this variable, and optionally will show regression lines for all cases and for each subgroup.

Examples

When you click a point on the regression line, the program will give the x-value and the f(x) value calculated using the regression equation.
You can press Ctrl+P to print the scatter diagram, or function key F10 to save the picture as file on disk. To define other titles or colors in the graph, or change the axis scaling, see p. 16.
If you want to repeat the scatter diagram, possibly to select a different regression equation, then you only have to press function key F7. The dialog box will re-appear with the previous entries (see p. 24).

**Extrapolation**

MedCalc only shows the regression line in the range of observed values. As a rule, it is not recommended to extrapolate the regression line beyond the observed range. For particular applications however, such as evaluation of stability data, extrapolation may be useful.

To allow extrapolation, right-click in the graph and select *Allow extrapolation* in the pop-up menu.

**Heteroscedasticity**

In regression analysis heteroscedasticity means a situation in which the variance of the dependent variable (Y) varies across the levels of the independent data (X). Heteroscedasticity can complicate analysis because regression analysis is based on an assumption of equal variance across the levels of the independent data.

Homoscedasticity is the absence of such variation.
Weighted regression can be used to correct for heteroscedasticity. In a Weighted regression procedure more weight is given to the observations with smaller variance because these observations provide more reliable information about the regression function than those with large variances.

**Residuals plot**

When you select the option *Residuals plot* in the *Regression line* dialog box, the program will display a second window with the residuals plot. *Residuals* are the differences between the predicted values and the observed values for the dependent variable. The residual plot allows for the visual evaluation of the goodness of fit of the selected model or equation. Residuals may point to possible outliers (unusual values) in the data or problems with the regression model. If the residuals display a certain pattern, you should consider selecting a different regression model.

![Residuals plot](image)

**Regression equations & curves**

The theoretical shape of the different regression equations is represented in the following figures (linear scaling for both dependent and independent variable). If the scatter diagram (with linear scaling) shows a pattern corresponding with one of the following curves, you should use the corresponding regression equation.
Multiple regression

Multiple regression is a method used to examine the relationship between one dependent variable $Y$ and one or more independent variables $X_i$. The regression parameters or coefficients $b_i$ in the regression equation

$$ Y = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + \ldots + b_k X_k $$

are estimated using the method of least squares. In this method, the sum of squared residuals between the regression plane and the observed values of the dependent variable are minimized. The regression equation represents a (hyper)plane in a $k+1$ dimensional space in which $k$ is the number of independent variables $X_1, X_2, X_3, \ldots, X_k$, plus one dimension for the dependent variable $Y$.

The following need to be entered in the **Multiple regression** dialog box:

![Multiple regression dialog box](image)

**Variables**

- **Dependent variable**: the variable whose values you want to predict.
- **Independent variables**: select at least one variable you expect to influence or predict the value of the dependent variable. Also called predictor variables or explanatory variables.
- **Weights**: optionally select a variable containing relative weights that should be given to each observation (for weighted multiple least-squares regression). Select the dummy variable "AutoWeight 1/SD^2" for an automatic weighted regression procedure to correct for heteroscedasticity (see p. 95) (Neter et al., 1996). This dummy variable appears as the first item in the drop-down list for Weights.
- **Filter**: optionally enter a data filter in order to include only a selected subgroup of cases in the analysis.

**Options**

- **Method**: select the way independent variables are entered into the model.
  - Enter: enter all variables in the model in one single step, without checking
  - Forward: enter significant variables sequentially
  - Backward: first enter all variables into the model and next remove the non-significant variables sequentially
  - Stepwise: enter significant variables sequentially; after entering a variable in the model, check and possibly remove variables that became non-significant.
- **Enter variable if $P<$**
  A variable is entered into the model if its associated significance level is less than this $P$-value.
- **Remove variable if $P>$**
  A variable is removed from the model if its associated significance level is greater than this $P$-value.
- **Report Variance Inflation Factor (VIF):** option to show the Variance Inflation Factor in the report. A high Variance Inflation Factor is an indicator of multicollinearity of the independent variables. Multicollinearity refers to a situation in which two or more explanatory variables in a multiple regression model are highly linearly related.

- **Zero-order and simple correlation coefficients:** option to create a table with correlation coefficients between the dependent variable and all independent variables separately, and between all independent variables.

- **Residuals:** you can select a Test for Normal distribution of the residuals. For further analysis of residuals, see p. 92.

### Results

If you want to repeat the *Multiple regression* procedure, possibly to add or remove variables in the model, then you only have to press function key \textit{F7}. The dialog box will re-appear with the previous entries (see p 24).

In the *results* window, the following statistics are displayed:

**Sample size:** the number of data records \( n \)

**Coefficient of determination:** this is the proportion of the variation in the dependent variable explained by the regression model, and is a measure of the goodness of fit of the model. It can range from 0 to 1, and is calculated as follows:

\[
R^2 = \frac{\text{explained variation}}{\text{total variation}} = \frac{\sum(Y_{\text{est}} - \overline{Y})^2}{\sum(Y - \overline{Y})^2}
\]

where \( Y \) are the observed values for the dependent variable, \( \overline{Y} \) is the average of the observed values and \( Y_{\text{est}} \) are predicted values for the dependent variable (the predicted values are calculated using the regression equation).
**R²-adjusted**: this is the coefficient of determination adjusted for the number of independent variables in the regression model. Unlike the coefficient of determination, R²-adjusted may decrease if variables are entered in the model that do not add significantly to the model fit.

\[
R^2_{adj} = 1 - \frac{\text{unexplained variation/}(n - k - 1)}{\text{total variation/}(n - 1)}
\]

or

\[
R^2_{adj} = 1 - \frac{\sum(Y_{est} - \bar{Y})^2}{\sum(Y - \bar{Y})^2} \frac{n - 1}{n - k - 1}
\]

**Multiple correlation coefficient**: this coefficient is a measure of how tightly the data points cluster around the regression plane, and is calculated by taking the square root of the coefficient of determination.

When discussing multiple regression analysis results, generally the coefficient of multiple determination is used rather than the multiple correlation coefficient.

**Residual standard deviation**: the standard deviation of the residuals (residuals = differences between observed and predicted values). It is calculated as follows:

\[
s_{res} = \sqrt{\frac{\sum(Y - Y_{est})^2}{n - k - 1}}
\]

**The regression equation**: the different regression coefficients \(b_i\) with standard error \(s_{b_i}\), \(r_{partial}\), \(t\)-value, \(P\)-value, partial and semipartial correlation coefficients \(r_{partial}\) and \(r_{semipartial}\).

If \(P\) is less than the conventional 0.05, the regression coefficient can be considered to be significantly different from 0, and the corresponding variable contributes significantly to the prediction of the dependent variable.

Partial correlation coefficient \(r_{partial}\): partial correlation is the correlation between an independent variable and the dependent variable after the linear effects of the other variables have been removed from both the independent variable and the dependent variable (the correlation of the variable with the dependent variable, adjusted for the effect of the other variables in the model).

Semipartial correlation coefficient \(r_{semipartial}\) (in SPSS called part correlation): semipartial correlation is the correlation between an independent variable and the dependent variable after the linear effects of the other independent variables have been removed from the independent variable only. The squared semipartial correlation is the proportion of (unique) variance accounted for by the independent variable, relative to the total variance of the dependent variable \(Y\).

Optionally the table includes the Variance Inflation Factor (VIF). A high Variance Inflation Factor is an indicator of multicollinearity of the independent variables. Multicollinearity refers to a situation in which two or more explanatory variables in a multiple regression model are highly linearly related.

**Variables not included in the model**: variables are not included in the model because of 2 possible reasons:

- You have selected a stepwise model and the variable was removed because the \(P\)-value of its regression coefficient was above the threshold value.
- The tolerance of the variable was very low (less than 0.0001). The tolerance is the inverse of the Variance Inflation Factor (VIF) and equals 1 minus the squared multiple correlation of this variable with all other independent variables in the regression equation. If the tolerance of a variable in the regression equation is very small then the regression equation cannot be evaluated.

**Analysis of variance**: the analysis of variance table divides the total variation in the dependent variable into two components, one which can be attributed to the regression model (labeled \(Regression\)) and one which cannot (labeled \(Residual\)). If the significance level for the F-test is small (less than 0.05), then the hypothesis that there is no (linear) relationship can be rejected, and the multiple correlation coefficient can be called statistically significant.

**Zero-order and simple correlation coefficients**: this optional table shows the correlation coefficients between the dependent variable \(Y\) and all independent variables \(X_i\) separately, and between all independent variables.
Logistic regression

Logistic regression (Pampel, 2000; Hosmer, Lemeshow, Sturdivant, 2013) is a technique for analyzing problems in which there are one or more independent variables that determine an outcome. The outcome is measured with a dichotomous variable (in which there are only two possible outcomes).

In logistic regression, the dependent variable is binary or dichotomous, i.e. it only contains data coded as 1 (TRUE, success, pregnant, etc.) or 0 (FALSE, “failure”, “non-pregnant”, etc.).

The goal of logistic regression is to find the best fitting (yet biologically reasonable) model to describe the relationship between the dichotomous characteristic of interest (dependent variable = response or outcome variable) and a set of independent (predictor or explanatory) variables. Logistic regression generates the coefficients (and its standard errors and significance levels) of a formula to predict a logit transformation of the probability of presence of the characteristic of interest:

\[ \text{logit}(p) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_kX_k \]

where \( p \) is the probability of presence of the characteristic of interest. The logit transformation is defined as the logged odds:

\[ \text{odds} = \frac{p}{1-p} = \frac{\text{probability of presence of characteristic}}{\text{probability of absence of characteristic}} \]

and

\[ \text{logit}(p) = \ln \left( \frac{p}{1-p} \right) \]

Rather than choosing parameters that minimize the sum of squared errors (like in ordinary regression), estimation in logistic regression chooses parameters that maximize the likelihood of observing the sample values.

Required input

Dependent variable: the variable whose values you want to predict. The dependent variable must be binary or dichotomous, and should only contain data coded as 0 or 1. If your data are coded differently, you can use the Define status (see below, p. 105) tool to recode your data.

Independent variables: select the different variables that you expect to influence the dependent variable.

Filter: (optionally) enter a data filter in order to include only a selected subgroup of cases in the analysis.

Options

- Method: select the way independent variables are entered into the model.
  - Enter: enter all variables in the model in one single step, without checking
• Forward: enter significant variables sequentially
• Backward: first enter all variables into the model and next remove the non-significant variables sequentially
• Stepwise: enter significant variables sequentially; after entering a variable in the model, check and possibly remove variables that became non-significant.

• Enter variable if $P<$
  A variable is entered into the model if its associated significance level is less than this $P$-value.

• Remove variable if $P>$
  A variable is removed from the model if its associated significance level is greater than this $P$-value.

• **Classification table cutoff value**: a value between 0 and 1 which will be used as a cutoff value for a classification table. The classification table is a method to evaluate the logistic regression model. In this table, the observed values for the dependent outcome and the predicted values (at the selected cut-off value) are cross-classified.

• **Categorical**: click this button to identify nominal categorical variables.

• **Graph**: the option to plot a graph that shows the logistic regression curve is only available when there is just one single independent variable.

After you click OK, the following results are displayed in the results window:
Sample size and cases with negative and positive outcome

First the program gives sample size and the number and proportion of cases with a negative (Y=0) and positive (Y=1) outcome.
Overall model fit

The null model -2 Log Likelihood is given by -2 * ln(L_0) where L_0 is the likelihood of obtaining the observations if the independent variables had no effect on the outcome.

The full model -2 Log Likelihood is given by -2 * ln(L) where L is the likelihood of obtaining the observations with all independent variables incorporated in the model.

The difference of these two yields a Chi-Squared statistic, which is a measure of how well the independent variables affect the outcome or dependent variable.

If the P-value for the overall model fit statistic is less than the conventional 0.05 then there is evidence that at least one of the independent variables contributes to the prediction of the outcome.

Cox & Snell R^2 and Nagelkerke R^2 are other goodness of fit measures known as pseudo R-squareds. Note that Cox & Snell's pseudo R-squared has a maximum value that is not 1. Nagelkerke R^2 adjusts Cox & Snell's so that the range of possible values extends to 1.

Regression coefficients

The regression coefficients are the coefficients b_0, b_1, b_2, ... b_k of the regression equation:

\[ \logit(p) = b_0 + b_1 X_1 + b_2 X_2 + b_3 X_3 + \ldots + b_k X_k \]

An independent variable with a regression coefficient not significantly different from 0 (P>0.05) can be removed from the regression model (press function key F7 to repeat the logistic regression procedure). If P<0.05 then the variable contributes significantly to the prediction of the outcome variable.

The logistic regression coefficients show the change (increase when b>0, decrease when b<0) in the predicted logged odds of having the characteristic of interest for a one-unit change in the independent variables.

When the independent variables X_a and X_b are dichotomous variables (e.g. Smoking, Sex) then the influence of these variables on the dependent variable can simply be compared by comparing their regression coefficients b_a and b_b.

The Wald statistic is the regression coefficient divided by its standard error squared: \((b/SE)^2\)

Odds ratios with 95% CI

By taking the exponential of both sides of the regression equation as given above, the equation can be rewritten as:

\[ \text{odds} = \frac{p}{1-p} = e^{b_0} \times e^{b_1 X_1} \times e^{b_2 X_2} \times e^{b_3 X_3} \times \ldots \times e^{b_k X_k} \]

It is clear that when a variable X_i increases by 1 unit, with all other factors remaining unchanged, then the odds will increase by a factor \(e^{b_i}\).

\[ e^{b_i(1+X_i)} - e^{b_i X_i} = e^{b_i(1+X_i)} \times b_i X_i = e^{b_i} \]

This factor \(e^{b_i}\) is the odds ratio (O.R.) for the independent variable X_i and it gives the relative amount by which the odds of the outcome increase (O.R. greater than 1) or decrease (O.R. less than 1) when the value of the independent variable is increased by 1 units.

E.g. The variable SMOKING is coded as 0 (= no smoking) and 1 (= smoking), and the odds ratio for this variable is 2.64. This means that in the model the odds for a positive outcome in cases that do smoke are 2.64 times higher than in cases that do not smoke.

Interpretation of the fitted equation

The logistic regression equation is:

\[ \logit(p) = -8.986 + 0.251 \times \text{AGE} + 0.972 \times \text{SMOKING} \]

So for 40 years old cases who do smoke logit(p) equals 2.026. Logit(p) can be back-transformed to p by the following formula:

\[ p = \frac{1}{1 + e^{-\logit(p)}} \]

Alternatively, you can use the table on p. 331. For logit(p)=2.026 the probability p of having a positive outcome equals 0.88.
Hosmer-Lemeshow test

The Hosmer-Lemeshow test is a statistical test for goodness of fit for the logistic regression model. The data are divided into approximately ten groups defined by increasing order of estimated risk. The observed and expected number of cases in each group is calculated and a chi-squared statistic is calculated as follows:

$$\chi^2_{HL} = \sum_{g=1}^{G} \frac{(O_g - E_g)^2}{E_g(1 - E_g/n_g)}$$

with $O_g$, $E_g$, and $n_g$ denote the observed events, expected events and number of observations for the $g$th risk decile group, and $G$ is the number of groups. The test statistic follows a chi-squared distribution with $G-2$ degrees of freedom.

A large value of chi-squared (with small p-value < 0.05) indicates poor fit and small chi-squared values (with larger p-value closer to 1) indicate a good logistic regression model fit.

The Contingency Table for Hosmer and Lemeshow Test table shows the details of the test with observed and expected number of cases in each group.

Classification table

The classification table can be used to evaluate the predictive accuracy of the logistic regression model. In this table, the observed values for the dependent outcome and the predicted values (at a user defined cut-off value, for example p=0.50) are cross-classified. In our example, the model correctly predicts 70% of the cases.

ROC curve analysis

Another method to evaluate the logistic regression model makes use of ROC curve analysis. In this analysis, the power of the model's predicted values to discriminate between positive and negative cases is quantified by the Area under the ROC curve (AUC). The AUC, sometimes referred to as the c-statistic (or concordance index), is a value that varies from 0.5 (discriminating power not better than chance) to 1.0 (perfect discriminating power).

To perform a full ROC curve analysis on the predicted probabilities you can save the predicted probabilities and next use this new variable in ROC curve analysis (p. 222). The Dependent variable used in Logistic Regression then acts as the Classification variable in the ROC curve analysis dialog box.

Propensity scores

Propensity scores are predicted probabilities of a logistic regression model. To save the propensity scores in your datasheet, click the link “Save predicted probabilities” in the results window.

Graph

MedCalc can plot the logistic regression curve when there is only one single independent variable:

The following graph is created:
Define status

When MedCalc requires that a variable must be binary or dichotomous, and this variable can only contain data coded as 0 or 1, but your data are coded differently, you can use the Define status tool to recode your data.

Example

You have entered the text values No and Yes for a variable Diseased:

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No</td>
<td>23.5</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>No</td>
<td>21.6</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>No</td>
<td>18.8</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>No</td>
<td>20.6</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>No</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Yes</td>
<td>16.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Yes</td>
<td>19.5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Yes</td>
<td>18.1</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Yes</td>
<td>20.1</td>
<td></td>
</tr>
</tbody>
</table>

In the Define status dialog box you can identify the values that indicate the status of subjects. In the left column, you select the values of the variable that indicate positive (diseased, abnormal) subjects and in the right column you select values that indicate negative (healthy, normal) subjects.
In this example, the text value Yes indicates a positive or diseased status, and the text value No indicates a negative of healthy status. This means that for calculations the variable Diseased will be assigned the numeric value 1 for cases with the text value Yes, and the numeric value 0 for cases with the text value No.

When you do not select any values, then MedCalc will use the following default numeric values:

- 1 indicates positive (diseased, abnormal) subjects
- 0 indicates negative (healthy, normal) subjects

### Probit regression (Dose-Response analysis)

The probit regression procedure fits a probit sigmoid dose-response curve and calculates values (with 95% CI) of the dose variable that correspond to a series of probabilities. For example, the ED50 (median effective dose) or (LD50 median lethal dose) are the values corresponding to a probability of 0.50, the Limit-of-Detection (CLSI, 2012) is the value corresponding to a probability of 0.95.

The probit regression equation has the form:

$$ \text{probit}(p) = a + b \times X $$

Where X is the (possibly log-transformed) dose variable and probit(p) is the value of the inverse standard normal cumulative distribution function \( \Phi^{-1} \) corresponding with a probability p:

$$ \text{probit}(p) = \Phi^{-1}(p) $$

Probit(p) can be transformed to a probability p using the standard normal cumulative distribution function \( \Phi \):

$$ p = \Phi(\text{probit}(p)) $$

MedCalc fits the regression coefficients a and b using the method of maximum likelihood.

### How to enter data

You can enter the data in binary format or in grouped format.

**Binary**

In the binary format, you have 2 variables, one variable for the dose (concentration) and one for the binary response. For each single measurement, there is a row with the dose and the response, which is coded 0 (no response) and 1 (response).

For example:

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>Positive</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.2</td>
<td>1</td>
</tr>
<tr>
<td>4</td>
<td>0.1</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.5</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0.9</td>
<td>1</td>
</tr>
<tr>
<td>9</td>
<td>0.9</td>
<td>1</td>
</tr>
</tbody>
</table>

**Grouped**

In the grouped format, you have 3 variables, one variable for the dose, one for the total number of measurements, and one for the number of measurements with a response.

For example:
Required input

- **Data type**: select the option corresponding to the way you have entered the data: binary or grouped (see above).
- **Dose variable**: select the dose variable.
- **Variables in case of binary data**
  - Response variable: the response variable must be binary or dichotomous, and should only contain data coded as 0 (no response) or 1 (response). If your data are coded differently, you can use the Define status tool to recode your data.
- **Variables in case of grouped data**
  - Total number of cases: select the variable that contains the number of measurements for each dose.
  - Number of responses: select the variable that contains the number of responses for each dose.
- **Filter**: (optionally) enter a data filter in order to include only a selected subgroup of cases in the analysis.
- **Options**
  - Log transformation: select this option if the dose variable requires a logarithmic transformation. When the dose variable contains 0 values, MedCalc will automatically add a small number to the data in order to make the logarithmic transformation possible. This small number will be subtracted when the results are backtransformed for presentation.
  - Dose-response plot: select this option to obtain a dose-response plot.
    - Markers: click this option to have the data represented in the graph as markers. Note that when you have selected logarithmic transformation and the dose variable contains 0 values, these values cannot be represented in the graph as markers.

**Results**
Sample size and cases with negative and positive outcome: first the program gives sample size and the number and proportion of cases with and without response.
Overall model fit

The null model -2 Log Likelihood is given by -2 * ln(L0) where L0 is the likelihood of obtaining the observations in the "null" model, a model without the dose variable.

The full model -2 Log Likelihood is given by -2 * ln(L) where L is the likelihood of obtaining the observations with the dose variable incorporated in the model.

The difference of these two yields a Chi-Squared statistic which is a measure of how well the dose variable affects the response variable.

Cox & Snell R² and Nagelkerke R² are other goodness of fit measures known as pseudo R-squareds. Note that Cox & Snell's pseudo R-squared has a maximum value that is not 1. Nagelkerke R² adjusts Cox & Snell's so that the range of possible values extends to 1.

Regression coefficients

The regression coefficients are the coefficients a (constant) and b (slope) of the regression equation:

\[ \text{probit}(p) = a + b \times X \]

The Wald statistic is the regression coefficient divided by its standard error squared: (b/SE)².

Log transformation

When you have selected logarithmic transformation of the dose variable, then a and b are in fact the coefficients of the regression equation:

\[ \text{probit}(p) = a + b \times \log(X) \]

Use of the fitted equation

The predicted probability of a positive response can be calculated using the regression equation.

When the regression equation is for example:

\[ \text{Probit} = -2.61 + 6.36 \times \text{Dose} \]

then for a Dose of 0.500 Probit(p) equals 0.57. Probit(p) can be transformed to p by the MedCalc spreadsheet function NORMSDIST(z) or the equivalent Excel function.

Alternatively, you can use the following table.

<table>
<thead>
<tr>
<th>Probit(p)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.326</td>
<td>0.99</td>
</tr>
<tr>
<td>1.645</td>
<td>0.95</td>
</tr>
<tr>
<td>1.282</td>
<td>0.90</td>
</tr>
<tr>
<td>0.842</td>
<td>0.80</td>
</tr>
<tr>
<td>0.000</td>
<td>0.50</td>
</tr>
<tr>
<td>-0.842</td>
<td>0.20</td>
</tr>
<tr>
<td>-1.282</td>
<td>0.10</td>
</tr>
<tr>
<td>-1.645</td>
<td>0.05</td>
</tr>
<tr>
<td>-2.326</td>
<td>0.01</td>
</tr>
</tbody>
</table>

In the example, with Probit(p) equal to 0.57, p = 0.72.

A probability p can be transformed to Probit(p) using the table above or using the MedCalc spreadsheet function NORMSINV(p) or the equivalent Excel function.

For a probability p=0.5 you find in the table that Probit(p)=0. When the regression equation is

\[ \text{Probit} = -2.61 + 6.36 \times \text{Dose} \]

then

\[ \text{Dose} = (\text{Probit}+2.61)/6.36 \]

and therefore dose = 2.61/6.36 = 0.41.
Dose-Response table
This table lists a series of Probabilities with corresponding Dose, with a 95% confidence interval for the dose (Finney, 1947). Values in light gray text color are dose values that fall outside the observed range of the dose variable.

Log transformation
When you have selected logarithmic transformation of the dose variable, MedCalc will backtransform the results and display the dose variable on its original scale in the Dose-Response table.

Graph
This graph shows the probabilities, ranging from 0 to 1, and the corresponding dose. Two additional curves represent the 95% confidence interval for the dose.

Nonlinear regression
Nonlinear regression is a regression technique in which a nonlinear mathematical model is used to describe the relationship between two variables (Glantz & Slinker, 2001).

For example:
\[ y = \frac{1}{1+\exp(a+b^*x)} \]

where
- \( y \) is the dependent variable
- \( x \) is the independent variable
- \( a \) and \( b \) are the parameters to be determined by the software

To find the model's parameters, MedCalc uses the Levenberg-Marquardt iterative procedure (Press et al., 2007) that requires the user to supply initial estimates or best guesses of the parameters.
Required input

- **Regression equation**: select or enter the model to be fitted, for example: \( y = \frac{1}{1+\exp(a+bx)} \) (note that "y=" is already displayed and does not need to be entered). In this example, \( a \) and \( b \) are the parameters to be estimated. The nonlinear regression equation must include the symbol \( x \), which refers to the independent variable that is selected in a different input box (see below).

The different parameters can be represented by single characters \( a .. z \), excluding the characters \( x \) and \( y \). The parameters can also be represented by more meaningful names such as for example "slope". Parameter names must not be equal to any variable name in the spreadsheet, but just like variables, parameter names cannot include spaces, nor the following characters: \( - + / * = < > ^ { } [ ] \{ \} \& ? \$ " ' : ,. In addition, parameter names should not start with a number and must be different from reserved words such as TRUE, FALSE, ROW and COLUMN.

- **Variable Y**: select the dependent variable.
- **Variable X**: select the independent variable.
- **Filter**: space for an optional filter to include a subset of data in the analysis.
- **Parameters**
  - **Get parameters from equation**: let the program extract the parameter names from the regression equation. When not all intended parameters are extracted, you probably have made some error(s) in naming the parameters or in the regression equation.
  - **Parameters list and initial values**: enter initial values (best estimates) for the different parameters.

To enter initial values, you can make use of the different statistical spreadsheet functions on variables. These functions can refer to the selected X- and Y-variables by means of the symbols \&X and \&Y respectively. The symbol \&FILTER can be used to refer to the selected data filter.

For example: when "Response" is selected as the dependent variable, then you can use the function VMAX(&Y) as the initial value of a parameter, and VMAX(&Y) will return the Maximum value of the variable "Response".

Note: \&X, \&Y, and \&FILTER can only be used in the manner described here in the context of parameter initialization for nonlinear regression. These symbols do not have any significance in any other part of the program.

- **Fit options**
  - **Convergence tolerance**: the iteration process completes when the difference between successive model fits is less than this value. The convergence tolerance influences the precision of the parameter estimates.
  - **Maximum numbers of iterations**: the iteration process stops when the maximum number of iterations is reached (when the number of iterations is unexpectedly large, the model or initial parameter values may be inaccurate).

- **Graph options**
  - **Show scatter diagram & fitted line**: option to create a scatter diagram with fitted line.
  - **Show residuals window**: option to create a residuals plot.
Results

This section shows the tolerance and iterations settings.

Next the reason of iteration process termination is given:
- **Convergence tolerance criterion met**: the iteration process has completed because the difference between successive model fits became less than the Convergence tolerance value.
- **Maximum numbers of iterations exceeded**: the iteration process stopped because the maximum number of iterations was reached. This may indicate a poor model fit or poor initial parameter values.
- **Bad model or bad initial parameters**: the program failed to find a solution for the given model using the supplied initial parameters.
- **Function not defined for all values of independent variable**: the calculation of the model resulted in an error, for example a division by zero.

Results
- **Sample size**: the number of (selected) data pairs.
- **Residual standard deviation**: the standard deviation of the residuals.

Regression equation
The parameter estimates are reported with standard error and 95% Confidence Interval. The Confidence Interval is used to test whether a parameter estimate is significantly different from a particular value \( k \). If a value \( k \) is not in the Confidence Interval, then it can be concluded that the parameter estimate is significantly different from \( k \).
For example, when the parameter estimate is 1.28 with 95% CI 1.10 to 1.46 then this parameter estimate is significantly different (P<0.05) from 1.

**Analysis of variance**

The Analysis of Variance tables gives the Regression model, Residual and Total sum of squares. When MedCalc determines that the model does not include an intercept the "uncorrected" sum of squares is reported and is used for the F-test. When MedCalc determines that the model does include an intercept, the "corrected" sum of squares is reported and is used for the F-test.

**Correlation of parameter estimates**

This table reports the correlation coefficients between the different parameter estimates. When you find 2 or more parameters to be highly correlated, you may consider reducing the number of parameters or selecting another model.

**Scatter diagram & fitted line**

This graph displays a scatter diagram and the fitted nonlinear regression line.

![Nonlinear regression](image)

**Residuals plot**

Residuals are the differences between the predicted values and the observed values for the dependent variable. The residuals plot allows for the visual evaluation of the goodness of fit of the model. Residuals may point to possible outliers (unusual values) in the data or problems with the fitted model. If the residuals display a certain pattern, the selected model may be inaccurate.

![Nonlinear regression - residuals](image)
T-tests

One sample t-test

Use the one sample t-test to test whether the average of observations differs significantly from a test value.

Required input

- The variable of interest. You can use the button to select variables and filters.
- The test value you want to compare the sample data with.

Options

- Logarithmic transformation: select this option if the data are positively skewed.

Results

The results window first displays the summary statistics of the observations.

The One sample t-test table shows:

- The test value
• The difference Sample mean - Test value
• The 95% Confidence Interval (CI) for this difference
• The Degrees of Freedom (DF), t-statistic, and corresponding (two-sided) P-value.

If the calculated P-value is less than 0.05, the conclusion is that, statistically, the sample mean is significantly different from the test value.

Logarithmic transformation

If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of the observations, but reports the back-transformed summary statistics.

For the One sample t-test, the difference between sample mean and test value, with 95% confidence interval, are given on the log-transformed scale. Next, the results are transformed back and the interpretation is as follows: the back-transformed difference of the logs is ratio of the sample mean / test value on the original scale.

Independent samples t-test

The independent samples t-test is used to compare the means of two independent samples.

Required input

Select the variables for sample 1 and sample 2. Use the button to select variables and filters in the respective lists.

Options

• Logarithmic transformation: select this option if the data are positively skewed.
• Correction for unequal variances: select the t-test assuming equal variances, or the t-test corrected for unequal variances (Welch test, Armitage et al., 2002). With the option "Automatic" the software will select the appropriate test based on the F-test (comparison of variances).
• Residuals: optionally, select a Test for Normal distribution of the residuals. In the independent samples t-test, residuals are the differences between the observations and their group or sample mean. For further analysis of residuals, see p. 92.

Results

After you have clicked OK, the program displays the summary statistics of the two samples, followed by the statistical tests.
First an F-test is performed. If the P-value is low (P<0.05) the variances of the two samples cannot be assumed to be equal and it should be considered to use the t-test with a correction for unequal variances (Welch test) (see above).

The independent samples t-test is used to test the hypothesis that the difference between the means of two samples is equal to 0 (this hypothesis is therefore called the null hypothesis). The program displays the difference between the two means, and the 95% Confidence Interval (CI) of this difference. Next follow the test statistic t, the Degrees of Freedom (DF) and the two-tailed probability P. When the P-value is less than the conventional 0.05, the null hypothesis is rejected and the conclusion is that the two means do indeed differ significantly.

Logarithmic transformation

If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of the observations, but reports the back-transformed summary statistics.

For the t-test, the difference and 95% confidence are given, and the test is performed, on the log-transformed scale.

Next, the results of the t-test are transformed back and the interpretation is as follows: the back-transformed difference of the means of the logs is the ratio of the geometric means of the two samples (see Bland, 2000).

One-sided or two-sided tests

In MedCalc, P-values are always two-sided (as recommended by Fleiss, 1981, and Altman, 1991) and not one-sided.

- A two-sided (or two-tailed) P-value is appropriate when the difference between the two means can occur in both directions: it may be either negative or positive; the mean of one sample may either be smaller or larger than that of the other sample.
- A one-sided test should only be performed when, before the start of the study, it has already been established that a difference can only occur in one direction. E.g. when the mean of sample A must be more than the mean of sample B for reasons other than those connected with the sample(s).

Interpretation of P-values

P-values should not be interpreted too strictly. Although a significance level of 5% is generally accepted as a cut-off point for a significant versus a non-significant result, it would be a mistake to interpret a shift of P-value from e.g. 0.045 to 0.055 as a change from significance to non-significance. Therefore the real P-values are preferably reported, P=0.045 or P=0.055, instead of P<0.05 or P>0.05, so the reader can make his own interpretation.

With regards to the interpretation of P-values as significant versus not-significant, it is has been recommended to select a smaller significance level of for example 0.01 when it is necessary to be quite certain that a difference exists before accepting it. When a study is designed to uncover a difference, or when a life-saving drug is being studied, we should be willing to accept that...
there is a difference even when the P-value is as large as 0.10 or even 0.20 (Lentner, 1982). The latter states: “The tendency in medical and biological investigations is to use too small a significance probability”.

Confidence intervals
Whereas the P-value may give information on the statistical significance of the result, the 95% confidence interval gives information to assess the clinical importance of the result.

When the number of cases included in the study is large, a biologically unimportant difference can be statistically highly significant. A statistically significant result does not necessarily indicate a real biological difference.

On the other hand, a high P-value can lead to the conclusion of statistically non-significant difference although the difference is clinically meaningful and relevant, especially when the number of cases is small. A non-significant result does not mean that there is no real biological difference.

Confidence intervals are therefore helpful in interpretation of a difference, whether or not it is statistically significant (Altman et al., 1983).

Presentation of results
It is recommended to report the results of the t-test (and other tests) not by a simple statement such as P<0.05, but by giving full statistical information, as in the following example by Gardner & Altman (1986):

The difference between the sample mean systolic blood pressure in diabetics and non-diabetics was 6.0 mm Hg, with a 95% confidence interval from 1.1 to 10.9 mm Hg; the t test statistic was 2.4, with 198 degrees of freedom and an associated P value of P=0.02.

In short:
Mean 6.0 mm Hg, 95% CI 1.1 to 10.9; t=2.4, df=198, P=0.02

See also
To perform different tests in one single procedure, see Comparison of independent samples, p. 243.

Paired samples t-test

The paired samples t-test is used to test the null hypothesis that the average of the differences between a series of paired observations is zero. Observations are paired when, for example, they are performed on the same samples or subjects.

Required input

First select the variables for sample 1 and sample 2, and a possible data filter for the data pairs. Use the button to select variables and filters in the respective lists.

Options
- Logarithmic transformation: select this option if the data are positively skewed.
- You can select an optional Test for Normal distribution of the differences between the paired observations. For further analysis of the distribution of differences, see analysis of residuiales p. 92.
Results

The results window for the paired samples t-test displays the summary statistics of the two samples. Note that the sample size will always be equal because only cases are included with data available for the two variables.

Next, the arithmetic mean of the differences (mean difference) between the paired observations is given, the standard deviation of these differences and the standard error of the mean difference followed by the 95% confidence interval for the mean difference.

Differences are calculated as sample 2 - sample 1.

In the paired samples t-test the null hypothesis is that the average of the differences between the paired observations in the two samples is zero. If the calculated P-value is less than 0.05, the conclusion is that, statistically, the mean difference between the paired observations is significantly different from 0.

Note that in MedCalc P-values are always two-sided.

Logarithmic transformation

If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of the observations, but reports the back-transformed summary statistics.

For the paired t-test, the mean difference and 95% confidence are given on the log-transformed scale.

Next, the results of the t-test are transformed back and the interpretation is as follows: the back-transformed mean difference of the logs is the geometric mean of the ratio of paired values on the original scale (see Altman, 1991).

See also

To perform different tests in one single procedure, see Comparison of paired samples, p. 244.
Rank sum tests

Signed rank sum test

The Signed rank sum test is a test for symmetry about a test value. This test is the non-parametric alternative for the One sample t-test. It can be used when the observations are not Normally distributed.

Required input

- The variable of interest. You can use the button to select variables and filters.
- The test value you want to compare the sample data with.

Results

The results windows for the Signed rank sum test first displays summary statistics of the sample.

The Signed rank sum test ranks the absolute values of the differences between the sample data and the test value, and calculates a statistic on the number of negative and positive differences.

If the resulting P-value is small (P<0.05), then the sample data are not symmetrical about the test value and therefore a statistically significant difference can be accepted between the sample median and the test value.
The statistics also include the Hodges-Lehmann location estimator (sometimes called the Hodges-Lehmann median) and its 95% confidence interval (Conover, 1999; CLSI, 2013). The Hodges-Lehmann location estimator of a sample with sample size n is calculated as follows. For each possible set of 2 observations, the average is calculated. The Hodges-Lehmann location estimator is the median of all n × (n+1) / 2 averages. The confidence interval is derived according to Conover (1999, p. 360).

**Mann-Whitney test (independent samples)**

The Mann-Whitney test is the non-parametric equivalent of the independent samples t-test. It should be used when the sample data are not Normally distributed, and they cannot be transformed to a Normal distribution by means of a logarithmic transformation.

**Required input**

Select the variables for sample 1 and sample 2. Use the button to select variables and filters in the respective lists.

**Results**

The **Mann-Whitney test** combines and ranks the data from sample 1 and sample 2 and calculates a statistic on the difference between the sum of the ranks of sample 1 and sample 2.

If the resulting P-value is small (P<0.05) then a statistically significant difference between the two samples can be accepted.

When either or both sample sizes are large (>20) then MedCalc uses the Normal approximation (Lentner, 1982) to calculate the P-value. For small sample sizes, in the absence of ties, MedCalc calculates the exact probability (Conover, 1999).

The statistics also include the Hodges-Lehmann median difference (the Hodges-Lehmann estimate of location shift) and its 95% confidence interval (Conover, 1999). For two independent samples with sample size m and n, the Hodges-Lehmann median difference is the median of all m × n paired differences between the observations in the two samples. Differences are calculated as sample 2 − sample 1. The confidence interval is derived according to Conover (1999, p. 281).

Note that the Hodges-Lehmann median difference is not necessarily the same as the difference between the two medians.
Wilcoxon test (paired samples)

The Wilcoxon test for paired samples is the non-parametric equivalent of the paired samples t-test. It should be used when the sample data are not Normally distributed, and they cannot be transformed to a Normal distribution by means of a logarithmic transformation.

Required input

Select the variables for sample 1 and sample 2, and a possible data filter for the cases to be included. Use the button to select variables and filters in the respective lists.
Results

The **Wilcoxon test** for paired samples ranks the absolute values of the differences between the paired data in sample 1 and sample 2 and calculates a statistic on the number of negative and positive differences (differences are calculated as sample 2 - sample 1).

If the resulting P-value is small (P<0.05) then it can be accepted that the median of the differences between the paired observations is statistically significantly different from 0.

The statistics also include the Hodges-Lehmann median difference (the Hodges-Lehmann estimate of location shift) and its 95% confidence interval (Conover, 1999). The Hodges-Lehmann median difference between two paired samples with sample size n is calculated as follows: first the n paired differences are calculated. For each possible set of 2 differences, the average is calculated. The Hodges-Lehmann median difference is the median of all \( n \times (n+1) / 2 \) averages. The confidence interval is derived according to Conover (1999, p. 360).

Note that the Hodges-Lehmann median difference is not necessarily the same as the difference between the medians.

See also

To perform different tests in one single procedure, see Comparison of paired samples, p. 244.

**Variance ratio test (F-test)**

The **Variance ratio test (F-test)** is used to compare the variances of two samples.

**Required input**

In the dialog box first identify the variables for sample 1 and sample 2. Use the \( \square \) button to select variables and filters in the respective lists.
Options
Logarithmic transformation: select this option if the data are positively skewed.

Results

The program displays summary statistics and the variances of the two samples. Next the results of the variance ratio test and the F-statistic is given, which is the ratio of the larger variance over the smaller, with its associated (two-sided) P-value. If the P-value is less than the conventional 0.05, the null hypothesis is rejected and the conclusion is that the two variances differ significantly.

Logarithmic transformation
If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of the observations, but reports the back-transformed summary statistics.

The variance of the logs cannot be back-transformed meaningfully and therefore the variances and the variance ratio are given on the log-transformed scale.
Analysis of variance and related procedures

One-way analysis of variance

One-way analysis of variance is used to test the difference between the means of several subgroups of a variable (multiple testing). For a graphical representation of ANOVA, refer to Multiple comparison graphs (p. 249).

Data

The following figure illustrates how data need to be entered. For ANOVA, you need one continuous variable (concentration) and one qualitative variable (grade). The data for each case are entered on one row of the spreadsheet. The qualitative variable may contain character or numeric codes. These codes are used to break-up the data into several subgroups for the ANOVA procedure, to calculate the Between groups and Within groups variation.

Required input
For *Data*, select a continuous variable, and for *Factor codes* the qualitative factor.

**Options**

- **Logarithmic transformation**: if the data require a logarithmic transformation (e.g. when the data are positively skewed), select the Logarithmic transformation option.
- **Post-hoc test**: this is the test used for pairwise comparison of subgroups, when the ANOVA test is positive (i.e. P is less than the selected significance level, see below). MedCalc offers 3 post-hoc tests (in order of decreasing power): Student-Newman-Keuls test, Tukey-Kramer test and Scheffé’s test.
- **Significance level**: the desired significance level for the post-hoc test. If the ANOVA test results in a P-value less than this significance level, MedCalc performs the selected post-hoc test.
- **Residuals**: optionally, select a Test for Normal distribution of the residuals. For further analysis of residuals, see p. 93.

**Results**

Levene’s Test for Equality of Variances

Prior to the ANOVA test, Levene’s Test for Equality of Variances is performed. If the Levene test is positive (P<0.05) then the variances in the different groups are different (the groups are not homogeneous) and you may need to apply a logarithmic transformation to the data, or use a non-parametric statistic.

**ANOVA**

The results of the ANOVA are presented in an ANOVA table, followed by the F statistic and associated P value. If the P value is less than 0.05 (or another preselected significance level), then you can accept the hypothesis that the means of at least two of the subgroups differ significantly.

**Post-hoc test**

If the ANOVA test is positive (P less than the selected significance level) then MedCalc performs a post hoc test (using either Student-Newman-Keuls', Tukey-Kramer's or Scheffé's method) for pairwise comparison of subgroups.
Logarithmic transformation

If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of the dependent variable, but the different means are back-transformed and reported as the geometric means.

Two-way analysis of variance

The two-way analysis of variance is an extension to the one-way analysis of variance. There are two qualitative factors (A and B) on one dependent variable Y.
Three null hypotheses are tested in this procedure:

- factor A does not influence variable Y,
- factor B does not influence variable Y,
- the effect of factor A on variable Y does not depend on factor B (i.e. there is no interaction of factors A and B).

Two-way analysis of variance requires that there are data for each combination of the two qualitative factors A and B.

Required input

Select the (continuous) dependent variable (Y) and two discrete variables for the qualitative factors (A and B) suspected to influence the dependent variable. The qualitative factors A and B may either consist of numeric or alphanumeric data. A filter can also be defined in order to include only a selected subgroup of cases.

Options

- Residuals: optionally, select a Test for Normal distribution of the residuals. For further analysis of residuals, see p. 93.
Results

Levene’s test for equality of variances

Prior to the ANOVA test, Levene’s test for equality of variances is performed. If the Levene test is positive (P<0.05) then the variances in the groups are different (the groups are not homogeneous), and a 2-way analysis of variance is not appropriate.

Tests of Between-Subjects Effects

If the calculated P-values for the two main factors A and B, or for the 2-factor interaction is less than the conventional 0.05 (5%), then the corresponding null hypothesis is rejected, and you accept the alternative hypothesis that there is indeed a difference between groups.

When the 2-factor interaction is significant the effect of factor A is dependent on the level of factor B, and it is not recommended to interpret the means and differences between means (see below) of the main factors.
Estimated marginal means

In the following tables, the means with standard error and 95% Confidence Interval are given for all levels of the two factors. Also, differences between groups, with Standard Error, and Bonferroni corrected P-value and 95% Confidence Interval of the difference are reported.

Analysis of covariance

Description

Analysis of covariance (ANCOVA) allows to compare one variable in 2 or more groups taking into account (or to correct for) variability of other variables, called covariates.

Analysis of covariance combines one-way or two-way analysis of variance with linear regression (General Linear Model, GLM).

How to enter data

In this example (data from Wildt & Ahtola, 1978) data are entered for 2 factor variables named "FactorA" and "FactorB". The variable "VarY" is the dependent variable and there is one covariate "VarX".
Required input

In the dialog box for ANCOVA you select:

- **Dependent variable**: the (continuous) dependent variable
- **Factors**: use one categorical variable for a one-way ANCOVA or two categorical variables for a two-way factorial ANCOVA.
- **Covariates**: one or more covariates.
- **Filter**: an optional data filter in order to include only a selected subgroup of cases.
- **Residuals**: optionally, select a Test for Normal distribution of the residuals. For further analysis of residuals, see p. 93.

Results
Levene’s test for equality of variances

Prior to the ANCOVA test, Levene’s test for equality of variances is performed. If the Levene test is positive (P<0.05) then the variances in the groups are different (the groups are not homogeneous), and therefore the assumptions for ANCOVA are not met.

Homogeneity of regression slopes

The interpretation of ANCOVA and the associated adjusted means relies on the assumption of homogeneous regression slopes for the various groups (Huitema, 1980). If this assumption is not met (P<0.05) the ANCOVA results are unreliable.

Tests of Between-Subjects Effects

If the calculated P-values for the two main factors A and B, or for the 2-factor interaction is less than the conventional 0.05 (5%), then the corresponding null hypothesis is rejected, and you accept the alternative hypothesis that there are indeed differences among groups.

When the 2-factor interaction (FactorA*FactorB) is significant the effect of factor A is dependent on the level of factor B, and it is not recommended to interpret the means and differences between means (see below) of the main factors.

Estimated marginal means

In the following tables, the marginal means (sometimes referred to as “corrected means”) with standard error and 95% Confidence Interval are given for all levels of the two factors. Also, differences between groups, with Standard Error, and Bonferroni corrected P-value and 95% Confidence Interval of the differences are reported.

General Linear Model

Since this ANCOVA procedure is an implementation of the General Linear Model (GLM), the procedure:

• reverts to one-way ANOVA when you do not specify covariates and only one factor,
• reverts to a 2-way ANOVA when you specify 2 factors but no covariates,
• reverts to multiple regression when you do not specify factors.
Repeated measures analysis of variance

Repeated measures analysis of variances can be used when the same parameter has been measured under different conditions on the same subjects. Subjects can be divided into different groups (Two-factor study with repeated measures on one factor) or not (Single-factor study).

A distinction is made between a Single factor study (without Grouping variable) or a Two-factor study with repeated measures on one factor (when a grouping variable is specified).

A. Single factor study

How to enter data

![Girden Table 3.1]

In a first column, an identification number for each case is entered (not required). The next columns contain the data of the different measurements (example taken from Girden, 1992, table 3.1).

Required input

- Repeated measurements variables: the variables containing the different measurements. Note that the order in which you select the variables is important for trend analysis.
- Grouping variable: not used in a single factor study.
- Filter: an optional data filter to include only a selected subgroup of cases.
- Options
  - Logarithmic transformation: select this option if the data are positively skewed.
Results

The results window displays the number of subjects in the study. Note that subjects with missing values for any measurement are dropped from the analysis.

Sphericity

Sphericity refers to the equality of variances of the differences between measurements, which is an assumption of ANOVA with a repeated measures factor.

MedCalc reports the estimates (epsilon) of sphericity proposed by Greenhouse and Geisser (1959) and Huynh and Feldt (1976) (corrected by Lecoutre, 1991). The closer that epsilon is to 1, the more homogeneous are the variances of differences, and hence the closer the data are to being spherical. Both the Greenhouse-Geisser and Huynh-Feldt estimates are used as a correction factor that is applied to the degrees of freedom used to calculate the P-value for the observed value of F.

Test of Within Subjects Effects

In this table, the variation attributed to "Factor" and "Residual" variation is displayed. If the P-value next to "Factor" is low (P<0.05) it can be concluded that there is significant difference between the different measurements.

0.75 then the correction according to Huynh and Feldt should be used. If epsilon < 0.75 then the more conservative correction according to Greenhouse-Geisser is preferred.

**Trend analysis**

The Trend analysis table shows whether the measurements show a linear or non-linear (quadratic, cubic) trend.

![Linear, Quadratic, Cubic Trends](image)

**Within-subjects factors**

The within-subjects factors are summarized in a table with Mean, Standard Error and 95% Confidence Interval.

**Pairwise comparisons**

In the Pairwise comparisons table, the different measurements are compared to each other. The mean difference with standard error, P-value, and 95% Confidence Interval of the difference is given. Bonferroni correction for multiple comparisons is applied for P-values and confidence intervals.

**B. Two-factor study with repeated measures on one factor**

**How to enter data**

![Data Entry Example](image)

In this example the first column indicates group membership. “Male” has been coded as 0, “female” as 1. The next columns contain the data of the different measurements (example taken from Girden ER, 1992, table 5.1).
Required input

- Repeated measurements variables: the variables containing the different measurements.
- Grouping variable: a categorical variable that divides the data into groups (between-subjects factor).
- Filter: an optional data filter to include only a selected subgroup of cases.
- **Options**
  - Logarithmic transformation: select this option if the data are positively skewed.
Results

Between-subjects factors (subject groups)
The first table lists the different subject groups and the number of observations.

Sphericity
Sphericity refers to the equality of variances of the differences between measurements, which is an assumption of ANOVA with a repeated measures factor.

MedCalc reports the estimates (epsilon) of sphericity proposed by Greenhouse and Geisser (1959) and Huynh and Feldt (1976) (corrected by Lecoutre, 1991). The closer that epsilon is to 1, the more homogeneous are the variances of differences, and hence the closer the data are to being spherical. Both the Greenhouse-Geisser and Huynh-Feldt estimates are used as a correction factor that is applied to the degrees of freedom used to calculate the P-value for the observed value of F.

Test of Between-Subjects Effects
In this table, the variation attributed to "Groups" (between-subjects) and "Residual" variation are displayed.
- If the P-value for "Groups" is low (P<0.05) it can be concluded that there is significant difference between groups.

Test of Within-Subjects Effects
In this table, the source of variation attributed to "Factor" (within-subjects), "Group" and "Factor" interaction, "Residual" variation is displayed.
- If the P-value for "Factor" is low (P<0.05) it can be concluded that there is significant difference between measurements.
- If the P-value for "Group x Factor interaction" is low (P<0.05) it can be concluded that the difference between measurements depends on group membership.
MedCalc produces two corrections based upon the estimates of sphericity by Greenhouse and Geisser (1959) and Huynh and Feldt (1976) (corrected by Lecoutre, 1991). Girden (1992) recommends that when epsilon (Greenhouse-Geisser estimate) > 0.75 then the correction according to Huynh and Feldt should be used. If epsilon < 0.75 then the more conservative correction according to Greenhouse-Geisser is preferred.

**Logarithmic transformation**

If you selected the Logarithmic transformation option, the program performs the calculations on the logarithms of all measurements, but backtransforms the results to the original scale for presentation.

- In the Within-Subjects factors table, the geometric mean with its 95% Confidence is given.
- In the Pairwise comparison table, the geometric mean of the ratios of paired observations is given (which is the backtransformed mean difference of the logarithms of the paired observations).

**Kruskal-Wallis test**

The *Kruskal-Wallis test* (*H*-test) is an extension of the *Wilcoxon* test and can be used to test the hypothesis that a number of unpaired samples originate from the same population (Conover, 1999). In MedCalc, *Factor codes* are used to break-up the (ordinal) data in one variable into different sample subgroups. If the null-hypothesis, being the hypothesis that the samples originate from the same population, is rejected (*P*<0.05), then the conclusion is that there is a statistically significant difference between at least two of the subgroups.

The following need to be entered in the dialog box: for *Data* select the variable containing the data, and for *Factor codes* the qualitative factor. The qualitative factor may either be character or numeric codes. These are the codes that will be used to break-up the data into several subgroups.

**Options**

- Post-hoc test: this is the test used for pairwise comparison of subgroups, when the Kruskal-Wallis test is positive (i.e. *P* is less than the selected significance level, see below). MedCalc offers 2 post-hoc tests: the test according to Dunn (1964) and Conover (1999).
- Significance level: the desired significance level for the post-hoc test. If the Kruskal-Wallis test results in a *P*-value less than this significance level, MedCalc performs the selected post-hoc test.
- Jonckheere-Terpstra trend test: when the qualitative factor is ordered the Jonckheere-Terpstra trend test can be used to test the hypothesis that the medians are ordered (increase or decrease) according to the order of the qualitative factor (Bewick et al., 2004; Sheskin, 2011).

You obtain the results after you click OK.
In this example, it is tested whether there is a difference of the variable *Pain relief* for the different treatment regimens coded A, B and C in the variable *Treatment*. Pain relief was recorded on an ordinal scale from 0 to 9. Since the null-hypothesis is not rejected (P=0.1995), the conclusion is that there is no statistically significant difference between treatments.

For a graphical representation of this test, refer to *Multiple comparison graphs* (p. 249).

**Post-hoc analysis**

If the Kruskal-Wallis test is positive (P less than the selected significance level) then MedCalc performs a test for pairwise comparison of subgroups according to Conover, 1999.
**Friedman test**

The Friedman test is a non-parametric test for testing the difference between several related samples (Conover, 1999). It is an alternative for Repeated measures analysis of variances which is used when the same parameter has been measured under different conditions on the same subjects.

**How to enter data**

![Data](image)

The columns contain the data of the different measurements (example adapted from Conover, 1999).

**Required input**

- **Variables**: the variables that contain the related observations.
- **Filter**: an optional data filter to include only a selected subgroup of cases.
- **Options**
  - **Significance level**: the desired significance level for the post-hoc test. If the Friedman test results in a P-value less than this significance level, MedCalc performs a test for pairwise comparison of variables according to Conover, 1999.
Results

Descriptive statistics
This table gives the descriptive statistics for the different variables: number of cases (n), minimum, 25th percentile, median, 75th percentile and maximum. Since the Friedman test is for related samples, cases with missing observations for one or more of the variables are excluded from the analysis, and the sample size is the same for each variable.

Friedman test
The null hypothesis for the Friedman test is that there are no differences between the variables. If the calculated probability is low (P<0.05) the null-hypothesis is rejected and it can be concluded that at least 2 of the variables are significantly different from each other.

Multiple comparisons
When the Friedman test is positive (P less than the selected significance level) then a table is displayed showing which of the variables is significantly different from which other variables. The post-hoc test is performed according to Conover, 1999. In the example variable (1), which is TREATMENT1, is significantly different from the variables (2) and (3), which correspond to TREATMENT2 and TREATMENT3.
Crosstabs

Chi-squared test

The Chi-squared test can be used

- to test the hypothesis that for **one classification factor** (e.g. gender), all classification levels have the same frequency.
- to test the relationship between **two classification factors** (e.g. gender and profession).

In the following example we have two categorical variables. For the variable OUTCOME a code 1 is entered for a positive outcome and a code 0 for a negative outcome. For the variable SMOKING a code 1 is used for the subjects that smoke and a code 0 for the subjects that do not smoke. The data of each case is entered on one row of the spreadsheet.

![Data table](image)

In the *Chi-squared test* dialog box, one or two discrete variables with the classification data must be identified. Classification data may either be numeric or alphanumeric (string) values. If required, you can convert a continuous variable into a discrete variable using the CATEGORISE function (see p. 324) or IF function (see p. 325).

![Chi-squared test dialog box](image)

After you have completed the dialog box, click the OK button, or press the *Enter* key to obtain the frequency table with the relevant statistics.
Classification table

When you select the option **Show all percentages** in the results window, all percentages are shown in the table as follows:

In this example the number 42 in the upper left cell (for both Codes X and Coded Y equal to 0) is 67.7% of the row total of 62 cases; 75% of the column total of 56 cases and 42% of the grand total of 100 cases.

**Chi-squared test**

**Single classification factor**

- When you want to test the hypothesis that for one single classification table (e.g. gender), all classification levels have the same frequency, then identify only one discrete variable in the dialog form. In this case the null hypothesis is that all classification levels have the same frequency. If the calculated P-value is low (P<0.05), then you reject the null hypothesis and the alternative hypothesis that there is a significant difference between the frequencies of the different classification levels must be accepted.
• In a single classification table the *mode* of the observations is the most common observation or category (the observation with the highest frequency). A unimodal distribution has one mode; a bimodal distribution, two modes.

**Two classification factors**

• When you want to study the relationship between *two classification factors* (e.g. gender and profession), then identify the two discrete variables in the dialog form. In this case the null hypothesis is that the two factors are independent. If the calculated *P*-value is low (*P*<0.05), then the null hypothesis is rejected and you accept the alternative hypothesis that there is a relation between the two factors.

**Chi-squared test for trend**

If the table has two columns and three or more rows (or two rows and three or more columns), and the categories can be quantified, MedCalc will also perform a *Chi-squared test for trend*. The Cochran-Armitage test for trend (Cochran, 1954; Armitage, 1955) tests whether there is a linear trend between row (or column) number and the fraction of subjects in the left column (or top row). The Cochran-Armitage test for trend provides a more powerful test than the unordered independence test above.

If there is no meaningful order in the row (or column) categories, then you should ignore this calculation.

**Analysis of 2x2 table**

For a 2x2 table, MedCalc uses the "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011). The use of Yates' continuity correction is no longer recommended.

If the classification table is a 2x2 table then you should **not** use the *Chi-squared test* procedure when:

• the number of expected frequencies in the 2x2 table is low (in case the total number of observations is less than 20), the table should be tested using *Fisher's exact test* (see below);

• the two classification factors are not independent, or when you want to test the difference between proportions in related or paired observations (e.g. in studies in which patients serve as their own control), you must use the *McNemar test* (p. 143).

**Fisher’s exact test**

If you have a 2x2 frequency table with small numbers of expected frequencies (in case the total number of observations is less than 20), you should not perform the *Chi-squared test* as described above, but you should use *Fisher's exact test*.

In the *Fisher’s exact test* dialog box, two discrete dichotomous variables with the classification data must be identified. Classification data may either be numeric or alphanumeric (string) values. If required, you can convert a continuous variable into a dichotomous variable using the CATEGORISE function (see p. 324) or IF function (see p. 325).

For example: in a study including 20 patients, 9 women and 11 men, the success of a treatment is recorded (1 = successful, 0 = no success). Is there a difference between the success rate in men and women?

The data are entered as follows in the spreadsheet:
The dialog box for the Fisher’s exact test is completed as follows:

After you have completed the dialog box, click the OK button, or press the Enter key to obtain the frequency table with the relevant statistics.

**Classification table**

The program displays the 2x2 classification table.

When you select the option **Show all percentages** in the results window, all percentages are shown in the table as follows:
In this example the number 1 in the upper left cell (for Classification X equal to "F" and Classification Y equal to 0) is 12.5% of the row total of 8 cases; 11.1% of the column total of 9 cases and 5.0% of the grand total of 20 cases.

**P-value**

When the (two-sided) P-value (the probability of obtaining the observed result or a more extreme result) is less than the conventional 0.05, the conclusion is that there is a significant relationship between the two classification factors.

In the example? P=0.028 and the conclusion therefore is that the success rate in men and women differs (or that the success rate is related to gender).

**McNemar test**

The McNemar test is a test on a 2x2 classification table when the two classification factors are dependent, or when you want to test the difference between paired proportions, e.g. in studies in which patients serve as their own control, or in studies with “before and after” design.

In the McNemar test dialog box, two discrete dichotomous variables with related classification data must be identified. Classification data may either be numeric or alphanumeric (string) values. If required, you can convert a continuous variable into a dichotomous variable using the CATEGORISE function (see p. 324) or IF function (see p. 325).

The variables together cannot contain more than 2 different classification values.

For example, in a study a test is performed before treatment and after treatment in 20 patients. The results of the test are coded 0 and 1. Is there a significant change in the test result before and after treatment?

The data are entered as follows in the spreadsheet:
The dialog box for the McNemar test is completed as follows:

Select two discrete variables with related classification data. Classification data may either be numeric or alphanumeric (string) values, but both variables cannot contain more than 2 different classification values.

After you have completed the dialog box, click OK, or press the **Enter** key to obtain the classification table with the relevant statistics.

**Classification table**

The program displays the 2x2 classification table.
**Difference and P-value**

The program gives the difference between the proportions (expressed as a percentage) with 95% confidence interval. When the (two-sided) P-value is less than the conventional 0.05, the conclusion is that there is a significant difference between the two proportions.

In the example, 45% of cases were positive before treatment (Classification A = 1) and 35% were positive after treatment (Classification B = 1). The difference before and after treatment is -10% with 95% CI from -29.1% to 9.1%, which is not significant (P=0.625, n=20).

**Note**

The two-sided P-value is based on the cumulative binomial distribution.
The 95% confidence interval is calculated according to Sheskin, 2011.

**Cochran's Q test**

Cochran's Q test (Sheskin, 2004) is an extension to the McNemar test for related samples that provides a method for testing for differences between three or more matched sets of frequencies or proportions.

Example: 12 subjects are asked to perform 3 tasks. The outcome of each task is a dichotomous value, success or failure.

**How to enter the data in the spreadsheet**

The results are coded 0 for failure and 1 for success. In the example, subject 1 was successful in task 2 but failed tasks 1 and 3.
Required input

- Variables: the variables that contain the related observations. Data must be coded 0 to represent failure (or absence) and 1 to represent success (or presence).
- Filter: an optional data filter to include only a selected subgroup of cases.
- Options
  - Significance level: the desired significance level for the post-hoc test. If the Cochran's Q test results in a P-value less than this significance level, MedCalc performs a test for pairwise comparison of variables according to Sheskin, 2004.

Results

Frequencies
This table gives the frequencies of the values coded 0 (meaning absence or failure) and 1 (meaning presence or success) in the different variables, the proportion (expressed as a percentage) of values coded 1. Since Cochran's Q test is for related samples, cases with missing observations for one or more of the variables are excluded from the analysis, and the number of cases is the same for each variable.
Cochran's Q test

The null hypothesis for the Cochran's Q test is that there are no differences between the variables. If the calculated probability is low (P<0.05) the null-hypothesis is rejected, and it can be concluded that the proportions in at least 2 of the variables are significantly different from each other.

Multiple comparisons

When the Cochran's Q test is positive (P less than the selected significance level) then a minimum required difference for a significant difference between two proportions is calculated (Sheskin, 2011) and a table is displayed showing which of the proportions are significantly different from which other proportions.

Relative risk & Odds ratio

Use this procedure to compile a 2x2 table from the data and calculate the Relative risk and Odds ratio for the observed data.

How to enter the data in the spreadsheet

The calculation of Relative risk & Odds ratio requires two categorical variables, one for outcome and one for group. In the example we have a variable "Recurrence" for outcome and a variable "Treatment" for group.

Outcome is preferentially coded 0 for negative (the event of interest was not observed) and 1 for positive (the event of interest was observed). In the example disease recurrence is the event of interest and cases in which disease recurrence was observed have code 1 and cases in which disease recurrence was not observed have code 0 for the variable "Recurrence".

The variable for group can be coded freely, but should not define more than 2 groups. In the example, cases belonging to the treated group have code 1 and cases belonging to the placebo group have code 0 for the variable "Treatment".

Required input

- **Outcome**: select a dichotomous variable where a positive outcome is coded 1 and a negative outcome is coded 0.
- **Group**: select a variable with codes that identify 2 groups (e.g. treated and controls).
• **Filter**: an optional filter to include a subset of data in the analysis.

• **Options**:
  - **Relative risk**: option to calculate the Relative risk
    - Option: calculate Number Needed to Treat (NNT)
  - **Odds ratio**: option to calculate the Odds ratio

**Results**

![Relative risk & Odds ratio](image)

**Frequency table**

The 2x2 classification table.

**Selection of Exposed group**

MedCalc assumes the second group (in alphanumerical order) to be the exposed group by default. If in your data the first group is the exposed group, you can select this as the Exposed group and the results will be adapted accordingly.

**Relative risk**

The program reports the relative risk with its 95% confidence interval (Altman 1991, Daly 1998, Sheskin 2004). The relative risk is the ratio of the proportions of cases having a positive outcome in the two groups. The program also calculates the z-statistic and associated P-value. If P is less than 0.05 it can be concluded that the relative risk is significantly different from 1 and that there is an increased risk in one group compared to the other.

**Number Needed to Treat (NNT)**

The number needed to treat (NNT) is the estimated number of patients who need to be treated with the new treatment rather than the standard treatment for one additional patient to benefit (Altman 1998).

A negative number for the number needed to treat has been called the number needed to harm.

MedCalc uses the terminology suggested by Altman (1998) with NNT(Benefit) and NNT(Harm) being the number of patients needed to be treated for one additional patient to benefit or to be harmed respectively.

The 95% confidence interval is calculated according to Daly (1998) and is reported as suggested by Altman (1998).
Odds ratio

The program reports the odds ratio with its 95% confidence interval. MedCalc also reports the z-statistic and associated P-value. If P is less than 0.05 it can be concluded that the odds ratio is significantly different from 1 and that the odds in one group are higher than in the other.

Frequencies bar chart

Use the Frequencies bar chart command to graph categorical data.

Required input

In the Frequencies bar chart dialog box, one or two discrete variables with the classification data must be identified. Classification data may either be numeric or alphanumeric (string) values.

Graph types

Simple column chart (one classification factor). The chart contains a single bar for each category. The height of the bars is the number of cases in the category.

Clustered column (two classification factors). Like simple column chart, but containing a group of bars for each category in the first classification category. The height of the bars is the number of cases in the category.

Stacked column (two classification factors). Bar segments are stacked on top of one another. There is one bar stack for each category in the first classification factor. Segments within each stack represent the contribution of categories in the second classification factor.

100% Stacked column (two classification factors). Bar segments are stacked on top of one another, the total equals 100%. There is one bar stack for each category in the first classification factor. Segments within each stack represent the relative contribution of categories in the second classification factor.
Options
Relative frequency: option to represent the data as percentages, not counts. This option is applicable to the Simple and Clustered column charts only. The Stacked column graph always shows counts, the 100% Stacked column graph always shows percentages.

Example
Survival analysis

Kaplan-Meier survival curve

In clinical trials the investigator is often interested in the time until participants in a study present a specific event or endpoint. This event usually is a clinical outcome such as death, disappearance of a tumor, etc. The participants will be followed beginning at a certain starting-point, and the time will be recorded needed for the event of interest to occur.

Usually, the end of the study is reached before all participants have presented this event, and the outcome of the remaining patients is unknown. Also, the outcome is unknown of those participants who have withdrawn from the study. For all these cases the time of follow-up is recorded (censored data).

In MedCalc, these data can be analyzed by means of a *life-table*, or *Kaplan-Meier curve* (Altman, 1991), which is the most common method to describe survival characteristics. In order to be able to analyze the data, you need to enter the data in the spreadsheet as follows:

- in one column, a code can be entered to assign the case to a particular group (study group - control group).
- in a second column, the survival time must be recorded
- in a third column, it must be recorded whether or not the case has reached the endpoint (by entering the code 1) or whether the time is censored, i.e. the outcome is unknown (by entering the code 0);

The order of these columns is of course not important. Also, the rows do not have to be sorted in any way.

The case in row 1 belonged to group 1, and reached the endpoint after 10 units of time. The case in row 3 also belonged to group 1 and was followed for 9 units of time. The outcome of this case is unknown (withdrawn from study, or end of study) (data from Freireich et al., Blood 1963; 21:699-716).

From these data, MedCalc can easily calculate and construct the Kaplan-Meier curve. After you have selected the *Kaplan-Meier survival curve* option in the *Statistics* menu, the following dialog box is displayed:
In this dialog box the following data need to be entered:

- **Survival time**
  The name of the variable containing the time to reach the event of interest, or the time of follow-up.

- **Endpoint**
  The name of a variable containing codes 1 for the cases that reached the endpoint, or code 0 for the cases that have not reached the endpoint, either because they withdrew from the study, or the end of the study was reached.
  If your data are coded differently, you can use the Define status (see p. 105) tool to recode your data.

- **Factor**
  For Factor select a qualitative or discrete variable (grouping variable - GROUP in the example). This qualitative factor may either be character or numeric codes. These codes are used to break-up the data into several subgroups. If you want to study the effect of a continuous variable on survival time, you can convert this continuous variable into a discrete variable using the CATEGORISE function (see p. 324) or IF function (see p. 325).
  MedCalc will allow comparison of survival curves for up to 6 subgroups.
  If no Factor variable is selected, then MedCalc will display only one survival curve (all data are considered to belong to one group).

- **Filter**
  An optional data filter to include only a selected subgroup of cases in the analysis.

- **Options**
  - **Linear trend for factor levels**: Allows testing for a linear trend across levels of the factor. It is appropriate if factor levels have a natural ordering (for example, factor codes represent doses applied to different groups). Kaplan-Meier assumes that the factor levels are equally spaced.
  - **Graph**:
    - Survival probability (%): plot Survival probability (%) against time (descending curves)
    - 100 - Survival probability (%): plot 100 - Survival probability (%) against time (ascending curves)
  - **Include 95% CI in graph**: Option to plot the 95% confidence interval for the survival curves.
  - **Mark censored data in graph**: Mark censored data in the graph with a small vertical line.
  - **Number at risk table below graph**: Shows a table below the graph with the number of subjects at risk.

When all data have been entered click OK, and the program will open 2 windows: one with the survival graphs and one with the results in a text window.
Graph

The survival curves are drawn as a step function, as shown in the following example:

With the option “Include 95% CI in graph” selected, the graph looks like this:

When the option "Number at risk table below graph" is selected, the result is:
Results

Cases summary
This table shows the number of cases that reached the endpoint (Number of events), the number of cases that did not reach the endpoint (Number censored), and the total number of cases.

Mean and median survival
The mean and median survival time are reported with their 95% confidence interval (CI).
The mean survival time is estimated as the area under the survival curve in the interval 0 to \( t_{\text{max}} \) (Klein & Moeschberger, 2003). The median survival is the smallest time at which the survival probability drops to 0.5 (50%) or below. If the survival curve does not drop to 0.5 or below then the median time cannot be computed. The median survival time and its 95% CI is calculated according to Brookmeyer & Crowley, 1982.

Survival table
At each observed timepoint, the survival proportions (with standard error) are listed for all groups, as well as the overall survival proportion.

Comparison of survival curves (Logrank test)
When you scroll down (press the Page Down key), you see the result of the logrank test for the comparison between the two survival curves: 9 cases in group 1 and 21 cases in group 2 presented the outcome of interest, the chi-squared statistic was 16.79 with associated P-value of less than 0.0001. The conclusion therefore is that, statistically, the two survival curves differ significantly, or that the grouping variable has a significant influence on survival time.
Hazard ratios with 95% Confidence Interval

When you have specified a factor then MedCalc also calculates the hazard ratios with 95% confidence interval (CI). Hazard is a measure of how rapidly the event of interest occurs. The hazard ratio compares the hazards in two groups.

In the example the hazard ratio is 5.1462 so that the estimated relative risk of the event of interest occurring in group 2 is 5.1462 higher than in group 1. This hazard ratio is significantly different from the value 1 (corresponding to equal hazards) since the confidence interval 2.3506 to 11.2663 does not include the value 1.

Note that the computation of the hazard ratio assumes that the ratio is consistent over time, so therefore if the survival curves cross, the hazard ratio statistic should be ignored.

The hazard ratios and confidence intervals are calculated according to Altman et al., 2000.

Logrank test for trend

If more than two survival curves are compared, and there is a natural ordering of the groups, then MedCalc can also perform the logrank test for trend. This tests the probability that there is a trend in survival scores across the groups.

Cox proportional-hazards regression

Whereas the Kaplan-Meier method with log-rank test is useful for comparing survival curves in two or more groups, Cox proportional-hazards regression allows analyzing the effect of several risk factors on survival.

The probability of the endpoint (death, or any other event of interest, e.g. recurrence of disease) is called the hazard. The hazard is modeled as:

\[ H(t) = H_0(t) \times \exp(b_1X_1 + b_2X_2 + b_3X_3 + \cdots + b_kX_k) \]

where \( X_1 \ldots X_k \) are a collection of predictor variables and \( H_0(t) \) is the baseline hazard at time \( t \), representing the hazard for a person with the value 0 for all the predictor variables.

By dividing both sides of the above equation by \( H_0(t) \) and taking logarithms, we obtain:
\[ \ln \left( \frac{H(t)}{H_0(t)} \right) = b_1 X_1 + b_2 X_2 + b_3 X_3 + \cdots + b_k X_k \]

We call \( H(t) / H_0(t) \) the hazard ratio. The coefficients \( b_1, \ldots, b_k \) are estimated by Cox regression and can be interpreted in a similar manner to that of multiple logistic regression.

Suppose the covariate (risk factor) is dichotomous, and that the covariate is coded 1 if present and 0 if absent. Then the quantity \( \exp(b) \) can be interpreted as the instantaneous relative risk of an event, at any time, for an individual with the risk factor present compared with an individual with the risk factor absent, given both individuals are the same on all other covariates.

Suppose the covariate is continuous, then the quantity \( \exp(b) \) is the instantaneous relative risk of an event, at any time, for an individual with an increase of 1 in the value of the covariate compared with another individual, given both individuals are the same on all other covariates.

**Required input**

- **Survival time**: The name of the variable containing the time to reach the event of interest, or the time of follow-up.
- **Endpoint**: The name of a variable containing codes 1 for the cases that reached the endpoint, or code 0 for the cases that have not reached the endpoint, either because they withdrew from the study, or the end of the study was reached.
- **Predictor variables**: Names of variables that you expect to predict survival time. The Cox proportional regression model assumes that the effects of the predictor variables are constant over time. Furthermore, there should be a linear relationship between the endpoint and predictor variables. Predictor variables that have a highly skewed distribution may require logarithmic transformation to reduce the effect of extreme values. Logarithmic transformation of a variable \( \text{var} \) can be obtained by entering \( \text{LOG(var)} \) as predictor variable.

**Filter**: A data filter to include only a selected subgroup of cases in the graph.

**Options**

- Method: select the way independent variables are entered into the model.
  - Enter: enter all variables in the model in one single step, without checking
  - Forward: enter significant variables sequentially
  - Backward: first enter all variables into the model and next remove the non-significant variables sequentially
  - Stepwise: enter significant variables sequentially; after entering a variable in the model, check and possibly remove variables that became non-significant.
- Enter variable if \( P< \)
  - A variable is entered into the model if its associated significance level is less than this \( P \)-value.
- Remove variable if \( P> \)
A variable is removed from the model if its associated significance level is greater than this P-value.

**Categorical**: click this button to identify nominal categorical variables.

**Graph options**
- **Graph**:
  - Survival probability (%): plot Survival probability (%) against time (descending curves)
  - 100 - Survival probability (%): plot 100 - Survival probability (%) against time (ascending curves)
- **Graph subgroups**: here you can select one of the predictor variables. The graph will display different survival curves for all values in this covariate (which must be categorical and may not contain more than 8 categories). If no covariate is selected here, then the graph will display the survival at mean of the covariates in the model.

![Subgroup variable dialog box](image)

**Results**

In the example (taken from Bland, 2000), “survival time” is the time to recurrence of gallstones following dissolution (variable *Time*). Recurrence is coded in the variable *Recurrence* (1 = yes, 0 = No). Predictor variables are *Dis* (= number of months previous gallstones took to dissolve), *Mult* (1 in case of multiple previous gallstones, 0 in case of single previous gallstones), and *Diam* (maximum diameter of previous gallstones).
Cases summary

This table shows the number of cases that reached the endpoint (Number of events), the number of cases that did not reach the endpoint (Number censored), and the total number of cases.

Overall Model Fit

The Chi-squared statistic tests the relationship between time and all the covariates in the model.

Coefficients and Standard Errors

Using the Forward selection method, the two covariates Dis and Mult were entered in the model which significantly (0.0096 for Dis and 0.0063 for Mult) contribute to the prediction of time.

MedCalc lists the regression coefficient b, its standard error, Wald statistic (b/SE)^2, P value, Exp(b) and the 95% confidence interval for Exp(b).

The coefficient for months for dissolution (continuous variable Dis) is 0.0429. Exp(b) = Exp(0.0429) is 1.0439 (with 95% Confidence Interval 1.0107 to 1.0781), meaning that for an increase of 1 month to dissolution of previous gallstones, the hazard ratio for recurrence increases by a factor 1.04. For 2 months the hazard ratio increases by a factor 1.04^2.

The coefficient for multiple gallstones (dichotomous variable Mult) is 0.9335. Exp(b) = Exp(0.9335) is 2.6208 (with 95% Confidence Interval 1.3173 to 5.2141), meaning that a case with previous gallstones is 2.62 more likely to have a recurrence than a case with a single stone.

Variables not included in the model

The variable Diam was found not to significantly contribute to the prediction of time, and was not included in the model.
Baseline cumulative hazard function

Finally, the program lists the baseline cumulative hazard \( H_0(t) \), with the cumulative hazard and survival at mean of all covariates in the model.

The baseline cumulative hazard can be used to calculate the survival probability \( S(t) \) for any case at time \( t \):

\[
S(t) = \exp(-H_0(t) \times PI)
\]

where PI is a prognostic index:

\[
PI = x_1b_1 + x_2b_2 + x_3b_3 + \cdots + x_kb_k
\]

Graph

The graph displays the survival curves for all categories of the categorical variable Mult (1 in case of multiple previous gallstones, 0 in case of single previous gallstones), and for mean values for all other covariates in the model.

If no covariate was selected for Graph – Subgroups, or if the selected variable was not included in the model, then the graph displays a single survival curve at mean of all covariates in the model.
Meta-analysis

Meta-analysis: introduction

A meta-analysis integrates the quantitative findings from separate but similar studies and provides a numerical estimate of the overall effect of interest (Petrie et al., 2003).

Different weights are assigned to the different studies for calculating the summary or pooled effect. The weighing is related with the inverse of the standard error (and therefore indirectly to the sample size) reported in the studies. Studies with smaller standard error and larger sample size are given more weight in the calculation of the pooled effect size.

The effect of interest can be:

- an average of a continuous variable
- a correlation between two variables
- an odds ratio, suitable for analyzing retrospective studies
- a relative risk (risk ratio) or risk difference, suitable for analyzing prospective studies
- a proportion

The agreement or disagreement between the studies is examined using different measures of heterogeneity.

Fixed and random effects model

Under the fixed effects model, it is assumed that the studies share a common true effect, and the summary effect is an estimate of the common effect size.

Under the random effects model the true effects in the studies are assumed to vary between studies and the summary effect is the weighted average of the effects reported in the different studies (Borenstein et al., 2009).

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree when there is no heterogeneity. When heterogeneity is present (see below) the random effects model should be the preferred model.

Heterogeneity

Cohran's Q

Q is the weighted sum of squares on a standardized scale. It is reported with a P value with low P-values indicating presence of heterogeneity. This test however is known to have low power to detect heterogeneity and it is suggested to use a value of 0.10 as a cut-off for significance (Higgins et al., 2003). Conversely, Q has too much power as a test of heterogeneity if the number of studies is large.

I^2 statistic

I^2 is the percentage of observed total variation across studies that is due to real heterogeneity rather than chance. It is calculated as $I^2 = 100 \times (Q - df)/Q$, where Q is Cochran's heterogeneity statistic and df the degrees of freedom. Negative values of $I^2$ are put equal to zero so that $I^2$ lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity (Higgins et al., 2003).

Forest plot

The results of the different studies, with 95% CI, and the overall effect (under the fixed and random effects model) with 95% CI are illustrated in a graph called "forest plot", for example:
In this example the markers representing the effect size all have the same size. Optionally, the marker size may vary in size according to the weights assigned to the different studies. In addition, the pooled effects can be represented using a diamond. The location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate, for example:

**Funnel plot**

In a funnel plot (Egger et al., 1997) treatment effect is plotted on the horizontal axis and MedCalc plots the standard error on the vertical axis (Sterne & Egger, 2001). Publication bias results in asymmetry of the funnel plot. If publication bias is present, the smaller studies will show the larger effects. See Sterne et al. (2011) for interpreting funnel plot asymmetry. The funnel plot may not always be a reliable tool, in particular when the number of studies included in the analysis is small.

Example of symmetrical funnel plot

Example of asymmetrical funnel plot
Meta-analysis: continuous measure

For meta-analysis of studies with a continuous measure (comparison of means between treated cases and controls), MedCalc uses the Hedges g (Hedges & Olkin, 1985) statistic as a formulation for the standardized mean difference under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary standardized mean difference under the random effects model (DerSimonian & Laird, 1986).

The standardized mean difference Hedges g is the difference between the two means divided by the pooled standard deviation, with a correction for small sample bias:

\[
s_{pooled} = \sqrt{\frac{(n_1 - 1)s_1^2 + (n_2 - 1)s_2^2}{n_1 + n_2 - 2}}
\]

\[
g = \frac{\bar{x}_1 - \bar{x}_2}{s_{pooled}}
\]

\[
J(n) = \frac{\Gamma(n/2)}{\sqrt{n/2} \Gamma((n-1)/2)}
\]

\[
g_{corrected} = g \times J(n_1 + n_2 - 2)
\]

where \(\Gamma\) is the Gamma function.

**Required input**

The data of different studies can be entered as follows in the spreadsheet:

In this example, in a first study 40 cases were treated and the mean of the parameter of interest was 23.52 with a standard deviation of 1.38. In 40 control cases the mean was 20.12 with standard deviation of 3.36. On the next rows of the spreadsheet follow the data of 4 other studies.

The dialog box for “Meta-analysis: continuous measure” can then be completed as follows:
• **Studies**: a variable containing an identification of the different studies.

• Intervention groups & Control groups:
  ▪ **Number of cases, Mean, Standard deviation**: variables containing the number of cases, mean and standard deviation observed in the different studies, in the intervention groups and control groups respectively.

• **Filter**: a filter to include only a selected subgroup of studies in the meta-analysis.

• **Options**
  ▪ **Forest plot**: creates a forest plot.
    – **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    – **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
    – **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
    – **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
  ▪ **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).
The program lists the results of the individual studies: number of positive cases, total number of cases, the standardized mean difference (SMD) with 95% CI.

The total Standardized Mean Difference with 95% CI is given both for the Fixed effects model and the Random effects model. If the value 0 is not within the 95% CI, then the SMD is statistically significant at the 5% level (P<0.05).

Cohen’s rule of thumb for interpretation of the SMD statistic is: a value of 0.2 indicates a small effect, a value of 0.5 indicates a medium effect and a value of 0.8 or larger indicates a large effect.

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and I². When heterogeneity is present the random effects model should be the preferred model.

**Meta-analysis: correlation**

MedCalc uses the Hedges-Olkin (1985) method for calculating the weighted summary Correlation coefficient under the fixed effects model, using a Fisher Z transformation of the correlation coefficients. Next the heterogeneity statistic is incorporated to calculate the summary Correlation coefficient under the random effects model (DerSimonian and Laird, 1986).

**How to enter data**

The data of different studies can be entered as follows in the spreadsheet:
Required input
The dialog box for "Meta-analysis: correlation" can then be completed as follows:

- **Studies**: a variable containing an identification of the different studies.
- **Data**
  - **Number of cases**: a variable containing the total number of cases included in the different studies.
  - **Correlation coefficients**: a variable containing the correlation coefficient reported in the different studies.
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
    - **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    - **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
    - **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
    - **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
  - **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).
Results

The program lists the results of the individual studies included in the meta-analysis: number of cases, the correlation coefficient with 95% CI.

The pooled correlation coefficient with 95% CI is given both for the Fixed effects model and the Random effects model. The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran’s Q and $I^2$. When heterogeneity is present the random effects model should be the preferred model.

Meta-analysis: proportion

MedCalc uses a Freeman-Tukey transformation (arcsine square root transformation; Freeman and Tukey, 1950) to calculate the weighted summary Proportion under the fixed and random effects model (DerSimonian & Laird, 1986).

How to enter data

The data of different studies can be entered as follows in the spreadsheet:
Required input
The dialog box for "Meta-analysis: proportion" can then be completed as follows:

- **Studies**: a variable containing an identification of the different studies.
- **Data**
  - **Total number of cases**: a variable containing the total number of cases in the different studies.
  - **Number of positive cases**: a variable containing the number of positive cases in the different studies.
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
    - **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    - **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
    - **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
    - **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
  - **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).
Results

The program lists the proportions (expressed as a percentage), with their 95% CI, found in the individual studies included in the meta-analysis.

The pooled proportion with 95% CI is given both for the Fixed effects model and the Random effects model. The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and I². When heterogeneity is present the random effects model should be the preferred model.

Meta-analysis: relative risk

MedCalc uses the Mantel-Haenszel method (based on Mantel & Haenszel, 1959) for calculating the weighted pooled relative risk under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary relative risk under the random effects model (DerSimonian & Laird, 1986).

How to enter data

The data of different studies can be entered as follows in the spreadsheet:
Required input

The dialog box for "Meta-analysis: relative risk" can then be completed as follows:

- **Studies**: a variable containing an identification of the different studies.
- **Intervention groups**
  - Total number of cases: a variable containing the total number of cases in the intervention groups of the different studies
  - Number with positive outcome: a variable containing the number of cases with positive outcome in the intervention groups of the different studies
- **Control groups**
  - Total number of cases: a variable containing the total number of cases in the control groups of the different studies
  - Number with positive outcome: a variable containing the number of cases with positive outcome in the control groups of the different studies
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
    - Marker size relative to study weight: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
Plot pooled effect - fixed effects model: option to include the pooled effect under the fixed effects model in the forest plot.

Plot pooled effect - random effect model: option to include the pooled effect under the random effects model in the forest plot.

Diamonds for pooled effects: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).

Funnel plot: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).

Results

The program lists the results of the individual studies: number of positive cases, total number of cases, and the relative risk with 95% CI.

The pooled relative risk with 95% CI is given both for the Fixed effects model and the Random effects model. If the value 1 is not within the 95% CI, then the relative risk is statistically significant at the 5% level (P<0.05).

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and \( I^2 \). When heterogeneity is present the random effects model should be the preferred model.

Note that when a study reports no events (or all events) in both intervention and control groups the study provides no information about relative probability of the event and is automatically omitted from the meta-analysis (Higgins & Green, 2011).

Meta-analysis: risk difference

MedCalc uses the Mantel-Haenszel method (based on Mantel & Haenszel, 1959) for calculating the weighted pooled risk difference under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary risk difference under the random effects model (DerSimonian & Laird, 1986).
How to enter data

The data of different studies can be entered as follows in the spreadsheet:

![Spreadsheet](image1.png)

Required input

The dialog box for "Meta-analysis: risk difference" can then be completed as follows:

![Dialog box](image2.png)

- **Studies**: a variable containing an identification of the different studies.
- **Intervention groups**
  - **Total number of cases**: a variable containing the total number of cases in the intervention groups of the different studies
  - **Number with positive outcome**: a variable containing the number of cases with positive outcome in the intervention groups of the different studies
- **Control groups**
  - **Total number of cases**: a variable containing the total number of cases in the control groups of the different studies
  - **Number with positive outcome**: a variable containing the number of cases with positive outcome in the control groups of the different studies
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
- **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.

- **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.

- **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.

- **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).

- **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).

**Results**

The program lists the results of the individual studies: number of positive cases, total number of cases, and the risk difference with 95% CI.

The pooled risk difference with 95% CI is given both for the Fixed effects model and the Random effects model. If the value 0 is not within the 95% CI, then the risk difference is statistically significant at the 5% level (P<0.05).

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and I². When heterogeneity is present the random effects model should be the preferred model.
Meta-analysis: odds ratio

MedCalc uses the Mantel-Haenszel method (Mantel & Haenszel, 1959) for calculating the weighted pooled odds ratio under the fixed effects model. Next the heterogeneity statistic is incorporated to calculate the summary odds ratio under the random effects model (DerSimonian & Laird, 1986).

How to enter data

The data of different studies can be entered as follows in the spreadsheet:

![Spreadsheet example](image)

In this example, in a first study 73 cases were treated with an active substance and of these, 15 had a positive outcome. 23 cases received a placebo and 3 of these had a positive outcome. On the next rows of the spreadsheet follow the data of 4 other studies.

Required input

The dialog box for “Meta-analysis: odds ratio” can then be completed as follows:

![Dialog box example](image)

- **Studies**: a variable containing an identification of the different studies.
- **Intervention groups**
  - **Total number of cases**: a variable containing the total number of cases in the intervention groups of the different studies
  - **Number with positive outcome**: a variable containing the number of cases with positive outcome in the intervention groups of the different studies

- **Control groups**
  - **Total number of cases**: a variable containing the total number of cases in the control groups of the different studies
  - **Number with positive outcome**: a variable containing the number of cases with positive outcome in the control groups of the different studies
• Control groups
  ▪ **Total number of cases**: a variable containing the total number of cases in the control groups of the different studies
  ▪ **Number with positive outcome**: a variable containing the number of cases with positive outcome in the control groups of the different studies

• Filter: a data filter to include only a selected subgroup of studies in the meta-analysis.

• Options
  ▪ **Forest plot**: creates a forest plot.
    − **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    − **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
    − **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
    − **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
  ▪ **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).

### Results

The program lists the results of the individual studies: number of positive cases, total number of cases, and the odds ratio with 95% CI.

The pooled odds ratio with 95% CI is given both for the Fixed effects model and the Random effects model. If the value 1 is not within the 95% CI, then the Odds ratio is statistically significant at the 5% level (P<0.05).

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and $I^2$. When heterogeneity is present the random effects model should be the preferred model.

Note that when a study reports no events (or all events) in both intervention and control groups the study provides no information about relative probability of the event and is automatically omitted from the meta-analysis (Higgins & Green, 2011).
Meta-analysis: area under ROC curve

MedCalc uses the methods described by Zhou et al. (2002) for calculating the weighted summary Area under the ROC curve under the fixed effects model and random effects model.

How to enter data
The data of different studies can be entered as follows in the spreadsheet (example taken from Zhou et al., 2002):

![Spreadsheet example](image)

Required input
The dialog box for “Meta-analysis: Area under ROC curve” can then be completed as follows:

![Dialog box example](image)

- **Studies**: a variable containing an identification of the different studies.
- **Data**
  - **Area under ROC curve (AUC)**: a variable containing the Area under the ROC curve reported in the different studies.
  - **Standard error of AUC**: a variable containing the Standard error of the Area under the ROC curve reported in the different studies.
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
    - **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    - **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
- **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
- **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
- **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).

## Results

The program lists the results of the individual studies included in the meta-analysis: the area under the ROC curve, its standard error and 95% confidence interval.

The pooled Area under the ROC curve with 95% CI is given both for the Fixed effects model and the Random effects model (Zhou et al., 2002).

The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cohran's Q and $I^2$. When heterogeneity is present the random effects model should be the preferred model.

### Meta-analysis: generic inverse variance method

If none of the above procedures for meta-analysis is applicable or suitable, you can use the "generic inverse variance method" procedure. In this procedure estimates and their standard errors are entered directly into MedCalc. For ratio measures of intervention effect, the data should be entered as natural logarithms (for example as a log Hazard ratio and the standard error of the log Hazard ratio).

In the inverse variance method the weight given to each study is the inverse of the variance of the effect estimate (i.e. one over the square of its standard error). Thus larger studies are given more weight than smaller studies, which have larger standard errors. This choice of weight minimizes the imprecision (uncertainty) of the pooled effect estimate.

### How to enter data

The data of different studies can be entered as follows in the spreadsheet:
Required input

- **Studies**: a variable containing an identification of the different studies.
- **Data**
  - **Estimate**: a variable containing the estimate of interest reported in the different studies.
  - **Standard error**: a variable containing the Standard error of the estimate reported in the different studies.
- **Filter**: a data filter to include only a selected subgroup of studies in the meta-analysis.
- **Options**
  - **Forest plot**: creates a forest plot.
    - **Marker size relative to study weight**: option to have the size of the markers that represent the effects of the studies vary in size according to the weights assigned to the different studies. You can choose the fixed effect model weights or random effect model weights.
    - **Plot pooled effect - fixed effects model**: option to include the pooled effect under the fixed effects model in the forest plot.
    - **Plot pooled effect - random effect model**: option to include the pooled effect under the random effects model in the forest plot.
    - **Diamonds for pooled effects**: option to represent the pooled effects using a diamond (the location of the diamond represents the estimated effect size and the width of the diamond reflects the precision of the estimate).
  - **Funnel plot**: creates a funnel plot to check for the existence of publication bias (see Meta-analysis: introduction, p. 161).
Results

The program lists the results of the individual studies included in the meta-analysis: the estimate and 95% confidence interval. The pooled value for the estimate, with 95% CI, is given both for the Fixed effects model and the Random effects model. Under the fixed effects model, it is assumed that the studies share a common true effect, and the summary effect is an estimate of the common effect size. Under the random effects model (DerSimonian and Laird) the true effects in the studies are assumed to vary between studies and the summary effect is the weighted average of the effects reported in the different studies (Borenstein et al., 2009). The random effects model will tend to give a more conservative estimate (i.e. with wider confidence interval), but the results from the two models usually agree where there is no heterogeneity. See the introduction (p. 160) for interpretation of the heterogeneity statistics Cochrane’s Q and $I^2$. When heterogeneity is present the random effects model should be the preferred model.

Forest plot

The Forest plot shows the estimate (with 95% CI) found in the different studies included in the meta-analysis, and the overall effect with 95% CI.
Funnel plot

A funnel plot is a graphical tool for detecting bias in meta-analysis (see Meta-analysis: introduction, p. 161).

Note that when the option “Data are entered as natural logarithms” was selected (see above), then the Standard Errors on the Y-axis are natural logarithms.
Serial measurements

Description
When serial measurements have been performed, e.g. in a glucose tolerance test, it is often useful to summarize the data on every subject into one or more summarizing measures (Bland 2000; Mathews et al., 1990), such as:

- height of peak (maximum value)
- time to reach peak
- difference last-first value
- area under the curve.

These summary measures can be obtained, and analyzed statistically, with the Serial measurements command. The program will create a graph for the observations, and perform an appropriate statistical test to evaluate whether the summary measure differs between the different subgroups.

Data input
While for any other statistical procedure in MedCalc, the data of one case have to be entered on one single row of the spreadsheet, for serial measurements MedCalc requires the data for all cases to be entered in one single column (Value in the example). Other columns in the spreadsheet must contain:

- a variable for the time: time should be entered as numbers and should be expressed in the same unit (e.g. hours, days); time intervals can be unequal
- a categorical variable that identifies cases
- an (optional) categorical variable that identifies the group a case belongs to.

In the example, case 1 belongs to groups "Malabsorption" and the value 0.08 was measured at time 0, value 5.70 at time 30 and 3.22 at time 45.
The dialog box

Variable Y (data): this variable contains the serial measurements of all cases.
Variable X (time): this variable contains the time of the different measurements.
Case identification: a categorical variable containing case identification data.
Groups: a categorical variable containing group identification data.
Summary measure: here you select the summary measure of interest for statistical analysis
- Minimum, and Time to reach minimum
- Maximum, and Time to reach maximum
- First observation, Last observation
- Difference Last-First observation
- % Change Last-First observation, calculated as 100x(Last-First)/First
  Note that in order to calculate this summary measure, the first observation should never be equal to zero.
- Maximum difference with first observation
- % Maximum difference with first observation, calculated as 100x(Max difference/First )
  Note that in order to calculate this summary measure, the first observation should never be equal to zero.
- Time-weighted average is calculated as the case AUC (baseline 0) divided by its total time interval (time of last observation minus time of first observation). If there is only one observation, this value is taken as the time-weighted average.
- Area under the curve (AUC)
  The area under the curve can be calculated in 3 different ways, depending on what is taken as the baseline value: 0, first observation, or minimum (when the first observation is taken as the baseline value, the area under the curve can be a negative number).
  Note that for the AUC, MedCalc requires that for all cases the first and last observations are set at the same time. If this is not the case, the alternative is to use the Time-weighted average as a summary measure.
- % Time above, above or equal to, below, or below or equal to a threshold value.

Options
- Left-align time: left-align time by subtracting the first time value of a case from all other time values of that case. As a result, the start time of each case is set at 0.
**Statistical analysis**

- **Automatic**: let MedCalc decide how to analyze the data. If this option is selected, MedCalc will analyze the summary statistics in the different groups and perform a test for Normal distribution (the test for Normal distribution is performed on the whole sample, after the values are transformed, per group, to z-scores). If the data have a Normal distribution, the software will perform a parametric test. If the data do not have a Normal distribution, the software will attempt a Logarithmic transformation. If the data have a Normal distribution after logarithmic transformation, a statistical test will be performed on the log transformed data; if not, a non-parametric test will be used on the non-transformed data.

- **Parametric test**: assume the summary measure has a Normal distribution and use a parametric test

- **Parametric test after Logarithmic transformation**: perform a Logarithmic transformation on the summary measure and then do a parametric test.

- **Non-parametric test**: use a non-parametric test.

For a parametric test, MedCalc uses the t-test when there are 2 groups or One-way analysis of variance (ANOVA) when there are more than 2 groups.

For a non-parametric test, MedCalc uses the Mann-Whitney when there are 2 groups or the Kruskal-Wallis test when there are more than 2 groups.

**Test for Normal distribution**: the option to select a test for Normal distribution is only available when you select "Automatic" statistical analysis.

**Results**

The results window displays the statistics (sample size, mean, SD, etc.) for the selected summary measure in the different subgroups.

Next, a statistical test is performed to test the hypothesis that there is no difference between the subgroups. If the resulting P-value is less than 0.05, the conclusion is that there is a significant difference of the summary measure between the different subgroups.
Graph

The Serial measurements diagram plots the serial data consecutively, for every case.

If there are many cases, you may want to create different graphs for each subgroup. To create a serial measurements graph for all cases in the "normal" group, enter the following in the Select box:
This gives the following graph:

For the “Malabsorption” group, you enter:

This gives the following graph:
Reference intervals

Reference interval

A Reference interval (Reference range, Normal range) can be calculated using the following two methods: (a) using the Normal distribution, (b) using a non-parametrical percentile method, and (c) optionally a "robust method" as described in the CLSI Guidelines C28-A3.

In the dialog box you identify the variable with the measurements. You can click the button to obtain a list of variables. In this list you can select a variable by clicking the variable's name. You can also enter a data filter in the Filter field, in order to include only a selected subgroup of measurements in the statistical procedure, as described in the Introduction part of this manual.

Options

- **Reference interval**: select a 90%, 95%, 99%, 99.9% or 99.99% reference interval. A 95% interval is the most usual and preferred setting.
- **Double sided, left or right sided**: Select Double sided when there is both a lower and upper limit of normality (both low and high values are suspicious). Select Left sided when there is only a lower limit of normality and no upper limit of normality (only low values are suspicious). Select Right sided when there is only an upper limit of normality and no lower limit of normality (only high values are suspicious).
Test for outliers: select the method based on Reed et al. (1971) or Tukey (1977) to automatically check the measurements for outliers (alternatively select none for no outlier testing). The method by Reed et al. will test only the minimum and maximum observations; the Tukey test can identify more values as outliers. The tests will create a list of possible outlying observations, but these will not automatically be excluded from the analysis. The possible outliers should be inspected by the investigator who can decide to exclude the values (see Exclude & Include, p. 51).

Follow CLSI guidelines for percentiles and their CIs: select this option to follow the NCCLS and Clinical and Laboratory Standards Institute (CLSI) guidelines C28-A2 and C28-A3 for estimating percentiles and their 90% confidence intervals. In these guidelines, percentiles are calculated as the observations corresponding to rank \( r=p*(n+1) \). Also for the 90% confidence intervals of the reference limits the CLSI guidelines are followed and conservative confidence intervals are calculated using integer ranks (and therefore the confidence intervals are at least 90% wide). If you do not select this option, MedCalc calculates percentiles as the observations corresponding to rank \( r=p*n+0.5 \) (Lentner, 1982; Schoonjans et al., 2011), and calculates a less conservative and more precise confidence interval using an iterative method.

Robust method: select this option to calculate the reference limits with the "robust method" (CLSI Guidelines C28-A3). Recommended for smaller sample sizes (less than 120). With the Robust method, the confidence intervals for the reference limits are estimated using bootstrapping (percentile interval method, Efron & Tibshirani, 1993). Click the Advanced... button for bootstrapping settings such as number of replications and random-number seed.

Logarithmic transformation

Box-Cox transformation: this will allow to perform a Box-Cox transformation with the following parameters:
- **Lambda**: the power parameter \( \lambda \)
- **Shift parameter**: the shift parameter is a constant \( c \) that needs to be added to the data when some of the data are negative.
- **Button Get from data**: click this button to estimate the optimal value for Lambda, and suggest a value for the shift parameter \( c \) when some of the observations are negative. The program will suggest a value for Lambda with 2 to 3 significant digits.

The Box-Cox transformation is defined as follows:
\[
x(\lambda) = \frac{(x+c)^\lambda - 1}{\lambda} \quad \text{when } \lambda \neq 0
\]
\[
x(\lambda) = \log(x+c) \quad \text{when } \lambda = 0
\]

When you perform a Box-Cox transformation, MedCalc will automatically transform the measurements with the selected parameters and will back-transform the results to the original scale for presentation.

Shapiro-Wilk test, Shapiro-Francia test, Kolmogorov-Smirnov test, Chi-squared test, or D'Agostino-Pearson test for Normal distribution (see p. 70).

Graph: graph option (see below).

Advanced: bootstrapping options for the calculation of confidence intervals with the Robust method.

Results

The results window for Reference interval displays the following information:
Sample size: the number of cases N is the number of numerical entries for the measurements variable that fulfill the data filter.

Range: the lowest and highest value of all observations.

Arithmetic mean: the arithmetic mean is the sum of all observations divided by the number of observations.

Median: when you have 100 observations, and these are sorted from smaller to larger, then the median is equal to the middle value. If the distribution of the data is Normal, then the median is equal to the arithmetic mean.

Standard Deviation: the standard deviation (SD) is the square root of the variance. When the distribution of the observations is Normal, then 95% of observations are located in the interval Mean ± 2SD.

Skewness: degree of symmetry of the sample distribution (see p. 73).

Kurtosis: degree of tailedness of the sample distribution (see p. 74).

Test for Normal Distribution: The result of this test is expressed as 'accept Normality' or 'reject Normality', with P value. If P is higher than 0.05, it may be assumed that the data follow a Normal distribution and the conclusion 'accept Normality' is displayed. If P is less than 0.05, then the hypothesis that the distribution of the observations in the sample is Normal, should be rejected, and the conclusion 'reject Normality' is displayed.

Logarithmic transformation
If the option Logarithmic transformation was selected, the program will display the back-transformed results. The back-transformed mean is named the Geometric mean. The Standard deviation cannot be back-transformed meaningfully and is not reported.

Suspected outliers
The program produces a list of possible outliers, detected by the methods based on Reed et al. (1971) or Tukey (1977). The method by Reed et al. tests only the minimum and maximum observations; the Tukey test can identify more values as outliers. Note that this does not automatically exclude any values from the analysis. The observations should be further inspected by the investigator who can decide to exclude the values. Click on the listed values, which are displayed as hyperlinks, to show the corresponding data in the spreadsheet (see Exclude & Include, p. 51).
Reference interval

The program will give the 90, 95, 99, 99.9 or 99.99% Reference interval, double sided or left or right sided only, as selected in the dialog box.

The reference interval is calculated using 3 different methods: (a) using the Normal distribution (Bland 2000; CLSI 2008), (b) using a non-parametrical percentile method, and (c) optionally a "robust method" as described in the CLSI Guidelines C28-A3 (CLSI 2008).

90% Confidence Intervals are given for the reference limits.

For the robust method, the confidence intervals are estimated with the bootstrap (percentile interval method, Efron & Tibshirani, 1993). When sample size is very small and/or the sample contains too many equal values, it may be impossible to calculate the CIs.

The results from the Normal distribution method are not appropriate when the Test for Normal distribution (see above) fails. If sample size is large (120 or more) the CLSI C28-A3 guideline recommends the percentile method and for smaller sample sizes the "robust method" is recommended.

The minimal sample size of 120 for the percentile method is the minimum number required to calculate 90% Confidence Intervals for the reference limits. A higher number of cases is required to achieve more reliable reference limits with more narrow 90% Confidence Intervals.

Graph

Click the Graph button in the dialog box shown above to obtain the following Reference Interval Graph box:

![Reference Interval Graph](image-url)

This results in the following graph:

![Reference Interval Graph](image-url)
Age-related reference interval

An age-related reference interval is a reference interval that varies with the patients’ age.

The methodology that MedCalc uses to model the reference interval on age is based on the methods described by Altman (1993), Altman & Chitty, 1993 and Wright & Royston 1997a.

The method includes the following steps:

1. If the distribution of the measurements (the variable for which to establish a reference interval) shows skewness at different levels of age, the measurements are transformed logarithmically or using a Box-Cox power transformation.
2. The transformed measurements are modelled on age using weighted polynomial regression (Altman & Chitty, 1994). This regression model gives the mean of the (transformed) measurements as a function of age: mean(age).
3. The residuals of this regression model are calculated.
4. The absolute residuals, multiplied by $\sqrt{\pi/2}$ are modelled on age using weighted polynomial regression (Altman, 1993). This second regression model gives the standard deviation of the (transformed) measurements as a function of age: SD(age).
5. For every age in the observed range, the reference interval is calculated by taking mean(age) ± z x SD(age). For a 95% reference interval z=1.96. If the data were initially transformed in step 1, the resulting values are backtransformed to their original scale.
6. The model is evaluated by analyzing and plotting z-scores for all observations. The z-score for an observed value $y$ is calculated by

   \[ z = \frac{y - \text{mean}(age)}{\text{SD}(age)} \]

   The z-scores should be normally distributed. If they are not, the model may not be appropriate and other powers for the polynomial model may be selected.

Required input

The example makes use of the data on biparietal diameter (outer-inner) from Chitty et al., 1994 (data downloaded from http://www.stata.com/stb/stb38/sbe15/bpd.dta).

Measurements and age variables

In the dialog box you identify the variable for the measurements and the variable for age. You can also enter or select a filter in order to include only a selected subgroup of cases in the statistical procedure, as described in the Introduction part of this manual.
Reference interval options

- Report centiles: you can select the different centiles of interest. For example, for a 95% double sided reference interval you select the centiles 2.5 and 97.5.

Powers for polynomial model

- Powers: select the powers for the polynomial model for Mean and for SD. The special value 0 means logarithmic transformation (base 10). For example, when you select the powers 0, 1 and 2 the model will include Log(age), age^1=age and age^2:
  \[ Y = b_0 + b_1 \text{Log}(age) + b_2 \text{age} + b_3 \text{age}^2 \]
  The values b_i are the coefficients to be estimated by the software. The value b0 is the constant term in the regression model.

Options for Measurements variable

- Logarithmic transformation: if the measurements data require a logarithmic transformation (e.g. when the data are positively skewed), select the Logarithmic transformation option.
- Box-Cox transformation: this will allow to perform a Box-Cox transformation with the following parameters:
  - Lambda: the power parameter \( \lambda \)
  - Shift parameter: the shift parameter is a constant c that needs to be added to the data when some of the data are negative.
  - Button Get from data: click this button to estimate the optimal value for Lambda, and suggest a value for the shift parameter c when some of the observations are negative. The program will suggest a value for Lambda with 2 to 3 significant digits.
  The Box-Cox transformation is defined as follows:
  \[
  x(\lambda) = \begin{cases} 
  \frac{((x+c)^\lambda - 1)}{\lambda} & \text{when } \lambda \neq 0 \\
  \log(x+c) & \text{when } \lambda = 0
  \end{cases}
  \]
  When you perform a Box-Cox transformation, MedCalc will automatically transform the measurements with the selected parameters and will back-transform the results to the original scale for presentation.
- Test for outliers: select the method based on Reed et al. (1971) or Tukey (1977) to automatically check the data for outliers (alternatively select none for no outlier testing). The method by Reed et al. will test only the minimum and maximum observations; the Tukey test can identify more values as outliers. The tests will create a list of possible outlying observations, but these will not automatically be excluded from the analysis. The possible outliers should be inspected by the investigator who can decide to exclude the values (see Exclude & Include, p. 51).
  For other methods for outlier detection see Outlier detection (p. 75).

z-scores

- Test for Normal distribution: select a statistical test to evaluate if the distribution of the z-scores is compatible with a Normal distribution (see p. 70).
Results

Suspected outliers

The program produces a list of possible outliers of the measurements, detected by the methods based on Reed et al. (1971) or Tukey (1977). The method by Reed et al. tests only the minimum and maximum observations; the Tukey test can identify more values as outliers. Note that this does not automatically exclude any values from the analysis. The observations should be further inspected by the investigator who can decide to exclude the values. Click on the listed values (which are displayed as hyperlinks) to show the corresponding data in the spreadsheet (see Exclude & Include, p. 51).

Model summary

This table gives a summary of the model.

The first row shows the outcome variable.

• If no transformation was selected, the outcome variable is the measurements variable (e.g. BPD).
• If a logarithmic transformation was selected, the outcome variable is the base 10 logarithm of the measurements variable, and will be shown as Log(BPD).
• If a Box-Cox transformation was selected, the outcome variable is Box-Cox transformed measurements variable, and will be shown as (BPD+c)^λ
Next the regression equation is given for Mean and SD of the outcome variable.

- If no transformation was selected, the equations directly give the estimated Mean and SD of the measurements variable.
- If a logarithmic transformation or Box-Cox transformation was selected, the equations give the estimated Mean and SD of the transformed measurements, and the results must be back-transformed to their original scale. MedCalc back-transforms the results automatically in the following table (Centiles) and graphs.

Centiles
This table lists the centiles at different ages (for about 6 to 12 values of age). Below this table there is a hyperlink to get a more comprehensive table in Excel format, for about 60 to 120 values of age. This Excel file includes the formulae for the different centiles and therefore can easily be shortened or expanded to your needs.

Fitted equations for Mean and Standard Deviation
This table lists the details of the weighted regression for the Mean of the measurements and next for the Standard Deviation. The different coefficients are listed with their standard error and P-value. The P-values should not be given too much attention. Specifically, they must not be used to decide if a term should remain or should be removed from the model. It is the magnitude of the coefficient itself that is of interest.

z-scores
The analysis of the z-scores is an important step in the evaluation of how well the model fits the data.

- Range: the lowest and highest value of z-scores.
- Skewness: the coefficient of Skewness (Sheskin, 2011) is a measure for the degree of symmetry in the variable distribution. The coefficient of Skewness should be close to 0 (see p. 73).
- Kurtosis: The coefficient of Kurtosis (Westfall, 2014) is a measure for the degree of tailedness in the variable distribution. The coefficient of Kurtosis should be close to 0 (see p. 73).
- Test for Normal Distribution: The result of this test is expressed as 'accept Normality' or 'reject Normality', with P value. If P is higher than 0.05, it may be assumed that the z-scores follow a Normal distribution and the conclusion 'accept Normality' is displayed.

Graphs

Scatter plot with centile curves
This plot shows a scatter diagram of the measurements versus age with the calculated mean (central line) and centile curves.
**z-scores**

This graph shows the z-scores plotted against age.

Horizontal lines are drawn at z-scores of -1.645 and 1.645. The central line (red in the example) is an 80% smoothed LOESS (Local Regression Smoothing) trendline. The z-scores should not display any pattern and must be randomly scattered about 0 at all ages (Altman & Chitty, 1993). It is expected that 5% of cases lie above the line corresponding to $z=1.645$ and 5% of cases are expected to lie below the line corresponding with $z=-1.645$; and these cases should be randomly distributed across the observed age range. Any deviation from this indicates that the model needs modification. In the graph’s Info panel, the exact number of observations below $z=-1.645$ and above $z=1.645$ is reported.

**Confidence intervals**

MedCalc allows to calculate confidence intervals for the reference limits using bootstrapping (Wright & Royston, 1997b). Proceed as follows:

- Select only one or two centiles. MedCalc cannot calculate confidence intervals for more centiles at the same time.
- Next click the Confidence intervals button and complete the new dialog box as follows:
  
  - **Bootstrap confidence intervals**: select None if you do not want to calculate confidence intervals; otherwise select a 90% or 95% confidence interval.
  - **Bootstrap replications**: enter the number of bootstrap replications. High numbers increase accuracy but also increase processing time.
• Random-number seed: this is the seed for the random number generator. Enter 0 for a random seed; this can result in different confidence intervals when the procedure is repeated. Any other value will give a repeatable "random" sequence, which will result in repeatable values for the confidence intervals.

Click OK to return to the main dialog box.

• When you return to the main dialog box, select Box-Cox transformation and click Get from data to automatically get the best values for Lambda and Shift parameter.

This step is necessary because at every step in the bootstrap procedure, MedCalc will do an automatic Box-Cox transformation to estimate and model the skewness of each bootstrap sample (Wright & Royston 1997a). By doing a Box-Cox transformation in the original procedure, you align the results of the centiles with the confidence intervals.

• Click OK to proceed. The calculations can take a few minutes to complete.

• The confidence intervals are displayed in the report table:

<table>
<thead>
<tr>
<th>Age variable</th>
<th>0.05 (90% CI)</th>
<th>0.95 (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>25.2243</td>
<td>33.1266</td>
</tr>
<tr>
<td>20</td>
<td>42.4764</td>
<td>51.3550</td>
</tr>
<tr>
<td>25</td>
<td>57.1975</td>
<td>67.1804</td>
</tr>
<tr>
<td>30</td>
<td>69.7257</td>
<td>80.8841</td>
</tr>
<tr>
<td>35</td>
<td>80.1412</td>
<td>92.4986</td>
</tr>
<tr>
<td>40</td>
<td>88.3649</td>
<td>101.9643</td>
</tr>
</tbody>
</table>

* BC$_2$ bootstrap confidence interval (5000 iterations; random number seed: 978).
Method comparison & method evaluation

Bland-Altman plot

The Bland-Altman plot (Bland & Altman, 1986 and 1999; Hanneman 2008), or difference plot, is a graphical method to compare two measurements techniques. In this graphical method, the differences (or alternatively the ratios) between the two techniques are plotted against the averages of the two techniques. Alternatively, (Krouwer, 2008) the differences can be plotted against one of the two methods, if this method is a reference or "gold standard" method.

Horizontal lines are drawn at the mean difference, and at the limits of agreement, which are defined as the mean difference plus and minus 1.96 times the standard deviation of the differences.

After you have selected Bland-Altman plot in the menu, enter the variables for the two different techniques in the following dialog box:

You can select the following variations of the Bland-Altman plot (see Bland & Altman, 1995; Bland & Altman, 1999; Krouwer, 2008):

- **Plot against (X-axis)**
  - In the original Bland-Altman plot (Bland & Altman, 1986) the differences* between the two methods are plotted against the averages of the two methods.
  - Alternatively, you can choose to plot the differences*
    - against one of the two methods, if this is a reference or "gold standard" method (Krouwer, 2008).
    - against the geometric mean of both methods.
    - against the sample rank (where the samples are ranked by the average of the two methods), the rank of the first method, or the rank of the second method; these options will give a "Ranked order difference plot" according to CLSI, 2013.
  - * or ratios when this option is selected (see below).

- **Plot differences**
  - This is the default option corresponding to the methodology of Bland & Altman, 1986.

- **Plot differences as %**
  - When selecting this option, the differences will be expressed as percentages of the observations represented on the X-axis (i.e. proportionally to the magnitude of measurements). This option is useful when there is an increase in variability of the differences as the magnitude of the measurement increases.

- **Plot ratios**
  - When this option is selected then the ratios of the measurements will be plotted instead of the differences (MedCalc performs the calculations on log-transformed data in the background). This option as well is useful when there is an increase
in variability of the differences as the magnitude of the measurement increases. However, the program will give a warning when either one of the two techniques includes zero values.

Options

- **Maximum allowed difference between methods**: (optionally) the pre-defined clinical agreement limit $D$. Depending on the option (Plot differences or ratios) selected above, a difference, a difference expressed as a percentage, or a ratio must be entered.
  
  The value $D$ must be chosen so that differences in the range $-D$ to $D$ (for ratios $1/D$ to $D$) are clinically irrelevant or negligible.

- **Draw line of equality**: useful for detecting a systematic difference.

- **95% CI of mean difference**: the 95% Confidence Interval of the mean difference illustrates the magnitude of the systematic difference. If the line of equality is not in the interval, there is a significant systematic difference.

- **95% CI of limits of agreement**: shows error bars representing the 95% confidence interval for both the upper and lower limits of agreement.

- **Draw regression line of differences** versus averages: this regression line may help to detect a proportional difference. The regression parameters are shown in the graph's info panel. Optionally, you can select to show the 95% confidence interval of this regression line.

* or ratios when this option was selected.

Click the **Subgroups** button if you want to identify subgroups in the scatter diagram. A new dialog box is displayed in which you can select a categorical variable. The graph will display different markers for the different categories in this variable.

After clicking the OK button, you obtain the following graph:

This graph displays a scatter diagram of the differences plotted against the averages of the two measurements. Horizontal lines are drawn at the mean difference, and at the limits of agreement.

The limits of agreement (LoA) are defined as the mean difference $\pm 1.96$ SD of differences. If these limits do not exceed the maximum allowed difference between methods $\Delta$ (the differences within mean $\pm 1.96$ SD are not clinically important), the two methods are considered to be in agreement and may be used interchangeably.

Proper interpretation (Stöckl et al., 2004) takes into account the 95% confidence interval of the LoA, and to be 95% certain that the methods do not disagree, $\Delta$ must be higher than the upper 95 CI limit of the higher LoA and $-\Delta$ must be less than the lower 95 CI limit of the lower LoA:
To get more statistical information, right-click in the graph window and select the **Info** option in the pop-up menu. A new window appears inside the graph window:

The Bland-Altman plot is useful to reveal a possible relationship between the differences and the averages (examples 1 & 2), to look for any systematic bias (example 3) and to identify possible outliers. If there is a consistent bias, it can be adjusted for by subtracting the mean difference from the new method.

If the differences within mean ± 1.96 SD are not *clinically* important, the two methods may be used interchangeably.

Some typical situations are shown in the following examples.

**Example 1: Case of a proportional error.**
Example 2: Case where the variation of at least one method depends strongly on the magnitude of measurements.

Example 3: Case of an absolute systematic error.

Repeatability

The Bland and Altman plot may also be used to assess the *repeatability* of a method by comparing repeated measurements using one single method on a series of subjects. The graph can then also be used to check whether the variability or precision of a method is related to the size of the characteristic being measured.

Since for the repeated measurements the same method is used, the mean difference should be zero. Therefore the *Coefficient of Repeatability* (CR) can be calculated as 1.96 times the standard deviation of the differences between the two measurements ($d_2$ and $d_1$) (Bland & Altman, 1986; Bland 2005):

$$CR = 1.96 \times \sqrt{\frac{\sum (d_2 - d_1)^2}{n}}$$

The 95% confidence interval for the Coefficient of Repeatability is calculated according to Barnhart & Barborial, 2009.

To obtain this coefficient in MedCalc you
- Create a Bland-Altman plot for the two measurements
- Right-click in the display and select *Info* in the pop-up menu.
- In the info panel, click *Coefficient of Repeatability*
The coefficient of repeatability is not reported when you have selected the "Plot ratios" method.

**Bland-Altman plot with multiple measurements per subject**

Use this command to create a Bland-Altman plot for method comparison when there is more than one measurement per subject with each laboratory method.

**How to enter data**

This procedure requires that you have your data organized like illustrated in the following example (data from Bland & Altman, 2007):

<table>
<thead>
<tr>
<th>Subject</th>
<th>RV</th>
<th>IC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.83</td>
<td>6.57</td>
</tr>
<tr>
<td>2</td>
<td>7.42</td>
<td>5.62</td>
</tr>
<tr>
<td>3</td>
<td>7.89</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>7.12</td>
<td>6.57</td>
</tr>
<tr>
<td>5</td>
<td>7.88</td>
<td>6.35</td>
</tr>
<tr>
<td>6</td>
<td>6.16</td>
<td>4.06</td>
</tr>
<tr>
<td>7</td>
<td>7.26</td>
<td>4.29</td>
</tr>
<tr>
<td>8</td>
<td>6.71</td>
<td>4.26</td>
</tr>
<tr>
<td>9</td>
<td>6.54</td>
<td>4.09</td>
</tr>
<tr>
<td>10</td>
<td>4.75</td>
<td>4.71</td>
</tr>
<tr>
<td>11</td>
<td>5.24</td>
<td>5.5</td>
</tr>
<tr>
<td>12</td>
<td>4.86</td>
<td>5.08</td>
</tr>
</tbody>
</table>

There is one column for subject identification (Subject) and one column for the measurements for each method (RV and IC). If you have your data organized in a different format, such as the data for the multiple measurements in different columns, you can use the Stack columns tool to reorganize your data (see p. 52).
Required input

![Bland-Altman plot for multiple observations per individual](image)

- **Data**
  
  *First method, Second method*: Select the variables for the two techniques you want to compare.
  
  *Subject identification*: Select the variable that contains the subject identification.

- **Model**
  
  *True value is constant in each subject*: Select this option if the true value is constant in each subject (e.g., with both methods several measurements were performed on the same sample).
  
  In the True value is constant in each subject model (see Bland & Altman, 2007) there is only one marker for each subject in the graph. The marker size is relative to the number of observations for the subject. The number of markers is equal to the number of subjects.
  
  In the alternative model, where the *True value varies*, there is one marker for each observation pair.

- **Options**
  
  - **Plot against (X-axis):**
    
    In the original Bland-Altman plot (Bland & Altman, 1986) the differences between the two methods are plotted against the averages of the two methods (recommended, Bland & Altman, 1995).
    
    Alternatively, you can choose to plot the differences against one of the two methods, if this is a reference or "gold standard" method (Krouwer, 2008). Finally, you can also plot the differences against the geometric mean of both methods.
  
  - **Plot differences or ratios**
    
    Plot differences: this is the default option corresponding to the methodology of Bland & Altman, 1986.
    
    Plot ratios: when this option is selected then the ratios of the measurements will be plotted instead of the differences (MedCalc performs the calculations on log-transformed data in the background). This option as well is useful when there is an increase in variability of the differences as the magnitude of the measurement increases. However, the program will give a warning when either one of the two techniques includes zero values.
  
  - **Maximum allowed difference between methods**: (optionally) the pre-defined clinical agreement limit \( D \). Depending on the option (Plot differences or ratios) selected above, a difference or a ratio must be entered.
    
    The value \( D \) must be chosen so that differences in the range \(-D\) to \( D\) (for ratios \(1/D\) to \( D\)) are clinically irrelevant or neglectable.
  
  - **Draw line of equality**: useful for detecting a systematic difference.
  
  - **95% CI of limits of agreement**: shows error bars representing the 95% confidence interval for both the upper and lower limits of agreement.

Calculations

The calculations are performed as described by Zou (2013). For the estimation of the confidence intervals of the limits of agreement, the MOVER method is used (Zou, 2013).

Graph

This is the graph in the *True value is constant in each subject* model:
In the *True value is constant in each subject* model there is only one marker for each subject in the graph, and the marker size is relative to the number of observations for the subject. The number of markers is equal to the number of subjects.

In the alternative model, where the *True value varies*, there is one marker for each observation pair:

### Comparison of multiple methods

Comparison of multiple methods is an extension of the Bland-Altman plot (Bland & Altman, 1986 and 1999) (p. 195) for more than two methods. For each method, the differences with a reference method are plotted against the values of this reference method (Krouwer, 2008).

The procedure produces multiple bias plots in one single display with all axes aligned to facilitate comparison of the different methods.

If duplicate or multiple measurements (with two methods) were performed per subject, you should use Bland-Altman plot with multiple measurements per subject (p. 199).

**Required input**

First select the variables for the methods you want to compare.
Options

- First method is the reference method: the measurements of first selected method are the reference values (informational, this option is fixed).
- Plot differences or ratios
  - Plot differences: This is the default option corresponding to the methodology of Bland & Altman, 1986. Differences are calculated as measurement-reference so a positive difference is an overestimation and a negative difference is an underestimation.
  - Plot differences as %: With this option the differences will be expressed as percentages of the values on the axis (i.e. proportionally to the magnitude of measurements). This option is useful when there is an increase in variability of the differences as the magnitude of the measurement increases.
  - Plot ratios: When this option is selected then the ratios of the measurements will be plotted instead of the differences (avoiding the need for logarithmic transformation). This option as well is useful when there is an increase in variability of the differences as the magnitude of the measurement increases. Ratios are calculated as measurement/reference so a ratio > 1 indicates an overestimation and a ratio < 1 indicates an underestimation.
- Draw line of equality: useful for detecting a systematic difference.
- 95% CI of mean difference*: the 95% Confidence Interval of the mean difference illustrates the magnitude of the systematic difference. If the line of equality is not in the interval, there is a significant systematic difference.
- 95% CI of limits of agreement: shows error bars representing the 95% confidence interval for both the upper and lower limits of agreement.
- Draw regression line of differences*: this regression line may help to detect a proportional difference. Optionally, you can select to show the 95% confidence interval of this regression line.

*or ratios when this option was selected.
Results

The results panel displays the following information:

- **Identifier for the reference value:** the variable for the reference method.
- **Systematic differences:** n (sample size), mean, SD and 95% CI of the differences.
- **Limits of agreement:** the lower and upper limits of agreement with 95% CI.
- **Parameters of the regression of the differences against the reference value:** intercept and slope with 95% CI, and P-value for slope.
- **Absolute percentage error:** the absolute percentage error (APE) is calculated as $100 \times \frac{\text{ABS}(y - \text{ref})}{\text{ref}}$ where y is the observation and ref is the reference value. MedCalc calculates the median APE (MdAPE) and the 95th percentile of the absolute percentage error. The 95th percentile APE is interpreted as follows: the percentage difference between a measurement and the reference value is not expected, with 95% certainty, to exceed this value. MedCalc also reports the 95% confidence intervals for both statistics, if sample size is large enough.
Graph

The graphical display consists of multiple frames with Bland-Altman plots using the selected options. Unlike other MedCalc graphs, this graphical display has limited editing possibilities:

- you cannot add reference lines or draw boxes, arrows or add text frames.
- the scaling of the axes is the same in each frame.
- the titles are the same for each frame. To create variations in the titles for the different frames, you can use the following symbolic fields:
  - !#/: this will insert the frame number in the title
  - !a!: this will insert a character A, B, ..., corresponding with the frame number, in the title
  - !var!: this will insert the variable name in the title

Mountain plot

A *mountain plot* (or "folded empirical cumulative distribution plot") is created by computing a percentile for each ranked difference between a new method and a reference method. To get a folded plot, the following transformation is performed for all percentiles above 50: percentile = 100 - percentile. These percentiles are then plotted against the differences between the two methods (Krouwer & Monti, 1995; CLSI, 2003).

The mountain plot is a useful complementary plot to the Bland-Altman plot. In particular, the mountain plot offers the following advantages:

- It is easier to find the central 95% of the data, even when the data are not Normally distributed.
- Different distributions can be compared more easily.

In the dialog box for *Mountain plot* you enter the variables for the two or three techniques you want to compare.
You can enter variables for two or three laboratory assays. In case of three assays, the second and third assay will be compared with the first reference assay. You can select an option to include all the data points in the graph. This option is very useful to identify outliers.

The mountain plot provides information about the distribution of the differences between methods. If two assays are unbiased with respect to each other, the mountain will be centered over zero. Long tails in the plot reflect large differences between the methods.

In the example, the median of the differences is close to zero for both methods Assay2 and Assay3 as compared with Assay 1. The differences of Assay 1 with Assay3 tend to be smaller than the differences of Assay 1 with Assay2. Therefore Assay3 corresponds better with Assay1 than Assay2 does.

When you click an individual observation in the graph, the corresponding case is identified in a pop-up window (see also Select variable for case identification command, p. 66).
If you double-click an observation, the spreadsheet window will open with the corresponding case highlighted. Select *Info* in the shortcut menu (which appears after right-clicking in the graph window) to get precise information on sample size, median, minimum and maximum and the most important percentiles of the distribution(s).

**Deming regression**

Whereas the ordinary linear regression method assumes that only the Y measurements are associated with random measurement errors, the Deming method takes measurement errors for both methods into account.

**Required input**

Select the variables for the two techniques you want to compare. For each of both techniques you can either enter 2 variables (which contain repeated measurements) or you can enter only one variable, in which case you will have to enter an already established Coefficient of Variation (expressed as a percentage). As an option, you can create 2 graphs:
- A scatter diagram with the regression line
- The *residuals* plot.

Use the *Subgroups* button if you want to identify subgroups in the scatter diagram and residuals plot. A new dialog box is displayed in which you can select a categorical variable. The graph will display different markers for the different categories in this variable.
Results
The results are displayed in the following text window:

![Deming regression window]

- Mean and Coefficient of Variation (%) for both methods
- Sample size: the number of (selected) data pairs
- Variance ratio: this is the ratio of the measurement errors of X and Y.
- The regression equation, Intercept and Slope with 95% confidence interval
  - The Intercept and Slope are calculated according to Cornbleet & Gochman, 1979. The standard errors and confidence intervals are estimated using the jackknife method (Armitage et al., 2002).
  - The 95% confidence interval for the Intercept can be used to test the hypothesis that $A=0$. This hypothesis is accepted if the confidence interval for $A$ contains the value 0. If the hypothesis is rejected, then it is concluded that $A$ is significantly different from 0 and both methods differ at least by a constant amount.
  - The 95% confidence interval for the Slope can be used to test the hypothesis that $B=1$. This hypothesis is accepted if the confidence interval for $B$ contains the value 1. If the hypothesis is rejected, then it is concluded that $B$ is significantly different from 1 and there is at least a proportional difference between the two methods.

Graphs
The first graph window displays the scatter diagram with regression line (solid line) and identity line ($x=y$, dotted line)

![Deming regression graph]

The second graph window displays the residuals:
Passing & Bablok regression

Passing & Bablok (1983) have described a linear regression procedure with no special assumptions regarding the distribution of the samples and the measurement errors. The result does not depend on the assignment of the methods (or instruments) to X and Y. The slope B and intercept A are calculated with their 95% confidence interval. These confidence intervals are used to determine whether there is only a chance difference between B and 1 and between A and 0.

Required input

- Variable Y and Variable X: select the variables for the two techniques you want to compare.
- Filter: an optional data filter.
- Options
  - Calculate perpendicular residuals: select this option to calculate the residuals perpendicular to the regression line (see Passing & Bablok, 1983). This is different from the traditional (least squares) method which measures residuals parallel to the y-axis.
- Spearman rank correlation coefficient: select this option to include Spearman's rank correlation coefficient in the report.

- Graphic windows
  - Scatter diagram & regression line: a graph window with scatter diagram and regression line, including confidence interval for the regression line and identity line (x=y).
  - Residuals: a graph window with a residuals plot. As an option, the Residuals can be plotted by rank number (see Passing & Bablok, 1983).
  - Subgroups: click the Subgroups button if you want to identify subgroups in the scatter diagram and residuals plot. A new dialog box is displayed in which you can select a categorical variable. The graph will display different markers for the different categories in this variable.

- Advanced: click the Advanced button so select Advanced options for the Passing-Bablok procedure. These include the calculation of bootstrap parameters of the regression coefficients, or the calculation of expected bias at selected threshold values according to CLSI guideline EP09c (2018).

**Results**

When you have completed the dialog box, click the OK button to proceed. The following results will be displayed in a text window.

- Sample size: the number of (selected) data pairs
- Summary statistics for both variables: lowest and highest value, mean, median, standard deviation and standard error of the mean
- The regression equation: the regression equation with the calculated values for A and B according to Passing & Bablok (1983).
- Systematic differences. The intercept A is a measure of the systematic differences between the two methods. The 95% confidence interval for the intercept A can be used to test the hypothesis that A=0. This hypothesis is accepted if the confidence interval for A contains the value 0. If the hypothesis is rejected, then it is concluded that A is significantly different from 0 and both methods differ at least by a constant amount.
• **Proportional differences.** The slope $B$ is a measure of the proportional differences between the two methods. The 95% confidence interval for the slope $B$ can be used to test the hypothesis that $B=1$. This hypothesis is accepted if the confidence interval for $B$ contains the value 1. If the hypothesis is rejected, then it is concluded that $B$ is significantly different from 1 and there is at least a proportional difference between the two methods.

• **Random differences.** The residual standard deviation (RSD) is a measure of the random differences between the two methods. 95% of random differences are expected to lie in the interval $-1.96 \text{ RSD}$ to $+1.96 \text{ RSD}$. If this interval is large, the two methods may not be in agreement.

• **Linear model validity:** the Cusum test for linearity is used to evaluate how well a linear model fits the data. The Cusum test for linearity only tests the applicability of the Passing-Bablok method; it has no further interpretation with regards to comparability of the two laboratory methods. A small $P$ value ($P<0.05$) indicates that there is no linear relationship between the two measurements and therefore the Passing-Bablok method is not applicable.

Optionally, the program reports Spearman’s rank correlation coefficient (rho) with $P$-value and 95% Confidence Interval. Note that Passing & Bablok (1983) discourage reporting the correlation coefficient in method comparison studies. We have found that Passing & Bablok regression does not work when correlation is low; we report it not as a method-comparison statistic, but as a factor in the evaluation of the validity of the Passing-Bablok regression procedure itself.

**Graphs**

**Scatter diagram and regression line**

This graph displays a scatter diagram and the regression line according to Passing & Bablok (1983).

In addition to the regression line (solid line), the confidence interval for the regression line (dashed lines) and identity line ($x=y$, dotted line) are displayed.

![Passing and Bablok regression](image)

**Extrapolation**

MedCalc only shows the regression line in the range of observed values. As a rule, it is not recommended to extrapolate the regression line beyond the observed range. To allow extrapolation anyway, right-click in the graph and select Allow extrapolation in the pop-up menu.

![Allow extrapolation](image)

**Residuals plot**

Residuals are the differences between the predicted values and the observed values for the dependent variable.
The residual plot allows for the visual evaluation of the goodness of fit of the linear model. If the residuals display a certain pattern, you can expect the two variables not to have a linear relationship.

Since it is a non-parametric procedure, Passing-Bablok regression is not influenced by the presence of one or relative few outliers. Nevertheless, outliers - defined here as residuals outside the 4 SD limit - are plotted in a different color. Linnet & Boyd (2012) recommend that these measurements should not just be rejected automatically, but the reason for their presence should be scrutinized.

![Passing and Bablok regression - residuals](image)

### Coefficient of variation from duplicate measurements

The calculation of Coefficient of Variation (CV) from duplicate measurements made on a number of different subjects or materials is used to determine the reproducibility of the measurements as an alternative to making a large number of observations on a single subject or material to estimate the within-run imprecision directly (Jones & Payne 1997).

**Required input**

In the dialog box you select the variables that contain the data for the two measurements.

You can select one of three methods to calculate the Coefficient of Variation:

- Root mean square method
- Logarithmic method
- Within-subject standard deviation method

The Root mean square and Logarithmic methods allow the calculation of a confidence interval for the CV and are the recommended methods.

The Within-subject standard deviation method can only be used when the standard deviation can be assumed reasonable constant across the concentration interval.
Results

With \( n \) being the number of data pairs and \( x_1 \) and \( x_2 \) duplicate measurements, the overall mean is given by:

\[
\text{Mean} = \frac{\sum (x_1 + x_2)}{2n}
\]

Root mean square method

In this method (Hyslop & White, 2009), the CV (%) is calculated as:

\[
\text{CV(\%)} = 100 \times \sqrt{\frac{\sum (d/m)^2}{2n}}
\]

where \( d \) is the difference between two paired measurements and \( m \) is the mean of paired measurements.

The Root mean square method cannot be used when the mean of one or more pairs of measurements is 0.

Logarithmic method

In this method (Bland & Altman, 1996; Bland 2006), first the sum of squared differences between the logarithms of observations is calculated:

\[
s_l = \sum (\ln(x_1) - \ln(x_2))^2
\]

Next, the CV (%) is calculated as:

\[
\text{CV(\%)} = 100 \times (\exp \sqrt{\frac{s_l}{2n}} - 1)
\]

The Logarithmic method cannot be used when any value is 0 or negative.

Within-subject standard deviation method

The within-subject standard deviation is given by (Jones & Payne 1997; Synek 2008):

\[
\text{SD} = \sqrt{\frac{\sum (x_1 - x_2)^2}{2n}}
\]

The coefficient of variation is the standard deviation divided by the mean (\( x \times 100 \)):

\[
\text{CV(\%)} = 100 \times \frac{\text{SD}}{\text{Mean}}
\]

In this method, no confidence interval is reported.

The Within-subject standard deviation method cannot be used when the overall mean of measurements is 0.
Intraclass correlation coefficient

The Intraclass Correlation Coefficient (ICC) is a measure of the reliability of measurements or ratings. For the purpose of assessing inter-rater reliability and the ICC, two or preferably more raters rate a number of study subjects. A distinction is made between two study models: (1) each subject is rated by a different and random selection of a pool of raters, and (2) each subject is rated by the same raters. In the first model, the ICC is always a measure for Absolute agreement; in the second model a choice can be made between two types: Consistency when systematic differences between raters are irrelevant, and Absolute agreement, when systematic differences are relevant.

For example: the paired ratings (2,4), (4,6) and (6,8) are in perfect agreement, with a consistency of 1.0, but with an absolute agreement of 0.6667.

How to enter data

In this example (taken from Shrout PE & Fleiss JL, 1979) data are available for 4 raters on 6 subjects. The data for each subject are entered in the 4 columns.

If not all subjects are rated by the same 4 raters, the data are still entered in 4 columns, the order of which then being unimportant.

Required input

- **Measurements**: variables that contain the measurements of the different raters.
- **Filter**: an optional data filter to include only a selected subgroup of cases.
- **Options**
- Model
  - Raters for each subject were selected at random: the raters were not the same for all subjects, a random selection or raters rated each subject.
  - The same raters for all subjects: all subjects were rated by the same raters.

- Type
  - Consistency: systematic differences between raters are irrelevant.
  - Absolute agreement: systematic differences are relevant

Results

The Intraclass correlation coefficient table reports two coefficients with their respective 95% Confidence Interval (McGraw & Wong, 1996).

- **Single measures**: this ICC is an index for the reliability of the ratings for one, typical, single rater.
- **Average measures**: this ICC is an index for the reliability of different raters averaged together. This ICC is always higher than the Single measures ICC.
Concordance correlation coefficient

The concordance correlation coefficient (Lin, 1989; Lin, 2000) evaluates the degree to which pairs of observations fall on the 45° line through the origin.

Required input
Select the variables for the two techniques you want to compare.

Results
The concordance correlation coefficient $\rho_c$ contains a measurement of precision $\rho$ and accuracy $C_b$:

$$\rho_c = \rho C_b$$

where

- $\rho$ is the Pearson correlation coefficient, which measures how far each observation deviates from the best-fit line, and is a measure of precision, and
- $C_b$ is a bias correction factor that measures how far the best-fit line deviates from the 45° line through the origin, and is a measure of accuracy.

Inter-rater agreement (kappa)

Inter-rater agreement is used to evaluate the agreement between two classifications (nominal or ordinal scales). Agreement is quantified by the Kappa ($K$) statistic (Cohen, 1960; Fleiss et al., 2003). $K$ is 1 when there is perfect agreement between the classification system; $K$ is 0 when there is no agreement better than chance; and $K$ is negative when agreement is worse than chance.
Data input

If you have the data already organized in a table, you can use the *Inter-rater agreement* command in the *Tests* menu (see p. 280).

![Data input screenshot](image)

Dialog box

In the *Inter-rater agreement* dialog box, two discrete variables with the classification data from the two methods or observers must be identified. Classification data may either be numeric or alphanumeric (string) values.

![Dialog box screenshot](image)

Weighted Kappa

Kappa does not take into account the degree of disagreement between observations and all disagreement is treated equally as *total* disagreement. Therefore when the categories are ordered, it is preferable to use *Weighted Kappa*, and assign different weights $w_i$ to subjects for whom the raters differ by $i$ categories, so that different levels of agreement can contribute to the value of Kappa.

MedCalc offers two sets of weights, called linear and quadratic. In the linear set, if there are $k$ categories, the weights are calculated as follows:

$$w_i = 1 - \frac{i}{k-1}$$

and in the quadratic set:

$$w_i = 1 - \frac{i^2}{(k-1)^2}$$

When there are 5 categories, the weights in the linear set are 1, 0.75, 0.50, 0.25 and 0 when there is a difference of 0 (=total agreement) or 1, 2, 3 and 4 categories respectively. In the quadratic set the weights are 1, 0.937, 0.750, 0.437 and 0.
Use linear weights when the difference between the first and second category has the same importance as a difference between the second and third category, etc. If the difference between the first and second category is less important than a difference between the second and third category, etc., use quadratic weights.

**Results**

MedCalc calculates the inter-rater agreement statistic Kappa with 95% confidence interval.

MedCalc calculates the inter-rater agreement statistic Kappa with 95% confidence interval (Fleiss et al., 2003). The standard errors reported by MedCalc are the appropriate standard errors for testing the hypothesis that the underlying value of weighted kappa is equal to a prespecified value other than zero (Fleiss et al., 2003).

The $K$ value can be interpreted as follows (Altman, 1991):

<table>
<thead>
<tr>
<th>Value of $K$</th>
<th>Strength of agreement</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt; 0.20$</td>
<td>Poor</td>
</tr>
<tr>
<td>$0.21 - 0.40$</td>
<td>Fair</td>
</tr>
<tr>
<td>$0.41 - 0.60$</td>
<td>Moderate</td>
</tr>
<tr>
<td>$0.61 - 0.80$</td>
<td>Good</td>
</tr>
<tr>
<td>$0.81 - 1.00$</td>
<td>Very good</td>
</tr>
</tbody>
</table>

**Cronbach’s alpha**

Cronbach's alpha is a statistic for investigating the internal consistency of a questionnaire (Cronbach, 1951; Bland & Altman, 1997).

**How to enter data**

Each question of the questionnaire results in one variable and the answers (numerically coded) are entered in the respective columns of the spreadsheet. The answers of one subject are entered on one row of the spreadsheet.
Required input

- **Variables**: the variables that contain the answers to the different questions of the questionnaire.
- **Filter**: an optional data filter to include only a selected subgroup of subjects (rows).
- **Options**
  - **Correct for scale reversal**: Some variables may be inversely related to other variables. When you select the option "Correct for scale reversal", MedCalc will detect these variables automatically (based on the correlation matrix) and reverse the values of those variables before analysis.
Results

In the example, the results of Question 3 were found to be inversely related to the results of the other questions. Therefore the results of Question 3 were reversed prior to analysis.

MedCalc reports Cronbach's alpha with its lower confidence limit (Feldt, 1965).

Next, MedCalc calculates the alpha obtained with each question in turn dropped. If the deletion of a question causes a considerable increase in alpha then you should consider dropping that question from the questionnaire.

MedCalc calculates Cronbach's alpha using the raw data and on the standardized variables (a transformation so that their mean is 0 and variance is 1). Using the "raw" data, questions that have more variability contribute more to the variability of the resulting scale; in the "standardized" form, each question gets equal weight.

For research purposes alpha should be more than 0.7 to 0.8, but for clinical purposes alpha should at least be 0.90 (Bland & Altman, 1997).
Responsiveness

Use this command to calculate several indices for responsiveness, which is the ability to detect any change (Husted et al., 2000; Norman et al., 2007).

Required input

- **1st and 2nd measurement**: the variables for a 1st and 2nd measurement.
- **Filter**: an optional data filter to include only a selected subgroup of subjects (rows).
- **Options**
  - **Paired data**: select this option when the variables for 1st and 2nd measurements contain paired data (measurements are repeated on the same subjects). If the 2 measurements are independent, unselect this option.
  - **Advanced**: the confidence intervals for the different indices of responsiveness are estimated using the bias-corrected and accelerated (BC$_a$) bootstrap (Efron, 1987; Efron & Tibshirani, 1993). Click the Advanced... button for bootstrapping options such as number of replications and random-number seed.

Results

**Summary statistics**

This table displays the sample size, mean, variance and standard deviation of the 1st and 2nd measurement.
Difference
This table reports the average difference between the two measurements with the pooled standard deviation and (in case of paired observations) the standard deviation of the paired differences.

Indices of responsiveness
- Effect size (ES) using baseline SD: this is the average difference divided by the standard deviation of the 1st measurement (this is Glass' Δ).
- Effect size (ES) using pooled SD: this is the average difference divided by the pooled standard deviation of both measurements (this is Cohen's d).
- Standardized response mean (SRM): this is the average difference divided by the standard deviation of the differences between the paired measurements.
**Receiver Operating Characteristic (ROC) curve analysis**

**ROC Curve analysis: introduction**

Often the clinical researcher is confronted with the question how accurate a particular laboratory test is in identifying diseased cases. The ability of a test to discriminate diseased cases from normal cases is evaluated using Receiver Operating Characteristic (ROC) curve analysis (Metz, 1978; Zweig & Campbell, 1993). ROC curves can also be used to compare the diagnostic performance of two or more laboratory or diagnostic tests (Griner et al., 1981).

When you consider the results of a particular test in two populations, one population with a disease, the other population without the disease, you will rarely observe a perfect separation between the two groups. Indeed, the distribution of the test results will overlap, as shown in the following figure.

For every possible cut-off point or criterion value you select to discriminate between the two populations, there will be some cases with the disease correctly classified as positive (TP = True Positive fraction), but some cases with the disease will be classified negative (FN = False Negative fraction). On the other hand, some cases without the disease will be correctly classified as negative (TN = True Negative fraction), but some cases without the disease will be classified as positive (FP = False Positive fraction).

**Table: Schematic outcomes of a test.**

<table>
<thead>
<tr>
<th>Test</th>
<th>Disease</th>
<th>Present</th>
<th>n</th>
<th>Absent</th>
<th>n</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>True Positive</td>
<td>a</td>
<td></td>
<td>False Positive</td>
<td>c</td>
<td>a + c</td>
</tr>
<tr>
<td>Negative</td>
<td>False Negative</td>
<td>b</td>
<td></td>
<td>True Negative</td>
<td>d</td>
<td>b + d</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>a + b</td>
<td></td>
<td>c + d</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Sensitivity**: probability that a test result will be positive when the disease is present (true positive rate, expressed as a percentage).
- **Specificity**: probability that a test result will be negative when the disease is not present (true negative rate, expressed as a percentage).
- **Positive likelihood ratio**: ratio between the probability of a positive test result given the *presence* of the disease and the probability of a positive test result given the *absence* of the disease, i.e.
- **Negative likelihood ratio**: ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease, i.e.

\[
\frac{\text{False Negative rate}}{\text{True Negative rate}}
\]

- **Positive predictive value**: probability that the disease is present when the test is positive (expressed as a percentage).
- **Negative predictive value**: probability that the disease is not present when the test is negative (expressed as a percentage).

**How to enter data for ROC curve analysis**

In order to perform ROC curve analysis in MedCalc you should have a measurement of interest (= the variable you want to study) and an independent diagnosis which classifies your study subjects into two distinct groups: a diseased and non-diseased group. The latter diagnosis should be independent from the measurement of interest.

In the spreadsheet, create a column DIAGNOSIS and a column for the variable of interest, e.g. TEST1. For every study subject enter a code for the diagnosis as follows: 1 for the diseased cases, and 0 for the non-diseased or normal cases. In the TEST1 column, enter the measurement of interest (this can be measurements, grades, etc. - if the data are categorical, code them with numerical values).
ROC curve analysis

To obtain a ROC curve you first select the *ROC curve analysis* option in the menu and complete the following box:

### Data
- **Variable**: select the variable of interest.
- **Classification variable**: select a dichotomous variable indicating diagnosis (0=negative, 1=positive). If your data are coded differently, you can use the Define status (see p. 105) tool to recode your data.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases (e.g. AGE>21, SEX="Male").

### Methodology
- **DeLong et al.**: use the method of DeLong et al. (1988) for the calculation of the Standard Error of the Area Under the Curve (recommended).
- **Binomial exact Confidence Interval for the AUC**: calculate an exact Binomial Confidence Interval for the Area Under the Curve (recommended). If this option is not selected, the Confidence Interval is calculated as AUC ± 1.96 its Standard Error.

### Disease prevalence
Whereas sensitivity and specificity, and therefore the ROC curve, and positive and negative likelihood ratio are independent of disease prevalence, positive and negative predictive values are highly dependent on disease prevalence or prior probability of disease. Therefore, when disease prevalence is unknown the program cannot calculate positive and negative predictive values. Clinically, the disease prevalence is the same as the probability of disease being present before the test is performed (prior probability of disease).
- **Unknown**: select this option when the disease prevalence is unknown, or irrelevant for the current statistical analysis.
- **The ratio of cases in the positive and negative groups reflects the prevalence of the disease**: if the sample sizes in the positive and negative group reflect the real prevalence of the disease in the population, this can be indicated by selecting this option.
- **Other value (%)**: alternatively, you can enter a value for the disease prevalence, expressed as a percentage.

### Options
- **List criterion values with test characteristics**: option to create a list of criterion values corresponding with the coordinates of the ROC curve, with associated sensitivity, specificity, likelihood ratios and predictive values (if disease prevalence is known).
Include all observed criterion values: When you select this option, the program will list sensitivity and specificity for all possible threshold values. If this option is not selected, then the program will only list the more important points of the ROC curve: for equal sensitivity/specificity it will give the threshold values (criterion values) with the highest specificity/sensitivity.

95% Confidence Interval for sensitivity/specificity, likelihood ratio and predictive values: select the Confidence Intervals you require.

Calculate optimal criterion value taking into account costs: option to calculate the optimal criterion value taking into account the disease prevalence and cost of false and true positive and negative decisions (Zweig & Campbell, 1993). This option is only available if disease prevalence is known (see above).

FPc: the cost of a false positive decision.
FNc: the cost of a false negative decision.
TPc: the cost of a true positive decision.
TNc: the cost of a true negative decision.

These data are used to calculate a parameter S as follows:

$$S = \left( \frac{FPc - TNc}{FNc - TPc} \right) \times \left( \frac{1 - P}{P} \right)$$

where P denotes the prevalence in the target population (Greiner et al., 2000). The point on the ROC curve where a line with this slope S touches the curve is the optimal operating point, taking into account prevalence and the costs of the different decisions.

Costs can be financial costs or health costs, but all 4 cost factors need to be expressed on a common scale. Benefits can be expressed as negative costs.

Suppose a false negative (FN) decision is judged to be twice as costly as a false positive (FP) decision, and no assumptions are made about the costs for true positive and true negative decisions. Then for FNc you enter 2, for FPc enter 1 and enter 0 for both TPc and TNc.

Because the slope S must be a positive number:

FPc cannot be equal to TNc
FNc cannot be equal to TPc
When TNc is larger than FPc then TPc must be larger than FNc
When TNc is smaller than FPc then TPc must be smaller than FNc

The parameter S is "cost-neutral" when \( \frac{FPc - TNc}{FNc - TPc} \) evaluates to 1, that is when FPc-TNc equals FNc-TPc. In this case S, and the "optimal criterion value" depends only on disease prevalence.

Advanced: click this button for advanced options including bootstrapping confidence intervals for the Youden index and its associated criterion value.

These options require bootstrapping and are computationally intensive and time consuming.

Estimation of sensitivity and specificity at fixed specificity and sensitivity: compile a table with estimation of sensitivity and specificity, with a BCa bootstrapped 95% confidence interval (Efron, 1987; Efron & Tibshirani, 1993), for a fixed and prespecified specificity and sensitivity of 80%, 90%, 95% and 97.5% (Zhou et al., 2002).

Bootstrap Youden index confidence interval: calculate a BCa bootstrapped 95% confidence interval (Efron, 1987; Efron & Tibshirani, 1993) for the Youden index and its associated criterion value.

Bootstrap replications: enter the number of bootstrap replications. 1000 is a number commonly encountered in the literature. High numbers increase accuracy but also increase processing time.

Random-number seed: this is the seed for the random number generator. Enter 0 for a random seed; this can result in different confidence intervals when the procedure is repeated. Any other value will give a repeatable "random" sequence, which will result in repeatable values for the confidence intervals.

Graphs:

Select Display ROC curve window to obtain the ROC plot in a separate window.

Options:

mark points corresponding to criterion values.
display 95% Confidence Bounds for the ROC curve (Hilgers, 1991).

A few moments after you have clicked the OK button, the following appears in the results window. The report may consist of several pages of text, and press the Page down key to see the next pages of the report.
Results

Sample size

<table>
<thead>
<tr>
<th>Variable</th>
<th>TEST1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Classification variable</td>
<td>DIAGNOSIS</td>
</tr>
</tbody>
</table>

| Sample size | 100 |
| Positive group : | DIAGNOSIS = 1 | 55 |
| Negative group : | DIAGNOSIS = 0 | 45 |
| Disease prevalence (%) | 10 |

First the program displays the number of observations in the two groups. Concerning sample size, it has been suggested that meaningful qualitative conclusions can be drawn from ROC experiments performed with a total of about 100 observations (Metz, 1978).

Area under the ROC curve, with standard error and 95% Confidence Interval

| Area under the ROC curve (AUC) | 0.947 |
| Standard Error*                | 0.0241 |
| 95% Confidence interval²       | 0.883 to 0.982 |
| z statistic                    | 18.644 |
| Significance level P (Area=0.5) | <0.0001 |

* DeLong et al., 1988

This value can be interpreted as follows (Zhou, Obuchowski & McClish, 2002):
- the average value of sensitivity for all possible values of specificity;
- the average value of specificity for all possible values of sensitivity;
- the probability that a randomly selected individual from the positive group has a test result indicating greater suspicion than that for a randomly chosen individual from the negative group.

When the variable under study cannot distinguish between the two groups, i.e. where there is no difference between the two distributions, the area will be equal to 0.5 (the ROC curve will coincide with the diagonal). When there is a perfect separation of the values of the two groups, i.e. there no overlapping of the distributions, the area under the ROC curve equals 1 (the ROC curve will reach the upper left corner of the plot).

The 95% Confidence Interval is the interval in which the true (population) Area under the ROC curve lies with 95% confidence.

The Significance level or P-value is the probability that the observed sample Area under the ROC curve is found when in fact, the true (population) Area under the ROC curve is 0.5 (null hypothesis: Area = 0.5). If P is small (P<0.05) then it can be concluded that the Area under the ROC curve is significantly different from 0.5 and that therefore there is evidence that the laboratory test does have an ability to distinguish between the two groups.

Youden index

<table>
<thead>
<tr>
<th>Youden index</th>
<th>0.0202</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% Confidence interval*</td>
<td>0.6979 to 0.9051</td>
</tr>
<tr>
<td>Associated criterion</td>
<td>&gt;108.9</td>
</tr>
<tr>
<td>95% Confidence interval²</td>
<td>&gt;107.9 to &gt;114.8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>90.91</td>
</tr>
<tr>
<td>Specificity</td>
<td>91.11</td>
</tr>
</tbody>
</table>

* BCa bootstrap confidence interval (1000 iterations; random number seed: 975).

The Youden index J (Youden, 1950) is defined as:

\[ J = \max \{ \text{sensitivity} \cdot c + \text{specificity} \cdot c - 1 \} \]

where c ranges over all possible criterion values.

Graphically, J is the maximum vertical distance between the ROC curve and the diagonal line.

The criterion value corresponding with the Youden index J is the optimal criterion value only when disease prevalence is 50%, equal weight is given to sensitivity and specificity, and costs of various decisions are ignored.
When the corresponding Advanced option has been selected, MedCalc will calculate $BC_a$ bootstrapped 95% confidence intervals (Efron, 1987; Efron & Tibshirani, 1993) for both the Youden index and its corresponding criterion value.

**Optimal criterion**

This panel is only displayed when disease prevalence and cost parameters are known.

<table>
<thead>
<tr>
<th>Optimal criterion</th>
<th>&gt;114.8</th>
</tr>
</thead>
<tbody>
<tr>
<td>95% Confidence interval</td>
<td>&gt;112.9 to &gt;114.8</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>76.36</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.78</td>
</tr>
</tbody>
</table>

* Taking into account disease prevalence (10%) and estimated costs: cost False Positive: 1; cost False Negative: 2; cost True Positive: 0; cost True Negative: 0

$BC_a$ bootstrap confidence interval (1000 iterations; random number seed: 978).

The optimal criterion value takes into account not only sensitivity and specificity, but also disease prevalence, and costs of various decisions. When these data are known, MedCalc will calculate the optimal criterion and associated sensitivity and specificity. And when the corresponding Advanced option has been selected, MedCalc will calculate $BC_a$ bootstrapped 95% confidence intervals (Efron, 1987; Efron & Tibshirani, 1993) for these parameters.

When a test is used either for the purpose of screening or to exclude a diagnostic possibility, a cut-off value with a higher sensitivity may be selected; and when a test is used to confirm a disease, a higher specificity may be required.

**Summary table**

This panel is only displayed when the corresponding Advanced option has been selected.

<table>
<thead>
<tr>
<th>Estimated specificity at fixed sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>80.00</td>
</tr>
<tr>
<td>90.00</td>
</tr>
<tr>
<td>95.00</td>
</tr>
<tr>
<td>97.50</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Estimated sensitivity at fixed specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specificity</td>
</tr>
<tr>
<td>------------</td>
</tr>
<tr>
<td>80.00</td>
</tr>
<tr>
<td>90.00</td>
</tr>
<tr>
<td>95.00</td>
</tr>
<tr>
<td>97.50</td>
</tr>
</tbody>
</table>

* $BC_a$ bootstrap confidence interval (1000 iterations; random number seed: 978).

The summary table displays the estimated specificity for a range of fixed and pre-specified sensitivities of 80, 90, 95 and 97.5% as well as estimated sensitivity for a range of fixed and pre-specified specificities (Zhou et al., 2002), with the corresponding criterion values.

Confidence intervals are $BC_a$ bootstrapped 95% confidence intervals (Efron, 1987; Efron & Tibshirani, 1993).
Criterion values and coordinates of the ROC curve

This section of the results window lists the different filters or cut-off values with their corresponding sensitivity and specificity of the test, and the positive (+LR) and negative likelihood ratio (-LR). When the disease prevalence is known, the program will also report the positive predictive value (+PV) and the negative predictive value (-PV).

When you did not select the option Include all observed criterion values, the program only lists the more important points of the ROC curve: for equal sensitivity (resp. specificity) it gives the threshold value (criterion value) with the highest specificity (resp. sensitivity). When you do select the option Include all observed criterion values, the program will list sensitivity and specificity for all possible threshold values.

- Sensitivity (with optional 95% Confidence Interval): Probability that a test result will be positive when the disease is present (true positive rate).
- Specificity (with optional 95% Confidence Interval): Probability that a test result will be negative when the disease is not present (true negative rate).
- Positive likelihood ratio (with optional 95% Confidence Interval): Ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease.
- Negative likelihood ratio (with optional 95% Confidence Interval): Ratio between the probability of a negative test result given the presence of the disease and the probability of a negative test result given the absence of the disease.
- Positive predictive value (with optional 95% Confidence Interval): Probability that the disease is present when the test is positive.
- Negative predictive value (with optional 95% Confidence Interval): Probability that the disease is not present when the test is negative.

Sensitivity, specificity, positive and negative predictive value as well as disease prevalence are expressed as percentages. Confidence intervals for sensitivity and specificity are "exact" Clopper-Pearson confidence intervals. Confidence intervals for the likelihood ratios are calculated using the "Log method" as given on page 109 of Altman et al. 2000. Confidence intervals for the predictive values are the standard logit confidence intervals given by Mercaldo et al. 2007.

Display ROC curve

The ROC curve will be displayed in a second window when you have selected the corresponding option in the dialog box.

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Sensitivity</th>
<th>95% CI</th>
<th>Specificity</th>
<th>95% CI</th>
<th>+LR</th>
<th>-LR</th>
<th>+PV</th>
<th>-PV</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;27.3</td>
<td>100.00</td>
<td>95.5 - 100.0</td>
<td>0.00</td>
<td>0.0 - 7.9</td>
<td>1.09</td>
<td>0.00</td>
<td>15.2</td>
<td>100.0</td>
<td>0.560</td>
</tr>
<tr>
<td>&gt;54.9</td>
<td>100.00</td>
<td>95.5 - 100.0</td>
<td>37.78</td>
<td>23.8 - 53.5</td>
<td>1.61</td>
<td>0.00</td>
<td>15.2</td>
<td>100.0</td>
<td>0.560</td>
</tr>
<tr>
<td>&gt;95</td>
<td>98.18</td>
<td>90.3 - 100.0</td>
<td>37.78</td>
<td>23.8 - 53.5</td>
<td>1.58</td>
<td>0.049</td>
<td>14.9</td>
<td>99.5</td>
<td>0.564</td>
</tr>
<tr>
<td>&gt;102.5</td>
<td>98.19</td>
<td>90.3 - 100.0</td>
<td>66.67</td>
<td>51.0 - 80.0</td>
<td>2.95</td>
<td>0.027</td>
<td>24.7</td>
<td>99.7</td>
<td>0.304</td>
</tr>
<tr>
<td>&gt;102.7</td>
<td>96.39</td>
<td>87.5 - 99.6</td>
<td>66.67</td>
<td>51.0 - 80.0</td>
<td>2.89</td>
<td>0.055</td>
<td>24.3</td>
<td>99.4</td>
<td>0.307</td>
</tr>
<tr>
<td>&gt;103.2</td>
<td>96.39</td>
<td>87.5 - 99.6</td>
<td>73.33</td>
<td>58.1 - 85.4</td>
<td>3.61</td>
<td>0.060</td>
<td>28.6</td>
<td>99.5</td>
<td>0.247</td>
</tr>
<tr>
<td>&gt;104</td>
<td>94.55</td>
<td>84.9 - 98.9</td>
<td>73.33</td>
<td>58.1 - 85.4</td>
<td>3.55</td>
<td>0.074</td>
<td>28.3</td>
<td>99.2</td>
<td>0.251</td>
</tr>
<tr>
<td>&gt;104.5</td>
<td>94.55</td>
<td>84.9 - 98.9</td>
<td>75.56</td>
<td>60.5 - 87.1</td>
<td>3.87</td>
<td>0.072</td>
<td>30.1</td>
<td>99.2</td>
<td>0.231</td>
</tr>
<tr>
<td>&gt;104.9</td>
<td>92.73</td>
<td>82.4 - 98.0</td>
<td>75.56</td>
<td>60.5 - 87.1</td>
<td>3.79</td>
<td>0.096</td>
<td>29.7</td>
<td>99.9</td>
<td>0.235</td>
</tr>
<tr>
<td>&gt;108.3</td>
<td>92.73</td>
<td>82.4 - 98.0</td>
<td>86.67</td>
<td>73.2 - 94.9</td>
<td>6.55</td>
<td>0.084</td>
<td>43.6</td>
<td>99.1</td>
<td>0.135</td>
</tr>
<tr>
<td>&gt;108.9</td>
<td>90.91</td>
<td>80.0 - 97.0</td>
<td>91.11</td>
<td>76.8 - 97.5</td>
<td>10.23</td>
<td>0.100</td>
<td>53.2</td>
<td>98.9</td>
<td>0.0962</td>
</tr>
<tr>
<td>&gt;110.7</td>
<td>81.82</td>
<td>69.1 - 90.9</td>
<td>91.11</td>
<td>76.8 - 97.5</td>
<td>9.26</td>
<td>0.20</td>
<td>50.6</td>
<td>97.8</td>
<td>0.116</td>
</tr>
<tr>
<td>&gt;112.2</td>
<td>81.82</td>
<td>69.1 - 90.9</td>
<td>93.33</td>
<td>81.7 - 96.6</td>
<td>12.27</td>
<td>0.19</td>
<td>57.7</td>
<td>97.9</td>
<td>0.0964</td>
</tr>
<tr>
<td>&gt;112.7</td>
<td>80.00</td>
<td>67.0 - 89.6</td>
<td>93.33</td>
<td>81.7 - 96.6</td>
<td>12.00</td>
<td>0.21</td>
<td>57.1</td>
<td>97.7</td>
<td>0.1000</td>
</tr>
<tr>
<td>&gt;112.9</td>
<td>80.00</td>
<td>67.0 - 89.6</td>
<td>95.66</td>
<td>84.9 - 99.5</td>
<td>16.00</td>
<td>0.21</td>
<td>66.7</td>
<td>97.7</td>
<td>0.0800</td>
</tr>
<tr>
<td>&gt;114.6</td>
<td>76.36</td>
<td>63.0 - 86.8</td>
<td>95.66</td>
<td>84.9 - 99.5</td>
<td>17.18</td>
<td>0.25</td>
<td>65.6</td>
<td>97.3</td>
<td>0.0873</td>
</tr>
<tr>
<td>&gt;114.8</td>
<td>76.36</td>
<td>63.0 - 86.8</td>
<td>97.78</td>
<td>88.2 - 99.9</td>
<td>34.36</td>
<td>0.24</td>
<td>79.2</td>
<td>97.4</td>
<td>0.0673</td>
</tr>
<tr>
<td>&gt;133.1</td>
<td>14.55</td>
<td>6.5 - 26.7</td>
<td>97.78</td>
<td>88.2 - 99.9</td>
<td>6.55</td>
<td>0.87</td>
<td>42.1</td>
<td>91.1</td>
<td>0.191</td>
</tr>
<tr>
<td>&gt;133.4</td>
<td>14.55</td>
<td>6.5 - 26.7</td>
<td>100.00</td>
<td>92.1 - 100.0</td>
<td>0.05</td>
<td>1.00</td>
<td>100.0</td>
<td>91.3</td>
<td>0.171</td>
</tr>
<tr>
<td>&gt;143.6</td>
<td>0.00</td>
<td>0.0 - 6.5</td>
<td>100.00</td>
<td>92.1 - 100.0</td>
<td>1.00</td>
<td>0.00</td>
<td>100.0</td>
<td>90.0</td>
<td>0.200</td>
</tr>
</tbody>
</table>

In a ROC curve the true positive rate (Sensitivity) is plotted in function of the false positive rate (100-Specificity) for different cut-off points. Each point on the ROC plot represents a sensitivity/specificity pair corresponding to a particular decision threshold. A test with perfect discrimination (no overlap in the two distributions) has a ROC plot that passes through the upper
left corner (100% sensitivity, 100% specificity). Therefore, the closer the ROC plot is to the upper left corner, the higher the overall accuracy of the test (Zweig & Campbell, 1993).

When you click on a specific point of the ROC curve, the corresponding cut-off point with sensitivity and specificity will be displayed in a small (non-printable) window.

**Presentation of results**

The prevalence of a disease may be different in different clinical settings. For instance, the pre-test probability for a positive test will be higher when a patient consults a specialist than when he consults a general practitioner. Since positive and negative predictive values are sensitive to the prevalence of the disease, it would be misleading to compare these values from different studies where the prevalence of the disease differs, or apply them in different settings.

The data from the results window can be summarized in a table. The sample size in the two groups should be clearly stated. The table can contain a column for the different criterion values, the corresponding sensitivity (with 95% CI), specificity (with 95% CI), and possibly the positive and negative predictive value. The table should not only contain the test’s characteristics for one single cut-off value, but preferably there should be a row for the values corresponding with a sensitivity of 90%, 95% and 97.5%, specificity of 90%, 95% and 97.5%, and the value corresponding with the Youden index or highest accuracy.

With these data, any reader can calculate the negative and positive predictive value applicable in his own clinical setting when he knows the prior probability of disease (pre-test probability or prevalence of disease) in this setting, by the following formulas based on Bayes’ theorem:

$$PPV = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

and

$$NPV = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)}$$

The negative and positive likelihood ratio must be handled with care because they are easily and commonly misinterpreted.
Interactive dot diagram

In addition to the ROC curve, MedCalc offers a second graphical display to study the accuracy of a diagnostic test, namely an *Interactive dot diagram*.

In the *Interactive dot diagram* the data of the negative and positive groups are displayed as dots on two vertical axes. Initially, a horizontal line indicates the cut-off point with the best separation (minimal false negative and false positive results) between the two groups. The corresponding test characteristics *sensitivity* and *specificity* are shown at the right side of the display.

**Required input**

- **Variable**: select the variable of interest.
- **Classification variable**: select a dichotomous variable indicating diagnosis (0=negative, 1=positive). If your data are coded differently, you can use the Define status (see p. 91) tool to recode your data.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases (e.g. AGE>21, SEX="Male").
- **Options**: Logarithmic transformation of data.

**Graph**

By clicking in the display, you can move the horizontal line to other values or cut-off points.

**Plot versus criterion values**

In this graph you can plot the following statistics against the criterion values:

- Sensitivity and specificity, and optionally their 95% Confidence Intervals
• Youden index
  The Youden index for a single point on the ROC curve is defined as
  \[
  \text{Youden index} = \frac{\text{sensitivity} + \text{specificity} - 1}{1}
  \]

• Positive predictive value (PPV)
  Probability that the disease is present when the test is positive.
  \[
  PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}
  \]

• Negative predictive value (NPV)
  Probability that the disease is not present when the test is negative.
  \[
  NPV = \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}
  \]

• Efficiency
  Efficiency is defined as (Greiner et al., 2000):
  \[
  \text{Efficiency} = P \times Se + (1 - P) \times Sp
  \]
  with \( P \) = Prevalence, \( Se \) = Sensitivity, and \( Sp \) = Specificity

• Cost
  The Cost is the average cost resulting from the use of the diagnostic test at a particular decision level.
  It takes into account disease prevalence and cost of true and false positive, and true and false negative decisions.
  \[
  Cost = FNc \times (1 - Se) \times P
  + FPc \times (1 - Sp) \times (1 - P)
  + TPc \times Se \times P
  + TNc \times Sp \times (1 - P)
  \]
  with \( P \) = Prevalence, \( Se \) = Sensitivity, \( Sp \) = Specificity, \( FNc \) the cost of a false negative decision and \( FPc \) the cost of a false positive decision, \( TPc \) the cost of a true positive decision and \( TNc \) the cost of a true negative decision.
  The Misclassification-Cost Term (MCT, Greiner et al., 2000) takes into account disease prevalence and cost of false positive and false negative decisions only:
  \[
  MCT = \frac{FNc}{FPc} \times P \times (1 - Se) + (1 - P) \times (1 - Sp)
  \]
  Costs can be financial costs or health costs, but all 4 cost factors need to be expressed on a common scale.
  The minimum value of Cost or MCT may be used as an indicator for an optimal selection criterion.

Required input
• Variable: select the variable of interest.
• Classification variable: select a dichotomous variable indicating diagnosis (0=negative, 1=positive). If your data are coded differently, you can use the Define status (see p. 91) tool to recode your data.
• Filter: (optionally) a data filter in order to include only a selected subgroup of cases (e.g. AGE>21, SEX="Male").
Options
You can select one of the following 2 plots: sensitivity/specificity or misclassification-cost term

- Sensitivity and specificity
  - Show 95% Confidence Intervals as:
    - **error bars**: show the 95% Confidence Interval of sensitivity and specificity as error bars
    - **connected lines**: show the 95% Confidence Interval of sensitivity and specificity as connected lines (recommended when number of criterion values is high)
    - **do not show CI**: do not show the 95% Confidence Interval of sensitivity and specificity in the graph.

- Youden index
- Positive Predictive Value
- Negative Predictive Value
- Efficiency
- Cost
  
  **Option Misclassification-Cost Term (MCT):** see above.
  
  You need to enter
  
  - FNC: the cost of a false negative decision
  - FPC: the cost of a false positive decision
  - TPC: the cost of a true positive decision - not required for the calculation of the Misclassification-Cost Term (MCT).
  - TNc: the cost of a true negative decision - not required for the calculation of the Misclassification-Cost Term (MCT).

For Positive and Negative Predictive Value, Efficiency, and Cost, data on disease prevalence are required. The program can create curves for different prevalences in the same graph.

- Select Observed prevalence if the number of cases in the positive and the negative group reflect the real prevalence of the disease in the population (this value will be indicated with an asterisk in the graph's legend).
- Or enter up to 4 different values for prevalence, expressed as percentages (0..100).

If the data require a logarithmic transformation (e.g. when the data are positively skewed), select the Logarithmic transformation option.

Graph

In the graph the selected statistic is plotted against the criterion value.

Sensitivity and specificity, Positive and Negative Predictive values are displayed as percentages.
The maximum values of Youden index and Efficiency, and the minimum values of Cost are reported in the graphs info box. To obtain the info box you right-click in the graph and select "Info" in the pop-up menu.

**Examples**

Plot of sensitivity and specificity versus criterion values:

![Plot of sensitivity and specificity](image1)

Plot of cost versus criterion values for different levels of disease prevalence:

![Plot of cost versus criterion](image2)

**Plot versus prevalence**

In this graph you can plot positive and negative predictive values against disease prevalence, for one pair of sensitivity/specificity values.

You obtain sensitivity and specificity values from ROC curve analysis or from the literature. For a definition of Positive and Negative predictive value see the previous section.

**Required input**

- Sensitivity and Specificity: enter sensitivity and specificity as a percentage.
- Options – See below.

For example, Giguère et al. (2016) studied the use of stall-side serum amyloid (SAA) for early detection of pneumonia on a farm endemic for R. equi. For an optimal cut-point of >53 μg/mL they found a sensitivity of 64% and a specificity of 77%.
In the graph the positive and negative predictive values are plotted against disease prevalence.

Plot the 95% confidence intervals

MedCalc can also draw the 95% confidence intervals in the graph. This requires you to enter the number of cases in the diseased and normal groups. These are the number of cases included in the study in which sensitivity and specificity were established.

First click the option 95% Confidence Interval and next enter the number of cases in the diseased and normal groups.

The study by Giguère et al. (2016) included 25 foals with a culture-confirmed R. equi pneumonia (the positive or diseased cases in which sensitivity was established), and 22 foals that remained clinically healthy during the entire breeding season (the negative or normal cases, in which specificity was established).
The new graph includes the 95% confidence intervals for positive and negative predictive values. MedCalc calculates the confidence intervals for the predictive values using the standard logit method given by Mercaldo et al. 2007.

Predictive values

When you do have access to the raw data to perform ROC curve analysis, you can still calculate positive and negative predictive values for a test when the sensitivity and specificity of the test as well as the disease prevalence (or the pretest probability of disease) are known, using Bayes' theorem (p. 229).

Required input

Enter the sensitivity and specificity of a test (expressed as percentages), and the disease prevalence (also expressed as a percentage).

Optionally you can enter the number of cases in the diseased and normal groups. These are the number of cases included in the study in which sensitivity and specificity were established. Input of these numbers will enable MedCalc to calculate 95% confidence intervals for the positive and negative predictive values.
Results
When you have entered the data, click the TEST button to obtain the positive predictive value and negative predictive value.

- Positive predictive value (PPV): probability that the disease is present when the test is positive (expressed as a percentage).
- Negative predictive value (NPV): probability that the disease is not present when the test is negative (expressed as a percentage).
- When the sample sizes in the diseased and normal groups are known, MedCalc calculates confidence intervals for the predictive values using the standard logit method given by Mercaldo et al. 2007.

Interval likelihood ratios

Description
This procedure allows the calculation of likelihood ratios (with 95% CI) for user-defined data intervals (Gardner & Greiner, 2006).

When test results have a continuous or ordinal outcome then valuable information is lost when the data are dichotomized for the calculation of sensitivity, specificity and likelihood ratios as in ROC curve analysis.

Interval likelihood ratios may be more powerful because they use more information contained in the data.

The likelihood ratio can be used to calculate the post-test probability of disease from the pre-test probability of disease.

Required input

- **Variable**: select the variable of interest.
- **Classification variable**: select a dichotomous variable indicating diagnosis (0=negative, 1=positive). If your data are coded differently, you can use the Define status (see p. 91) tool to recode your data.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases (e.g. AGE>21, SEX="Male").

Define intervals
After some calculations, a new dialog box is displayed with suggested data intervals which you can modify.
You can define up to 12 intervals. For each interval, you enter the lower and upper (inclusive) boundaries. For categorical variables, with few categories, it may suffice to enter only one number to define the “interval” as one single category.

Results

For each data interval, the program reports the number of positive and negative cases in the interval and the corresponding Likelihood ratio with 95% Confidence interval.

The likelihood ratio can be used to calculate the post-test odds from the pre-test odds off disease:

\[
\text{post-test odds} = \text{pre-test odds} \times \text{likelihood ratio}
\]

The relation between odds and probability is:

\[
\text{odds} = \frac{p}{1-p} \quad \text{and} \quad p = \frac{\text{odds}}{1 + \text{odds}}
\]

Using these equations, you can calculate the post-test probability of disease from the pre-test probability of disease.

If, for example, the pre-test probability of disease is 0.6 then the pre-test odds is 0.6/(1-0.6) = 1.5. For a patient with test result in the interval 50-60, corresponding with a likelihood ratio of 12, the post-test odds are 1.5 x 12 = 18. The post-test probability of disease is 18/(1+18) = 0.95.
Comparison of ROC curves

Select Comparison of ROC curves in the menu when you want to test the statistical significance of the difference between the areas under 2 to 6 dependent ROC curves (derived from the same cases).

Required input

Data

- **Variables**: select the different variables (at least 2, maximum 6).
- **Classification variable**: select a dichotomous variable indicating diagnosis (0=negative, 1=positive). If your data are coded differently, you can use the Define status (see p. 91) tool to recode your data.
- **Filter**: (optionally) a data filter in order to include only a selected subgroup of cases (e.g. AGE>21, SEX="Male").

Methodology

- **DeLong et al.**: use the method of Delong et al. (1988) for the calculation of the Standard Error of the Area Under the Curve (AUC) and of the difference between two AUCs (recommended).
- **Hanley & McNeil**: use the methods of Hanley & McNeil (1982, 1983) for the calculation of the Standard Error of the Area Under the Curve (AUC) and of the difference between two AUCs.
- **Binomial exact Confidence Interval for the AUC**: calculate exact Binomial Confidence Intervals for the Area Under the Curves (AUC) (recommended). If this option is not selected, the Confidence Intervals for the AUCs are calculated as AUC ± 1.96 SE (Standard Error). This option does not apply to the difference between two AUCs.

Graph

- Select Display ROC curves window to obtain the ROC plots in a separate graph window.
- Option: mark points corresponding to criterion values.

Results

The results window shows the data for the different ROC curves followed by the result of pairwise comparison of all ROC curves: the difference between the areas, the standard error, the 95% confidence interval for the difference and P-value. If P is less than the conventional 5% (P<0.05), the conclusion is that the two compared areas are significantly different.
Display ROC curves

When you have selected *Display ROC curves window* in the dialog box, the program will also open a graph window with the different ROC curves.
Create tables

Create summary statistics table

This allows creating a publication-ready summary statistics table of several variables with possible subgroups.

Required input

- **Variables**: select the variables of interest in the top left box and next click the right arrow button to move the selection to the list of selected variables.
- **Grouping variable**: (optionally) a categorical variable that defines subgroups.
- **Filter**: an optional data filter.
- **Statistics**: select the statistics to be displayed in the table: Sample size, mean, 95% CI for the mean, etc.
• Options:
  ▪ Try Logarithmic transformation if distribution is not Normal: if this option is selected the software will perform a test for Normal distribution for all variables. If the data of a variable are found not to be Normally distributed, a Logarithmic transformation is attempted. If after logarithmic transformation the data are found to agree better with a Normal distribution, the transformation is applied and the back-transformed results will be displayed in the table.
  ▪ Report variables vertically or horizontally: option to report the variables vertically (in rows below each other) or horizontally (in columns next to each other).

Results
The results window displays the summary statistics table.
• With the option ‘Report variables vertically’:

• With the option ‘Report variables horizontally’:
Create correlation table

This command allows creating a publication-ready table of correlation coefficients.

Required input

- **Variables**: select the variables of interest in the top left box and next click the right arrow button to move the selection to the list of selected variables.
- **Filter**: an optional data filter.
- **Method**: select Pearson correlation (parametric) or Spearman rank correlation (non-parametric).
- **Correlogram**: select this option for a correlogram. In a correlogram the table cells are colored according to the magnitude of the correlations (see below).

Results

The results window displays the correlation table.

Correlogram

In a correlogram the table cells are colored according to the magnitude of the correlations, ranging from dark red for positive correlations to dark blue for negative correlations. Furthermore, the variables are sorted so that "patterns" in the correlations can more easily be detected.
Comparison of independent samples

Allows to create a table with different comparison of independent samples tests.

Required input

- Variables: select the variables of interest in the top left box and next click the right arrow button to move the selection to the Selected variables list.
- Filter for group 1 and Filter for group 2: the filters used to identify the two groups in which the selected variables must be compared.
  
  For example:
  Filter for group 1: TREATMENT="A"
  Filter for group 2: TREATMENT="B"
  Differences will be calculated as Group2-Group1.
- Options: select Independent samples t-test (parametric) or the Mann-Whitney test (non-parametric).

Results

The program creates a table with the results of the selected test for each variable.
Comparison of paired samples

Allows to create a table with different comparison of paired samples tests.

Required input

- Variables: select the variables of interest in the top left box and next click the right arrow button to move the selection to the Paired variables list.
  - In the left box, you must select 2 variables or more.
  - When you click the right arrow button, all possible pairs that can be formed with the selected variables are added to the Paired variables list.
    When you have selected 2 variables A and B, 1 pair A-B will be added in the right box.
    When you have selected 3 variables A, B, and C, then 3 pairs A-B, A-C and B-C will be added in the right box.
  - To remove a pair from the right box, select the corresponding row and click left arrow button in the center.
    Differences will be calculated Variable2-Variable1. You can swap the variables of selected variable pairs by clicking the button.
- Filter: on optional filter to include only a selected subgroup of cases.
- Options: select Paired samples t-test (parametric) or the Wilcoxon test for paired samples (non-parametric).

Results

The program creates a table with the results of the selected test for each variable pair.
Multiple frequency tables

Description
Allows to create frequency tables for several categorical variables in one single procedure.

Required input

- Variables: select the categorical variables of interest in the top left box and next click the right arrow button to move the selection to the Selected variables list.
- Grouping variable: (optionally) a categorical variable that defines subgroups.
- Filter: on optional filter to include only a selected subgroup of cases.
- Options: select Paired samples t-test (parametric) or the Wilcoxon test for paired samples (non-parametric).

Examples
Example with multiple categorical variables, without grouping variable.
If a Grouping variable has been selected, the program creates crosstabulation tables of each variable with this grouping variable.

This results in the following display:
### Frequency Tables

<table>
<thead>
<tr>
<th>Classification X</th>
<th>GENDER</th>
<th>OUTCOME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>56</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>(56.0%)</td>
<td>(44.0%)</td>
</tr>
</tbody>
</table>

- Chi-squared: 0.391
- DF: 1
- Significance level: \( P = 0.5316 \)

<table>
<thead>
<tr>
<th>Classification X</th>
<th>SMOKING</th>
<th>GENDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>31</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>(62.0%)</td>
<td>(38.0%)</td>
</tr>
</tbody>
</table>

- Chi-squared: 0.065
- DF: 1
- Significance level: \( P = 0.7993 \)
Graphs menu

Data comparison graphs

In MedCalc, several graphs are available for comparison of 2 sets of data. You can select the graph type in the dialog box that appears after you have selected Data comparison graphs in the menu:

Several graphical elements can be selected to compose the graph, and some of these can be combined.

- **Bars, Horizontal lines, Markers and/or Connecting lines for means or medians.**
- **Error bars**: the following error bars are available if at least one of the graph types Bars, Horizontal lines, Markers and/or Connecting lines is selected:
  - If **mean** is selected: (none), or 95% CI for the mean, 1 SD, 2 SD, 3 SD, 1 SEM, range
    - Note that 2 SEM is not in this list: when the number of cases is large, mean ± 2 SEM corresponds to the 95% confidence interval (CI) for the mean. When the number of cases is small, then the 95% CI interval is calculated as mean ± t * SEM, where t is taken from a t-table (with DF=n-1 and area A=95%) (see SEM on p. 73).
    - Although 1 SEM gives the more narrow error bar, this option is not recommended since the resulting error bar may be highly misleading, especially when the number of cases in the groups is different. Preferably the 95% CI for the mean is used for providing a valid graphical comparison of means (Pocock, 1983), or use 2 SD as an indication for the variability of the data.
  - If **median** is selected: (none), or 95% CI for the median, 25-75 percentile, 10-90 percentile, 5-95 percentile, 1-99 percentile, range
    - When the number of cases is small, it is possible that the 95% CI for the median is not defined and that it will not be displayed in the graph.
    - When you use percentile ranges, take into account the number of observations: you need at least 100 observations for 1-99 percentiles, at least 20 for 5-95 percentiles, at least 10 for 10-90 percentile and at least 4 for 25-75th percentiles.
- The basic **Box-and-Whisker plot** (Tukey, 1977) is described on page 83.
- **Notched box-and-whisker plot**, in this variation of the box-and-whisker plot confidence intervals for the medians are provided by means of notches surrounding the medians (McGill et al., 1978). If the notches about two medians do not overlap, the medians are significantly different at a ± 95% confidence level.
- When you select **Dot plot**, all observations will be displayed in the graph.

If you want a logarithmic transformation of the values, select the **Logarithmic transformation** option.
Multiple comparison graphs

You can use Multiple comparison graphs to visualize the influence of a qualitative (discrete) factor on another (continuous) variable.

The graph can be composed from different elements: Bar, Horizontal Lines, Markers or Connecting lines for means or medians, with choice of different error bars for mean (95% CI, 1 SEM, 1 SD, 2 SD, 3 SD, range) or median (95% CI, 25-75 percentiles, 10-90 percentiles, 5-95 percentiles, 1-99 percentiles, range), Box-and-whisker plot (Tukey, 1977) or Notched box-and-whisker plot (McGill et al., 1978), and/or Dot plot (display all data) (see p. 248).

The following need to be entered in the dialog box: for Data select a continuous variable, and for Factor codes a qualitative factor. The qualitative factor may either be character or numeric codes. These codes are used to break-up the data into several subgroups.

When you want to use a continuous variable as the qualitative, discrete factor, you can convert the continuous data by using the CATEGORISE function (see p. 324) or IF function (see p. 325).

Several graphical elements can be selected to compose the graph, for a description, see p. 248. If logarithmic transformation of the data is required, select the Logarithmic transformation option.

After you have completed the form, click the OK button to obtain the graph.

Some combinations of graphs are shown in the following examples:
Clustered multiple comparison graphs can be used when you want to visualize the influence of two qualitative (discrete) factors on another (continuous) variable.

The qualitative factors may either be character or numeric codes. These codes are used to break-up the data into different subgroups.

The graph can be composed from different elements: Bar, Horizontal Lines, Markers or Connecting lines for means or medians, with choice of different error bars for mean (95% CI, 1 SEM, 1 SD, 2 SD, 3 SD, range) or median (95% CI, 25-75 percentiles, 10-90 percentiles, 5-95 percentiles, 1-99 percentiles, range), Box-and-whisker plot (Tukey, 1977) or Notched box-and-whisker plot (McGill et al., 1978), and/or Dot plot (display all data) (see p. 248)
How to enter data

You need to enter data for one continuous variable (MEASUREMENT1 in the example) and 2 categorical variables (GENDER and TREATMENT in the example).

Required input

The following need to be entered in the dialog box:

- **Data**: a continuous variable that will be represented in the graph;
- **Factor codes**: a categorical variable that contains codes to break-up the data into subgroups.
- **Define clusters by factor**: a second categorical variable to make a second subdivision in the subgroups.
- **Filter**: a data filter to include only a selected subgroup of cases in the graph.
- **Graphs**: several graphical elements can be selected to compose the graph, for a description, see p. 248.
- **Options**: Logarithmic transformation of data.
Multiple variables graphs

When you want to compare different variables, i.e. data entered in different columns of the spreadsheet, you can use *Multiple variables graphs*. In the dialog box, you select the different variables of interest, optionally followed by a data filter to include only a selected subgroup of cases in the graph.

Next select the different elements of the graph: *Bar, Horizontal Lines, Markers or Connecting lines* for means or medians, with choice of different error bars for mean (95% CI, 1 SEM, 1 SD, 2 SD, 3 SD, range) or median (95% CI, 25-75 percentiles, 10-90 percentiles, 5-95 percentiles, 1-99 percentiles, range), *Box-and-whisker plot* (Tukey, 1977) or *Notched box-and-whisker plot* (McGill et al., 1978), and/or *Dot plot* (display all data) (see p. 248).
You can select the option of logarithmic transformation of the data, or the option to include only complete cases in the graph. If the latter option is selected, only cases with valid numerical data for all variables entered in the dialog box will be included in the graph.

In addition to the graphical elements as for Data comparison graphs described on page 248, the Multiple variables graphs also include the multiple Dot and line diagram and Cumulative frequency distribution.

In the Dot and line diagram, all observations are plotted as individual dots, and observations from the different cases (rows in the spreadsheet) are connected by a line.

Clustered multiple variables graph

When you want to compare subgroups across different variables, you can use Clustered multiple variables graphs. Clustered multiple variables graphs include: Bar, Horizontal Lines, Markers or Connecting lines for means or medians, with choice of different error bars for mean (95% CI, 1 SEM, 1 SD, 2 SD, 3 SD, range) or median (95% CI, 25-75 percentiles, 10-90 percentiles, 5-95 percentiles, 1-99 percentiles, range), Box-and-whisker plot (Tukey, 1977) or Notched box-and-whisker plot (McGill et al., 1978), and/or Dot plot (display all data) (see p. 248)
In this dialog box, you enter:

- **Variables**: the different variables of interest.
- **Define clusters by**: a categorical variable containing codes to break-up the data into subgroups.
- **Filter**: a data filter to include only a selected subgroup of cases in the graph.
- **Graphs**: several graphical elements can be selected to compose the graph, for a description, see p. 248.
- **Options**:
  - Logarithmic transformation: Logarithmic transformation of all data.
  - Complete cases only: Option to include only complete cases in the graph. If selected, only cases with valid numerical data for all variables selected in the dialog box will be included in the graph.
  - Clustered by variables: Let clusters be defined by the Variables (X-axis will display groups defined by the Categorical variable, list of variables will appear in the Legend block).

This is the same graph, but with the option “Clustered by variables” selected:
This is an example of a graph with option "Connecting lines" selected:
Multiple line graph

Description
With this command you create graphs that show consecutive observations of different variables.

Required input

Select the variables of interest, and optionally a data filter to include only particular cases in the graph. Also you can enter a variable containing labels for the X-axis (e.g. dates).

Options
- Logarithmic transformation: select this option to transform all data logarithmically
- Complete cases only: a case (spreadsheet row) will only be included in the graph when data are available for all variables.
- Markers: mark observations in the graph.

Example
To obtain a quality control chart select *Control chart* in the *Graphs* menu. In this chart the data are plotted consecutively, together with a line at the mean, and at -2s, +2s, -3s and +3s (s = standard deviation), i.e. at 95% and 99.7% confidence limits (Westgard et al., 1981).

In the *Quality control* input box define the data to be represented in the quality control chart. First, enter the variable's name in the variable input field. Optionally, you may also enter a data filter in order to include only a subgroup of data in the graph, e.g. measurements by a particular technician. Also you can enter a variable containing labels for the X-axis (e.g. dates).

Next select the type of control limits:

- The control limits can be based on the data and in this case the program will calculate the mean and standard deviation of the selected data.
  
  Option: "until n =": if the control limits must be based on the first observations only, you can enter the required number here. E.g. if you have 40 observations to be plotted in the control chart, but the control limits must be based on the first 20 observations only, you enter the number 20 here.

- You can select ‘Standard’ and in this case enter the Mean and Standard Deviation (SD) of the standard used.

- Finally, you can enter the reference value with upper and lower control and warning limits. In this case the upper and lower control and warning limits can be asymmetrical.

**Rules**: see below

In the following example, a control chart is created for the technician with code 2.

The result is displayed in the following figure:
Rules

When you click the Select rules button, the following dialog box is displayed, in which you can select a combination of rules to be applied in the control chart:

1:2S rule

If you select the 1:2S rule then the software will check all following rules only if the measurement exceeds the mean ± 2SD (or the warning limits).
If this rule is not selected, then the following rules will be checked also when the measurement does not exceed the mean ± 2SD warning limits.
This will particularly influence the 4:1S rule and 10:X rule.

1:3S rule

If the measurement exceeds the mean + 3SD or mean - 3SD, then the run is considered out of control.
This rule mainly detects random error, but may also be an indication of a large systematic error.

2:2S rule

The run is considered out of control when 2 consecutive measurements exceed the same mean + 2S or the same mean - 2S limit.
This rule detects systematic error.

4:1S rule

The run is considered out of control when 4 or more consecutive measurements exceed the same (mean + 1S) or (mean - 1S) limit.
This rule detects systematic bias.
10:X rule

The run is considered out of control when 10 or more consecutive measurements are on the same side of the mean. The software allows you to select a different value less than 10 for a higher sensitivity or more than 10 for a lower sensitivity of this rule.

This rule detects systematic bias.

Example

When the option *Apply rules* is selected in the Control chart dialog box, and the 1:3S rule is selected in the Multirules dialog box, then when a measurement exceeds the mean + 3SD or mean - 3SD, this value will be indicated in the graph (using a marker drawn in the "warning" color). Click the value to display information on this measurement:

![Control chart image]

Custom control chart

When there are no data available for the variable, the program will ask whether you want to create a custom control chart, i.e. a blank control chart that you can print and on which the lab technician can mark the control measurements manually.

Youden plot

The Youden plot is a graphical method to analyze inter-laboratory data, where all laboratories have analyzed 2 samples. The plot visualizes within-laboratory variability as well as between-laboratory variability.

In medical literature you may encounter different graphs referred to as *Youden plot*.

Youden plots

1. The original Youden plot

For the original Youden plot (Youden, 1959) the two samples must be *similar and reasonably close in the magnitude of the property evaluated*.

The axes in this plot are drawn on the same scale: one unit on the x-axis has the same length as one unit on the y-axis.

Each point in the plot corresponds to the results of one laboratory and is defined by a first response variable on the horizontal axis (i.e. run 1 or product 1 response value) and a second response variable 2 (i.e., run 2 or product 2 response value) on the vertical axis.

A horizontal median line is drawn parallel to the x-axis so that there are as many points above the line as there are below it. A second median line is drawn parallel to the y-axis so that there are as many points on the left as there are on the right of this line. Outliers are not used in determining the position of the median lines. The intersection of the two median lines is called the Manhattan median.

A circle is drawn that should include 95% of the laboratories *if individual constant errors could be eliminated*. A 45-degree reference line is drawn through the Manhattan median.
Interpretation

Points that lie near the 45-degree reference line but far from the Manhattan median indicate large systematic error. Points that lie far from the 45-degree line indicate large random error. Points outside the circle indicate large total error.

2. The Youden plot adapted for non-comparable samples

If two different products are being tested, MedCalc draws a Youden plot as described above, but the axes of the plot are not drawn on the same scale, but in this case, one standard deviation on the X-axis has the same length as one standard deviation on the y-axis. Analogous to the 45-degree reference line in the original Youden plot, a reference line is drawn which in this case represents a constant ratio of the two samples. The interpretation is the same as for the original Youden plot.

3. Other variations of the Youden plot

A common variation of the Youden plot is a scatter diagram as described above, but the circle is replaced with one or more rectangles representing 1, 2 or 3SD on both the x-axis and y-axis.

The Youden dialog box

Sample A and Sample B: select the variables for the first and second sample. Filter: an (optional) data filter to include only a selected subgroup of cases in the graph. Options

- Areas – Circles:
  - 90%, 95% or 99% Coverage probability: circles can be drawn that include 90%, 95% or 99% of the laboratories if individual constant errors could be eliminated.
  - Samples are similar: select this option if the samples similar and reasonably close in the magnitude of the property evaluated.
- Areas – Rectangles:
  - 1 SD, 2SD or 3SD: draws rectangles representing 1, 2 or 3 SD on both the x-axis and y-axis.
- Outlier detection: MedCalc will detect outliers automatically and exclude them for calculations.
- Diagonal line: draws a diagonal reference line
- Subgroups: use the Subgroups button if you want to identify subgroups in the plot. A new dialog box is displayed in which you can select a categorical variable. The graph will use different markers for the different categories in this variable.
Examples

Fig. 1.
The original Youden plot. PR_A and PR_B represent similar samples. Notice the two outliers in the upper right corner of the graph. Circle represents 95% coverage probability.

Fig 2.
Example of a Youden plot adapted for samples that are not similar. Circle represents 95% coverage probability.

Fig. 3
Variation of Youden plot. The data are the same as in Figure 2. Rectangles represent 1 and 2 SD.

Print all
To print multiple copies of the Youden plot, with each copy highlighting one laboratory:
• right-click in the Youden plot
• select Print all in the pop-up menu
Polar plot

A polar plot is the plot of data expressed in polar coordinates, with radius $r$ as a function of angle $\theta$. The radius $r$ is the distance from the central point and $\theta$ is the angle from the x-axis:

The Polar plot dialog box

- **Radius**: a variable containing the Radius data
- **Angle**: a variable containing the Angle data
- **Filter**: an optional filter to include a subset of data in the plot
- **Options**
  - **Angle unit**: select whether the values for Angle are expressed in Radians (1 circle = $2\pi$) or Degrees (1 circle = $360^\circ$), or are Percentages (1 circle = 100).
  - **Rotation**: the plot can be rotated clockwise or counterclockwise
- **Zero angle**: the angle origin can be North, East, South or West.
- **Connect points**: an option to connect consecutive points in the plot.

**Example**

Polar plot with counterclockwise rotation and angle origin East:

Polar plot with clockwise rotation and angle origin North:

**Forest plot**

A Forest plot presents a series of central values and their confidence intervals in a graphic manner, so that they can easily be compared. The central values are represented by markers and the confidence intervals by horizontal lines.

**How to enter the data**

On different rows of the spreadsheet you enter a descriptive label, the central value and the low and high values of the confidence interval.
Required input

- **Variables**
  - **Labels**: a variable that contains labels to be displayed at the left side of the graph
  - **Central value**: a variable that contains the central values
  - **Confidence Interval Low value**: a variable that contains the low values of the confidence intervals
  - **Confidence Interval High value**: a variable that contains the high values of the confidence intervals

- **Filter**
  - Optionally, enter a **Filter** in order to include only a selected subgroup of cases in the graph.

- **Options**
  - Logarithmic scale
  - Single line style and marker type: when you select this option, all items will have the same line and marker style and color.
Result

![Forest plot image]

**Function plot**

The function plot can be used to plot a standard user-defined mathematical function such as $y = \sin(x)$ or $y = \exp(-x^2/2)/\sqrt{2\pi}$.

**The Function plot dialog box**

- **Functions**: the dialog box allows to enter up to 6 functions. For the function $y = \sin(x)$ you just enter $\sin(x)$. To build a more complex function, click the $\mathbb{F}$ button to call the Formula editor dialog box.
- **Graph options**
  - $X$-axis: enter the range over which you want to plot the function.
  - $Y$-axis: select the option "automatic" to let the program format the $Y$-axis, or you can enter the range for the $Y$-axis in the corresponding input fields.
Tests menu

The Tests menu includes statistical tests on tabulated or summarized data. These tests are useful when you do not have the raw data available in the spreadsheet, e.g. when you want to compare e.g. two means reported in the literature, and you do not have access to the raw data.

Test for one mean

The Test for one mean is used to test the hypothesis that a sample mean is equal to a given mean (with unknown standard deviation) or certified value.

![Test for one mean dialog box]

First enter the sample mean, standard deviation and sample size (n) in the dialog box. Next, in the input field Test mean is equal to: you enter the value to compare the mean to. As an example, a sample mean of 98 with standard deviation of 2.8 and sample size 8 is compared with the certified value 100.

When all data have been entered click the Test button.

First the program displays a 95% confidence interval for the mean. Next, the t-value, degrees of freedom and probability (P) are displayed. If the P-value is less than 0.05, then the hypothesis that the mean is equal to the given value is rejected, and the alternative hypothesis that there is a significant difference between the two values can be accepted.

In the example, the calculated P-value is 0.0831 so you do not reject the hypothesis that the sample mean of 98 is equal to 100.

In the Comment input field you can enter a comment or conclusion that will be included on the printed report.
Test for one proportion

Description

The Test for one proportion in the Tests menu can be used to test the hypothesis that an observed proportion is equal to a pre-specified proportion.

This test is not performed on data in the spreadsheet, but on statistics you enter in a dialog box.

Required input

- **Observed proportion (%)**: the observed proportion, expressed as a percentage.
- **Sample size**: the sample size or total number of observations.
- **Null Hypothesis value (%)**: the pre-specified proportion (the value to compare the observed proportion to), expressed as a percentage.

When all data have been entered click the Test button.

Results

The results panel displays:

- the 95% Confidence Interval of the observed proportion.
- z statistic and associated P-value. If the P-value is less than 0.05, the hypothesis that the observed proportion is equal to the pre-specified proportion value is rejected, and the alternative hypothesis that there is a significant difference between the two proportions can be accepted.

Chi-squared test

You can use the Chi-squared test in the Tests menu to test the statistical significance of differences in a classification system (one-way classification) or the relationship between two classification systems (two-way classification).

To perform this Chi-squared test, you must already have the data classified in a frequency table (for the test on raw data, see p. 139).

A frequency table shows the number of cases that belong simultaneously to two or more distinct categories, e.g. patients cross-classified according to both gender and age group. The data of the contingency table have to be entered in the table in the
dialog form. Either a one-way classification can be used (occupying one single row or one single column), or a two-way classification table up to a 6 x 9 table. Optionally, you can select a **Chi-squared test for trend.** The Cochran-Armitage test for trend (Armitage, 1955) provides a more powerful test than the unordered test, but this test is only applicable if your classification table has 2 columns and 3 or more rows (or 2 rows and 3 or more columns), and if the data originate from ordered categories.

After you click the Test button the program will automatically calculate the expected frequencies for every cell in the table, and the following results will be displayed:

- **Chi-squared with degrees of freedom** and **P-value.** The Chi-squared statistic is the sum of the squares of the differences of observed and expected frequency divided by the expected frequency for every cell:

\[
\chi^2 = \sum \frac{(observed \ count - expected \ count)^2}{expected \ count}
\]

For a 2x2 table, MedCalc uses the "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011). The use of Yates' continuity correction is no longer recommended. If the calculated P-value is less than 0.05, then there is a statistically significant relationship between the two classifications.

- **The Contingency Coefficient** is a measure of the degree of relationship, association of dependence of the classifications in the frequency table. The coefficient is calculated as follows (n is the total number of cases in the table):

\[
C = \sqrt{\frac{\chi^2}{\chi^2 + n}}
\]

The larger the value of this coefficient, the greater the degree of association is. The maximum value of the coefficient, which is never greater than 1, is determined by the number of rows and columns in the table.
Fisher’s exact test for a 2x2 table

When the number of expected frequencies in a 2x2 table is low (in case the total number of observations is less than 20), the table should be tested using Fisher’s exact test. The data (representing number of cases) for the 2x2 table are entered in the dialog box.

Example: treatment A resulted in 6 successes and 1 failure (6/7 = 85.7%) whereas treatment B resulted in 2 success and 8 failures (2/10 = 20%). The following is entered in the dialog box:

The P-value (the probability of obtaining the observed result or a more extreme result) is calculated when you click the Test button.

The result, P=0.015 in the example, indicates that the 2 treatments gave significantly different results.

In the Comment input field you can enter a comment or conclusion that will be included on the printed report.

McNemar test

The McNemar test is a test on a 2x2 classification table when the two classification factors are dependent, or when you want to test the difference between paired proportions, e.g. in studies in which patients serve as their own control, or in studies with “before and after” design.

In the example used by Bland (2000) 1319 schoolchildren were questioned on the prevalence of symptoms of severe cold at the age of 12 and again at the age of 14 years. At age 12, 356 (27%) children were reported to have severe colds in the past 12 months compared to 468 (35.5%) at age 14.

<table>
<thead>
<tr>
<th>Severe colds at age 12</th>
<th>Severe colds at age 14</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>Yes</td>
<td>212</td>
</tr>
<tr>
<td>No</td>
<td>No</td>
<td>256</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>468</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>144</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>707</td>
</tr>
<tr>
<td></td>
<td></td>
<td>851</td>
</tr>
</tbody>
</table>

Was there a significant increase of the prevalence of severe cold?

The data are entered as follows in the dialog box:
Difference and P-value

The program gives the difference between the proportions (expressed as a percentage) with 95% confidence interval. When the (two-sided) P-value is less than the conventional 0.05, the conclusion is that there is a significant difference between the two proportions.

In the example, the difference between the prevalence at age 12 and age 14 is 8.49% with 95% CI from 5.55% to 11.43%, and is highly significant (P<0.0001).

Note

The two-sided P-value is based on the cumulative binomial distribution.
The 95% confidence interval is calculated according to Sheskin, 2011.

Comparison of means (t-test)

When you want to compare the known mean of two independent samples, select Means in the Tests menu. In the dialog box, enter the mean, standard deviation and number of cases for both sets of data. Next you select Test to test the statistical significance of the difference between the two means, using a Student’s t-test.

The program displays the difference between the two means, and a 95% confidence interval for this difference. Next, the P value is displayed: when this P value is less than 0.05, the conclusion is that the two means are significantly different.

In the example, the mean 256 (standard deviation 22 and sample size 50) of the first sample, is compared with the mean 232 (standard deviation 32 and sample size 50) of the second sample. The difference between the two means is -24. The 95% confidence interval for this difference ranges from -34.9 to -13.1 (note that this interval excludes the value 0). The hypothesis test results in a P-value less than 0.0001, and the conclusion therefore is that, statistically, there is a significant difference between the two means.
Comparison of standard deviations (F-test)

When you want to test the statistical significance of the difference between known standard deviations of two independent samples, use the Comparison of ... Standard deviations command in the Tests menu.

In the dialog box, enter the two standard deviations that you want to compare, and the corresponding number of cases. Next select Test to perform the F-test or variance ratio test. In this test, the square of the standard deviations is calculated to obtain the corresponding variances. If the two variances are not significantly different, then their ratio will be close to 1.
When the calculated $P$ value is less than 0.05 ($P<0.05$), the conclusion is that the two standard deviations are statistically significantly different.

In the example, the standard deviation was 25.6 and sample size was 60 for the first sample, and for the second sample the standard deviation was 23.2 with sample size equal to 80. The resulting $F$-statistic was 1.2176 and the associated $P$-value was 0.412. Since $P$ was not less than 0.05, you can conclude that there is no significant difference between the two standard deviations.

If you want to compare two known variances, first calculate the standard deviations, by taking the square root, and next you can compare the two standard deviations.

### Comparison of correlation coefficients

Use Correlation coefficients in the Tests menu when you want to test the statistical significance of the difference between two independent correlation coefficients.

In the dialog box you enter the correlation coefficients and the corresponding number of cases. Next select Test to calculate the statistical significance of the difference between the two correlation coefficients.

![Comparison of correlation coefficients dialog box](image)

When the calculated $P$ value is less than 0.05, the conclusion is that the two coefficients indeed are significantly different.

In the example a correlation coefficient of 0.86 (sample size = 42) is compared with a correlation coefficient of 0.62 (sample size = 42). The resulting $z$-statistic is 2.5097, which is associated with a $P$-value of 0.0140. Since this $P$-value is less than 0.05, it is concluded that the two correlation coefficients differ significantly.

### Comparison of two proportions

When you want to compare two independent proportions (expressed as percentages), select Comparison of proportions in the Tests menu. In the dialog box, you can enter the two proportions (expressed as percentages) and the total number of cases. Next you click the TEST button to test the statistical significance of the difference between the two proportions (using a chi-squared test).

For example, when the prevalence of a disease in one sample of a total of 120 patients is 80%, and the prevalence of the disease in another sample of a total of 210 patients is 70%, you will enter the following in the dialog box:
After you have selected the Test button, the results of the test are displayed:

- the difference between the two proportions and a 95% confidence interval for this difference;
- Chi-squared test and P value: when this P value is less than 0.05, the conclusion is that the two proportions indeed differ significantly.

MedCalc uses the "N-1" Chi-squared test as recommended by Campbell (2007) and Richardson (2011).

Note that when the total number of cases is less than 20, it may be more appropriate to perform Fisher’s exact test (see p. 270).

**Comparison of Coefficients of variation**

**Description**
Performs a test for the comparison of two coefficients of variation from independent samples
This test is not performed on data in the spreadsheet, but on statistics you enter in a dialog box.

**Required input**
In the dialog box, you enter the two coefficients of variation, expressed as percentages, and the corresponding number of cases.
Click the Test button to test the statistical significance of the difference between the two coefficients of variation.
Results
When the calculated P value is less than 0.05, the conclusion is that the two coefficients of variation are significantly different. The test is performed according to Forkman (2009).

Comparison of areas under independent ROC curves

Description
This procedure is used to compare the Area under the Curve (AUC) of two independent ROC curves. This test is not performed on data in the spreadsheet, but on statistics you enter in a dialog box.

Required input
Enter the Area under the Curve (AUC) and Standard Error (SE) for the two ROC curves.
Click the Test button to test the statistical significance of the difference between the two AUCs.

**Results**

When the calculated P value is less than 0.05 (P<0.05), the conclusion is that the two AUCs are significantly different.

### Confidence interval for a rate

**Description**

A rate is a ratio between a count and another measurement, for example the ratio of a number of events observed and the total number of person-years of observation.

This test is not performed on data in the spreadsheet, but on data you enter in a dialog box.

**Required input**

- **Numerator**: the observed number of events.
- **Denominator**: for example the total person-years.
- Option **Express result as 1:X**: when this option is selected the rate R will be displayed as 1:(1/R), e.g. the rate 10/200 equals 0.05 and can be represented as 1:20.

When all data have been entered click the Test button.
Results
The program displays:
- The Poisson 95% Confidence Interval for the number counted (the Numerator).
- The (incidence) rate.
- The 95% Confidence Interval for the incidence rate.
The calculations are based on Sahai & Khurshid, 1996.

Comparison of two rates

Description
This procedure allows to compare the rates observed in two groups (Sahai & Khurshid, 1996).
This test is not performed on data in the spreadsheet, but on data you enter in a dialog box.

Required input
- **Numerator**: the observed number of events in each group.
- **Denominator**: for example the total person-years for each group.
- Option **Express result as 1:X**: when this option is selected the rate R will be displayed as 1:(1/R), e.g. the rate 10/200 equals 0.05 and can be represented as 1:20.
When all data have been entered click the Test button.
Results

The program displays:
- The (incidence) rate in the two groups with their Poisson 95% Confidence Interval.
- The difference between the two rates $R_2 - R_1$ with its 95% Confidence Interval and associated P-value. If the P-value is less than 0.05 it can be concluded that there is a statistical significant difference between the two rates.
- The ratio of the two rates $R_1/R_2$ and its 95% Confidence Interval. If the value 1 is not in this interval, it can be concluded that the ratio $R_1/R_2$ is not significantly different from 1 (in which case the rates would be equal).

Relative risk – Number needed to treat

Description

This command is used to calculate a relative risk (or risk ratio). The relative risk is the ratio of the proportions of cases having a positive outcome in two groups included in a prospective study.

In a prospective study cases are allocated to two groups and it is observed how many times the event of interest occurs. The program calculates the relative risk and a 95% confidence interval. If the value 1 is not in the range of the confidence interval, it can be concluded that the proportions are significantly different in the two groups, and there is an increased risk in one group compared to the other.

The program optionally also calculates the Number Needed to Treat (NNT) with its 95% confidence interval. This test is not performed on data in the spreadsheet, but on statistics you enter in a dialog box.

Required input

In the dialog box enter the number of cases with a positive (bad) and negative (good) outcome in the exposed and control groups.
Click the Test button to perform the test.

Relative risk

The program calculates the relative risk and a 95% confidence interval (Altman 1991, Daly 1998, Sheskin 2011). The relative risk is the ratio of the proportions of cases having a positive outcome in the two groups. If the value 1 is not in the range of the confidence interval, it can be concluded that the proportions are significantly different in the two groups, and there is an increased risk in one group compared to the other.

In the example, there was a positive outcome in 6 cases and a negative outcome in 44 cases in a group given treatment A. In a second group without treatment, 18 cases had a positive and 32 cases had a negative outcome.

The risk in the first group was 0.12 (6/50) and in the second group 0.36 (18/50). The relative risk for a positive outcome was 0.3333 (0.12/0.36) with a 95% confidence interval ranging from 0.1444 to 0.7696; the z-statistic is 2.574 and the associated P-value is 0.01. The conclusion is that there is a 3-fold decreased risk in the treatment A group, and this decrease is statistically significant (P=0.01).

Number Needed to Treat (NNT)

The number needed to treat (NNT) is the estimated number of patients who need to be treated with the new treatment rather than the standard treatment for one additional patient to benefit (Altman 1998).

A negative number for the number needed to treat has been called the number needed to harm.

MedCalc uses the terminology suggested by Altman (1998) with NNT(Benefit) and NNT(Harm) being the number of patients needed to be treated for one additional patient to benefit or to be harmed respectively.

The 95% confidence interval is calculated according to Daly (1998) and is reported as suggested by Altman (1998).
Odds ratio

When you want to calculate the odds ratio in a retrospective case-control study (unpaired samples), select the command Odds ratio in the Tests menu.

In a retrospective study the cases with positive and negative outcome are known and they are subsequently grouped according to the occurrence of a specific characteristic.

In the dialog box you enter the number of cases in the 1st and 2nd group that have a positive (bad) or negative (good) outcome. Next click the Test button to perform the test.

The program will display the odds ratio, which is the ratio of the odds of the outcome in the two groups. The program also calculates a 95% confidence interval for the odds ratio (Altman, 1991; Sheskin, 2004). If the value 1 is not in the range of the confidence interval, then it can be concluded that the odds in one group are significantly higher than in the other.

In the example 30 cases with a positive outcome and 30 cases with a negative outcome were selected. Next the occurrence of a particular characteristic was retrospectively investigated. For the cases with a positive outcome, 8 cases presented the characteristic (were exposed to a particular risk) and 22 did not. For the cases with a negative outcome, 4 cases presented the characteristic and 26 did not.

The resulting odds ratio is 2.4 with a 95% confidence interval ranging from 0.6 to 8.9. The value 1, which means equal odds in both groups, is included in this interval and the conclusion is that although there is a 2.4-fold increased odds of a positive outcome, this increase is not statistically significant at the 5% level.

Inter-rater agreement

Select Inter-rater agreement in the menu when you want to evaluate the agreement between two classification systems. If the raw data are available in the spreadsheet, use Inter-rater agreement in the Statistics menu to create the classification table and calculate Kappa (for interpretation, see p. 215).

In the dialog form you can enter the two classification systems in a 6x6 frequency table.

Select Weighted Kappa if the data come from an ordered scale. If the data come from a nominal scale, do not select Weighted Kappa. Use linear weights when the difference between the first and second category has the same importance as a difference between the second and third category, etc. If the difference between the first and second category is less important than a difference between the second and third category, etc., use quadratic weights.
In this example, from the 6 cases that observer B has placed in class 1, observer A has placed 5 in class 1 and 1 in class 2; from the 19 cases that observer B has placed in class 2, observer A has placed 3 in class 1, 12 in class 2 and 4 in class 3; and from the 12 cases that observer B has placed in class 3, observer A has placed 2 in class 1, 2 in class 2 and 8 in class 3.

After you have entered the data, click the Test button. The program will display the value for Kappa with its Standard Error and 95% confidence interval (CI) (Fleiss et al., 2003).

For interpretation of the Kappa statistic, see p. 215.
Diagnostic test

Description

*Diagnostic test* is used to calculate test characteristics such as sensitivity, specificity, positive and negative likelihood ratio, disease prevalence as well as positive and negative predictive value from a 2x2 table (Griner et al., 1981; Hanley & McNeil 1982; Metz, 1978; Zweig & Campbell, 1993).

Required input

Enter the number of cases in the non-diseased group that test negative and positive (left column); and the number of cases in the diseased group that test negative and positive (right column).

You can change the order of columns and rows by clicking the central button.

Disease prevalence

If the sample sizes in the positive (Disease present) and the negative (Disease absent) groups do not reflect the real prevalence of the disease, you can enter the disease prevalence in the corresponding input box. This will have an effect on the positive and negative predictive values.

Results

The following statistics are reported with their 95% Confidence intervals:

- **Sensitivity**: probability that a test result will be positive when the disease is present (true positive rate).
- **Specificity**: probability that a test result will be negative when the disease is not present (true negative rate).
- **AUC**: Area under the ROC curve
- **Positive likelihood ratio**: ratio between the probability of a positive test result given the presence of the disease and the probability of a positive test result given the absence of the disease, i.e.
  \[\text{Positive likelihood ratio} = \frac{\text{True positive rate}}{\text{False positive rate}} = \frac{\text{Sensitivity}}{1 - \text{Specificity}}\]
• **Negative likelihood ratio**: ratio between the probability of a negative test result given the *presence* of the disease and the probability of a negative test result given the *absence* of the disease, i.e.
  \[
  = \text{False negative rate} / \text{True negative rate} = (1 - \text{Sensitivity}) / \text{Specificity}
  \]

• **Positive predictive value**: probability that the disease is present when the test is positive.

\[
PPV = \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + (1 - \text{specificity}) \times (1 - \text{prevalence})}
\]

• **Negative predictive value**: probability that the disease is not present when the test is negative.

\[
NPV = \frac{\text{specificity} \times (1 - \text{prevalence})}{(1 - \text{sensitivity}) \times \text{prevalence} + \text{specificity} \times (1 - \text{prevalence})}
\]

Sensitivity, specificity, positive and negative predictive value as well as disease prevalence are expressed as percentages for ease of interpretation.

Confidence intervals for sensitivity and specificity are "exact" Clopper-Pearson confidence intervals.

Confidence intervals for the likelihood ratios are calculated using the "Log method" as given on page 109 of Altman et al. 2000.

Confidence intervals for the predictive values are the standard logit confidence intervals given by Mercaldo et al. 2007.

---

**Likelihood ratios (2xk table)**

**Description**

This procedure allows the calculation of likelihood ratios for different test levels from a 2xk table (Gardner & Greiner, 2006). When test results have a continuous or ordinal outcome then valuable information is lost when the data are dichotomized for the calculation of sensitivity, specificity and likelihood ratios as in ROC curve analysis.

**Interval likelihood ratios** may be more powerful because they use more information contained in the data.

The likelihood ratio can be used to calculate the post-test probability of disease from the pre-test probability of disease (see below).

**Required input**

Enter the number of cases in the diseased group that test positive and negative at the different test levels.
Results

For each test levels the program calculates corresponding Likelihood ratio with 95% Confidence interval. The likelihood ratio can be used to calculate the post-test odds from the pre-test odds of disease:

\[
\text{post-test odds} = \text{pre-test odds} \times \text{likelihood ratio}
\]

The relation between odds and probability is:

\[
\text{odds} = \frac{p}{1-p} \quad \text{and} \quad p = \frac{\text{odds}}{1 + \text{odds}}
\]

Using these equations, you can calculate the post-test probability of disease from the pre-test probability of disease.

If, for example, the pre-test probability of disease is 0.6 then the pre-test odds is 0.6/(1-0.6) = 1.5. For a case with a test result corresponding with diagnostic level 2, the likelihood ratio is 12, and the post-test odds is 1.5 \times 12 = 18. The post-test probability of disease is 18/(1+18) = 0.95.
Sample size

Sample size calculation: Introduction

In the Sample size menu, you can calculate the required sample size for some common problems, taking into account the magnitude of differences and the probability to make a correct or a false conclusion (Neely et al., 2007).

When you perform a statistical test, you will make a correct decision when you
• reject a false null hypothesis, or
• accept a true null hypothesis.

On the other hand, you can make two errors:
• you can reject a true null hypothesis, or
• you can accept a false null hypothesis.

These four situations are represented in the following table.

<table>
<thead>
<tr>
<th>Null hypothesis = TRUE</th>
<th>Null hypothesis = FALSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reject null hypothesis</td>
<td>Type I error ( \alpha )</td>
</tr>
<tr>
<td>Accept null hypothesis</td>
<td>Correct decision</td>
</tr>
</tbody>
</table>

For example, when you have rejected the null hypothesis in a statistical test (because \( P<0.05 \)), and therefore conclude that a difference between samples exists, you can either:
• have done so correctly, and uncovered a difference where one exists;
• have rejected the null hypothesis when in fact it is true, and uncovered a difference where in fact none exists. In this case you make a Type I error. \( \alpha \) is the (two-sided) probability of making a Type I error.

**Type I error = rejecting the null hypothesis when it is true**

You can avoid making a Type I error by selecting a lower significance level of the test, e.g. by rejecting the null hypothesis when \( P<0.01 \) instead of \( P<0.05 \).

On the other hand, when you accept the null hypothesis in a statistical test (because \( P>0.05 \)), and conclude that there is no difference between samples, you can either:
• have correctly concluded that there is no difference;
• have accepted the null hypothesis when in fact it is false, and therefore you have failed to uncover a difference where such a difference really exists. In this case you make a Type II error. \( \beta \) is the probability of making a Type II error.

**Type II error = accepting the null hypothesis when it is false**

The power of a test is \( 1-\beta \), this is the probability to uncover a difference when there really is one. For example, when \( \beta = 0.10 \), then the power of the test is 0.90 or 90%.

**Power = probability to achieve statistical significance**

You can avoid making a Type II error, and increase the power of the test to uncover a difference when there really is one, mainly by increasing the sample size.

To calculate the required sample size, you must decide beforehand on:
• the required probability \( \alpha \) of a Type I error, i.e. the required significance level (two-sided);
• the required probability \( \beta \) of a Type II error, i.e. the required power \( 1-\beta \) of the test;
• a quantification of the study objectives, i.e. decide what difference is biologically or clinically meaningful and worthwhile detecting.

In addition, you will sometimes need to have an idea about expected sample statistics such as e.g. the standard deviation. This can be known from previous studies.

## Single mean

### Description

With this procedure you calculate the required sample size for the comparison of a mean with a given value (Kirkwood & Sterne, 2003).

### Required input

- **Type I error - alpha**: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- **Type II error - beta**: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- **Mean**: the hypothesized mean (considered to be biologically significantly different from the null hypothesis value).
- **Standard deviation**: hypothesized standard deviation (known from previous studies or from the literature).
- **Null hypothesis value**: the null hypothesis value.

### Example

If for example the null hypothesis value is 50, and you consider a value of at least 60 to be significantly different, then you will enter these numbers for Null hypothesis value and Mean. From a previous study, you expect the standard deviation of the sample to be 14. For α-level you select 0.05 and for β-level you select 0.20.

### Results

After you click the **Calculate** button the program will display the required sample size (18 in the example). A table shows the required sample size for different Type I and Type II Error levels.
Comparison of two paired samples
To calculate the sample size required for the comparison of two paired samples, you use the same procedure as for a Single mean.
In the dialog box, for Mean, you enter the hypothesized mean difference; for Standard deviation, enter the hypothesized standard deviation of the differences, and for Null hypothesis value enter the value 0.

Single proportion

Description
With this procedure, you calculate the required sample size for the comparison of a proportion with a given proportion.

Required input

- Type I error - alpha: the probability of making a Type I error (\(\alpha\)-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (\(\beta\)-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Proportion (%): the hypothesized proportion (considered to be biologically significantly different from the null hypothesis value), expressed as a percentage.
- Null hypothesis value (%): the null hypothesis value (a proportion, expressed as a percentage).

Example
For example, if the null hypothesis value is 50%, and you consider a proportion of at least 70% to be significantly different, then you enter the numbers 70 and 50 in the dialog box. For \(\alpha\)-level you select 0.05 and for \(\beta\)-level you select 0.20.

Results
After you click the CALCULATE button the program will display the required sample size (47 in the example). A table shows the required sample size for different Type I and Type II Error levels.
Comparison of two means

Description
With this procedure, you calculate the required sample size for the comparison of two independent means.

Required input
- Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Difference: the hypothesized difference (considered to be biologically significant).
- Standard deviation 1: hypothesized standard deviation in the first sample.
- Standard deviation 2: hypothesized standard deviation in the second sample.

Example
For example, you are interested in detecting a difference between the sample means of at least 10. You expect the standard deviations in the two study groups to be equal to 16. Enter the value 10 for difference, and enter 16 for both standard deviations. For α-level you select 0.05 and for β-level you select 0.20.

Results
After you click the CALCULATE button the program will display the required sample size (41 in the example, meaning that you will need 41 cases in each group, or a total of 82 cases).
A table shows the required sample size for different Type I and Type II Error levels.

Comparison of two paired samples
To calculate the sample size required for the comparison of two paired samples, see Sampling for single mean, p. 286.
Sample size for paired samples t-test

This calculates the required sample size for the paired samples t-test (Machin et al., 2009).

Required input

- Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Mean difference: the hypothesized mean difference (considered to be biologically significantly different from the null hypothesis value 0).
- Standard deviation: hypothesized standard deviation of differences (known for example from a Paired samples t-test from previous studies, or from the literature).

Example

You consider an average difference between two paired observations before and after a study, of at least 8 to be meaningful. From a previous study you expect the standard deviation of the differences to be 12.

For α-level you select 0.05 and for β-level you select 0.20 (power is 80%). For mean difference, you enter 8 and for standard deviation enter 12.

Results

After you click Calculate the program displays the required number of data pairs (20 in the example). A table shows the required sample size for different Type I and Type II Error levels.
Comparison of two proportions

Description
With this procedure, you calculate the required sample size for the comparison of two proportions (Machin et al., 2009).

Required input
- Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- First proportion (%): hypothesized proportion in the first sample.
- Second proportion (%): hypothesized proportion in the second sample (the hypothesized difference with the first proportion is considered to be biologically significant).
- Statistical analysis: select the statistical test that will be used to analyse the study data: Chi-squared test or Fisher's exact test.

Example
You are interested in detecting a difference between two proportions of at least 15. You expect the two proportions to be equal to 75 and 60 in group 1 and 2 respectively. You will include twice as many cases in group 1 as in group 2. You plan to analyse the results of your study using a Chi-squared test. For α-level you select 0.05 and for β-level you select 0.20.

Results
After you click the Calculate button the program will display the required sample size, which is 224 in the first group and 112 in the second group, i.e. 336 cases in total.
A table shows the required sample size for different Type I and Type II Error levels.
Correlation coefficient

Description
With this procedure, you calculate the required sample size for a correlation coefficient (Bland, 2000). The sample size takes into account the required significance level and power of the test.

Required input
- Type I error - alpha: the probability of making a Type I error ($\alpha$-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error ($\beta$-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Correlation coefficient: the hypothesized or anticipated correlation coefficient.

Example
For example, the correlation coefficient between two variables is thought to be 0.60. How many patients are required for this correlation coefficient to be significantly different from 0.0? For $\alpha$-level you select 0.05 and for $\beta$-level you select 0.20.

Results
After you click the Calculate button the program will display the required sample size (19 in the example, meaning that you will need 19 cases in which both variables must be measured).
A table shows the required sample size for different Type I and Type II Error levels.

Survival analysis (logrank test)

Description
With this procedure, you calculate the required sample size for the comparison of survival rates in two independent groups (Machin et al., 2009).

Required input
- Type I error - alpha: the probability of making a Type I error ($\alpha$-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
• Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.

• Survival rate Group 1: the hypothesized survival rate in the first group.

• Survival rate Group 2: the hypothesized survival rate in the second group.

• Ratio of sample sizes in Group 1 / Group 2: the ratio of the sample sizes in group 1 and 2. Enter 1 for equal sample sizes in both groups. Enter 2 if the number of cases in group 1 must be double of the number of cases in group 2.

Example
You are interested in detecting a difference between survival rates of 0.4 and 0.6. You plan to have the same number of cases in both groups.

Enter the values 0.4 and 0.6 for the Survival rates in Group 1 and Group 2, and enter 1 for the Ratio of sample sizes. For α-level you select 0.05 and for β-level you select 0.20.

Results
After you click the Calculate button the program displays the required sample size.

In the example 98 cases are required in Group 1 and in Group 2, giving a total of 196 cases.

A table shows the required total sample size for different Type I and Type II Error levels.

McNemar test

Description
Calculates the required sample size for the comparison of two related proportions as analysed with the McNemar test. The sample size takes into account the required significance level and power of the test (Machin et al., 2009).

Required input
• Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
• Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.

• Proportion (%) of total expected to shift from Positive to Negative: hypothesized proportion of cases that will shift from positive to negative result or outcome.

• Proportion (%) of total expected to shift from Negative to Positive: hypothesized proportion of cases that will shift in the other direction, from negative to positive result or outcome.

Example

In a cross-over trial you expect that 20% of the total number of cases will shift from a positive to a negative response, and that 10% will shift from negative to positive. In the dialog box you enter 20 and 10 for the percentages. For α-level you select 0.05 and for β-level you select 0.20 (power is 80%).

Results

After you click the Calculate button the program displays the required total number of cases in the study. For the example the minimal required total sample size is 234.

A table shows the required sample size for different Type I and Type II Error levels.

Bland-Altman plot

Description

Calculates the required sample size for a method comparison study using the Bland-Altman plot.

In this method, limits of agreement (LoA) are calculated as the mean of differences between two measurements ± 1.96 x their standard deviation (Bland & Altman, 1986).

Two methods are considered to be in agreement when a pre-defined maximum allowed difference (Δ) is larger than the higher limit of agreement, and -Δ is lower than the lower limit of agreement.

Proper interpretation takes into account the 95% confidence interval of the LoA, and to be 95% certain that the methods do not disagree, Δ must be higher than the upper 95 CI limit of the higher LoA and -Δ must be less than the lower %95 CI limit of the lower LoA:
• With smaller sample sizes, the CI becomes larger and the probability that Δ lies within the 95 CI increases.
• With larger sample sizes, the CI becomes smaller and the probability that Δ lies within the 95 CI decreases.

To show that two methods are in agreement, an adequate sample size must be established to have a high probability (power) that Δ will fall outside the 95 CI of the Limits of Agreement.

**Required input**

- Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Expected mean of differences: the expected mean of differences between measurements by the 2 methods that are compared in the study.
- Expected Standard Deviation of differences: the expected Standard Deviation of differences between measurements by 2 methods.
- Maximum allowed difference between methods: this is the pre-defined clinical agreement limit. Differences below this limit are clinically irrelevant or neglectable. This difference must be larger than the expected mean + 1.96 x expected standard deviation of differences.

**Example**

You want to show that two laboratory methods are in agreement. A preliminary study has shown that the mean difference is 0.001167, and the standard deviation of the differences is 0.001129. The maximum allowed difference between the methods is 0.004 units (example by Lu et al., 2016).

You enter 0.001167 for Expected mean of differences, 0.001129 for Expected Standard Deviation of differences and 0.004 for Maximum allowed difference between methods.

For α-level you select 0.05 and for β-level you select 0.20 (power is 80%).
Results

After you click the Calculate button the program displays the required total number of cases in the study. The calculation may take some time to complete.

For the example, the minimal required total sample size is 83.

A table shows the required sample size for different Type I and Type II Error levels.

MedCalc uses the method by Lu et al. (2016) to calculate the sample sizes.

Note that the Bland-Altman plot implemented by MedCalc (and as described in Bland & Altman, 1986) has a fixed alpha level of 0.05.

Area under ROC curve

Description

With this procedure, you calculate the required sample size for the comparison of the area under a ROC curve with a null hypothesis value (Hanley & McNeil, 1982).

Required input

- Type I error - alpha: the probability of making a Type I error (α-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error (β-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Area under ROC curve: the hypothesized Area under the ROC curve (the AUC expected to be found in the study).
- Null hypothesis value: the null hypothesis AUC.
- Ratio of sample sizes in negative / positive groups: enter the desired ratio of negative and positive cases. If you desire both groups to have an equal number of cases you enter 1; when you desire twice as many cases in the negative than in the positive group, enter 2.

Example

If for example you want to show that the AUC of 0.725 for a particular test is significant from the null hypothesis value 0.5 (meaning no discriminating power), then you enter 0.725 for Area under ROC curve and 0.5 for Null Hypothesis value. You
expect to include twice as many negative cases than positive cases, so for the Ratio of sample sizes in negative / positive groups you enter 2.

For $\alpha$-level you select 0.05 and for $\beta$-level you select 0.20.

Results

In the example 19 cases are required in the positive group and 38 in the negative group, giving a total of 57 cases. A table shows the required sample size for different Type I and Type II Error levels.

Comparison of 2 ROC curves

Description

With this procedure, you calculate the required sample size for the comparison of the areas under two ROC curves (derived from the same cases) (Hanley & McNeil, 1982; 1983).

Required input

- Type I error - alpha: the probability of making a Type I error ($\alpha$-level, two-sided), i.e. the probability of rejecting the null hypothesis when in fact it is true.
- Type II error - beta: the probability of making a Type II error ($\beta$-level), i.e. the probability of accepting the null hypothesis when in fact it is false.
- Area under ROC curve 1: hypothesized area for the first ROC curve.
- Area under ROC curve 2: hypothesized area for the second ROC curve.
- Correlation in positive group: the hypothesized rank correlation coefficient in the positive group (abnormal cases)
- Correlation in negative group: the hypothesized rank correlation coefficient in the negative group (normal cases)
- Ratio of sample sizes in negative / positive groups: enter the desired ratio of negative and positive cases. If you desire both groups to have an equal number of cases you enter 1; when you desire twice as many cases in the negative than in the positive group, enter 2.
Example

For example: you are interested to show that the discriminating power of two assays (performed on the same cases), with an area under the ROC curve of 0.825 and 0.9, is significantly different. From previous studies, you know that the rank correlation between the two assays is 0.4 in both positive and negative cases.

You enter the values 0.825 and 0.9 for Area under ROC curve 1 and Area under ROC curve 2. Next you enter 0.4 for Correlation in positive group and Correlation in negative group. For $\alpha$-level you select 0.05 and for $\beta$-level you select 0.20.

![Sample size comparison of ROC curves](image)

Results

In the example 133 cases are required in the positive group and 266 in the negative group, giving a total of 399 cases. A table shows the required sample size for different Type I and Type II Error levels.
Sample size for Confidence Interval estimation & Precision

The following procedures allow to calculate the required number of cases to obtain confidence intervals with a pre-specified width.

Note that the calculation does not include a null hypothesis value or a factor for power (1−β). Therefore, the estimated sample size does not give a certainty that a particular value will fall inside or outside the confidence interval. The number of cases is only the number required to attain a specified confidence interval width.

Single mean

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for a single mean (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Standard deviation: the expected standard deviation (known from previous studies or from the literature)
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example when a mean is 35 with 95% Confidence Interval 30 to 40, then the confidence interval width is 10.

Example

![Sample size CI for single mean](image)

Single proportion

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for a single proportion (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Proportion (%): the expected proportion, expressed as a percentage.
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example, when a proportion is 60% with 95% Confidence Interval 55 to 65, then the confidence interval width is 10.
Example

Difference between means

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for a difference between two independent means (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Pooled standard deviation: you can find the pooled standard deviation in the output of the Independent samples t-test (see also Independent samples t-test: computational notes).
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example, when a difference is 25 with 95% Confidence Interval 20 to 30, then the confidence interval width is 10.
- Ratio of sample sizes in Group 1 / Group 2: enter 1 for equal sample sizes in both groups. Enter 2 if the number of cases in group 1 must be double of the number of cases in group 2.

Example
Mean difference between paired samples

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for an average difference between paired observations (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Standard deviation of differences: the expected standard deviation of the differences between the paired observations (known for example from a Paired samples t-test in previous studies, or from the literature).
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example, when a mean difference is 35 with 95% Confidence Interval 30 to 40, then the confidence interval width is 10.

Example

Difference between proportions

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for the difference between two independent proportions (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Proportion in group 1 (%): hypothesized proportion (expressed as a percentage) in the first sample.
- Proportion in group 2 (%): hypothesized proportion (expressed as a percentage) in the second sample.
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example, when a difference is 40% with 95% Confidence Interval 35 to 45, then the confidence interval width is 10.
- Ratio of sample sizes in Group 1 / Group 2: enter 1 for equal sample sizes in both groups. Enter 2 if the number of cases in group 1 must be double of the number of cases in group 2.
Example

Difference between paired proportions

This calculates the required minimum sample size for the estimation of a confidence interval with a required width for a difference between paired proportions (Machin et al., 2009).

Required input

- Confidence level (%): select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% Confidence Interval) is the most common selection. You can enter a different confidence level if required.
- Proportion in group 1 (%): the proportion in the first set of observations
- Proportion in group 2 (%): the proportion in the second set of observations
- Correlation coefficient: the correlation between the pairs of observations.
- Confidence interval width (2-sided): this is the required total width of the confidence interval. For example, when a difference is 40% with 95% Confidence Interval 35 to 45, then the confidence interval width is 10.
Calculates the required minimum sample size for the estimation of a confidence interval with a required width for the Coefficient of variation from duplicate measurements. The calculations are performed according to the general methodology given by Machin et al., 2009. It is assumed that the calculation of the Coefficient of variation uses the Logarithmic method.

**Required input**

- **Confidence level (%):** select the confidence level: 90, 95 or 99%. A 95% confidence level (the value for a 95% confidence interval) is the most common selection. You can enter a different confidence level if required.
- **Coefficient of variation (%):** the expected coefficient of variation, expressed as a percentage.
- **Confidence interval width (2-sided):** this is the required total width of the confidence interval. For example, when a CV is 8% with 95% Confidence Interval 6 to 10, then the confidence interval width is 4.

**Example**

A preliminary study in 20 sample pairs resulted in a coefficient of variation of 8% with 95% CI of 2.3 to 13.7%. The calculations used the logarithmic method.

The desired 95% confidence interval is 6 to 10%. How many sample pairs are needed for this more narrow confidence interval?

For confidence level you enter 95, for coefficient of variation 8 and for confidence interval width you enter 4 (=10−6).
Click Calculate.
The program gives a minimum required sample size of 37. This means that if the study is repeated with 37 sample pairs, and this new study again results in a coefficient of variation of 8%, the 95% confidence interval will be 6 to 10%.

Regression-based reference limits

With this procedure you can calculate the required sample size for the estimation of regression-based reference limits, such as Age-related reference limits, with a specified relative precision (Bellera & Hanley, 2007).

Required input

- Reference limit (%): the p% reference limit of interest, for example the 95% reference limit.
- Confidence interval (%): the A% confidence interval (two-sided) of the reference limit of interest, for example a 95% confidence interval.
- Reference range (%): the B% reference range, used for the calculation of the relative margin of error. The reference range encompasses the middle B% of the y values at any value of the covariate (age for example).
- Relative margin of error Δ (%): this is the margin of error relative to the reference range. It is defined as the ratio of the desired width of the confidence interval of the reference limit to the width of the reference range at any value of the covariate.

For example, look at the following output from an Age-related reference interval:

<table>
<thead>
<tr>
<th>Centiles</th>
<th>0.025</th>
<th>0.10</th>
<th>0.90</th>
<th>0.975</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAWKS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>24.7362</td>
<td>29.3356</td>
<td>32.1932</td>
<td>33.7436</td>
</tr>
<tr>
<td>20</td>
<td>41.3839</td>
<td>43.1065</td>
<td>49.0012</td>
<td>51.6842</td>
</tr>
<tr>
<td>25</td>
<td>56.3196</td>
<td>59.3245</td>
<td>55.9469</td>
<td>67.9948</td>
</tr>
<tr>
<td>30</td>
<td>69.1766</td>
<td>71.4237</td>
<td>79.9136</td>
<td>82.1507</td>
</tr>
<tr>
<td>35</td>
<td>79.5391</td>
<td>82.0165</td>
<td>91.3858</td>
<td>93.8852</td>
</tr>
<tr>
<td>40</td>
<td>86.9914</td>
<td>89.7031</td>
<td>95.9478</td>
<td>102.6594</td>
</tr>
</tbody>
</table>

- The 95% reference range at age 25 is 67.9618–56.3196 = 11.6422. A relative margin of error (Δ) of 10% corresponds with a width of the confidence interval of 10% of 11.6422 or about 1.2.
- Distribution: the distribution of the covariate in the sample.
  - Uniform distribution: select this option when the covariate follows a uniform distribution.
  - Low-Median-High groups: select this option when the covariate is grouped into 3 groups where one-third of the sample were taken at one age extreme, one-third are taken at the midpoint, and one-third are taken from the other extreme.
  - Normal distribution: select this option when the covariate follows a normal distribution.
  - Average age value: select this option if you are only interested in the reference limit at the average age value.

Example

You plan a study to obtain a 95% reference limit of blood pressure at different ages. For a 90% confidence interval, the desired relative margin of error is 10% compared with a 95% reference range (the middle 90% of observations). The distribution of age of the subjects is uniform.

You enter 95 for reference limit, 90 for confidence interval, 95 for reference range and 10 for relative margin of error. For distribution, you select Uniform distribution.
Click Calculate.
The minimum required sample size is 377.
Window menu

Cascade

Shortcut: Shift+F5

Use this command to layer the windows in the MedCalc application window so that the title bar of each window is visible.

Tile

Shortcut: Shift+F4

With this command you can arrange the windows in the MedCalc application window side by side and in equal sizes and so that all of them are visible.

Arrange icons

This command arranges the iconized windows (spreadsheet, graphs, results) across the bottom of the MedCalc application window.

Split window – Remove split

The spreadsheet window can be divided into two panes. The two panes scroll together vertically, but can scroll independently horizontally.

To split the window into panes:

- Select the Split window command in the Window menu.
- Drag the Split box (which is displayed in the bottom right corner of the spreadsheet window) into the spreadsheet.
- Double-click the Split box.

After you have performed one of these actions, the Split box changes into a Split bar dividing the spreadsheet into two panes. You can change the position of the Split bar by dragging it to the left or right in the window.
To remove the split:

- Choose *Remove split* from the *Window* menu.
- Drag the *Split box* to the utmost left or right of the spreadsheet.
- Double-click the *Split bar.*

**Close all**

With this command you can close all windows (spreadsheet, notes, graphs, results) in the MedCalc application window.
Help menu

On line help is always available by means of function key F1. In addition, you can select Contents and Index in the Help menu to obtain explanation on working with MedCalc.

MedCalc Help

You select MedCalc Help to browse the comprehensive on-line documentation. In Help, click one of the following tabs:
- Click the Contents tab to browse through topics by category.
- Click the Index tab to see a list of index entries, and then either type a word or scroll through the list.
- Click the Search tab to search for words or phrases that may be contained in a Help topic.

How to use Help

If you are new to Windows, or to the Windows Help system, select How to use Help. This command will activate the Windows documentation on how to use the Windows help system.

What’s new

Select What’s new in the Help menu to read more about what is new in your current copy of MedCalc.

MedCalc on the Web

When you select this command, the system will open your default web browser (e.g. Edge, Chrome, Internet Explorer, …) and establish a connection with the MedCalc Web site on the Internet.

The following options are available:
- MedCalc home page: connect to the MedCalc home page for general information
- Frequently asked questions: connect to the MedCalc web site for some frequently asked questions
- On line support: connect to the MedCalc web site for specific questions and comments
- On line manual: connect to the MedCalc web site containing the complete MedCalc manual
- MedCalc update: connect to the MedCalc web site for software updates.
Register

In this dialog box you can enter your user name and product key. This will end the trial period and you can use the software without limitations.

Unregister MedCalc from this computer

This command allows removing the MedCalc license from this computer. When you no longer user this computer it is advised to unregister MedCalc from it. In you want to do so, click the Yes button below. If you are in doubt, click Cancel. When you unregister MedCalc, the registration data are removed from the computer, but the software will not be uninstalled. After unregistering MedCalc, you may additionally completely remove it from this computer by selecting Control Panel, Add/Remove Programs, and click on MedCalc in the list of installed programs. All files that you created (data files, etc.) will not be deleted by any of these procedures.

About MedCalc

The About MedCalc box displays the program version number and copyright notice. Click OK to remove the info box from the screen.
MedCalc spreadsheet

Introduction

In MedCalc, as in other spreadsheets, a cell can contain a text or string entry, or it can contain a number or a formula. An example or a string entry is a name such as e.g. Howard. When used in a formula, literal strings must be placed between quotation marks, e.g. “Howard”.

A cell can also contain a number, negative or positive, and with or without a decimal fraction, e.g. 5, -23.5, 0.03. The number of decimals displayed globally in the spreadsheet is selected in the Format spreadsheet box (see p.49). However, a different number of decimals may be selected for a particular column.

A formula may be a simple mathematical formula, such as e.g. SQRT(36). This formula will return the value 6, which is the square root of the number 36. Alternatively, the number 36 may be entered in a different cell of the spreadsheet, and the SQRT function can take the address of this cell as an argument, e.g. SQRT(B5).

Most of the formulas available in MedCalc work similar to their equivalents in other spreadsheet programs. When a formula begins with a cell address, this must be preceded by a = or + sign, but MedCalc formulas must not be preceded by the = character.

Operators

Arithmetic operators

The arithmetic operators, in order of precedence, are:

- Exponentiation
- Negation
- Multiplication, division
- Addition, subtraction

Relational operators

Relational operators compare two numbers or two strings. The result is a logical value expressed as a number, either 1 (=TRUE), or 0 (=FALSE). The relational operators, in order of precedence, are:

= Equality
<> Inequality
< Less than
> Greater than
<= Less than or equal to
>= Greater than or equal to

Combination of operators

When arithmetic and relational operators are combined in one expression, the arithmetic are performed first. You have to use parentheses when you want to change the order in which the operations are performed. Operations within parentheses are performed first.

B6<5+3 Returns 1 if the contents of B6 is less than 8, otherwise this expression returns 0.
5+3*(A1>3) Returns 8 if cell A1 contains a value greater than 3 (since A1>3 = TRUE = 1). If A1 contains 3 or a number less than 3, this expression returns 5 (A1>3 = FALSE = 0).
Relative and absolute cell addresses

If you want to use the value of a cell in a formula in another cell of the spreadsheet, then you refer to this cell by means of its cell address. This cell address consists of a column indicator and a row number, e.g. cell D14 is the cell in column D, row 14. When a cell address includes a $ character before the column or row number, the address is considered as an absolute address. When cell C10 contains for instance the formula $B$5+$B$6, the actual addresses of these two cells are stored in memory. When the formula is copied or moved to cell C11, e.g. by inserting a row at row 9, the formula will still be $B$5+$B$6. When a cell address does not include any $ characters, the address is a relative address. This means that the program does not store the actual address, but instead the program stores the number of columns and rows calculated relative to the cell containing the formula. When cell B5 contains the cell address B4, then the program does not store the address B4 as such, but it stores how to get from cell B5 to cell B4, in this case one row up. When the formula $B$5+$B$6 is copied from cell B5 to cell D10, the formula will be changed to 2*D9.

When cell B1 contains the formula SUM(B2:B10), and this formula is copied to cell C1, the formula will be converted to SUM(C2:C10). When it is copied to cell D51, the formula will be converted to SUM(D52:D60).

A cell address or formula may contain a combination of absolute and relative cell addressing, e.g.: A$2, $B10, $C5, SUM(B3:B20)*$A$1.

Ranges of cells are identified by two cell addresses separated by a colon. These cell addresses may also include relative and absolute cell addresses, e.g. B2:E8, $A$10:$$A$25, D10:D10, etc.

When you design a spreadsheet, you should pay attention to when to use relative and when to use absolute cell addressing.

Complex numbers

A complex number is a number that can be expressed in the form $a + bi$ where $a$ and $b$ are real numbers and $i$ is the imaginary unit, satisfying the equation $i^2 = -1$. The number $a$ is called the real part and the number $b$ is called the imaginary part of the complex number.

Any real number $r$ can be expressed as a complex number $r + 0i$.

The complex number $a + bi$ can be represented visually as follows:

![Diagram of a complex number](image)

The phase and norm (modulus) are alternative ways to define a complex number.

Create a complex number

You create a complex number using the COMPLEX function or by entering the number directly in the form $a+bi$. COMPLEX($a$, $b$) returns the number $a + bi$. For example, COMPLEX(2,3) returns 2+3i.
Basic mathematical operations

Multiplication or division of a complex number with a real number

\[ A \times r \] both real and imaginary part of the complex number \( A \) are multiplied by the real number \( r \).

\[ A / r \] both real and imaginary part of the complex number \( A \) divided by the real number \( r \).

Addition or subtraction of a matrix with a real number

\[ A + r \] the real number \( r \) is added to the real part of the complex number \( A \).

\[ A - r \] the real number \( r \) is subtracted from the real part of the complex number \( A \).

Addition or subtraction of complex numbers

\[ A + B \] the corresponding parts of the two complex numbers are added.

\[ A - B \] the corresponding parts of the two complex numbers are subtracted.

Multiplication of complex numbers

\[ A \times B \] The multiplication of two complex numbers is defined as follows:

\[(a + bi)(c + di) = (ac - bd) + (bc + ad)i\]

Division of complex numbers

\[ A / B \] The division of two complex numbers is defined by as follows:

\[ \frac{a + bi}{c + di} = \left( \frac{ac + bd}{c^2 + d^2} \right) + \left( \frac{bc - ad}{c^2 + d^2} \right)i \]

Complex number functions

The following functions operate on complex numbers specifically:

- COMPLEX(\(a, b\)) Create complex number
- RE(\(A\)) Returns the real part of a complex number
- IM(\(A\)) Returns the imaginary part of a complex number
- NORM(\(A\)) Returns the norm (or modulus) of a complex number
- CONJ(\(A\)) Returns the complex conjugate of a complex number
- PHASE(\(A\)) Returns the phase angle (or angular component) of a complex number
- POLAR(\(\rho, \theta\)) Returns the complex number defined by its polar components
- CRND() Returns a random complex number.
- CSQRT(\(x\)) Square root function.

See p. 316 for more details.

Mathematical functions on complex numbers

The following mathematical functions accept a complex number as argument:

- ABS, EXP, INV, LN, LOG, SQRT
- ACOS, ACOSH, ASIN, ASINH, ATAN, ATANH, COS, COSH, SIN, SINH, TAN, TANH
- TRUNC, ROUND
Mathematical functions

**ABS Absolute value**
ABS(x) returns the absolute value of the number x.

**ALOGIT Antilogit function**
ALOGIT(l) returns the antilogit of the (logit) number l:

\[ \text{algorit(l)} = \frac{\exp(l)}{1 + \exp(l)} \]

**EXP Natural exponential function**
EXP(x) returns the natural exponential of x: \(2.718281828^x\). EXP is the inverse function of the LN function.

**INV Inverse function**
INV(x) returns the multiplicative inverse of x, so that \(x \cdot \text{INV}(x) = 1\).

**LN Natural logarithm function**
LN(x) returns the natural logarithm of the positive number x to the base e (\(e=2.718281828\)). The argument x must be greater than 0. LN is the inverse function of EXP.

**LOG Logarithm function**
LOG(x) returns the logarithm of the positive number x in the base 10. The argument x must be greater than 0.

**LOGIT Logit function**
LOGIT(p) returns the logit of the proportion p:

\[ \text{logit(p)} = \ln\left(\frac{p}{1-p}\right) \]

The argument p must be between 0 and 1.

**MOD Modulo function**
MOD(x,d) returns the remainder after x is divided by d. The result has the same sign as the divisor d.

**POWER Power function**
POWER(n,p) returns n raised to the power p.

**RAND Random number function (Uniform distribution)**
RAND(x) returns a computer-generated random number (a) when \(x \leq 1\) the result is a number between 0 and 1, or (b) when \(x > 1\) then the result is a number between 1 and x. The function will return a different value every time the spreadsheet is recalculated.

**RANDNORM Random number function (Normal distribution)**
The function RANDNORM(m,s) returns a random number from a Normal distribution with mean m and standard deviation s.

**SIGN Sign value**
SIGN(x) returns a number that indicates the sign x: -1 if x is negative; 0 if x equals 0; or 1 if x is positive.

**SQRT Square root function**
SQRT(x) returns the square root of the positive number x. SQRT(x) = \(x^{(1/2)}\). If the argument x of the function is negative, then the function returns an error (missing value).
**SQUARE Square function**

SQUARE(x) returns the square of the number x. SQUARE(x) = x^2.

**Rounding and truncation**

**CEIL** Rounds up

CEIL(x) rounds the number x up.

**FLOOR** Rounds down

FLOOR(x) rounds the number x down.

**INT** Integer value function

INT(x) rounds the number x down to an integer.

**ROUND** Round function

ROUND(x, n) rounds the number x to the number of digits n. If n is negative, then x is rounded to the left of the decimal point.

**TRUNC** Truncate function

TRUNC(x) truncates the number x to an integer by removing the fractional part of the number x.

**Prime number functions**

**ISPRIME** Primality test function

ISPRIME(x) checks whether a number is a prime number. The argument x must be less than 1000000000000 (10^{12}). The function returns 1 when the number is prime, 0 when not.

**NEXTPRIME** Next prime number function

NEXTPRIME(x) returns the first prime number larger than x. The argument x must be less than 999999999989 (the largest prime MedCalc will detect).

**PRND** Random prime function

PRND(min, max) returns a random prime number between min and max (inclusive). Max must be less than 1000000000000 (10^{12}).

**Trigonometric functions**

**PI** Pi function

The function PI() takes no argument and returns the value 3.14159265358979.

**RADIANS** Convert degrees to radians

RADIANS(x) converts an angle x expressed in degrees to radians.

**DEGREES** Convert radians to degrees

DEGREES(x) converts an angle x expressed in radians to degrees. The relation between the 2 units is as follows: 2 x Pi radians = 360 degrees.

**SIN** Sine function

SIN(x) returns the sine of the angle x. The result range is [-1..1]. The angle x must be expressed in radians. To convert an angle expressed in degrees to radians, use the RADIANS() function.
COS Cosine function
COS(x) returns the cosine of an angle x. The result range is [-1..1]. The angle x must be expressed in radians. To convert an angle expressed in degrees to radians, use the RADIANS() function.

TAN Tangent function
TAN(x) returns the tangent of the angle x. The angle x must be expressed in radians. To convert an angle expressed in degrees to radians, use the RADIANS() function.

ASIN Arc sine function
ASIN(x) returns the arcsine of x. The arcsine function is the inverse function of the sine function and calculates the angle for a given sine. X must be in the range [-1..1]. The result is an angle expressed in radians. To convert from radians to degrees, use the DEGREES() function.

ACOS Arc cosine function
ACOS(x) returns the arccosine of x. The arccosine function is the inverse function of the cosine function and calculates the angle for a given cosine. X must be in the [-1..1] range. The result is an angle expressed in radians. To convert from radians to degrees, use the DEGREES() function.

ATAN Arc tangent function
ATAN(x) returns the arctangent of x. The arctangent function is the inverse function of the tangent function and calculates the angle for a given tangent. The result is an angle expressed in radians. To convert from radians to degrees, use the DEGREES() function.

ATAN2 Arc tangent of two numbers
ATAN2(y,x) returns the arc tangent of the two numbers x and y. It is similar to calculating the arc tangent of y / x, except that the signs of both arguments are used to determine the quadrant of the result. The result is an angle expressed in radians. To convert from radians to degrees, use the DEGREES() function.

Hyperbolic functions

SINH Hyperbolic sine function
SINH(x) returns the hyperbolic sine of the angle x. The argument x must be expressed in radians. To convert degrees to radians you use the RADIANS() function.

COSH Hyperbolic cosine function
COSH(x) returns the hyperbolic cosine of the angle x. The argument x must be expressed in radians. To convert degrees to radians you use the RADIANS() function.

TANH Hyperbolic tangent function
TANH(x) returns the hyperbolic tangent of the angle x. The argument x must be expressed in radians. To convert degrees to radians you use the RADIANS() function.

ASINH Inverse hyperbolic sine function
ASINH(x) returns the inverse hyperbolic sine of x.

ACOSH Inverse hyperbolic cosine function
ACOSH(x) returns the inverse hyperbolic cosine of x. X must be greater than or equal to 1.

ATANH Inverse hyperbolic tangent function
ATANH(x) returns the inverse hyperbolic tangent of x. X must be in the range [-1..1].
Engineering functions

BESSELJ Bessel function of first kind
BESSELJ(x,n) returns the Bessel function of first kind. X is the value at which to evaluate the function, and n is the order of the Bessel function. If n is not an integer, it is truncated.

BESSELI Modified Bessel function of first kind
BESSELI(x,n) returns the modified Bessel function of first kind. X is the value at which to evaluate the function, and n is the order of the Bessel function. If n is not an integer, it is truncated.

BESSELY Bessel function of second kind
BESSELY(x,n) returns the Bessel function of second kind. X is the value at which to evaluate the function, and n is the order of the Bessel function. If n is not an integer, it is truncated.

BESSELK Modified Bessel function of second kind
BESSELK(x,n) returns the modified Bessel function of second kind. X is the value at which to evaluate the function, and n is the order of the Bessel function. If n is not an integer, it is truncated.

CONVERT Unit conversion function
CONVERT(x,From_unit,To_unit) converts the value x from the unit From_unit to a number in unit To_unit. See Appendix F (p. 335) for available units.

DEC2HEX Hexadecimal representation of a number
DEC2HEX(x) returns the hexadecimal representation of the integer number x.

ERF Error function
ERF(x) returns the error function integrated between zero and x.

\[
erf(x) = \frac{2}{\sqrt{\pi}} \int_0^x e^{-t^2} \, dt
\]

ERFC Complementary error function
ERFC(x) returns the error function integrated between x and infinity.

\[
erfc(x) = \frac{2}{\sqrt{\pi}} \int_x^\infty e^{-t^2} \, dt
\]

HEX2DEC Hexadecimal number to decimal number conversion
HEX2DEC(h) converts a hexadecimal number to a decimal number.

MD5 Hash function
MD5(str) returns the MD5 hash of a string. The MD5 algorithm processes a variable-length string into a fixed-length output of 128 bits (16 bytes), which are represented hexadecimal, resulting in a 32 characters string.

Gamma function and related functions

FACT Factorial function
FACT(x) returns the factorial of x. The factorial of a number n is equal to 1*2*3*...*n.

FACT(5) equals 120 (=1*2*3*4*5)
GAMMA Gamma function
GAMMA(r) returns the Gamma function of r.

GAMMALN function
GAMMALN(r) returns the logarithm of the Gamma function of r.

BETA function
BETA(a,b) returns the returns the Beta function of a and b.

Complex number functions

COMPLEX Create complex number
COMPLEX(a,b) returns the complex number a + bi.

RE Returns the real part of a complex number
RE(A) returns the real part a of the complex number A = a + bi.

IM Returns the imaginary part of a complex number
IM(A) returns the imaginary part b of the complex number A = a + bi.

NORM Returns the norm of a complex number
NORM(A) returns the norm (or modulus) of a complex number. The norm of the complex number A = a + bi is defined as

\[ \sqrt{a^2 + b^2} \]

This is equal to ABS(A) (in Excel this is the IMABS function).

CONJ Returns the complex conjugate of a complex number
CONJ(A) returns the complex conjugate of a complex number. The complex conjugate of the complex number A = a + bi is a - bi.

Note that:

\[ (a + bi) \times (a - bi) = abs(a + bi)^2 \]

PHASE Returns the phase angle of a complex number
PHASE(A) returns the phase angle (or angular component) of the complex number A, expressed in radians. This is Excel's IMARGUMENT function.

\[ \text{phase}(a + bi) = \arctan \left( \frac{b}{a + b}\right) \]

POLAR Returns the complex number defined by its polar components
POLAR(rho,theta) returns the complex number defined by its polar components rho and theta, where rho is the norm (modulus) and theta is the phase angle.

CRND Returns a random complex number
CRND() returns a random complex number. Both real and imaginary parts are independent random numbers in the range (0,1). The CRND() function takes no parameters.

CSQRT Square root function
CSQRT(x) takes a complex or real number as argument and returns its square root. When x is a negative real number the result is a complex number. CSQRT(-1) returns 0+1i.
Statistical functions

In the spreadsheet window, statistical functions can be entered that perform a calculation on one or two variables or ranges of cells containing numeric values. For all statistical functions that accept a range as argument, a list of ranges is also accepted as an argument. E.g. SUM(A1:A3,A10,B5:B6) will calculate the sum of cells A1, A2, A3, A10, B5 and B6.

AVEDDEV Average of absolute deviations

AVEDDEV(range) returns the average of absolute deviations of the data in range.

AVERAGE Average

AVERAGE(range) computes the arithmetic mean of the contents of the cells in the specified range. If one of the cells in the function’s range does not have a numeric value, but is empty or has a string value, then this cell will not be taken into account for calculating the average, or any of the other statistical functions.


COEFVAR Coefficient of variation

COEFVAR(range) returns the coefficient of variation of the data in range.

COUNT Count

COUNT(range) counts the number of cells in the specified range that have a numerical content. See also the COUNTS(range) function: this function counts the number of non-empty cells.

COUNT(A1:A5) Returns 4 if the contents of cells A1, A2,A3 and A5 is a number, and A4 is blank or contains non-numeric data.

The COUNT function has 2 variants:

COUNTNEG(range) counts the number of negative values in range (< 0);

COUNTPOS(range) counts the number of positive numbers in range (> 0);

COUNTS Count non-empty cells

COUNTS(range) counts the number of cells in range that are non-empty, irrespective if the cell contains a formula or a numeric or text value. This distinguishes the COUNTS function from the COUNT function that only counts cells containing a numeric value, or a formula resulting in a numeric value.

CORREL Correlation function

CORREL(range1,range2) returns the Pearson correlation coefficient of the data in range1 and range2.

COVAR Covariance function

COVAR(range1,range2) returns the covariance (the average of the products of deviations for each data point pair).

GEOMEAN Geometric mean

GEOMEAN(range) returns the geometric mean of the data in range. The geometric mean is calculated as follows:

$$\left( \prod_{i=1}^{n} x_i \right)^{\frac{1}{n}} = \sqrt[n]{x_1 x_2 \cdots x_n} = \exp \left[ \frac{1}{n} \sum_{i=1}^{n} \ln x_i \right]$$

The geometric mean is undefined for a data set that contains zero or negative values.

HARMEAN Harmonic mean

HARMEAN(range) computes the harmonic mean of the contents of the cells in the specified range. The harmonic mean is calculated as follows:
\[
\frac{1}{x_1} + \frac{1}{x_2} + \cdots + \frac{1}{x_n} = \frac{n}{\sum_{i=1}^{n} \frac{1}{x_i}}
\]

The harmonic mean is undefined for a data set that contains zero or negative values.

**MAX Maximum**

MAX(range) returns the maximum value of the contents of the cells in the specified range.

MAX(A1:D1,Z1) returns the maximum value of the contents of cells A1 to D1 (A1, B1, C1, D1) and cell Z1.

**MEDIAN Median**

MEDIAN(range) returns the median value (50th percentile) of the contents of the cells in the specified range.

**MIN Minimum**

MIN(range) returns the minimum value of the contents of the cells in the specified range.

**PERCENTILE Percentile**

PERCENTILE(p,range) returns the pth percentile of the data in range.

PERCENTILE(75,A1:A100) calculates the 75th percentile of the data in cells A1 to A100.

**PERC RANK Percentile rank**

PERC RANK(x,range) returns the percentile rank of a value in a sample given by the specified range.

**SEM Standard error of the mean**

SEM(range) returns the standard error of the mean of the data in range.

**STDEV Standard deviation - sample**

STDEV(range) calculates the ‘sample’ standard deviation of the data in range (divisor n-1).

STDEV(B3:E3) calculates the standard deviation of the contents of cells B3, C3, D3 and E3.

**SUM Sum**

SUM(range) computes the sum of the contents of the cells in the specified range. The SUM function is probably the most frequently used function in any spreadsheet model.

SUM(A1:D1) calculates the sum of the contents of cells A1, B1, C1 and D1.

The SUM function has 2 variants: SUMNEG(range) and SUMPOS(range) calculating the sum of respectively the negative and positive values in range.

**TrimMean**

TrimMean(k,range) computes the trimmed mean of the contents of the cells in the specified range.

If k is equal to or larger than 1 then i will be taken as the number of cases to drop at both sides (if k=1 then 2 cases will be dropped in total).

If k is smaller than 1 then k will be taken as a proportion and \((n^*k/2)\) cases will be dropped at both sides, so a total of \((n^*k)\) cases will be dropped (if k=0.1 then 10% of cases will be dropped).

**TrimMeanSEM**

TrimMeanSEM(k,range) computes the standard error of the trimmed mean of the contents of the cells in the specified range.

**TrimMeanLOW and TrimMeanHIGH**

TrimMeanLOW(k,ci,range) calculates the lower value of a confidence interval of a trimmed mean
TrimMeanHIGH(k,ci,range) calculates the higher value of a confidence interval of a trimmed mean

The confidence interval \(ci\) must be given in the range 0..100. A value of 95 will give the values of a 95% confidence interval.
VAR Variance - sample
VAR(range) computes the correct 'sample' variance of the data in the specified range (divisor n-1).

VAR(D8:G8) calculates the variance of the contents of cells D8 to G8.

Statistical test functions

NORMSDIST One-tailed probability from standardized Normal distribution
NORMSDIST(z) returns the one-tailed probability associated with the standardized Normal deviate z.

NORMSDIST(-1.96) returns 0.025 (rounded)
NORMSDIST(1.96) returns 0.975 (rounded)
NORMSDIST(0) returns 0.5

NORMSINV Returns a Standardized Normal deviate
NORMSINV(P) returns the standardized Normal deviate z corresponding with the one-tailed probability P. P must be a value between 0 and 1 (0<P<1). NORMSINV is the inverse function of the NORMSDIST function.

NORMSINV(0.025) returns -1.96 (rounded)
NORMSINV(0) returns an error

TDIST Two-tailed probability from the Student t distribution
TDIST(t,df) returns the two-tailed probability P associated with the test statistic t and df degrees of freedom.

TDIST(3.1693,10) returns 0.01 (rounded)

TINV Returns a value t from the Student t distribution
TINV(P,df) returns the t-value corresponding with the two-tailed P-value P and the specified degrees of freedom df. TINV is the inverse function of the TDIST function.

TINV(0.05,30) returns 2.0423 (rounded)

FDIST One-tailed probability from the F distribution
FDIST(F,v1,v2) returns the one-tailed probability P associated with the test statistic F with v1 degrees of freedom for the numerator and v2 degrees of freedom for the denominator.

FDIST(3.291,6,40) returns 0.01 (rounded)

FINV Inverse of the F probability distribution
FINV(p,v1,v2) returns the chi-squared value corresponding with the one-tailed P-value p and the specified degrees of freedom df. FINV is the inverse of the FDIST function.

CHIDIST One-tailed probability from the Chi Squared distribution
CHIDIST(chisquared,df) returns the probability P associated with the test statistic chisquared and df degrees of freedom.

CHIDIST(18.307,10) returns 0.05 (rounded)

CHIINV Returns the reverse of the chi-squared distribution
CHIINV(p,df) returns the chi-squared value corresponding with the one-tailed P-value p and the specified degrees of freedom df. CHIINV is the inverse of the CHIDIST function.
Probability distribution functions

Normal distribution functions

\text{PDFNormal}(x,mean, sd) \text{ returns the probability density at the value } x \text{ of the normal distribution with given } mean \text{ and standard deviation } sd.

\text{CDFNormal}(x,mean, sd) \text{ returns the value at } x \text{ of the normal cumulative distribution with given } mean \text{ and standard deviation } sd.

\text{RndNormal}(mean, sd) \text{ returns a random number from the normal distribution with given } mean \text{ and standard deviation } sd.

Log-normal distribution functions

\text{PDFLogNormal}(x, mu, sigma) \text{ returns the probability density at the value } x \text{ of the log-normal distribution with parameters } mu \text{ and sigma.}

\text{CDFLogNormal}(x, mu, sigma) \text{ returns the value at } x \text{ of the log-normal cumulative distribution with parameters } mu \text{ and sigma.}

\text{RndLogNormal}(mu, sigma) \text{ returns a random number from the log-normal distribution with parameters } mu \text{ and sigma.}

Exponential distribution functions

\text{PDFExponential}(x, mu) \text{ returns the probability density at the value } x \text{ of the exponential distribution with mean parameter } mu.

\text{CDFExponential}(x, mu) \text{ returns the value at } x \text{ of the exponential cumulative distribution with mean parameter } mu.

\text{RndExponential}(mu) \text{ returns a random number from the exponential distribution with mean parameter } mu.

T-distribution functions

\text{PDFStudentT}(x, df) \text{ returns the probability density at the value } x \text{ of a Student's t distribution with degrees of freedom } df.

\text{CDFStudentT}(x, df) \text{ returns the value at } x \text{ of the Student's t cumulative distribution with degrees of freedom } df.

\text{RndStudentT}(df) \text{ returns a random value of a Student's t distribution with degrees of freedom } df.

Chi-squared distribution functions

\text{PDFChi2}(x, df) \text{ returns the probability density at the value } x \text{ of a chi-squared distribution with degrees of freedom } df.

\text{CDFChi2}(x, df) \text{ returns the value at } x \text{ of the chi-squared cumulative distribution with degrees of freedom } df.

\text{RndChi2}(df) \text{ returns a random value of the chi-squared distribution with degrees of freedom } df.

F-distribution functions

\text{PDFF}(x, df1, df2) \text{ returns the probability density at the value } x \text{ of a F-distribution with degrees of freedom } df1 \text{ and } df2.

\text{CDFF}(x, df1, df2) \text{ returns the value at } x \text{ of the F cumulative distribution with degrees of freedom } df1 \text{ and } df2.

\text{RndF}(DF1, df2) \text{ returns a random value of a F distribution with degrees of freedom } df1 \text{ and } df2.

Uniform distribution functions (continuous)

\text{PDFUniform}(x, a, b) \text{ returns the probability density at the value } x \text{ of a uniform distribution with range } a \text{ to } b.

\text{CDFUniform}(x, a, b) \text{ returns the value at } x \text{ of the uniform cumulative distribution with range } a \text{ to } b.

\text{RndUniform}(a, b) \text{ returns a random value from the uniform distribution with range } a \text{ to } b.

Beta distribution functions

\text{PDFBeta}(x, a, b) \text{ returns the probability density at the value } x \text{ of the Beta distribution with parameters } a \text{ and } b.

\text{CDFBeta}(x, a, b) \text{ returns the value at } x \text{ of the cumulative Beta distribution with parameters } a \text{ and } b.

\text{RndBeta}(a, b) \text{ returns a random number of the Beta distribution with parameters } a \text{ and } b.

Gamma distribution functions

\text{PDFGamma}(x, a, b) \text{ returns the probability density at the value } x \text{ of the Gamma distribution with parameters } a \text{ and } b.

\text{CDFGamma}(x, a, b) \text{ returns the value at } x \text{ of the cumulative Gamma distribution with parameters } a \text{ and } b.

\text{RndGamma}(a, b) \text{ returns a random number of the Weibull distribution with parameters } a \text{ and } b.
**Poisson distribution functions**

PDFPoisson\((x,\lambda)\) returns the probability density at the value \(x\) of the Poisson distribution with parameter \(\lambda\).

CDFPoisson\((x,\lambda)\) returns the value at \(x\) of the Poisson cumulative distribution with parameter \(\lambda\).

RndPoisson\((\lambda)\) returns a random number from the Poisson distribution with parameter \(\lambda\).

**Binomial distribution functions**

PDFBinomial\((x,\text{trials},\text{probability})\) returns the binomial probability of obtaining exactly \(x\) 'events' in the specified number of \(\text{trials}\) and probability of success for each trial.

CDFBinomial\((x,\text{trials},\text{probability})\) returns the cumulative binomial probability of obtaining \(x\) or fewer 'events' in the specified number of \(\text{trials}\) and probability of success for each trial.

RNDDBinomial\((\text{trials},\text{probability})\) generates a random number from the binomial distribution with specified number of \(\text{trials}\) and probability of success.

**Weibull distribution functions**

PDFWeibull\((x,\alpha,\beta)\) returns the probability density at the value \(x\) of the Weibull distribution with parameters \(\alpha\) and \(\beta\).

CDFWeibull\((x,\alpha,\beta)\) returns the value at \(x\) of the cumulative Weibull distribution with parameters \(\alpha\) and \(\beta\).

RndWeibull\((\alpha,\beta)\) returns a random number of the Weibull distribution with parameters \(\alpha\) and \(\beta\).

**String functions**

String functions are functions that have a non-numerical result. A string is a sequence of characters not interpreted as a number, e.g. Jones, “25”.

**CELL Cell text/formula function**

CELL\((\text{column},\text{row})\) returns the contents of the cell with coordinates \(\text{column}\) and \(\text{row}\) as text.

CELL("A",5) returns the text 5*6 when cell A5 contains 5*6.

**CHAR Character function**

CHAR\((x)\) returns the Unicode character with code \(x\). The result is a string value of length 1 (if \(x>0\)).

CHAR(65.0) returns the string value ‘A’

CHAR(926) returns the string value “Ξ”

**CODE Character to Unicode code conversion**

CODE\((\text{str})\) returns the Unicode code number of the first character of the string \(\text{str}\). If the length of the string is 0, i.e. the string is empty, then the function returns 0.

CODE("Andy") returns 65.00

**CONCAT Concatenate strings**

CONCAT\((\text{str1},\text{str2},...)\) joins two or more strings (text items) into one single string.

CONCAT("Total ","value") returns "Total value".

**LEFT Left portion of string**

LEFT\((\text{str},n)\) returns the first \(n\) characters of \(\text{str}\). If \(n\) equals 0, then the LEFT function returns an empty string. If \(n\) is equal to or more than the length of the string \(\text{str}\), the function returns the complete string.

LEFT("Position",3) returns “Pos”
LEN Length of string
LEN(str) returns the length of the string str.

LOWER Lowercase function
LOWER(str) converts the string str to lowercase.

    LOWER('TOTAL') returns "total"

MID Middle portion of a string
MID(str,pos,n) returns n characters from str starting at position pos.

    MID("statistics",3,4) returns "atis"

REPT Repeat function
REPT(str,n) creates a string consisting of str repeated n time.

    REPT("***",5) returns "*****"

REVERSE Reverses a string
REVERSE(str) reverses the string str.

    REVERSE("total") returns "latot"

RIGHT Right portion of a string
RIGHT(str,n) returns the last n characters of str. If n equals 0, then the RIGHT function returns an empty string. If n is equal to or more than the length of the string str, the function returns the complete string.

STR Number to string conversion
STR(x,n) returns the numeric value x as a string, with n decimal places.

    STR(25.56,1) returns the string value "25.6"

UPPER Uppercase function
UPPER(str) converts the string str to uppercase.

    UPPER('total') returns "TOTAL"

VAL String to number conversion
VALUE(str) evaluates str as a number.

    VALUE("25.0") returns 25.0
    VALUE("text") returns an error

Date and time functions

DATE Serial date number to string
DATE(dnr) returns the date corresponding with the serial date number dnr expressed as a string.

    DATE(DATEVALUE(A1)+7) returns "6.9.96" when cell A1 contains the date string 30.8.96 or "30/8/96" (date format DD.MM.YY)

DATEVALUE String to serial date number
The function DATEVALUE(str) returns the serial date number for the date expressed in the string str.

    DATEVALUE("10.12.88") returns 68645 if the date format is DD.MM.YY.
DATEFRAC Fractional year-number

DATEFRAC(date) converts date into a fractional year-number. The integer part of this number is the year, and the decimal fraction ranges from 0.0 to 0.99..., representing the dates 01 Jan to 31 Dec.

```
DATEFRAC("01.07.2000")  returns 2000.5
```

DAY Day function

DAY(date) returns the day of the month of date. Date can either be a serial date number or a date string.

```
DAY("23.08.88") returns 23 (date format DD.MM.YY)
```

DAYNAME Day name function

DAYNAME(date[,languagecode]) returns the name of the day of date. Date can either be a serial date number or a date string. The optional argument languagecode is a two-character code that defines the language to be used (see page 332). When omitted, the name of the month is given in English.

```
DAYNAME("03.12.2001") returns "Monday" (date format DD.MM.YY)
DAYNAME("30.01.2012","KO") returns "월요일" (Korean)
```

MONTH Month function

MONTH(date) returns the month of the year of date. Date can either be a serial date number or a date string.

```
MONTH("23.08.88") returns 8 (date format DD.MM.YY)
```

MONTHNAME Month name function

MONTHNAME(date[,languagecode]) returns the name of the month of date. Date can either be a serial date number or a date string. The optional argument languagecode is a two-character code that defines the language to be used (see page 332). When omitted, the name of the month is given in English.

```
MONTHNAME("03.12.2001") returns "December" (date format DD.MM.YY)
MONTHNAME("30.01.2012","RU") returns "январь" (Russian)
```

NOW Current date and time function

The function NOW() takes no argument and returns the current date and time combined into one number. This number is the sum of the serial date number and the serial time number.

Note that the value of this function is not fixed and returns a different value each time the spreadsheet is recalculated.

```
NOW() returned 77695.71806 on September 20, 2013 at 17:14 PM.
77695.71806 is the sum of DATEVALUE("20.09.2013") and TIMEVALUE("17:14")
```

TIMEVALUE String to serial time number

TIMEVALUE(str) converts a time string (in "hh:mm" format) to a serial time number. A serial time number is a number ranging from 0.00 to 1.00 representing the time 0:00 to 24:00.

```
TIMEVALUE("06:30") returns 0.27084
TIMEVALUE("12:00") returns 0.5
```

TIME Serial time number to string

TIME(tnr) converts the serial time number tnr to a time string (hh:mm).

```
TIME(0.5) returns 12:00
```

TIMEFRAC Fractional time-number

TIMEFRAC(time) converts time into fractional time-number. The integer part of this number is the hour, and the decimal fraction ranges from 0.0 to 0.99, representing the minutes 0:00 to 0:59.

```
TIMEFRAC("12:30") returns 12.5
```
TODAY Today's date

The function TODAY() takes no argument and returns today's date. Note that the value of this function is not fixed, so if you use this function in a file and you reload this file the next day, the function will return the new date.

TODAY() returns 24.01.1998 if today is the 24th of January 1998 and the date format is DD.MM.YY.

DATEVALUE(TODAY()) returns the serial number of today’s date.

WEEKNUM Week number function

WEEKNUM(date) returns the number of the week of the year of date. Date can either be a serial date number or a date string.

WEEKNUM("01.01.98") returns 1
WEEKNUM("05.02.98") returns 2
WEEKNUM("25.12.98") returns 52

WEEKDAY Weekday number function

WEEKDAY(date) returns the weekday number of date. Days are numbered from Monday (=1) to Sunday (=7).

WEEKDAY("05.07.56") returns 4, this is the 4th day of the week (=Thursday).

YEAR Year function

YEAR(date) returns the year of date. Date can either be a serial date number or a date string.

YEAR("23.08.88") returns 88 (date format DD.MM.YY)
YEAR(TODAY()) returns today’s year.

Logical functions

AND And function

AND(condition1,condition2,...) returns 1 (=TRUE) of all of its arguments are TRUE. If one of the arguments, either condition1, condition2, etc. is FALSE (or 0), the function returns 0 (=FALSE). If one of the conditions cannot be evaluated (for example because of missing data), the function returns an error.

(LENGTH>160) AND (LENGTH<170) can be written as:

AND(LENGTH>160,LENGTH<170)

ANY Any function

ANY(test,value1,value2,...) returns 1 (=TRUE) if the value of test matches any of the subsequent values; returns 0 (=FALSE) otherwise.

CATEGORISE Categorise function

CATEGORISE("variable","condition1",value1,"condition2",value2,...,"conditionN",valueN [,defaultvalue] ) recodes a variable into different categories. If "condition1" is true then the function returns value1, else if "condition2" is true then the function returns value2, and so on.

The first parameter is the variable name and must be placed between quotation marks. The following parameters are a serious of conditions and values. The conditions must be placed between quotation marks. The list of conditions is evaluated from left to right. If a condition is true, the value that follows is returned as the result of the function.

The last (optional) parameter of the function specifies a default value which is returned when none of the conditions is true.

CATEGORISE("VALUE","=0","Zero","<0","Negative",">0","Positive") returns the string value “Zero” when the variable VALUE contains the value 0, the string value “Negative” is returned when the variable VALUE is less than 0.
CATEGORISE("AGE",">60","old",">25","middle-aged","young") returns the string value "old" when the variable AGE contains a value higher than 60, "middle-aged" is returned when AGE is higher than 25. In all other cases the function returns "young".

**IF If-then-else function**

IF(condition,x,y) returns x if the condition is TRUE (=1), but returns y if the condition is FALSE (=0).

- IF(C2<0,"NEG","POS") returns the string value "NEG" if the number in cell C2 is less than 0 (C2<0 = TRUE). If cell C2 contains a number equal to or more than 0, then this function returns the string value "POS".
- IF(A1>1,25,33) returns 25 if cell A1 contains a value greater than 1. If A1 contains 1 or a value less than 1, then this expression returns 33.

This function can also be used for converting continuous data into discrete data: the IF function can be nested in order to create 3 (or more) groups. When you want to convert the variable AGE into codes for age groups of less than 30 years, 30 to 39 years and 40 or more years, you can use the following formula:

\[
\text{IF( AGE < 30 , 1 , IF( AGE < 40 , 2 , 3 ) )}
\]

**ISEMPTY Cell-is-empty function**

ISEMPTY(var) returns the logical value 1 (=TRUE) if the calculation of var does not result in a numeric or text value.

**ISNUMBER Cell-is-number function**

ISNUMBER(var) results in the logical value 1 (=TRUE) if the calculation of var results in a number.

- ISNUMBER(25.6) returns 1
- ISNUMBER(B2) returns 0 (=FALSE) if cell B2 contains e.g. the string value "SMITH"

**ISSTRING Cell-is-string function**

ISSTRING(var) results in the logical value 1 (=TRUE) if the calculation of var does not result in a numeric value.

- ISSTRING(B2) returns 1 (=TRUE) if cell B2 contains a string value, e.g. "SMITH"
- ISSTRING(25.6) returns 0

**NOT Not function**

The function NOT(x) reverses the value of its argument x. If x is 0 or FALSE then NOT(x) returns 1 (= TRUE). If x is 1 or TRUE then NOT(x) returns 0 (= FALSE).

**ODD Odd number**

ODD(x) returns 1 (=TRUE) when x is an odd number, else this function returns 0 (=FALSE).

**OR Or function**

OR(condition1,condition2,...) returns 1 (=TRUE) of at least one of its arguments is TRUE (or 1). If one of the conditions cannot be evaluated (for example because of missing data), the function returns an error.

**Miscellaneous functions**

**CELLVALUE Value of spreadsheet cell**

CELLVALUE(column,row) returns the value of the cell in the specified column and row

**CHIGH Highest column number**

The CHIGH() function takes no argument and returns the highest column number used in the spreadsheet.
COLUMN Spreadsheet column identifier
COLUMN(cell) returns the zero-based column number of a cell in the spreadsheet.
The cell argument is optional and COLUMN() returns the column number of the cell in which the formula is used. COLUMN() can be shortened to COLUMN.

FALSE Logical constant FALSE
The logical constant FALSE corresponds to the numeric value 0.

RHIGH Highest row number
The RHIGH() function takes no argument and returns the highest row number used in the spreadsheet.

ROW Spreadsheet row identifier
ROW(cell) returns the row number (indicating cases) of a cell in the spreadsheet.
The cell argument is optional and ROW() returns the row number of the cell or row in which the formula is used. ROW() can be shortened to ROW.

TRUE Logical constant TRUE
The logical constants TRUE corresponds to the numeric value 1.
### Appendix A. Control keys

<table>
<thead>
<tr>
<th>Operation Description</th>
<th>Key Combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cascade windows</td>
<td>Shift+F5</td>
</tr>
<tr>
<td>Copy block (Text &amp; Spreadsheet window)</td>
<td>Ctrl+C</td>
</tr>
<tr>
<td>Cut block (Text &amp; Spreadsheet window)</td>
<td>Ctrl+X</td>
</tr>
<tr>
<td>Edit cell</td>
<td>F2</td>
</tr>
<tr>
<td>English user interface</td>
<td>Ctrl+Shift+E</td>
</tr>
<tr>
<td>Exit MedCalc program</td>
<td>Alt+F4</td>
</tr>
<tr>
<td>Export file (metafile, text file, ...)</td>
<td>F10</td>
</tr>
<tr>
<td>Save to or Append to Word file</td>
<td>Ctrl+W</td>
</tr>
<tr>
<td>Fill down</td>
<td>Ctrl+D</td>
</tr>
<tr>
<td>Fill right</td>
<td>Ctrl+R</td>
</tr>
<tr>
<td>Fill series</td>
<td>Ctrl+L</td>
</tr>
<tr>
<td>Find</td>
<td>Ctrl+F</td>
</tr>
<tr>
<td>Find and replace</td>
<td>Ctrl+H</td>
</tr>
<tr>
<td>Go to cell</td>
<td>Ctrl+G</td>
</tr>
<tr>
<td>Help</td>
<td>F1</td>
</tr>
<tr>
<td>Move cursor left (Text window)</td>
<td>←</td>
</tr>
<tr>
<td>Move cursor right (Text window)</td>
<td>→</td>
</tr>
<tr>
<td>Move cursor to previous line (Text window)</td>
<td>↑</td>
</tr>
<tr>
<td>Move cursor to previous word (Text window)</td>
<td>Ctrl+←</td>
</tr>
<tr>
<td>Move cursor to next line (Text window)</td>
<td>↓</td>
</tr>
<tr>
<td>Move cursor to next tab position (Text window)</td>
<td>Tab</td>
</tr>
<tr>
<td>Move cursor to next word (Text window)</td>
<td>Ctrl+→</td>
</tr>
<tr>
<td>On line help</td>
<td>F1</td>
</tr>
<tr>
<td>Open spreadsheet data file</td>
<td>Ctrl+O</td>
</tr>
<tr>
<td>Print window, graph, data, results</td>
<td>F9</td>
</tr>
<tr>
<td>Paste block (Text &amp; Spreadsheet window)</td>
<td>Ctrl+V</td>
</tr>
<tr>
<td>Recall dialog</td>
<td>F7</td>
</tr>
<tr>
<td>Recent dialogs</td>
<td>Ctrl+F7</td>
</tr>
<tr>
<td>Save data</td>
<td>Ctrl+S or F12</td>
</tr>
<tr>
<td>Save graph as a picture file (export)</td>
<td>F10</td>
</tr>
<tr>
<td>Save or Append to a Word (docx) file</td>
<td>Ctrl+W</td>
</tr>
<tr>
<td>Select all</td>
<td>Ctrl+A</td>
</tr>
<tr>
<td>Select the contents for a cell from a list of entries already in the column</td>
<td>Alt + ↓</td>
</tr>
<tr>
<td>Tile windows</td>
<td>Shift+F4</td>
</tr>
</tbody>
</table>
Appendix B. Notation and symbols

| x | absolute value of x |
| α | level of hypothesis test, usually 0.05 |
| β | probability of a Type I error |
| χ² | value from the Chi-squared distribution |
| CI | confidence interval |
| CR | coefficient of repeatability |
| DF | degrees of freedom |
| F | value from the F-distribution |
| K | kappa |
| n or N | sample size |
| P | probability of hypothesis |
| r | Pearson correlation coefficient |
| rs | Spearman rank correlation coefficient |
| R² | coefficient of determination |
| RSD | relative standard deviation |
| Σ | Greek letter sigma, denoting sum of. Σx is shorthand for \( \sum_{i=1}^{n} x_i \) |
| s | standard deviation |
| s² | variance |
| SD | standard deviation |
| SEM | standard error of the mean |
| t | value from the t-distribution |
| z | value from the Normal distribution |
Appendix C. Statistical tables

Table 1: Values of the Normal distribution

<table>
<thead>
<tr>
<th>area from $-\infty$ to $-z$ and $z$ to $+\infty$</th>
<th>area from $-z$ to $z$</th>
<th>$z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.999</td>
<td>3.291</td>
</tr>
<tr>
<td>0.005</td>
<td>0.995</td>
<td>2.807</td>
</tr>
<tr>
<td>0.01</td>
<td>0.99</td>
<td>2.576</td>
</tr>
<tr>
<td>0.05</td>
<td>0.95</td>
<td>1.960</td>
</tr>
<tr>
<td>0.10</td>
<td>0.90</td>
<td>1.645</td>
</tr>
<tr>
<td>0.20</td>
<td>0.80</td>
<td>1.282</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>0.675</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>area from $z$ to $\infty$</th>
<th>area from $-\infty$ to $z$</th>
<th>$z$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.999</td>
<td>3.090</td>
</tr>
<tr>
<td>0.005</td>
<td>0.995</td>
<td>2.576</td>
</tr>
<tr>
<td>0.01</td>
<td>0.99</td>
<td>2.326</td>
</tr>
<tr>
<td>0.05</td>
<td>0.95</td>
<td>1.645</td>
</tr>
<tr>
<td>0.10</td>
<td>0.90</td>
<td>1.282</td>
</tr>
<tr>
<td>0.20</td>
<td>0.80</td>
<td>0.842</td>
</tr>
<tr>
<td>0.50</td>
<td>0.50</td>
<td>0.000</td>
</tr>
</tbody>
</table>
Table 2: Values of the t-distribution (two-tailed)

<table>
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<tr>
<th>DF</th>
<th>0.80</th>
<th>0.90</th>
<th>0.95</th>
<th>0.98</th>
<th>0.99</th>
<th>0.995</th>
<th>0.998</th>
<th>0.999</th>
</tr>
</thead>
<tbody>
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<td>1</td>
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<td>6.314</td>
<td>12.706</td>
<td>31.820</td>
<td>63.657</td>
<td>127.32</td>
<td>318.30</td>
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<td>3.690</td>
<td>4.297</td>
<td>4.781</td>
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<td>2.228</td>
<td>2.764</td>
<td>3.169</td>
<td>3.581</td>
<td>4.144</td>
<td>4.587</td>
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<td>4.073</td>
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<td>3.922</td>
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<td>2.539</td>
<td>2.861</td>
<td>3.174</td>
<td>3.579</td>
<td>3.883</td>
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<td>20</td>
<td>1.325</td>
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<td>2.528</td>
<td>2.845</td>
<td>3.153</td>
<td>3.552</td>
<td>3.850</td>
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<td>1.721</td>
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<td>3.527</td>
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**Example**

The mean of a sample is 128.5, SEM 6.2, sample size 32. What is the 99% confidence interval of the mean?

Degrees of freedom (DF) is $n-1 = 31$, t-value in column for area 0.99 is 2.744. The 99% CI is:

$$
\text{mean} - t \ \text{SEM} \ \text{to} \ \text{mean} + t \ \text{SEM}
$$

$$
128.5 - 2.744 \times 6.2 \ \text{to} \ 128.5 + 2.744 \times 6.2
$$

$$
111.5 \ \text{to} \ 145.5
$$
Table 3: Logit transformation

\[
\logit(p) = \ln\left(\frac{p}{1-p}\right) \quad \text{and} \quad p = \frac{1}{1 + e^{-\logit(p)}}
\]

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## Appendix D. ISO language codes

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Appendix E. Bootstrapping

In bootstrapping (Efron & Tibshirani, 1993), the data of the sample are used to create a large set of new "bootstrap" samples, simply by randomly taking data from the original sample. In any given new sample, each of the same size as the original sample, some subjects will appear twice or more, and others will not.

The statistic of interest is computed in each of those bootstrap samples. The collection of these computed values is referred to as the bootstrap distribution of the statistic.

The percentile bootstrap is derived by using the 2.5 and the 97.5 percentiles of the bootstrap distribution as the 95% confidence interval of the statistics of interest. This percentile interval is used for the calculation of the confidence intervals for reference limits when estimated using the robust method.

The bias-corrected and accelerated (BCα) bootstrap (Efron, 1987; Efron & Tibshirani, 1993) adjusts for possible bias and skewness in the bootstrap distribution. The BCα bootstrap is used for Kendall's tau and in ROC curve analysis.

Random number generation

MedCalc uses the Mersenne twister as a random number generator (implementation MT19937) (Matsumoto & Nishimura, 1998).
Appendix F. Units for CONVERT function

The CONVERT function (see p. 315) converts a number from one measurement system to another. The available units are:

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<td>Foot</td>
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<td>Yard</td>
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<tr>
<td>Statute mile</td>
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<tr>
<td>Nautical mile</td>
<td>&quot;Nmi&quot;</td>
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<tr>
<td>Angstrom</td>
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<tr>
<td>Ell</td>
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<tr>
<td>Light-year</td>
<td>&quot;ly&quot;</td>
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<tr>
<td>Parsec</td>
<td>&quot;parsec&quot; or &quot;pc&quot;</td>
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<tr>
<td>Pica (1/72 inch)</td>
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<td>Day</td>
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<td>Hour</td>
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<td>Minute</td>
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<tr>
<td>Second</td>
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<td>mm of Mercury</td>
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<td><strong>Pond</strong></td>
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<tr>
<td><strong>Energy</strong></td>
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<td>Joule</td>
<td>&quot;J&quot;</td>
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<td>Erg</td>
<td>&quot;e&quot;</td>
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<td>IT calorie</td>
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<td>BTU</td>
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<td>Pferdestärke</td>
<td>&quot;PS&quot;</td>
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<td>Watt</td>
<td>&quot;W&quot; (or &quot;w&quot;)</td>
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<td>Tesla</td>
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<tr>
<td>Gauss</td>
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<td><strong>Volume (or liquid measure)</strong></td>
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<td>Liter</td>
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<td>&quot;in3&quot; or &quot;in^3&quot;</td>
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<td>Cubic feet</td>
<td>&quot;ft3&quot; or &quot;ft^3&quot;</td>
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<td>Cubic yard</td>
<td>&quot;yd3&quot; or &quot;yd^3&quot;</td>
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<tr>
<td>Cubic Mile</td>
<td>&quot;mi3&quot; or &quot;mi^3&quot;</td>
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<td>Cubic light-year</td>
<td>&quot;ly3&quot; or &quot;ly^3&quot;</td>
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<td>Cubic nautical mile</td>
<td>&quot;Nmi3&quot; or &quot;Nmi^3&quot;</td>
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The following abbreviated unit prefixes can be prepended to any metric From_unit or To_unit.

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<td>1.00E+24</td>
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<td>zetta</td>
<td>1.00E+21</td>
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<td>exa</td>
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<td>peta</td>
<td>1.00E+15</td>
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<td>tera</td>
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<td>1.00E+02</td>
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<td>1.00E+01</td>
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