

ISA Annual Conference

15/5/2007

# Statistical Aspects of Clinical Trials

*A special hands on workshop  
with computer simulations*

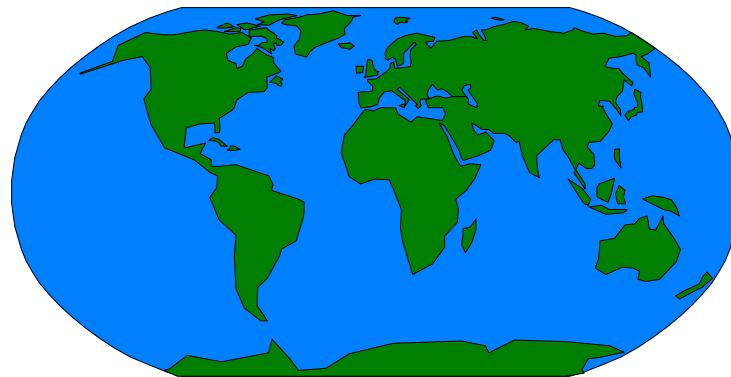
***Professor Tony Greenfield***

*tony@greenfieldresearch.co.uk*

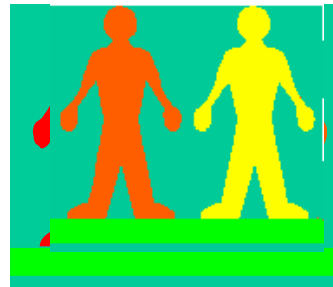
*with help of*

*Prof. Ron Kenett, ron@kpa.co.il*

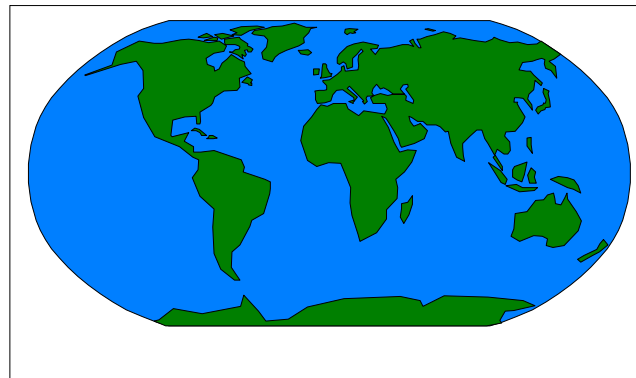
**A clinical trial is an experiment  
to discover something about  
the real world**



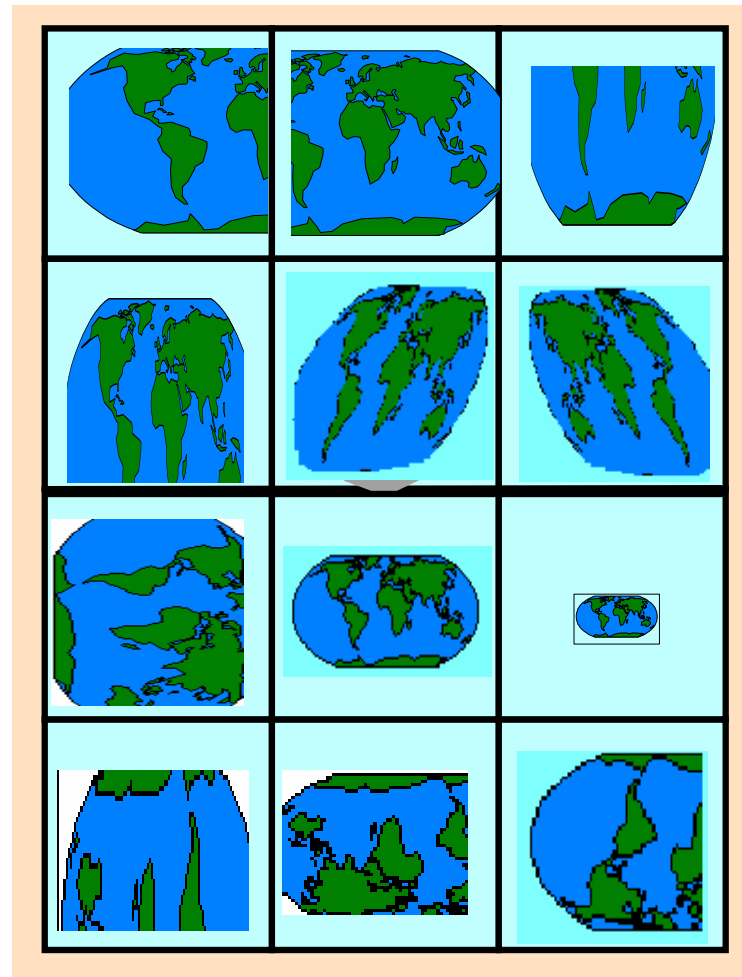
. . . **how people**  
**respond to clinical treatment**



# The protocol is the window we construct to look at the world

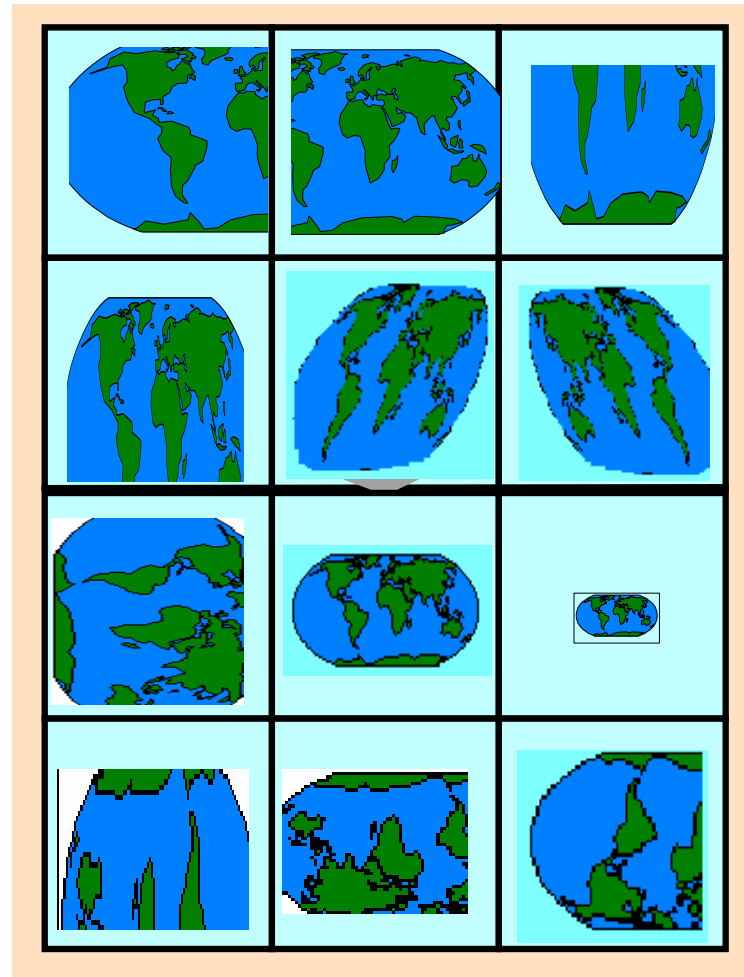


Different protocols will give different views of the world

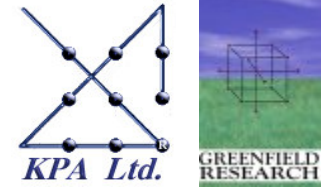


How can you be confident that your protocol is the best?

The efficiency and effectiveness and **cost** of a clinical trial depend on:

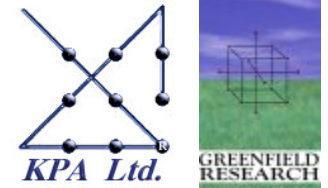


which window you choose to view the world



## The efficiency and effectiveness and **cost** of a clinical trial depend on:

- response to each treatment
- influence of other factors such as age, gender or life style
- number of patients
- how patients are selected for the trial
- how patients are allocated to treatments
- type of trial: parallel or crossover
- compliance of patients to treatments
- how data are recorded, analysed and interpreted



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- how patients are allocated to treatments
- type of trial: parallel or crossover
- compliance of patients to treatments
- how data are recorded, analysed and interpreted

All of these points should be discussed in the

**trial protocol**

**a statement of the design of the clinical trial and  
how it will be managed**

The protocol is the tool which is used to specify the way the trial will be run.

It is the glass through which the world will be observed.

through which we learn how people respond to clinical treatment



But it is used only once.

It can not be tried and retried until at last an efficient trial has been run



**MetaGen** will be used to develop and compare protocols  
for clinical trials  
to discover the best protocol for any situation  
in terms of scientific effectiveness  
as well as **cost** and effort

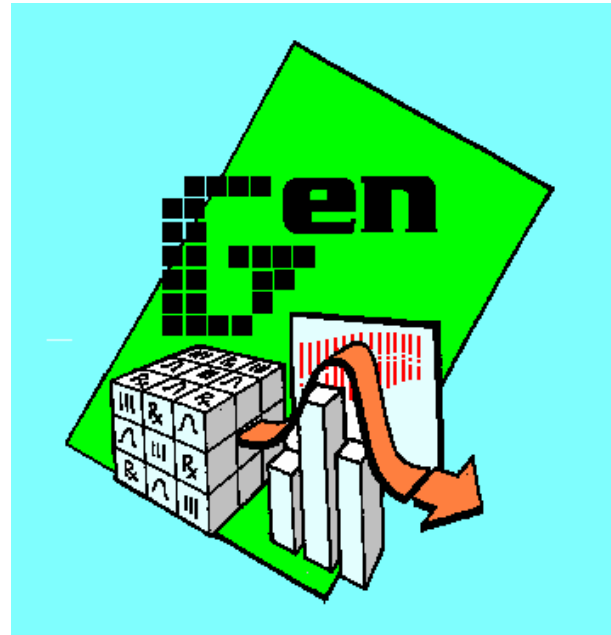


**MetaGen** has two components:

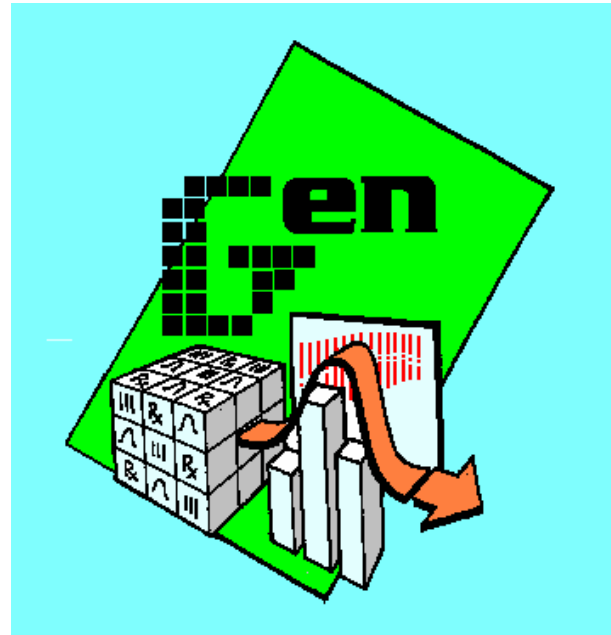


**META** is used to specify a model for study:

- treatments
- population variables
- response variables
- patient presentation and drop out rates

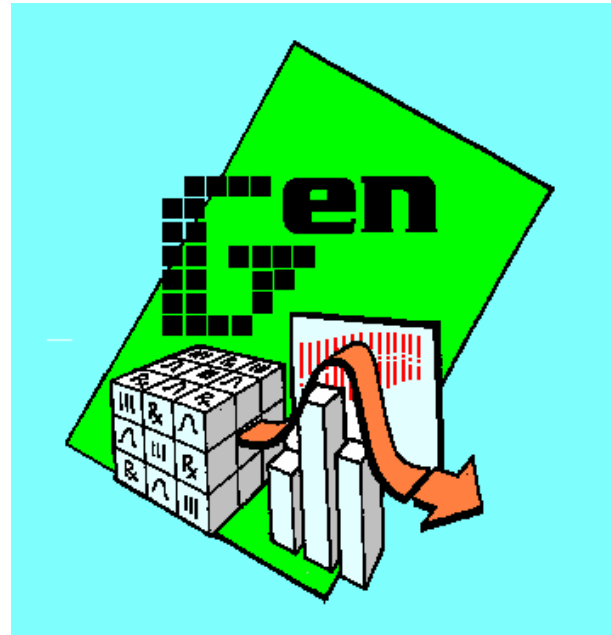


**GEN** allows the user to design a clinical trial  
with a view to discovering  
the model defined in **META**



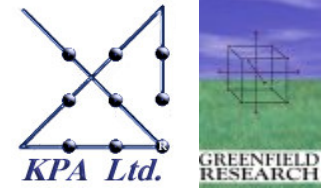
**GEN** will help the user to specify:

- treatments
- variables
- exclusion criteria
- schedule
- allocation procedure
- sample size



**GEN** will simulate a trial  
based on the protocol to produce:

- patient response data
- summary statistics
- charts



## Example: Nocturnal asthma

Three treatments:

- Wizerol
- Eezerol
- Placebo

Population variables:

- Gender
- Age

## Example: Nocturnal asthma

Response variables:

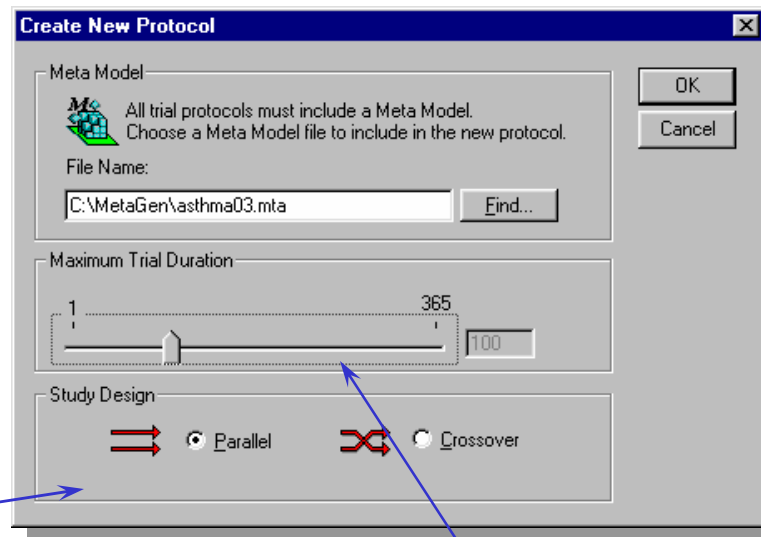
- blood pressure
- heart rate
- PEF (peak expiratory flow)
- FVC(forced vital capacity)
- FEV1(forced expiratory volume in one second)
- Symptom day score
- Symptom night score
- Tremors

## To create a new protocol:

attach a  
Meta  
model

specify a parallel  
or crossover trial

specify the overall trial duration



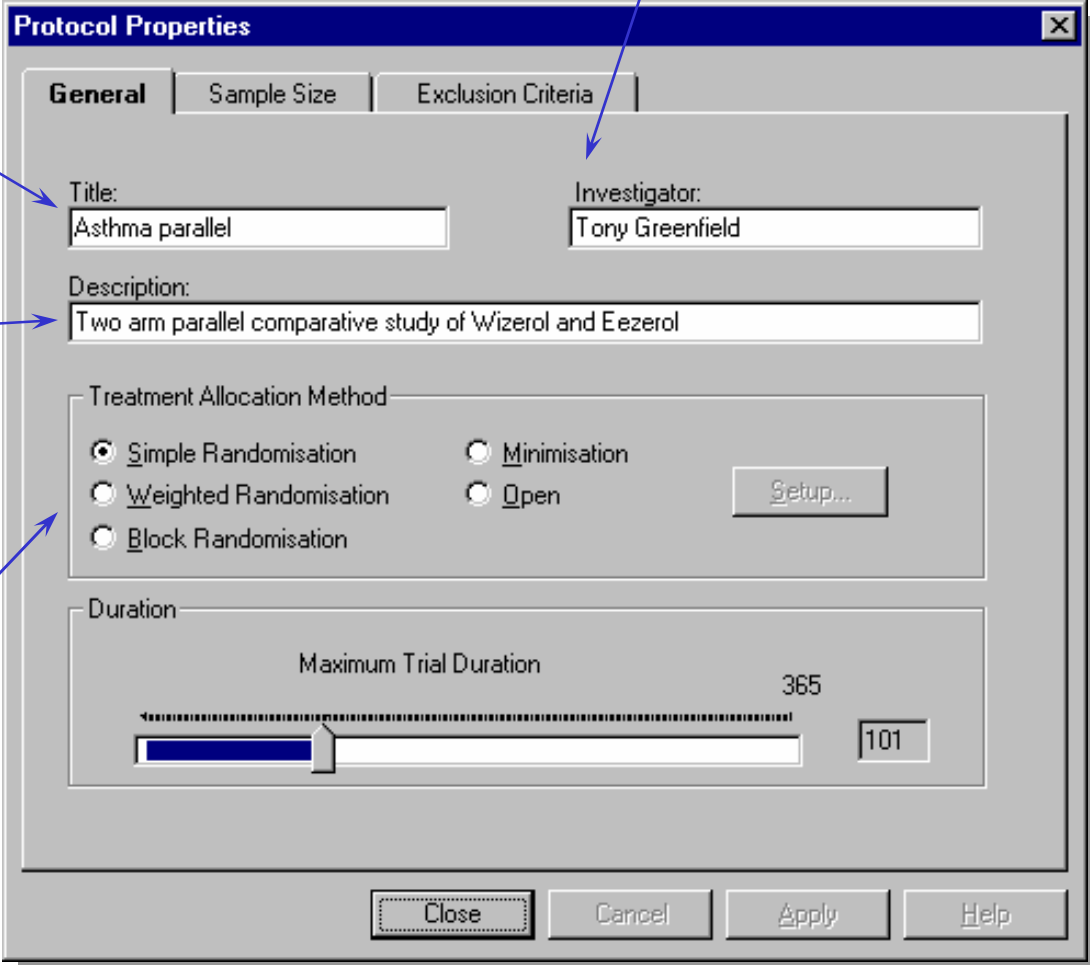
Enter

a title

investigator name

a description

specify the  
treatment  
allocation  
method



**Protocol Properties**

**General** | Sample Size | Exclusion Criteria

Title: Asthma parallel

Investigator: Tony Greenfield

Description: Two arm parallel comparative study of Wizerol and Eezerol

Treatment Allocation Method

Simple Randomisation     Minimisation

Weighted Randomisation     Open

Block Randomisation   

Duration

Maximum Trial Duration 365

101

## The arm designer allows you to:

create a diary of visits

allocate a treatment to a period

create new arms

delete arms

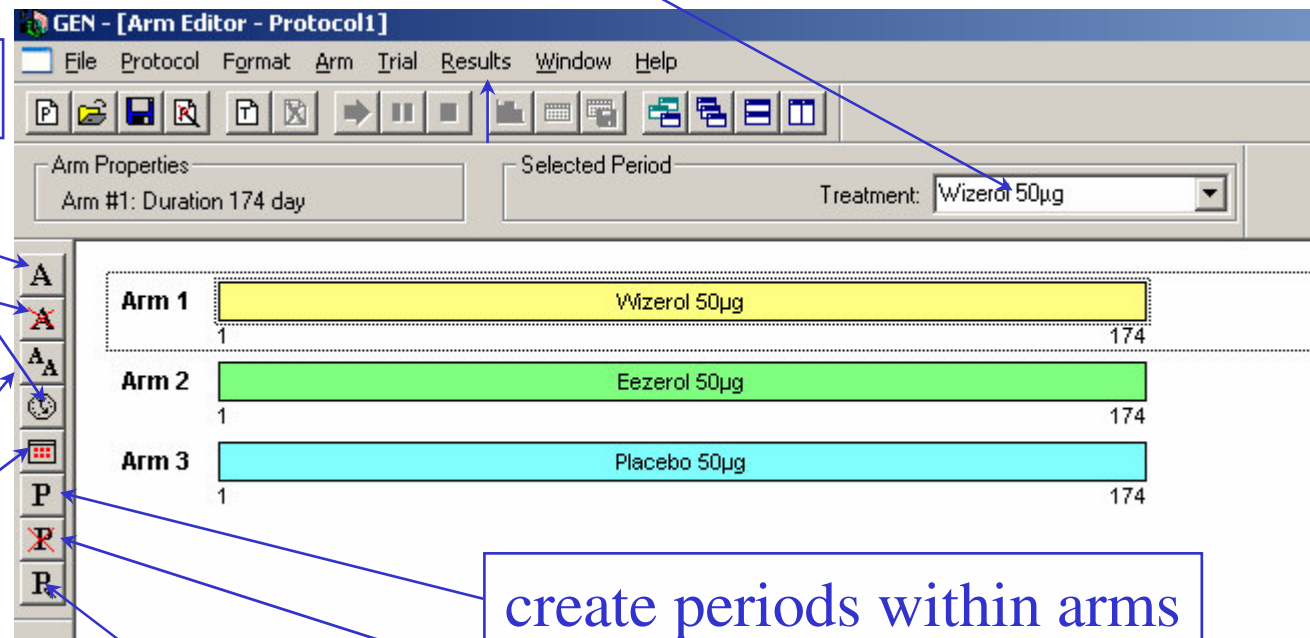
duplicate arms

schedule investigations

edit periods

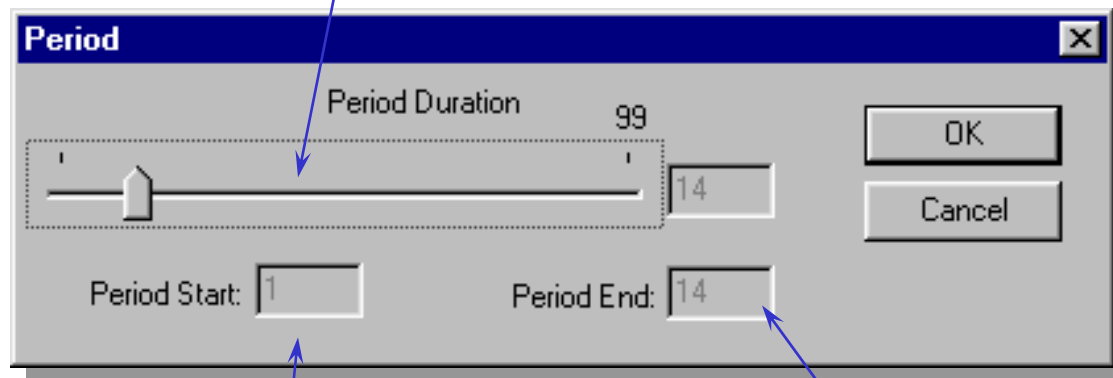
create periods within arms

delete periods



When you create a **new period** in a trial arm you can specify:

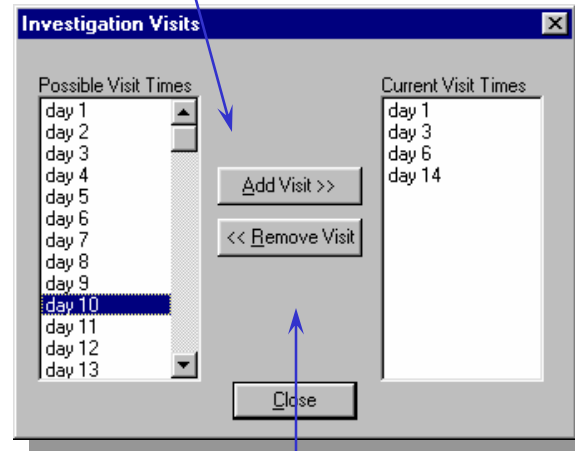
its duration



period start

period end

A **diary of visits** is created  
by moving possible times  
to the list of current visit times

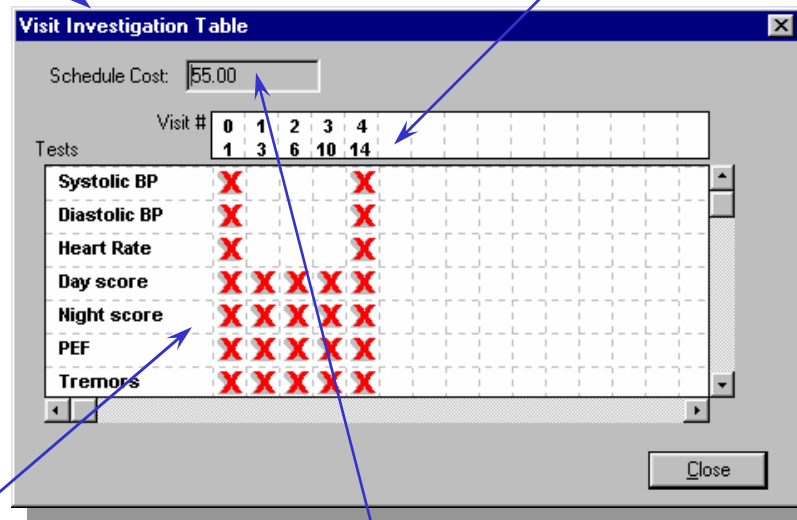


They can be removed too

The diary of visits is the basis for the investigation schedule

Some variables are recorded only by the investigator

Click on each square to add or remove crosses



Tests	0	1	2	3	4
Systolic BP		X			X
Diastolic BP		X			X
Heart Rate		X			X
Day score	X	X	X	X	X
Night score	X	X	X	X	X
PEF	X	X	X	X	X
Tremors	X	X	X	X	X

The schedule **cost**, for each patient, is updated according to your changes to the schedule

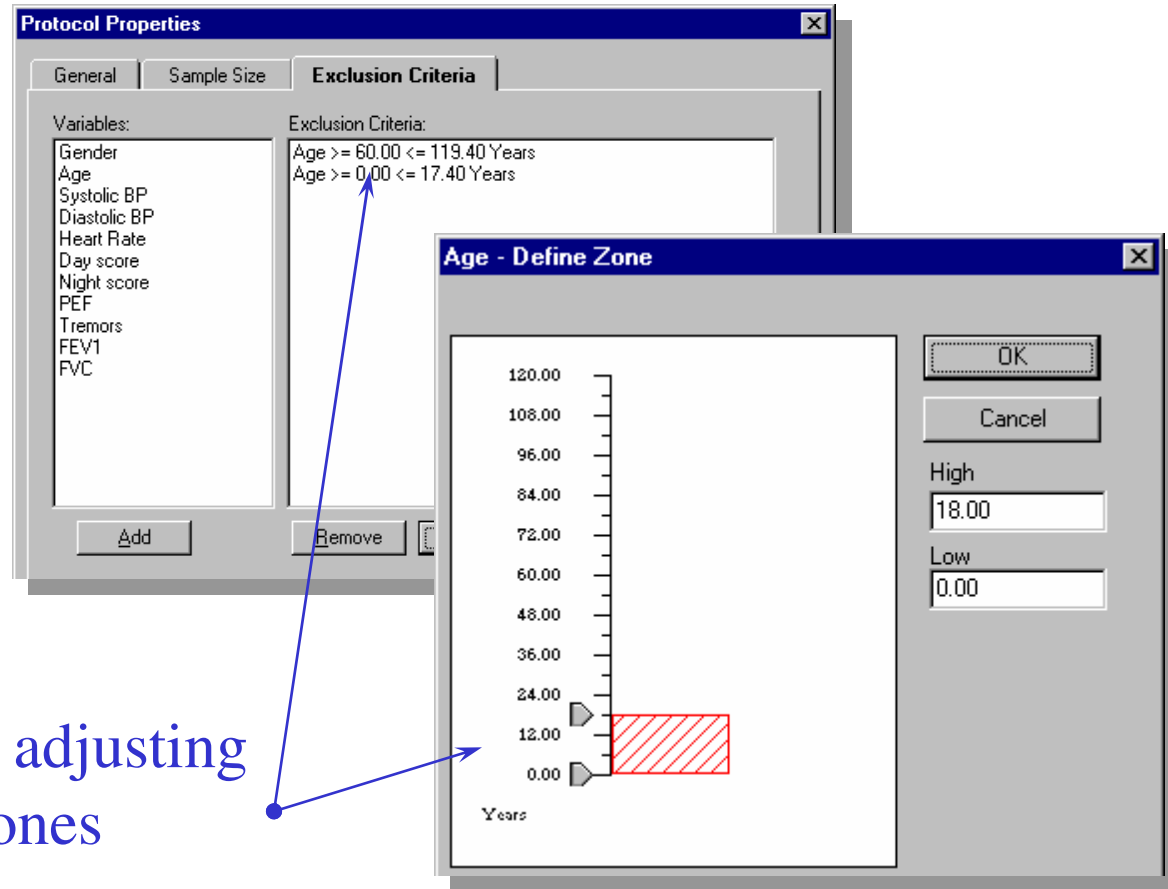
## Exclusion criteria can be defined using

population variables

or

response variables

and graphically adjusting the exclusion zones



The image shows two overlapping dialog boxes from a software application. The background dialog is titled "Protocol Properties" and has three tabs: "General", "Sample Size", and "Exclusion Criteria". The "Exclusion Criteria" tab is active, showing a list of variables on the left and a list of exclusion criteria on the right. The variables list includes Gender, Age, Systolic BP, Diastolic BP, Heart Rate, Day score, Night score, PEF, Tremors, FEV1, and FVC. The exclusion criteria list includes "Age >= 60.00 <= 119.40 Years" and "Age >= 0.00 <= 17.40 Years". The foreground dialog is titled "Age - Define Zone" and features a vertical axis labeled "Years" ranging from 0.00 to 120.00 in increments of 12.00. A red hatched rectangular zone is shown on the axis, spanning from 0.00 to approximately 18.00. To the right of the axis are input fields for "High" (set to 18.00) and "Low" (set to 0.00), along with "OK" and "Cancel" buttons.

## Sample size depends on

end point variable

standard deviation

clinically significant difference

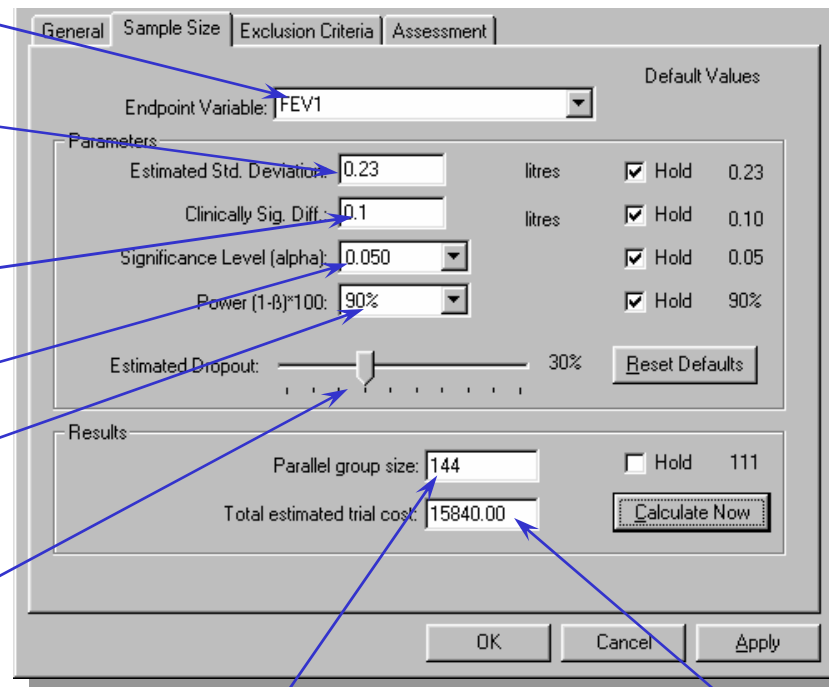
alpha value

power

allowance for drop outs

sample size

estimated trial cost



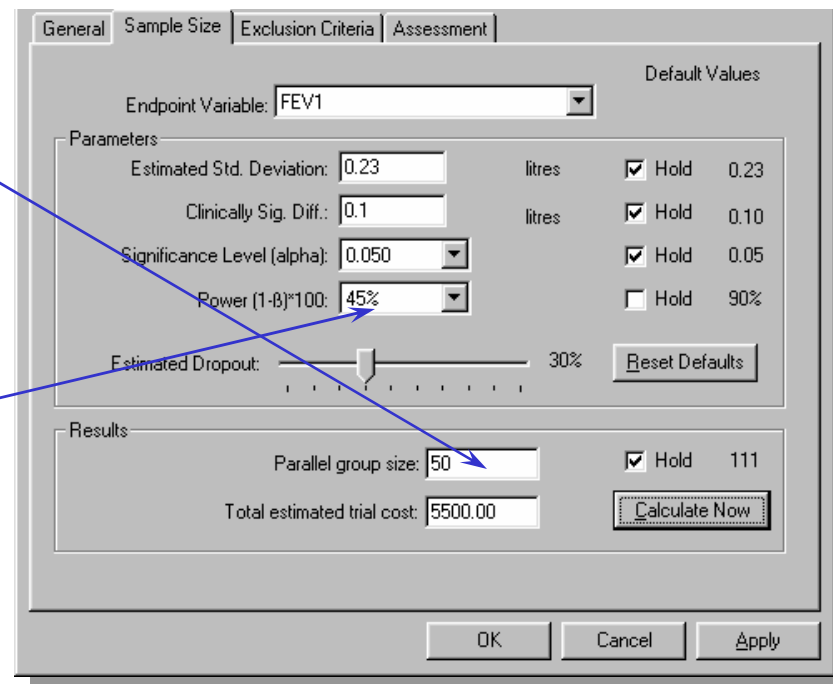
The screenshot shows a software window with tabs: General, Sample Size, Exclusion Criteria, and Assessment. The 'Sample Size' tab is active. It contains a 'Parameters' section and a 'Results' section. The 'Parameters' section includes: Endpoint Variable (FEV1), Estimated Std. Deviation (0.23 litres), Clinically Sig. Diff. (0.1 litres), Significance Level (alpha) (0.050), Power (1-β)\*100 (90%), and Estimated Dropout (30%). The 'Results' section shows: Parallel group size (144) and Total estimated trial cost (15840.00). A 'Calculate Now' button is present. A 'Reset Defaults' button is also visible. Blue arrows point from text labels on the left to specific fields in the software window.

Parameter	Value	Unit	Default Value
Endpoint Variable	FEV1		
Estimated Std. Deviation	0.23	litres	0.23
Clinically Sig. Diff.	0.1	litres	0.10
Significance Level (alpha)	0.050		0.05
Power (1-β)*100	90%		90%
Estimated Dropout	30%		
Parallel group size	144		111
Total estimated trial cost	15840.00		

Every parameter can be estimated in terms of the others

Set the **sample size** too low

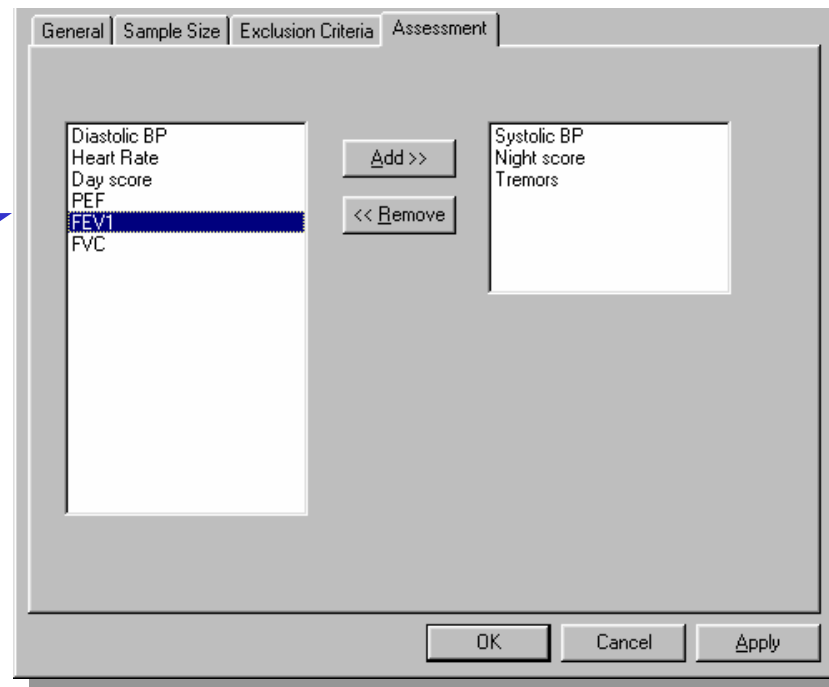
and the **power** drops appallingly



Parameter	Value	Unit	Hold	Default
Endpoint Variable	FEV1			
Estimated Std. Deviation	0.23	litres	<input checked="" type="checkbox"/>	0.23
Clinically Sig. Diff.	0.1	litres	<input checked="" type="checkbox"/>	0.10
Significance Level (alpha)	0.050		<input checked="" type="checkbox"/>	0.05
Power (1-β)*100	45%		<input type="checkbox"/>	90%
Estimated Dropout	30%			
Parallel group size	50		<input checked="" type="checkbox"/>	111
Total estimated trial cost	5500.00			

Some simple statistical tests are supplied in **Gen** for rapid assessment of simulated trials

Select variables for assessment tests



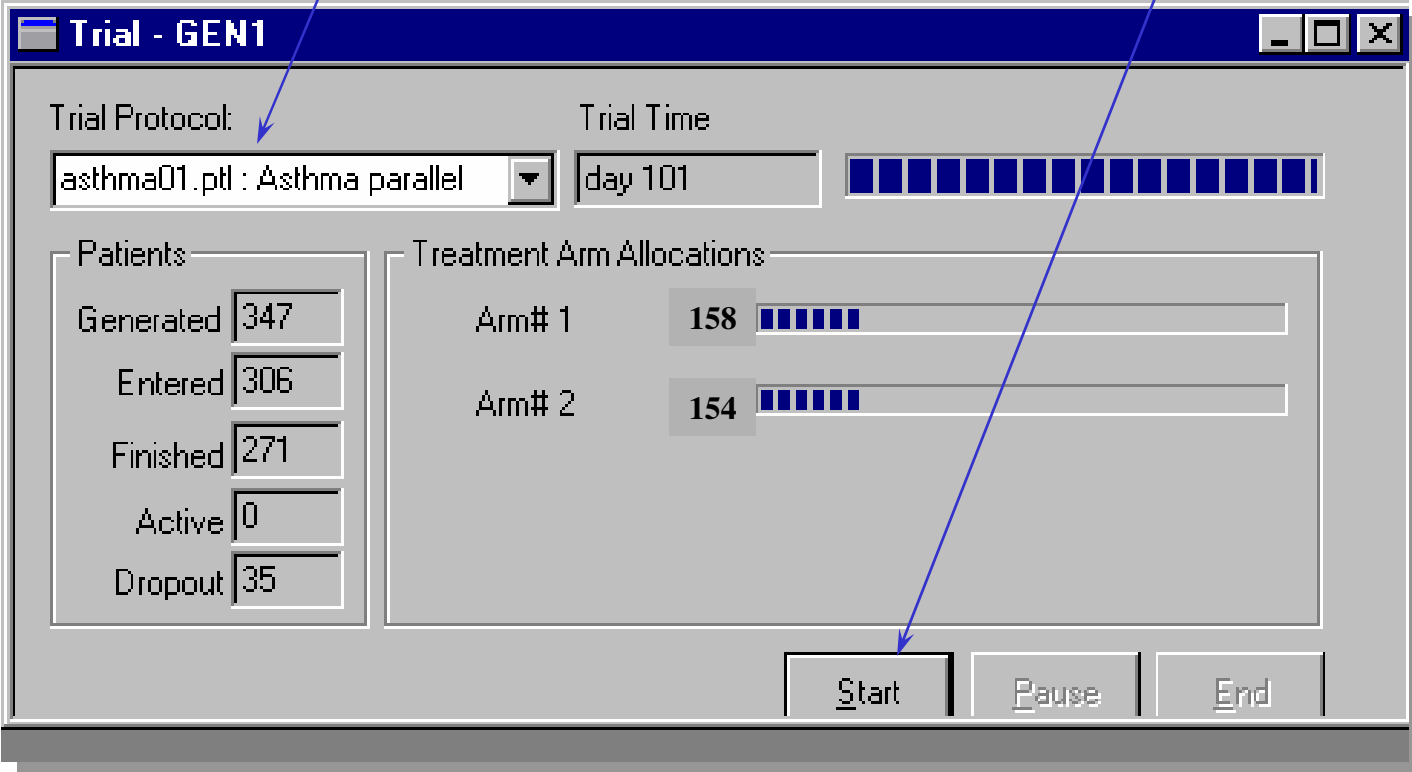
**Warning:**

**To be sure of applying the most appropriate tests export the data for analysis with a statistical analysis package**

## To simulate a trial:

choose a **trial protocol**

and click on Start



The screenshot shows the 'Trial - GEN1' window with the following data:

Patients	
Generated	347
Entered	306
Finished	271
Active	0
Dropout	35

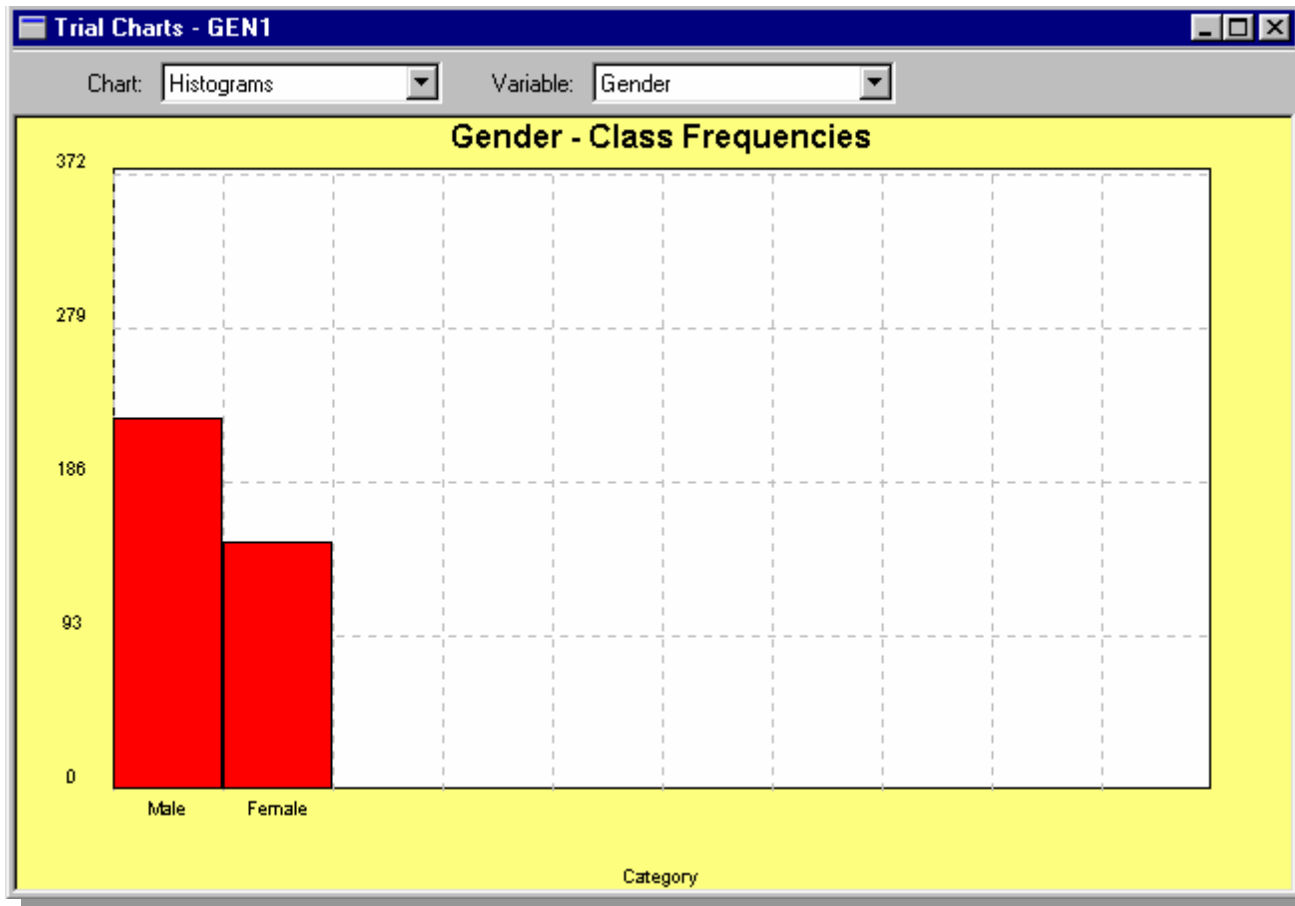
  

Treatment Arm Allocations	
Arm# 1	158
Arm# 2	154

Additional interface elements include: Trial Protocol: 'asthma01.ptl : Asthma parallel', Trial Time: 'day 101', and control buttons for 'Start', 'Pause', and 'End'.

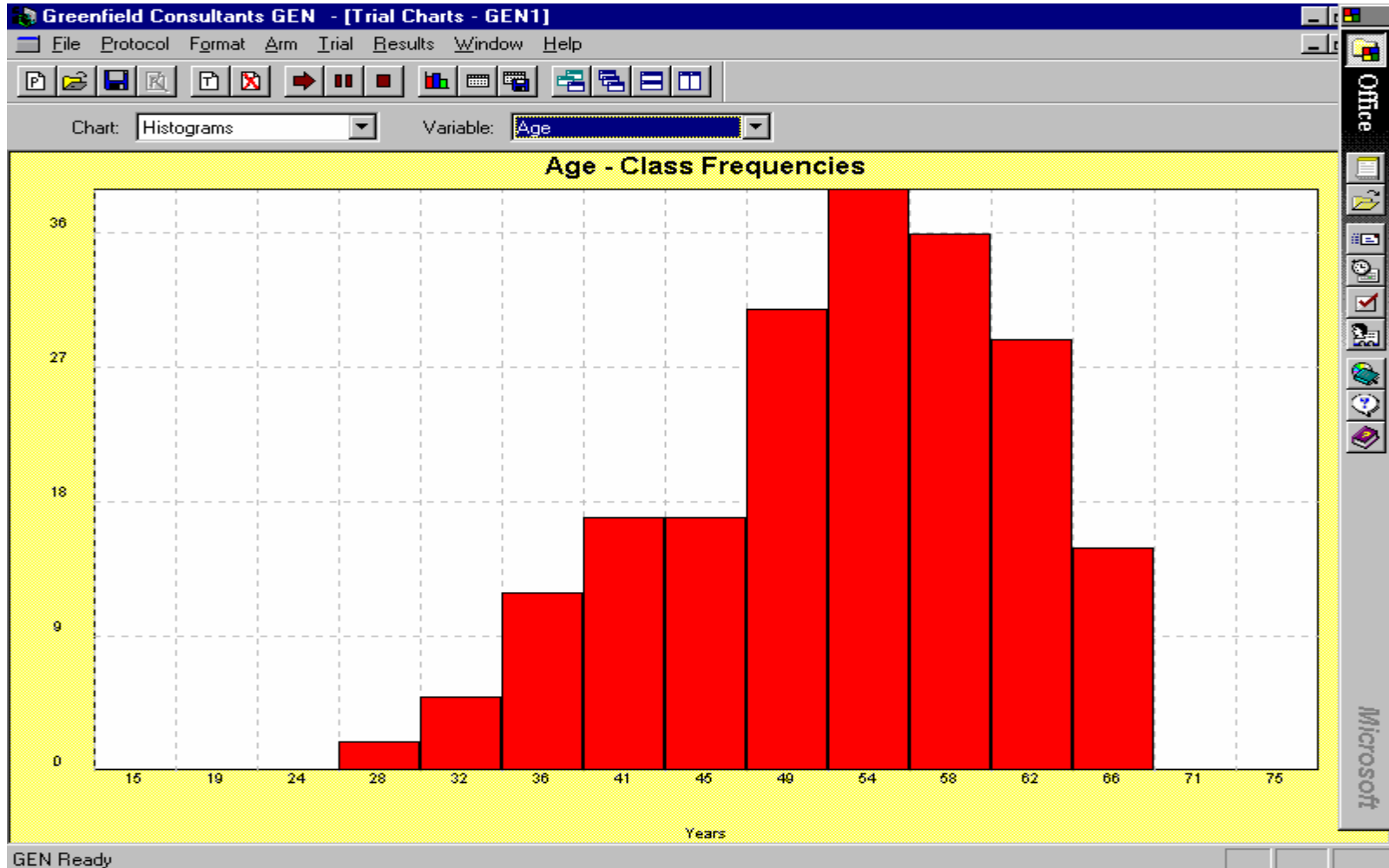
# Histograms:

Gender of patients entered into trial

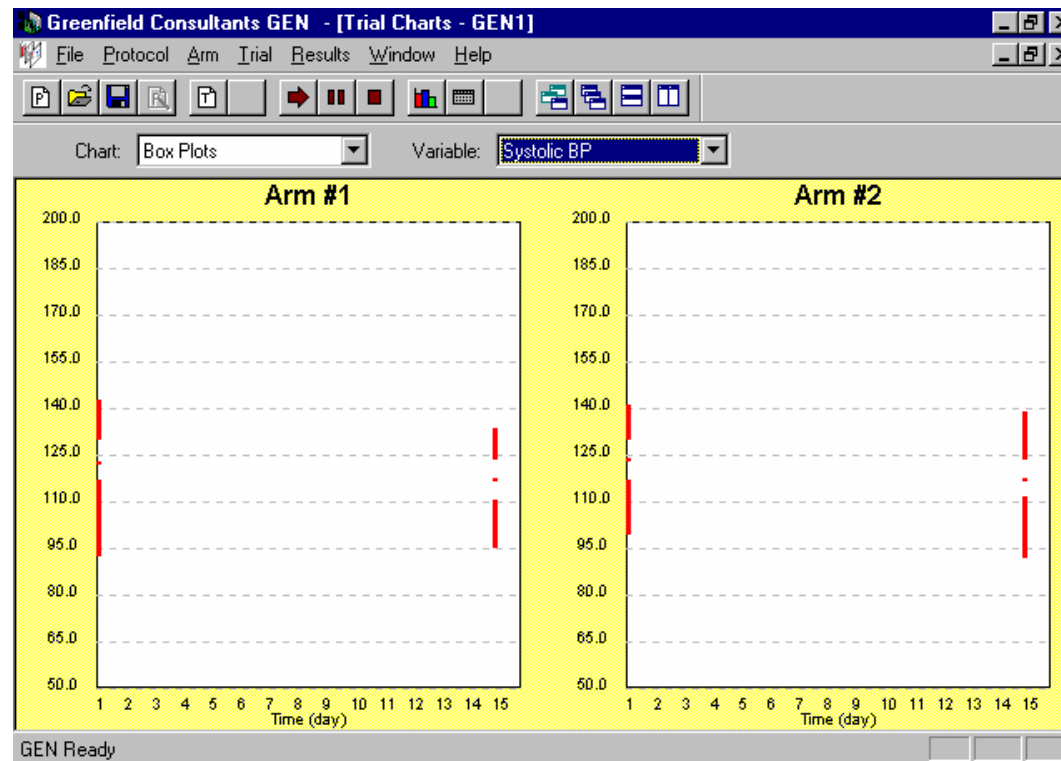


# Histograms:

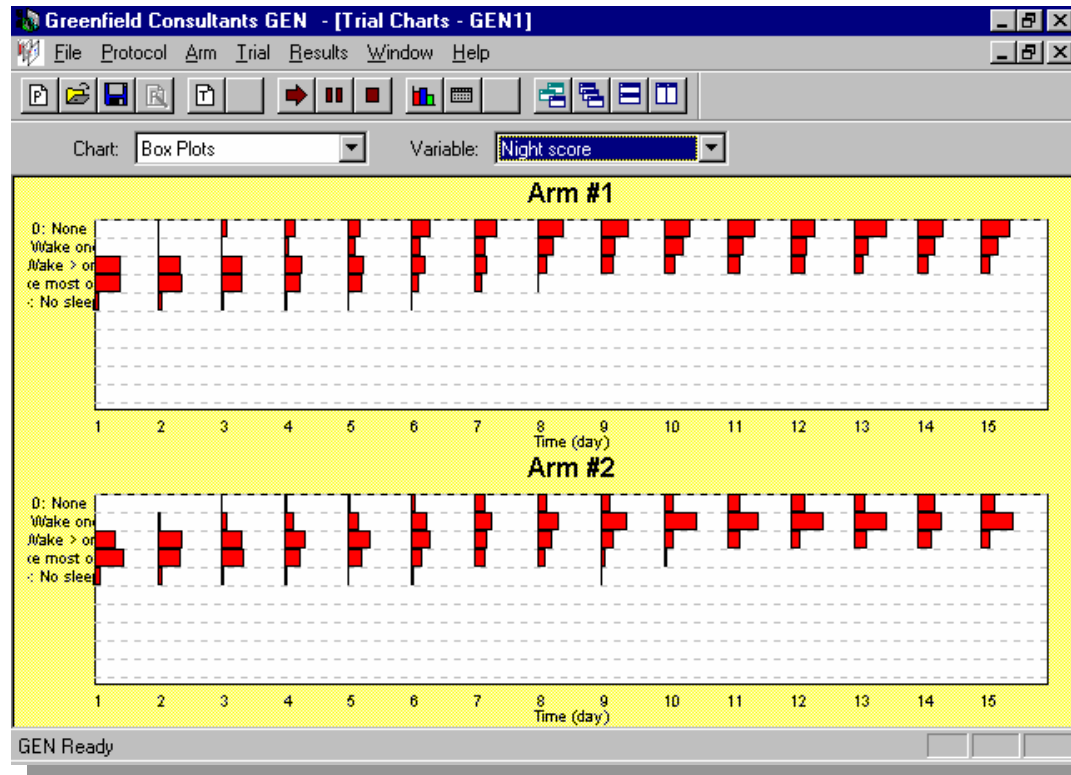
## Ages of patients entered into trial



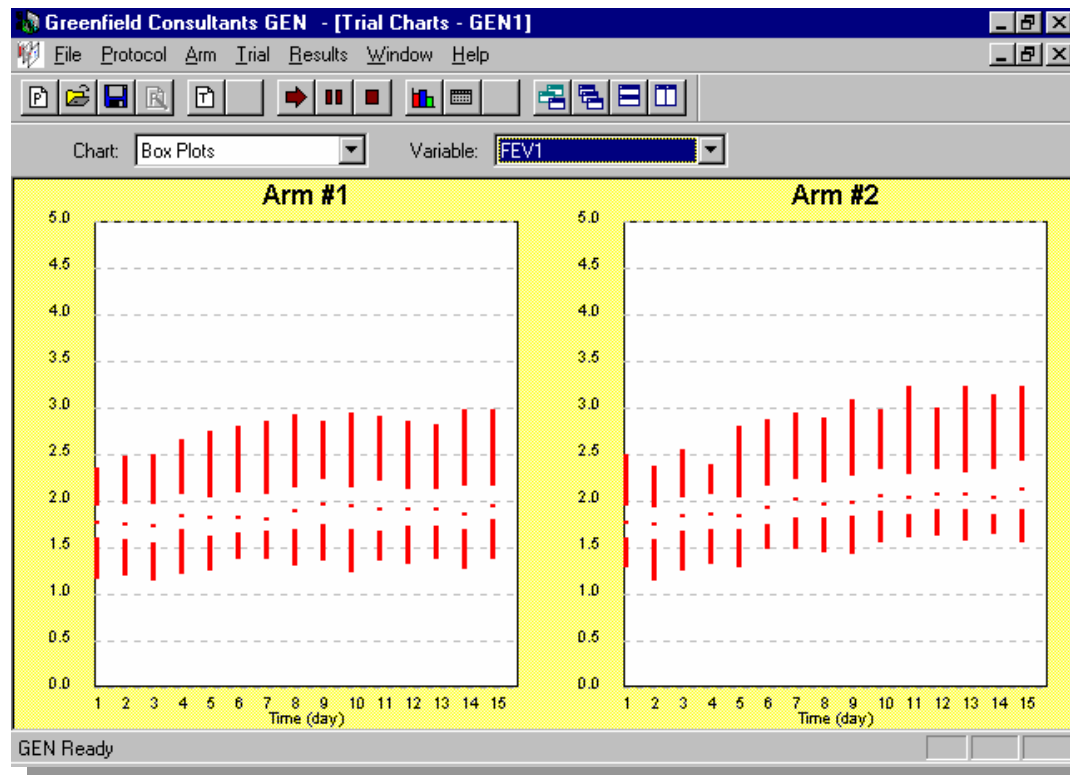
## Sample distributions of systolic blood pressure for both treatments: first and final visits

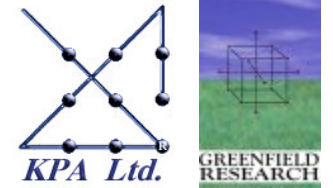


## Sample distributions of **night score** in diary records for both treatments



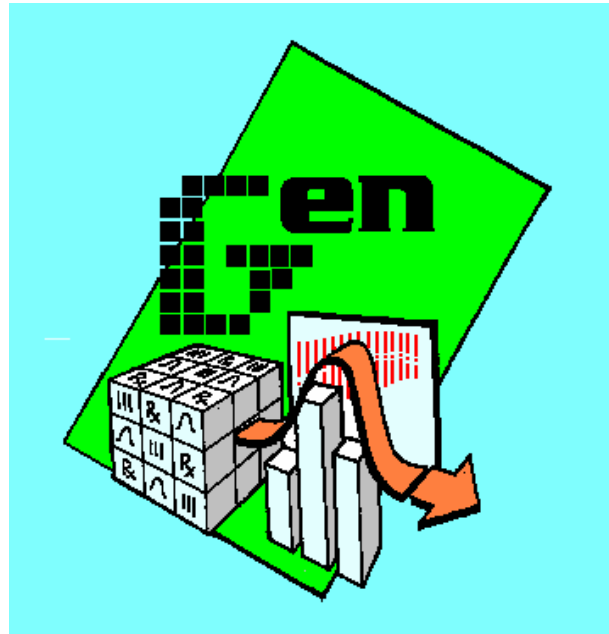
## Sample distributions of **FEV1** in diary records for both treatments





## Other results reported for each simulated trial:

- **tables of summary statistics for all variables**
- **tables of dropouts according to cause and treatment**
- **elementary statistical tests** (with the caution that reliable analysis requires export of data to a statistical analysis package)



Data can be exported for presentation and detailed analysis in other programs such as:

- Excel
- Word for Windows
- Minitab

# Asthma trial design

Investigator : Ron S. Kenett

Patient allocation : Simple Randomisation

Maximum trial duration is 365 day

Meta Model contained in this protocol : Asthma

Sample Size Parameters

End-point variable : FEV1

Estimated Standard Deviation : 0.13

Clinical Significant Difference : 0.10

Significance Level : 0.05

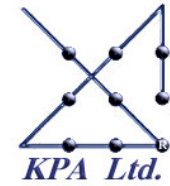
Power : 90%

Dropout %: 0

Required sample size per arm : 36

Total schedule cost : £9720.00

Exclusion Criteria



# Asthma trial patients allocation

In/Out	Arm#	Entry time	Gender	Age
In	2	1	0	64.08
In	3	1	1	33
In	2	2	0	33
In	3	3	0	60.68
In	2	3	0	64.76
In	3	3	0	52.5
In	3	3	0	54
In	2	3	0	42
In	2	4	0	65.44
Out	2	4	1	52.5
In	2	4	1	45
In	3	5	1	62.04
Out	1	5	0	66.12
Out	2	5	1	58.5
In	1	6	0	62.72

# Asthma trial results

Data	Arm#	Visit#	Systolic BP	Diastolic B	Heart rate	PEF	FEV1	Tremors
In	2	Visit#0	130.9	72	75	296.8	1.7	1
In	3	Visit#0	127.3	81.7	88.7	298.9	1.6	1
In	2	Visit#0	139.7	91.9	79.3	260	1.8	1
In	3	Visit#0	132.9	76	87.7	282	1.6	1
In	2	Visit#0	141.1	81.9	74.5	285.1	1.8	1
In	3	Visit#0	128.9	75	83	289.3	2	1
In	3	Visit#0	132.3	77.5	84.6	257	1.8	1
In	2	Visit#0	128.3	76.6	73.9	261	1.6	1
In	2	Visit#0	133.6	75.5	79.9	276	1.6	1
Out	2	Visit#0	124.1	71.2	68.5	270	1.7	1
In	2	Visit#0	136.3	86.6	77.7	266	1.6	1
In	3	Visit#0	129.6	74.3	83.5	271	1.8	1
Out	1	Visit#0	142.4	82.6	77.7	279	1.7	1

# FEV1 trial results

	Pre-Wizerol	Post-Wizerol	Pre-Eezerol	Post-Eezerol	Pre-Placebo	Post-Placebo
FEV1						
Number	45	45	49	48	33	30
Mean	1.69	1.83	1.70	1.84	1.66	1.67
Std.Dev.	0.12	0.16	0.13	0.13	0.13	0.14
Std.Err	0.02	0.02	0.02	0.02	0.02	0.02

## Assessments of significant difference

### FEV1

Wizerol 50µg v Eezerol 50µg - No significant difference

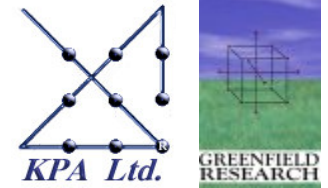
Wizerol 50µg v Placebo 50µg - Significant difference

Eezerol 50µg v Placebo 50µg - Significant difference

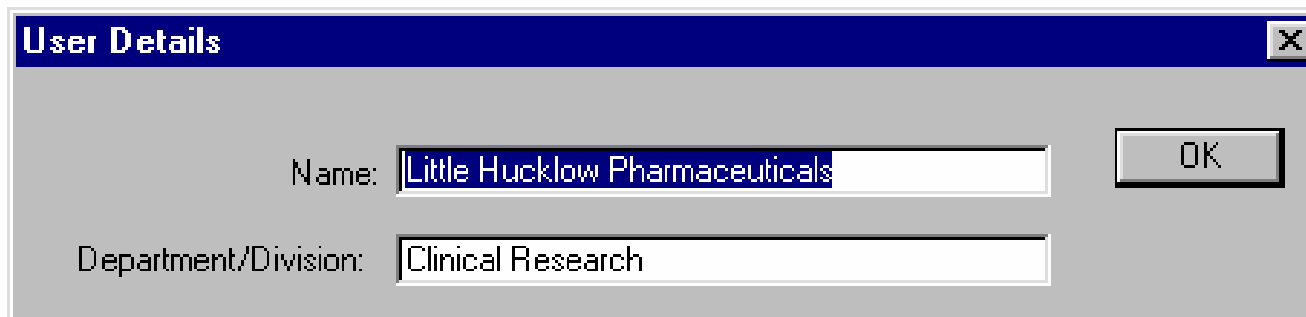


**META** is used to specify a model for study:

- treatments
- population variables
- response variables
- patient presentation and drop out rates



When you first use MetaGen,  
enter the company and division names.



**User Details** [X]

Name:

Department/Division:

OK

These will appear at the top of every report.

## Each new treatment is entered with

name

administration

effect on  
pulse pressure

dose

frequency

effective  
response  
time

relapse time

time units  
default is days

Treatment

Name: Wizerol

Dose

Quantity: 50 µg

Administration: tablet

Frequency: 2 daily

Pulse Pressure

Increases

Decreases

No Effect

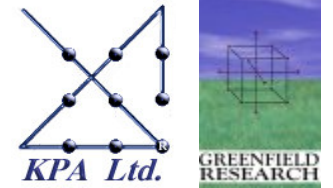
Treatment Response

Effective Time Span 8

Relapse Duration 5

Time Units: days

Cancel OK



**There is no limit to  
the number of treatments:  
all those you enter are candidates  
for inclusion in protocols  
created in Gen**

While a model is being created, using Meta,  
a report is automatically written, recording all the details

Meta Model Report

## Little Hucklow Pharmaceuticals

Clinical Research division

### Model details

Name :

Asthma

Creator:

Tony Greenfield

Condition :

Nocturnal Asthma

Test of proof:

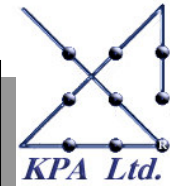
night score  $\geq 2$  in 3/7 days

Minimum presence of  
symptoms :

28 days

Date :

Monday, September 25, 1995

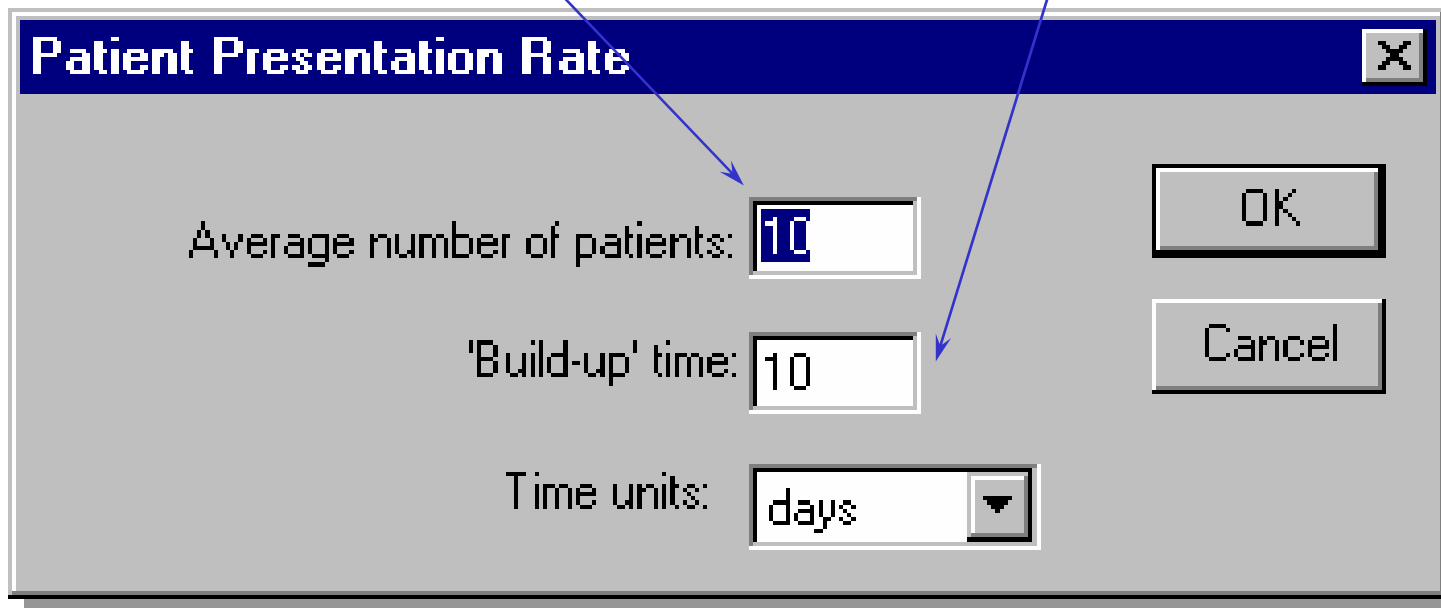


<b>Treatments</b>	
<b>Wizerol 50µg 2 daily</b>	
Administration: tablet	Pulse pressure: No effect
Effective response time: 8 days	Relapse time: 5 days
<b>Eezerol 50µg 2 daily</b>	
Administration: tablet	Pulse pressure: Decrease
Effective response time: 10 days	Relapse time: 7 days
<b>Placebo 50µg 2 daily</b>	
Administration: tablet	Pulse pressure: No effect
Effective response time: 5 days	Relapse time: 2 days

the report can be printed for reference

Enter the average patient presentation rate

including the time from the start of the trial to reach that rate



Patient Presentation Rate

Average number of patients: 10

'Build-up' time: 10

Time units: days

OK

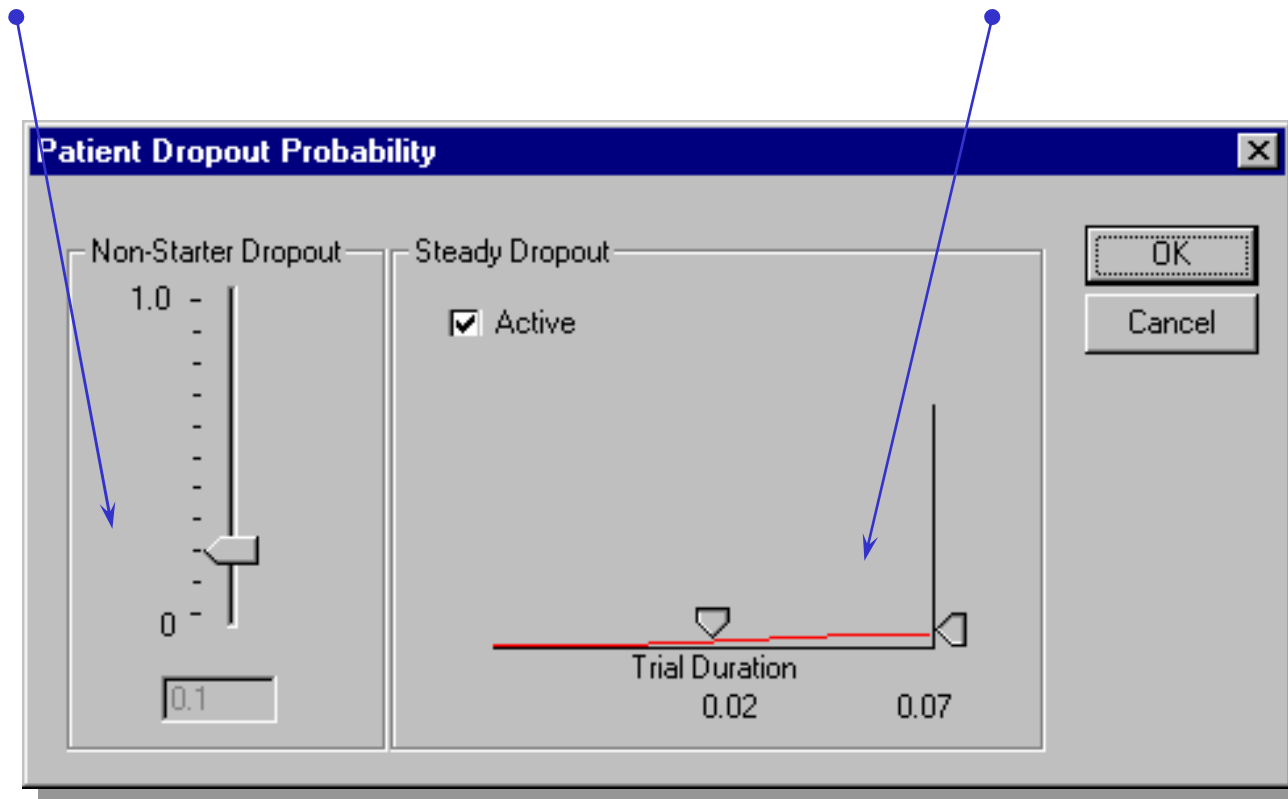
Cancel

note that this is the average rate

## Enter patient drop out rates during the trial

Some patients entered into the trial will fail to start

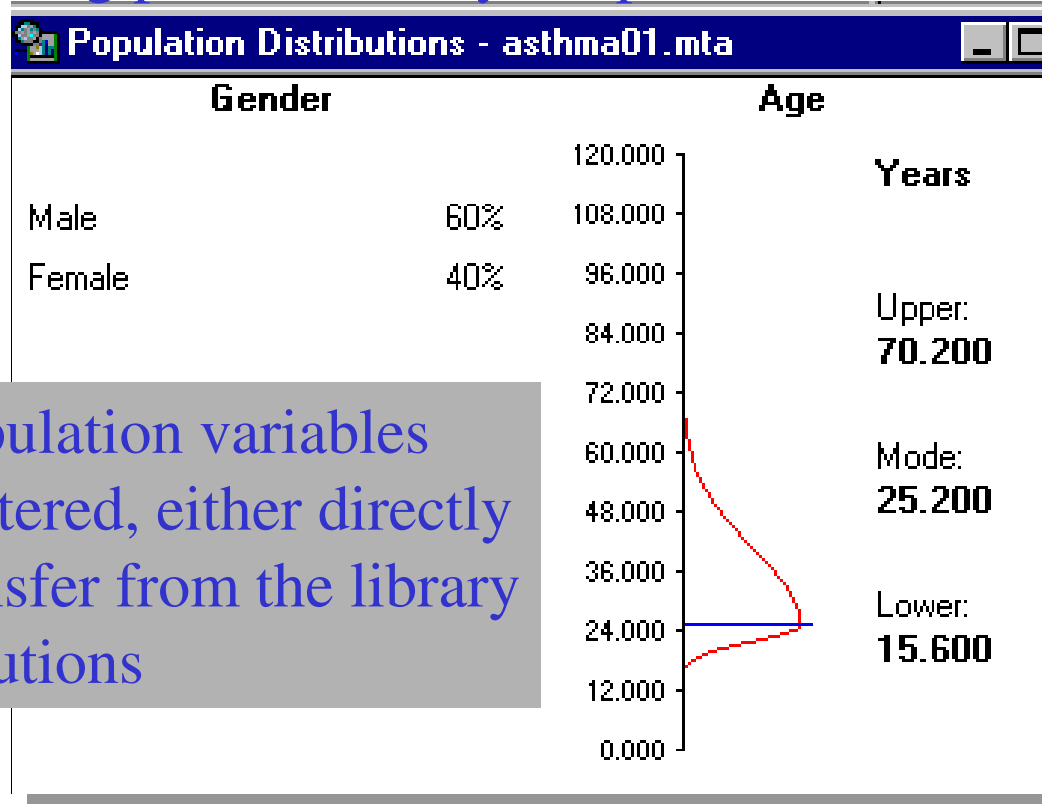
Others will drop out during the trial for no particular reason



Values are changed by mouse control of the sliders

Two standard population distributions are gender and age

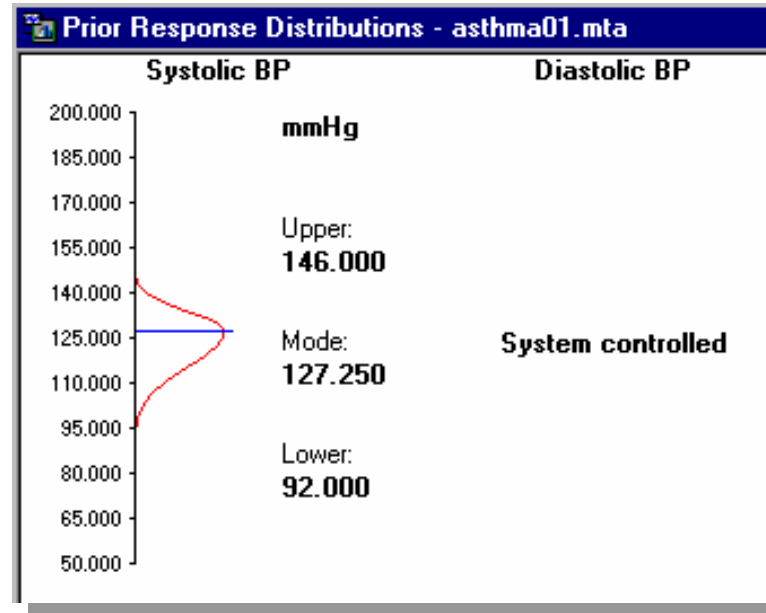
These can be adjusted to match your expectations of presenting patients . . . by simple mouse controls



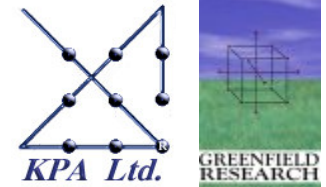
More population variables can be entered, either directly or by transfer from the library of distributions

Systolic blood pressure is a standard response variable

It can be adjusted by mouse control



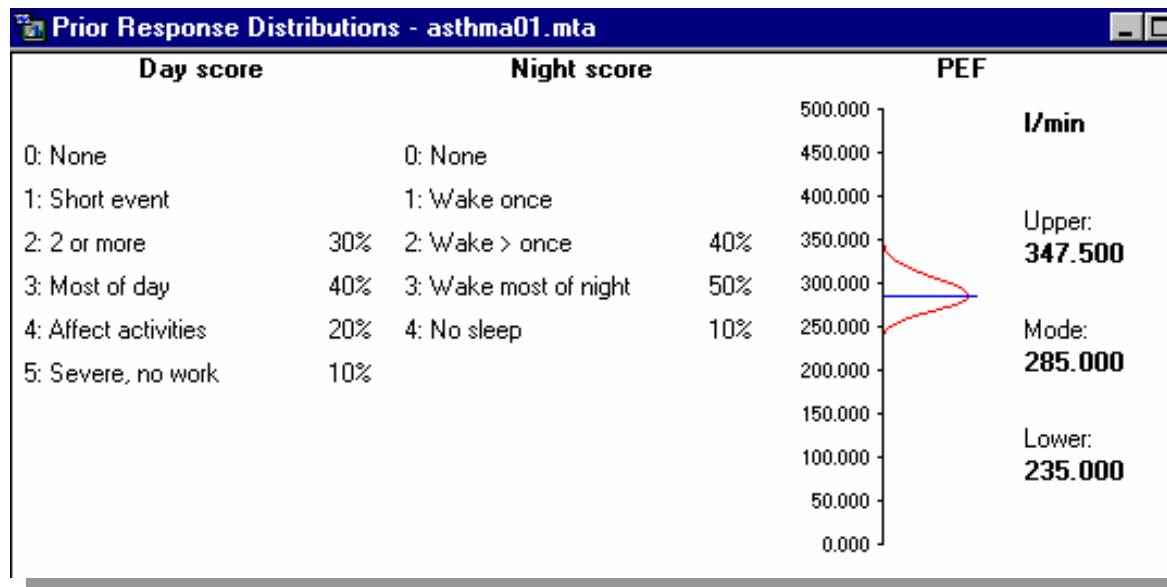
Diastolic blood pressure is system controlled: related to systolic by pulse pressure, in turn controlled by age and gender



More response variables can be entered,

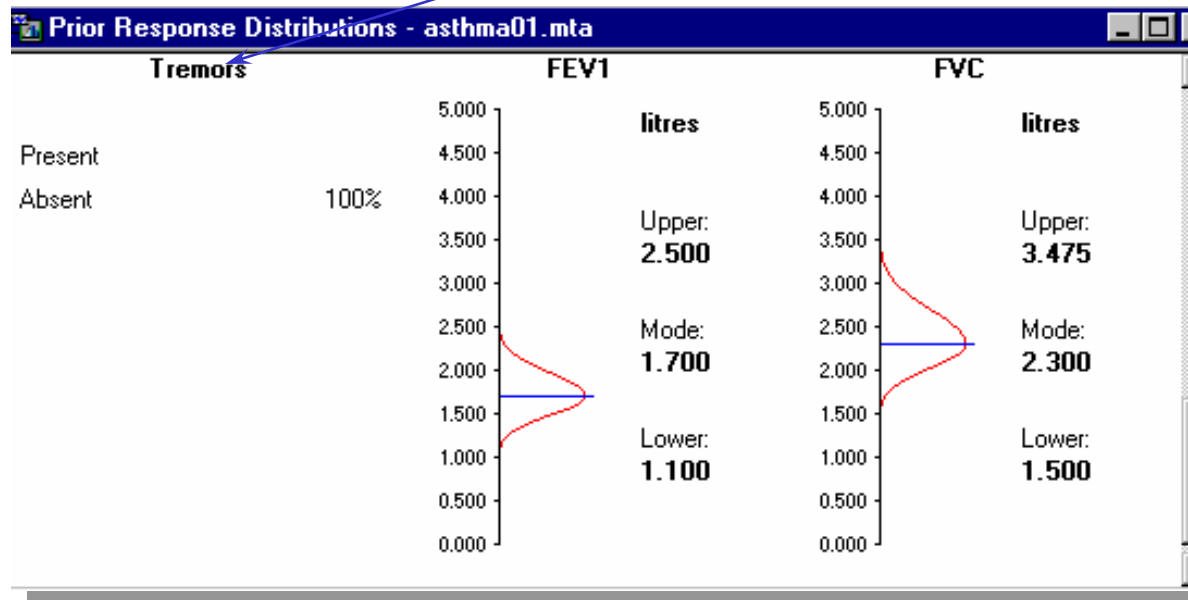
either **directly**

or by **transfer** from the **library of distributions**

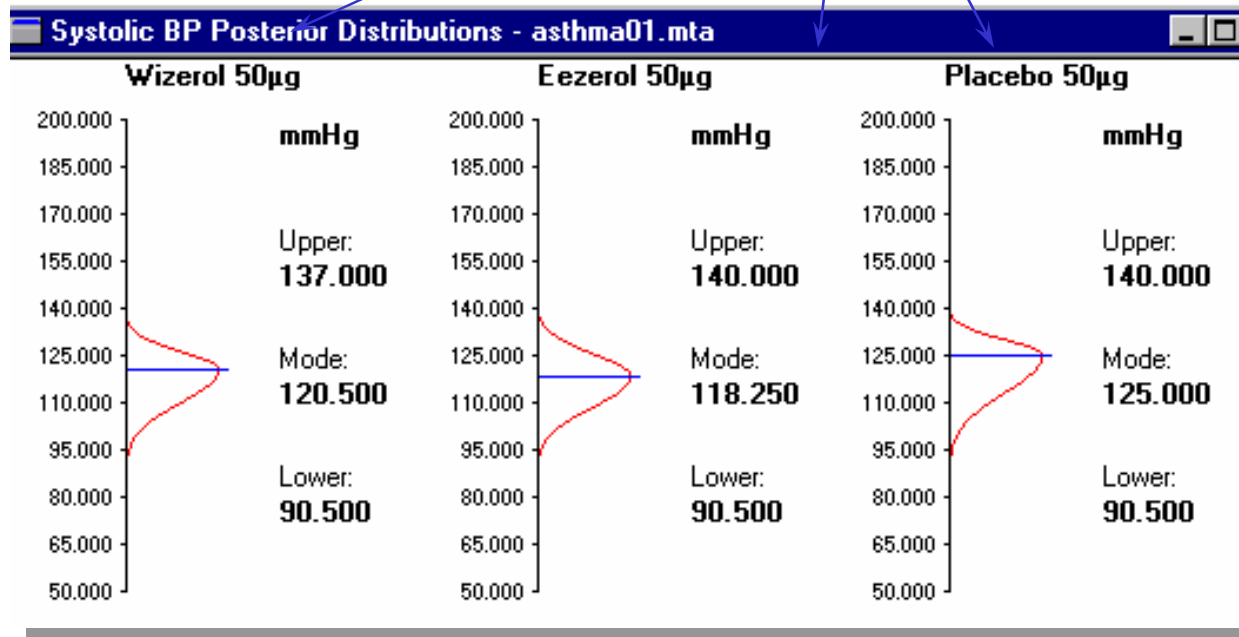


There is no limit to the number of variables that can be entered

The response variables should include expected **adverse responses** such as **tremors**

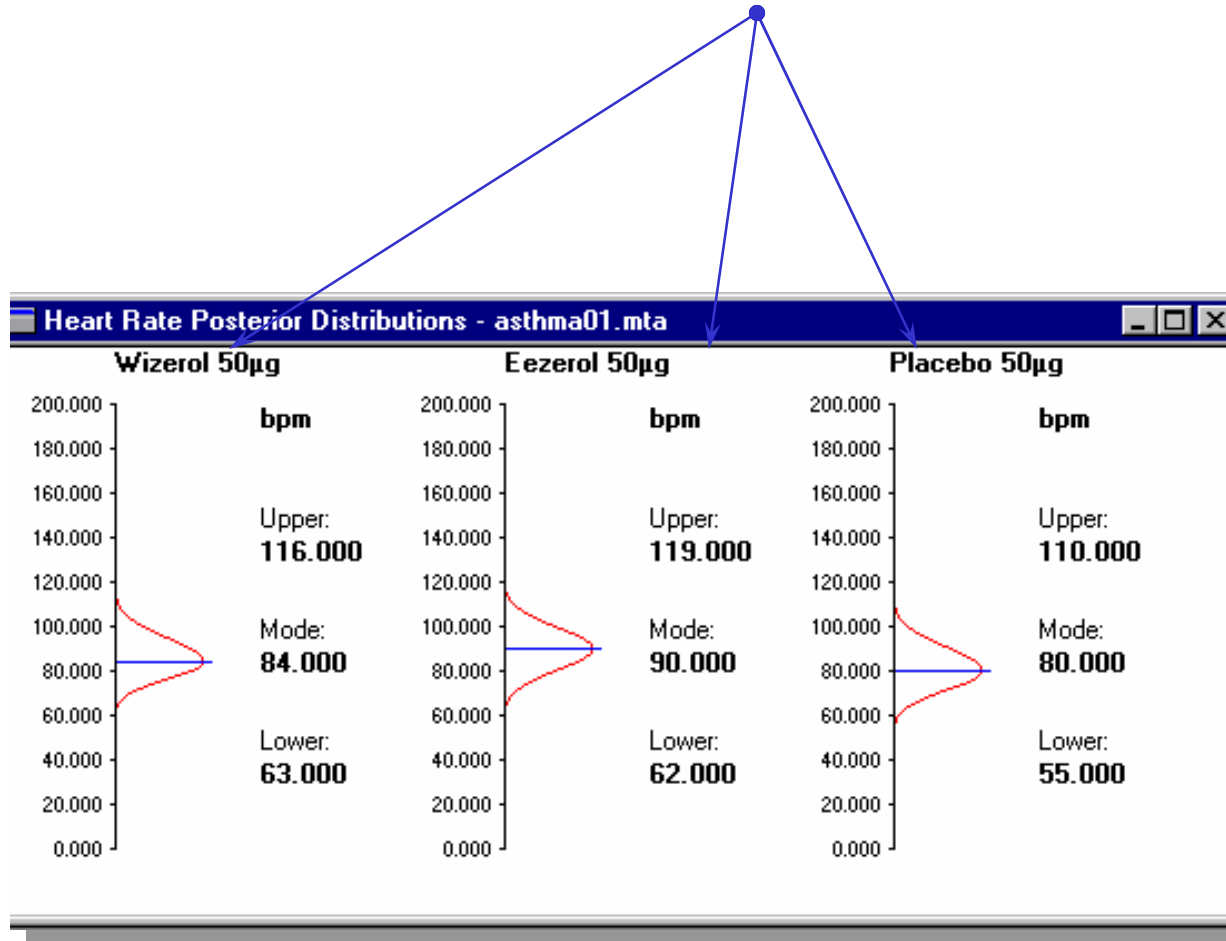


Treatment effects are shown as the **posterior distributions** of response variables one for each treatment

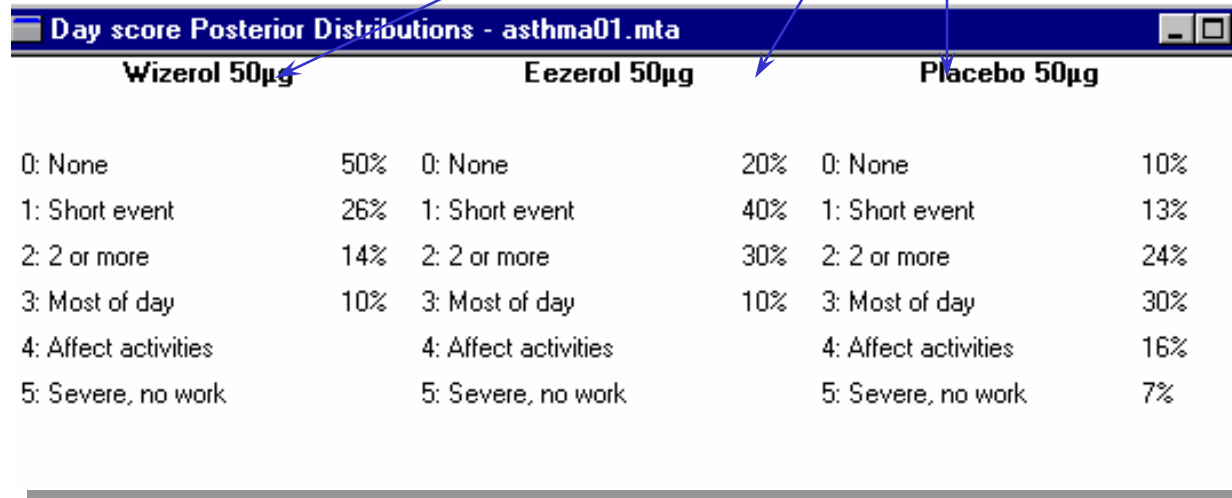


They are adjusted easily by mouse control

## The posterior distributions for heart rate . . .



and for a categorical variable: **day score**



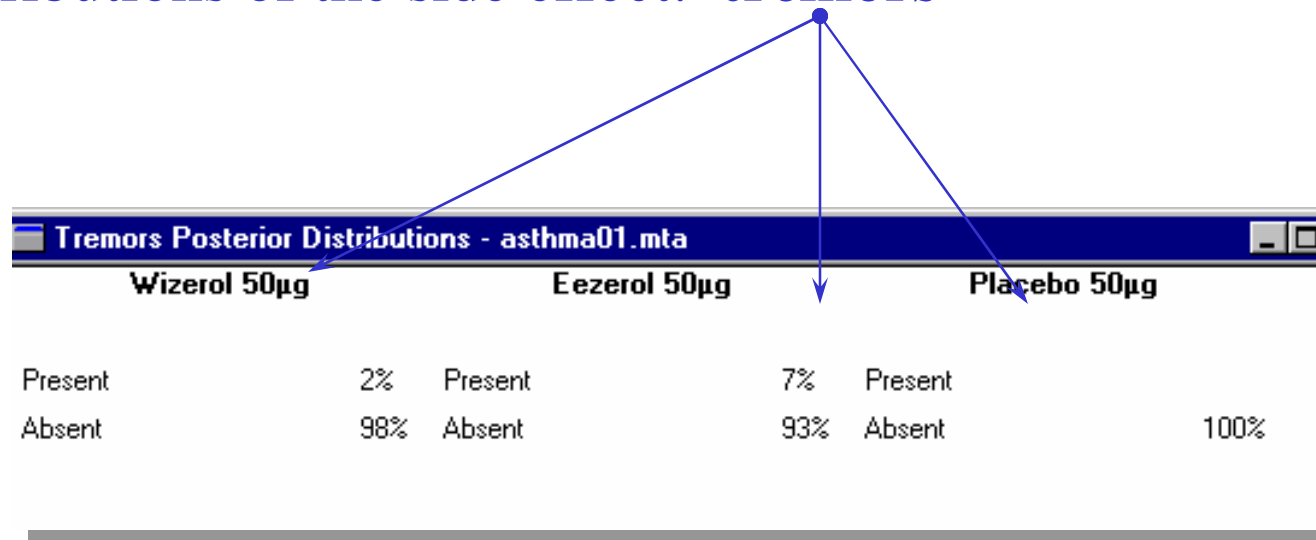
Day score Posterior Distributions - asthma01.mta					
Wizerol 50µg		Eezerol 50µg		Placebo 50µg	
0: None	50%	0: None	20%	0: None	10%
1: Short event	26%	1: Short event	40%	1: Short event	13%
2: 2 or more	14%	2: 2 or more	30%	2: 2 or more	24%
3: Most of day	10%	3: Most of day	10%	3: Most of day	30%
4: Affect activities		4: Affect activities		4: Affect activities	16%
5: Severe, no work		5: Severe, no work		5: Severe, no work	7%

## and night score

**Night score Posterior Distributions - asthma01.mta**

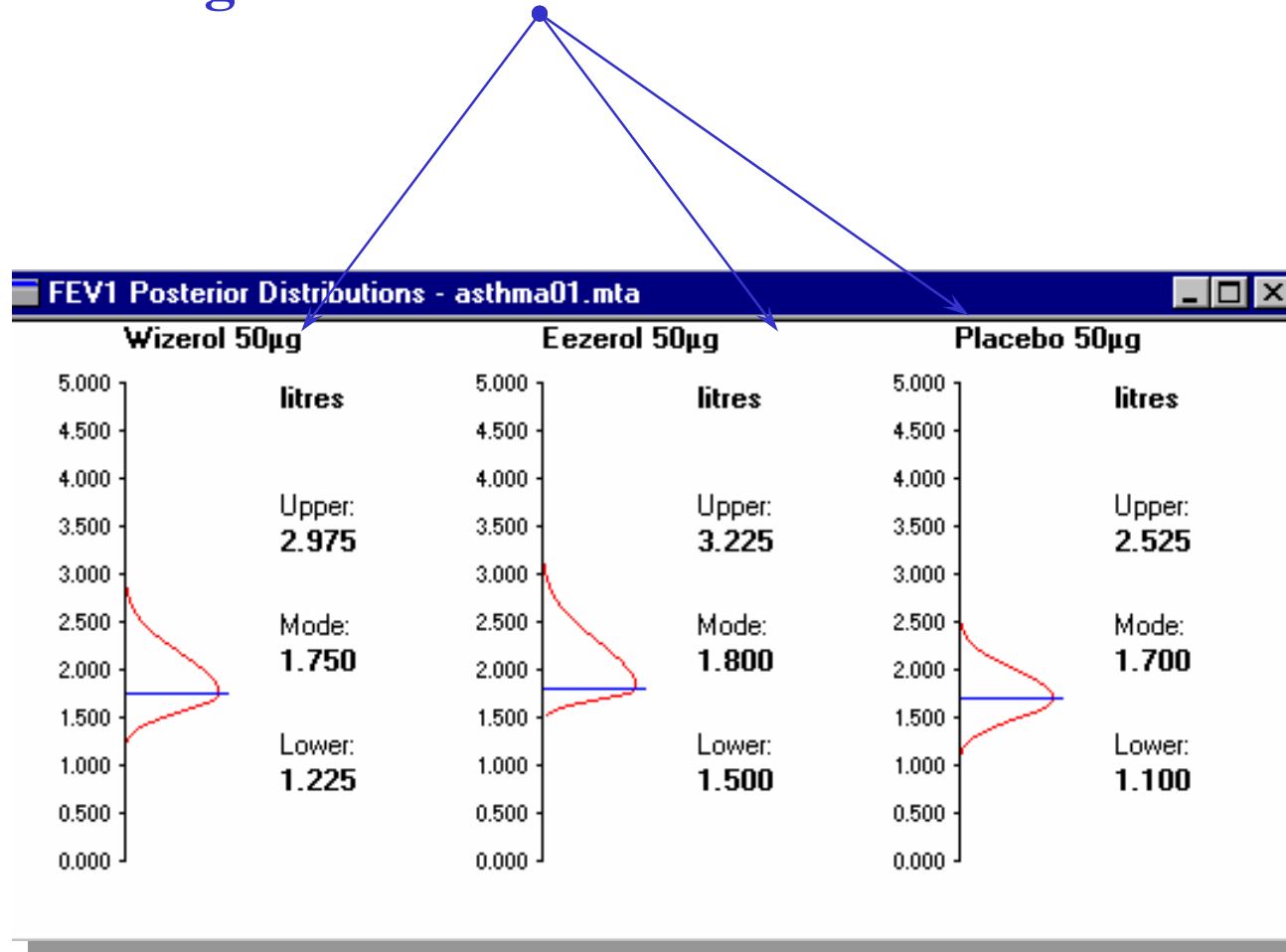
Wizerol 50µg		Eezerol 50µg		Placebo 50µg	
0: None	50%	0: None	25%	0: None	10%
1: Wake once	30%	1: Wake once	55%	1: Wake once	17%
2: Wake > once	20%	2: Wake > once	20%	2: Wake > once	34%
3: Wake most of night		3: Wake most of night		3: Wake most of night	34%
4: No sleep		4: No sleep		4: No sleep	5%

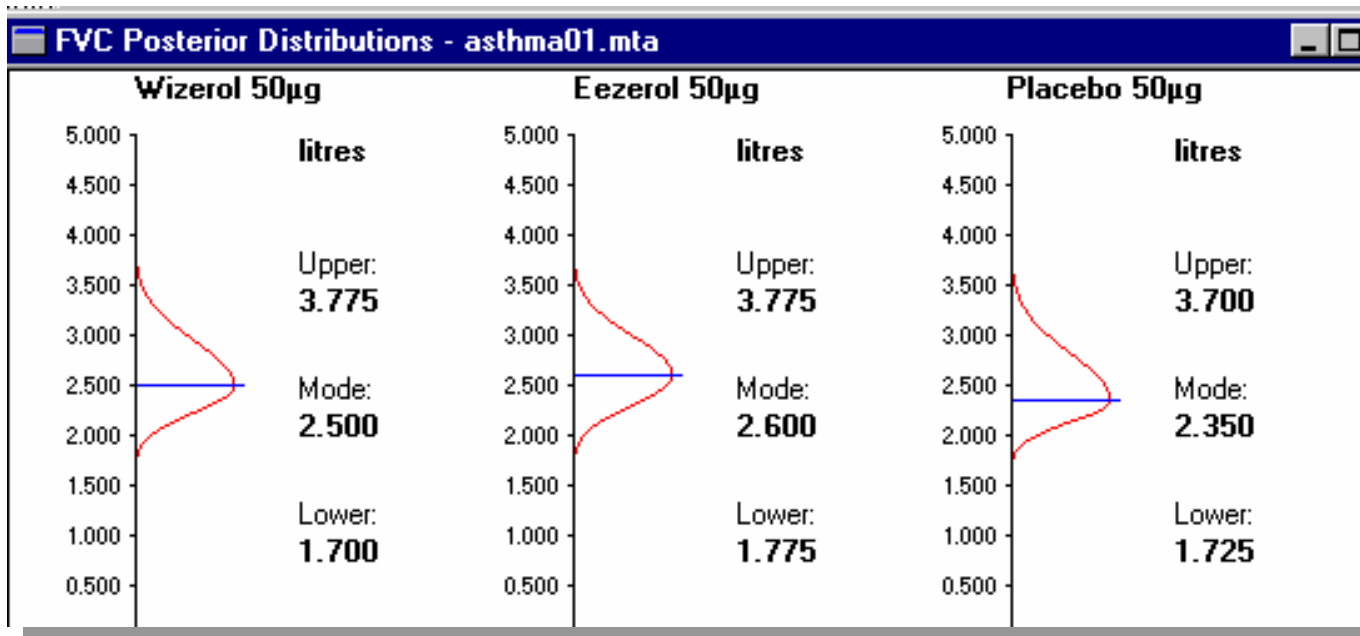
There are small differences between the posterior distributions of the side effect: **tremors**



**Will the trial, using the protocol you create in Gen, be able to detect such small differences?**

Will your trial be able to detect the small differences between **lung function** values?



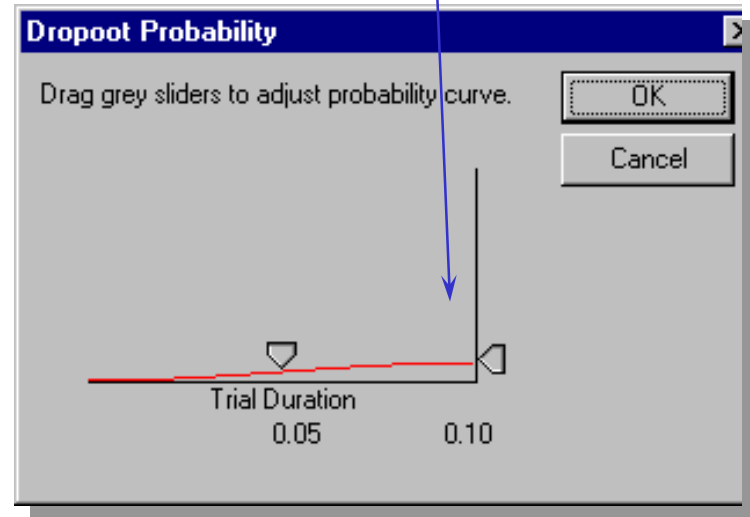
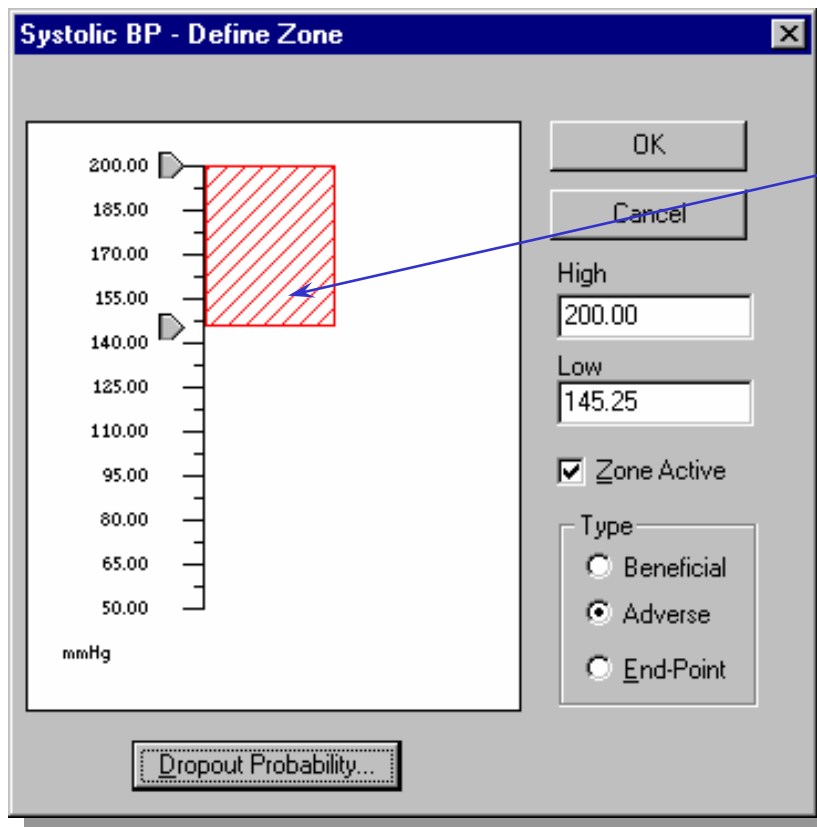


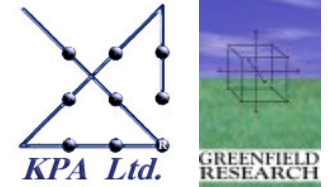
You can create several models in **Meta**, using larger or smaller differences between effects, to compare the protocols created in **Gen**

Some patients may drop out because they don't feel well

Such an adverse effect may be high blood pressure

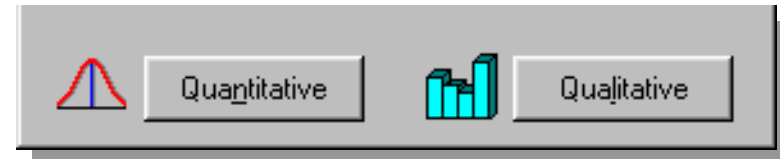
Estimate the probability that they will drop out





# Investigation costs

can be entered when  
distributions are entered



or they can be entered  
by transfer from the

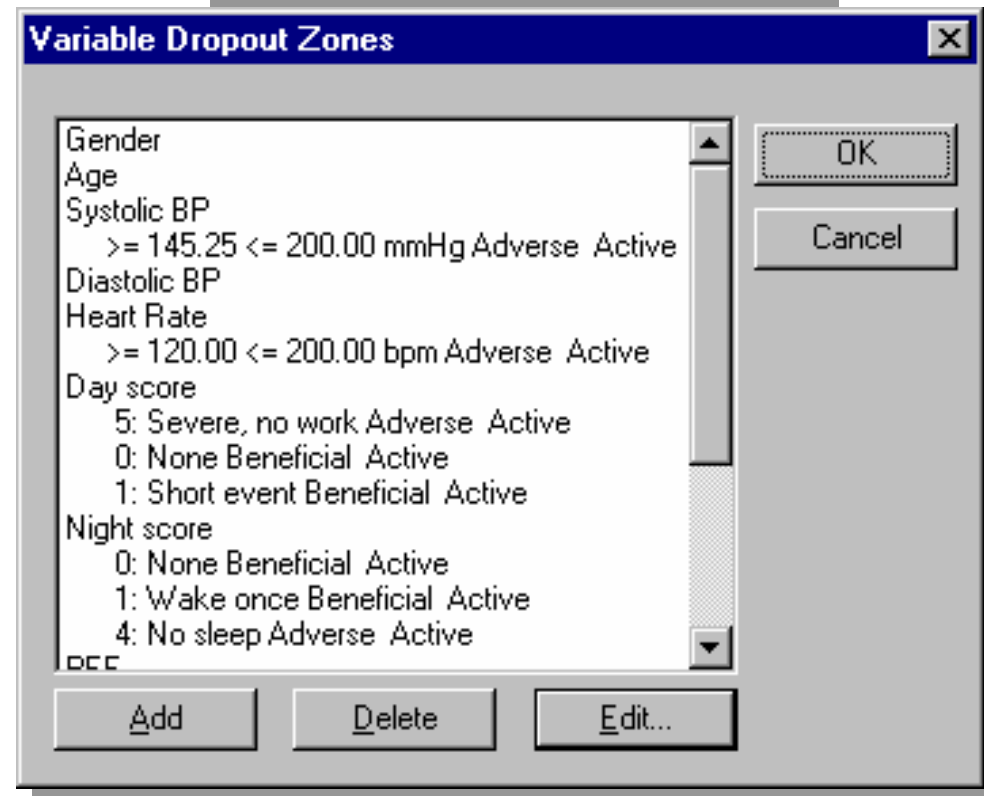
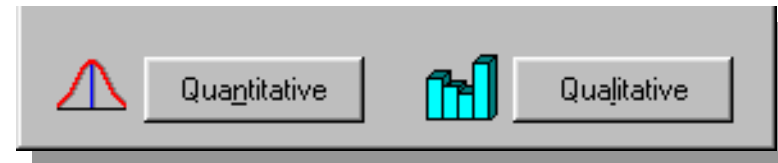


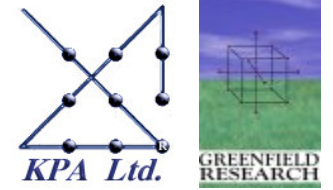
## Drop out zones

can be entered when distributions are entered

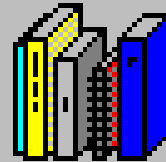
or they can be entered by transfer from the

or they can be entered and edited all together





# The library



Meta Library

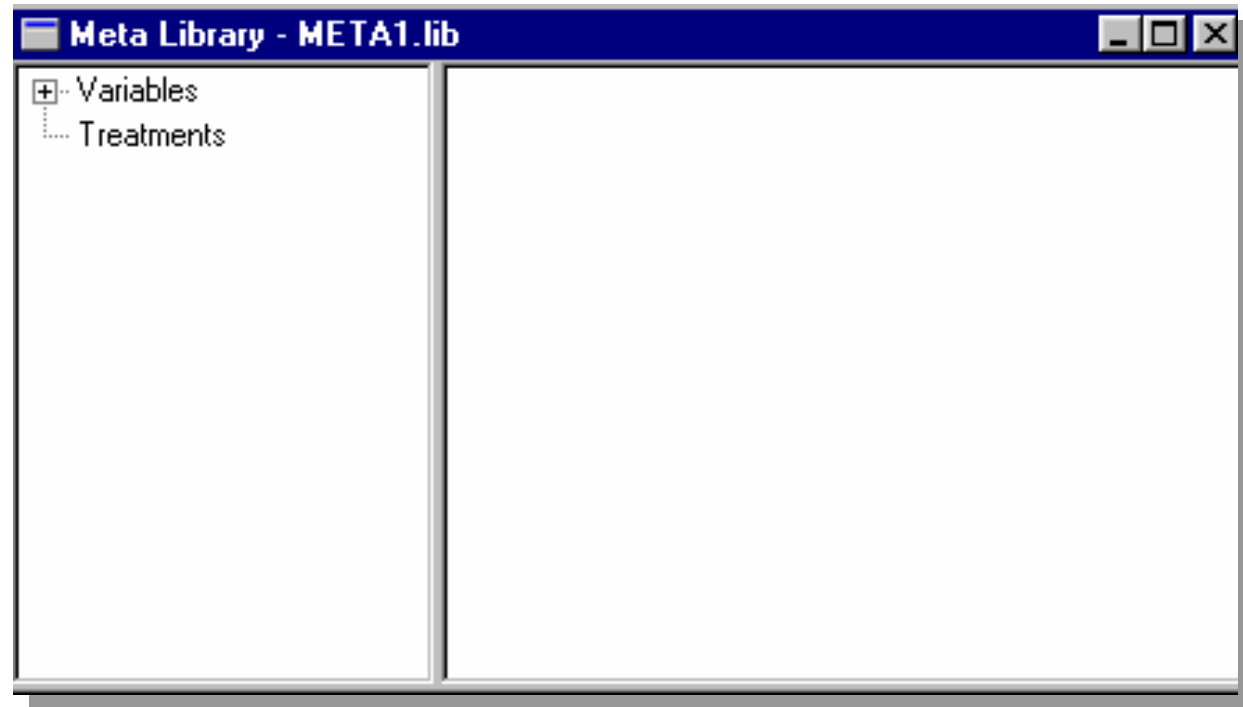
of treatments, distributions, and costs

The first level of categories in the library are

**variables**

and

**treatments**

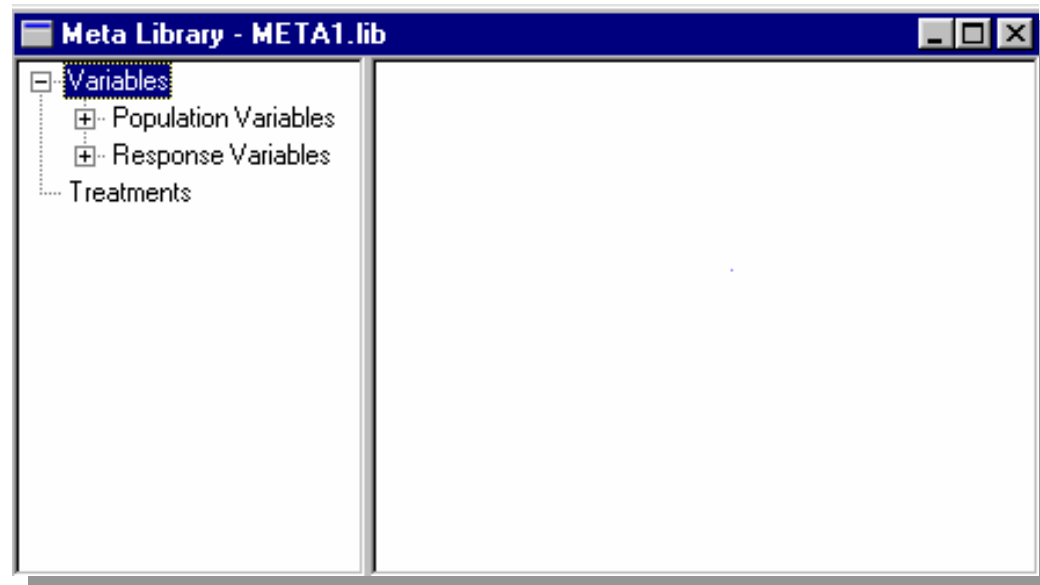


Variables are classed as

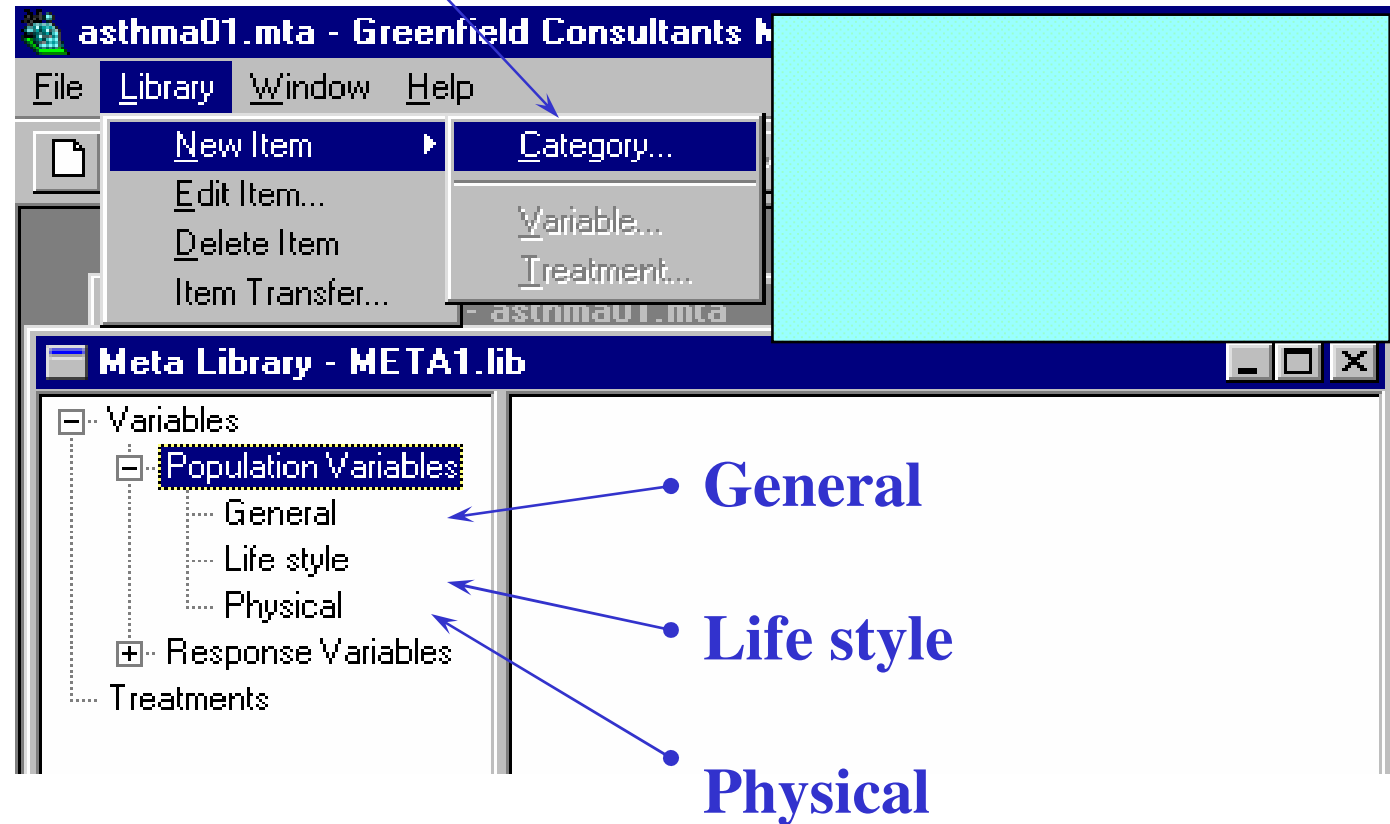
**population  
variables**

and

**response  
variables**



you can add **categories**



The screenshot shows a software window titled "asthma01.mta - Greenfield Consultants M...". The "Library" menu is open, showing options: "New Item", "Edit Item...", "Delete Item", "Item Transfer...", "Category...", "Variable...", and "Treatment...". A blue arrow points from the text "you can add categories" to the "Category..." option. Below the menu is a window titled "Meta Library - META1.lib" with a tree view structure:

- Variables
  - Population Variables
    - General
    - Life style
    - Physical
  - Response Variables
  - Treatments

Three blue arrows point from the text labels "General", "Life style", and "Physical" to their respective sub-items in the tree view. A large cyan rectangular area is present on the right side of the screenshot.

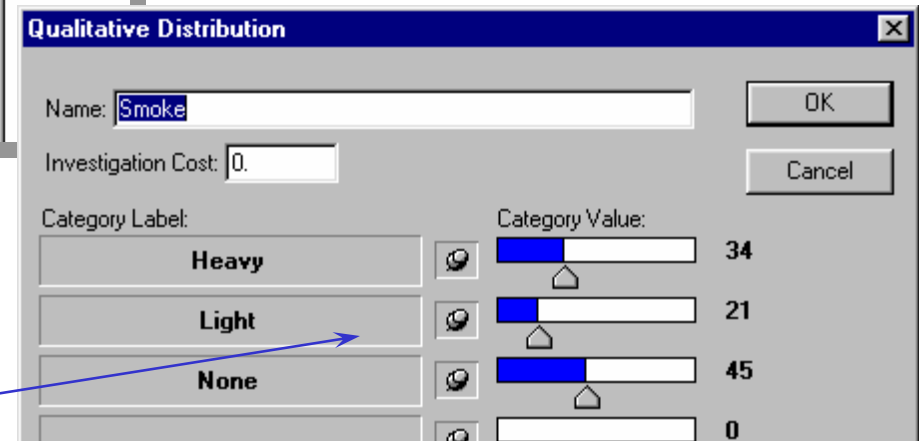
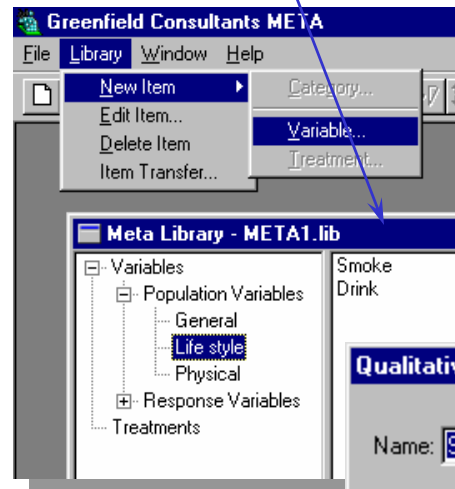
such as

**General**

**Life style**

**Physical**

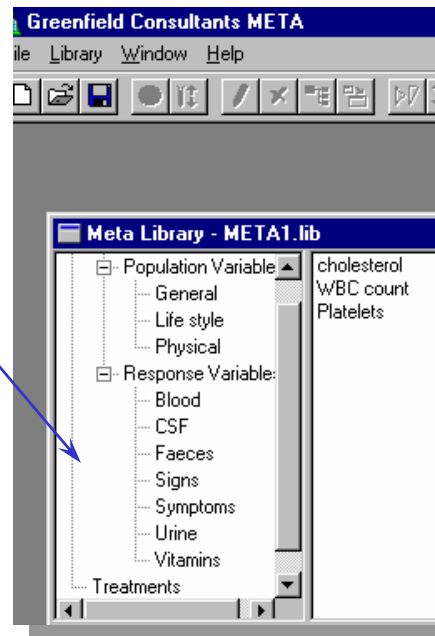
## Add a population variable



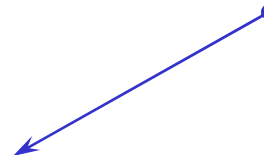
and enter its distribution  
using mouse controlled  
sliders

Create categories  
of response  
variables

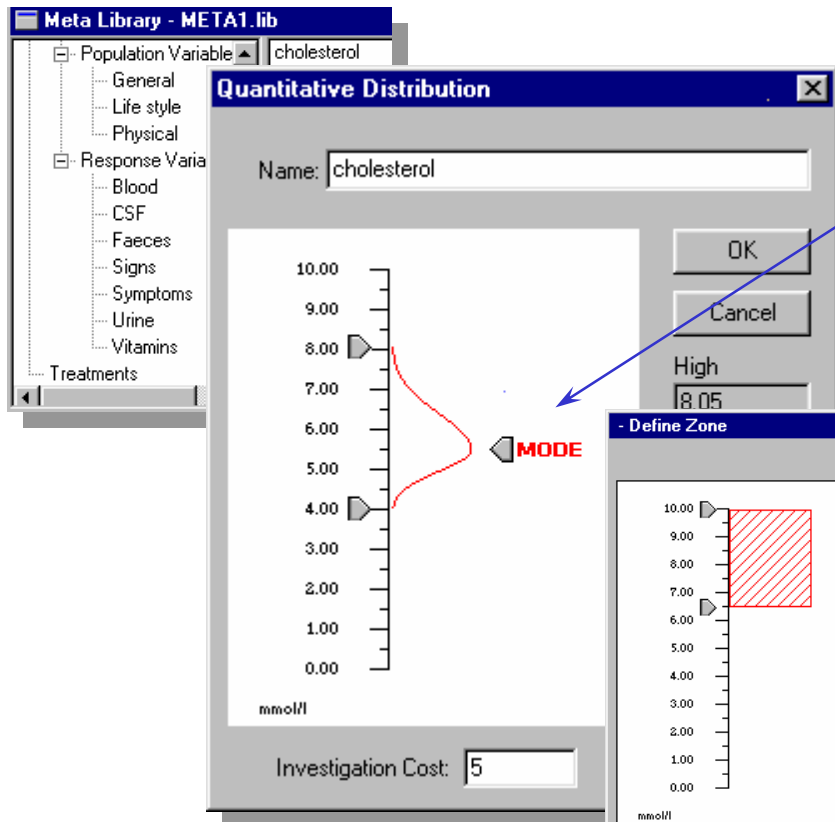
Blood  
CSF  
Faeces  
Signs  
Symptoms  
Urine  
Vitamins



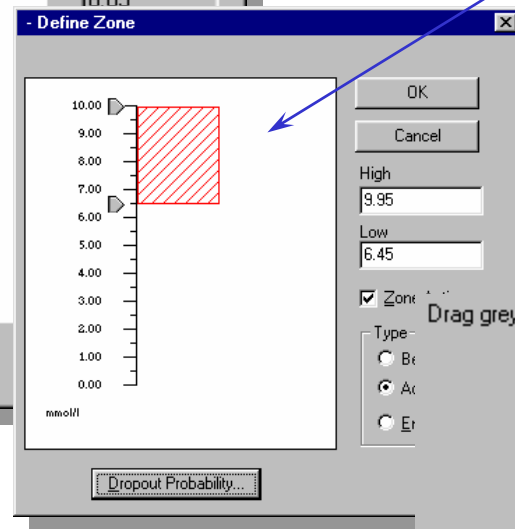
Introduce  
variables  
in the category  
of **blood**



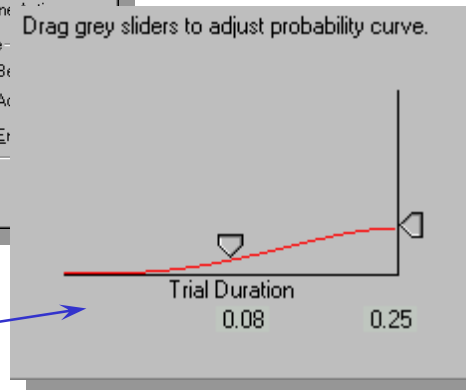
specify the distribution of cholesterol using sliders



define drop out zones

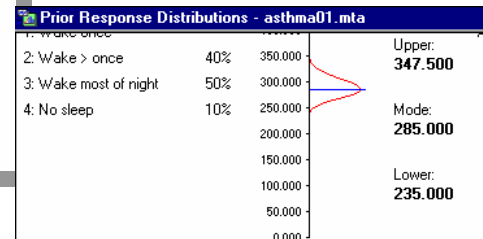
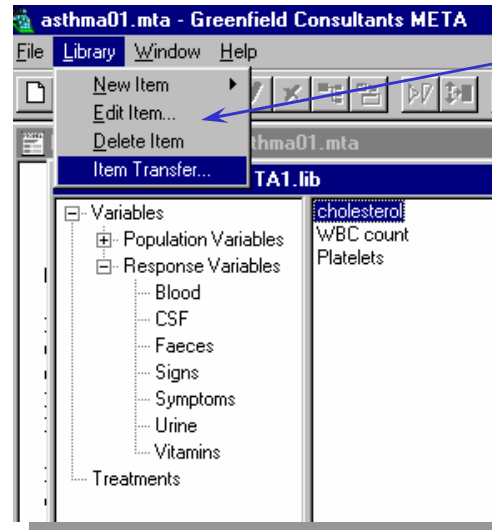


Drag grey sliders to adjust probability curve.

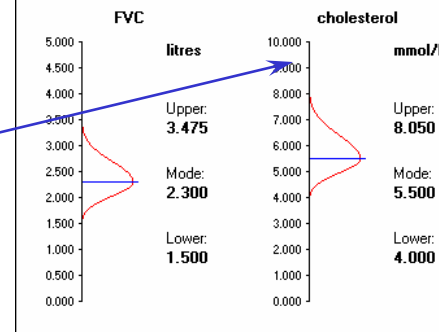


and add the probability of drop out

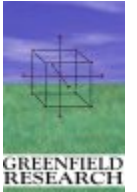
Transfer the cholesterol distribution from the library to the active Meta model



where it will be displayed with other response variables



drop out zones, probabilities, and costs will also be moved



**Thank you for your attention**