An ENBIS workshop

ISA Annual Conference
15/5/2007

Statistical Aspects of Clinical Trials

A special hands on workshop with computer simulations

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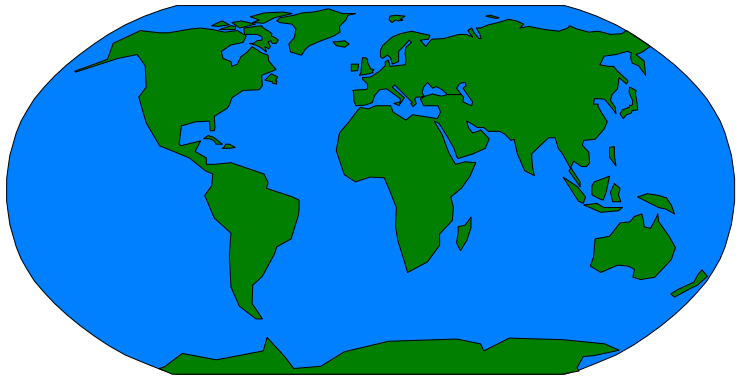
A clinical trial is an experiment

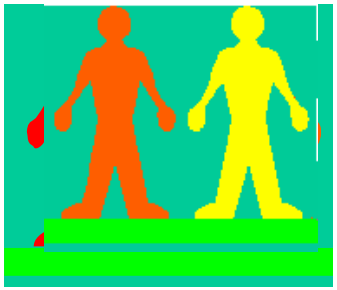
to discover something about

the real world



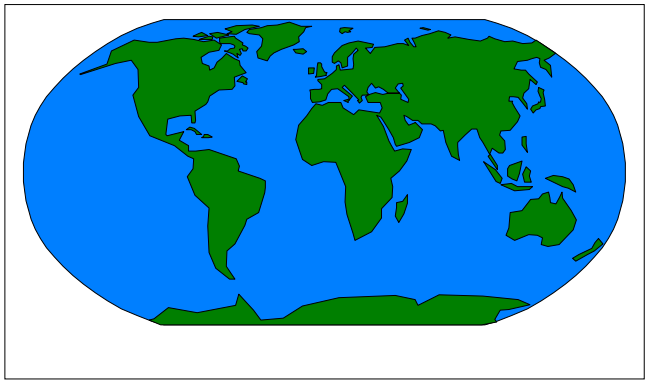
. . . how people

respond to clinical treatment

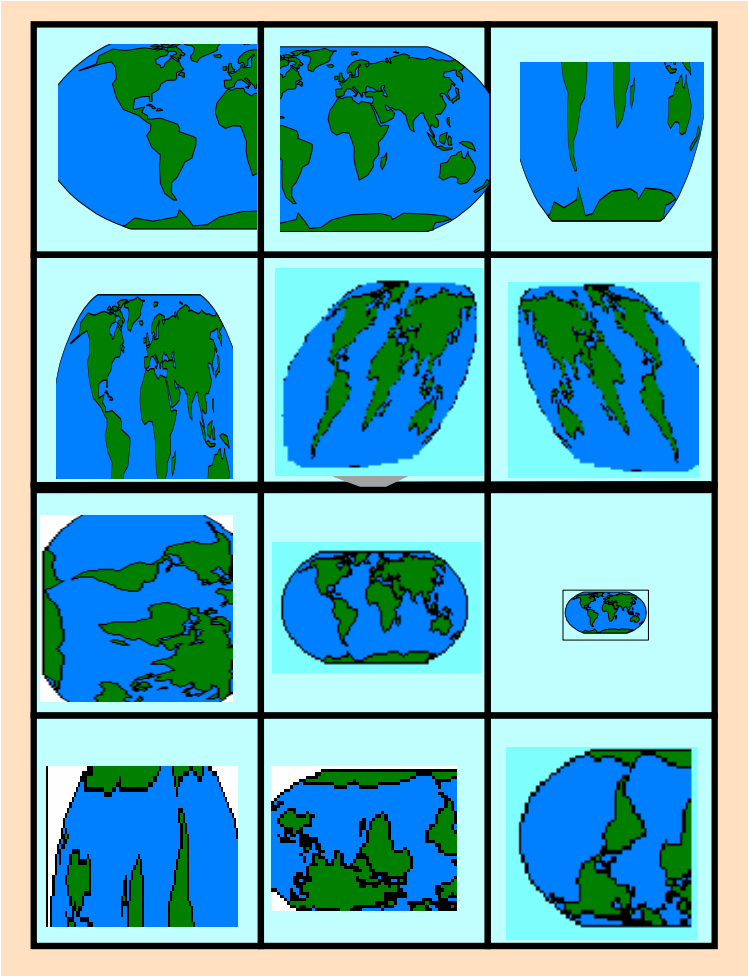


The protocol is the window

we construct to look at the world

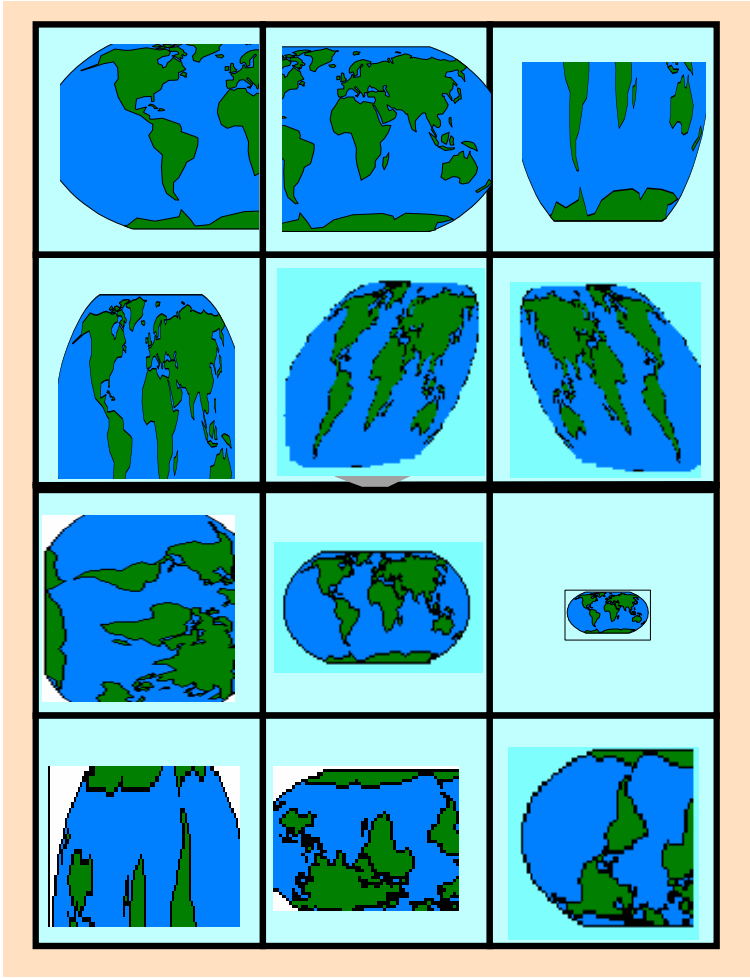


Different protocols will give different views of the world



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

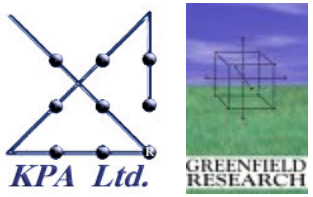
The efficiency and effectiveness and **cost** of a clinical trial depend on:



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**



- 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

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

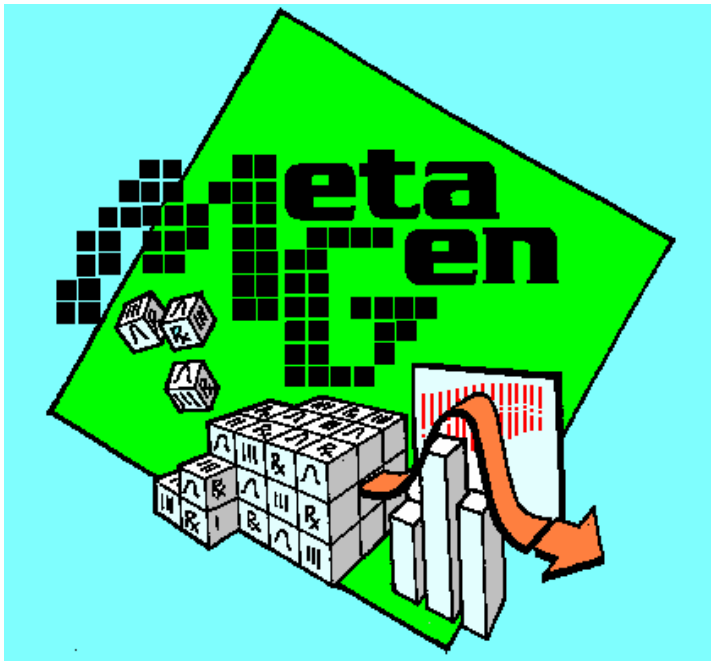
The protocol is the tool which is used to specify the way the trial will be run.

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

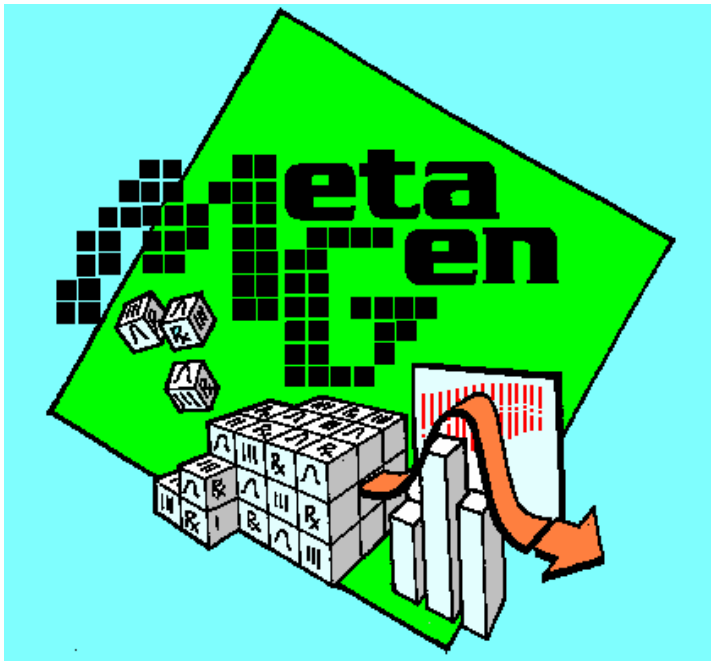
through which we learn how people respond to clinical treatment

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

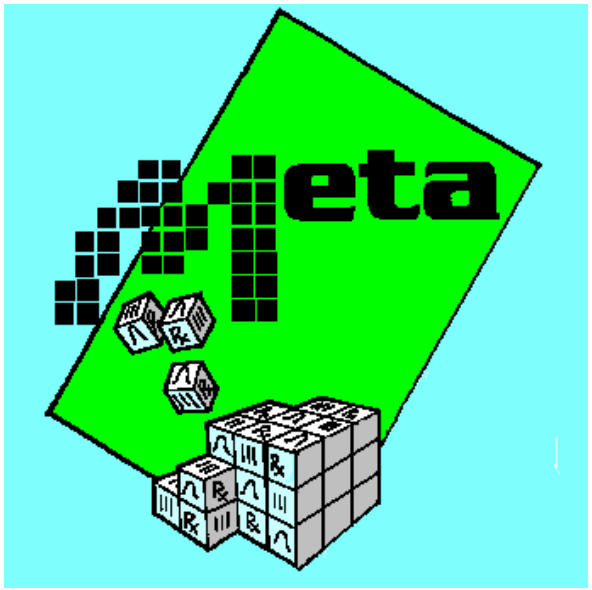
But it is used only once.



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

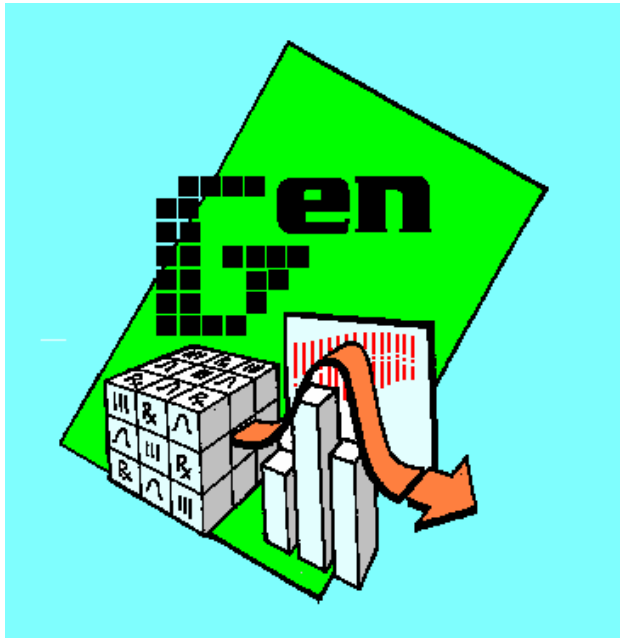


MetaGen has two components:

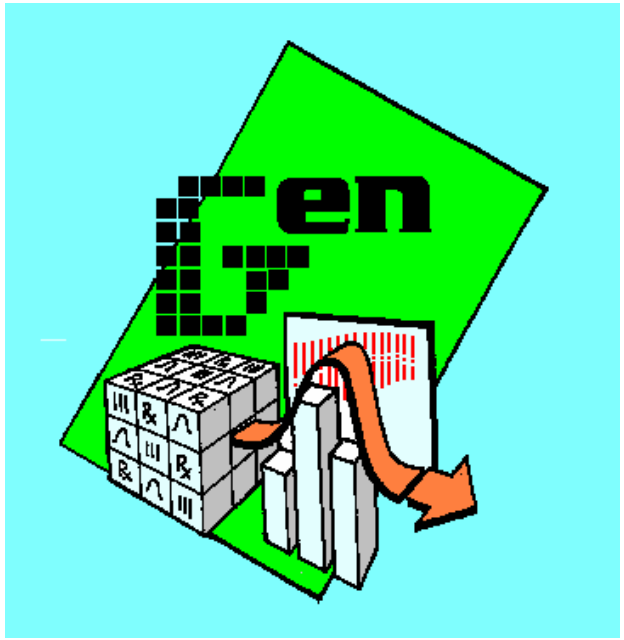


META is used to specify a model for study:

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

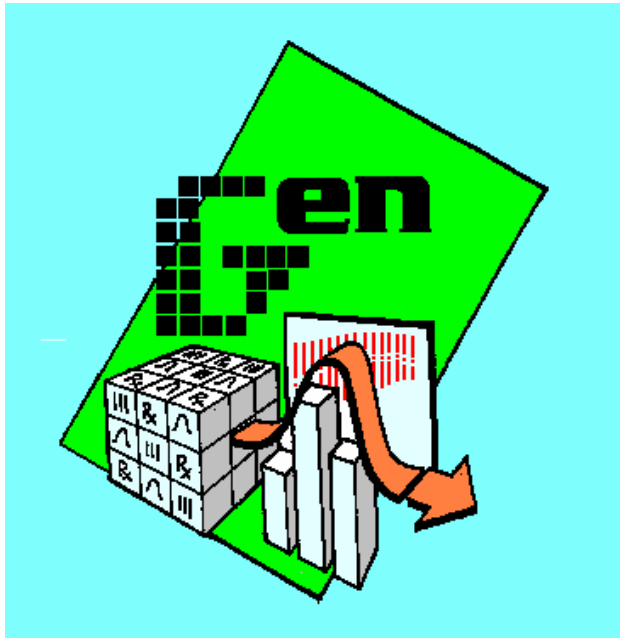


GEN allows the user to design a clinical trial
with a view to discovering
the model defined in **META**



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

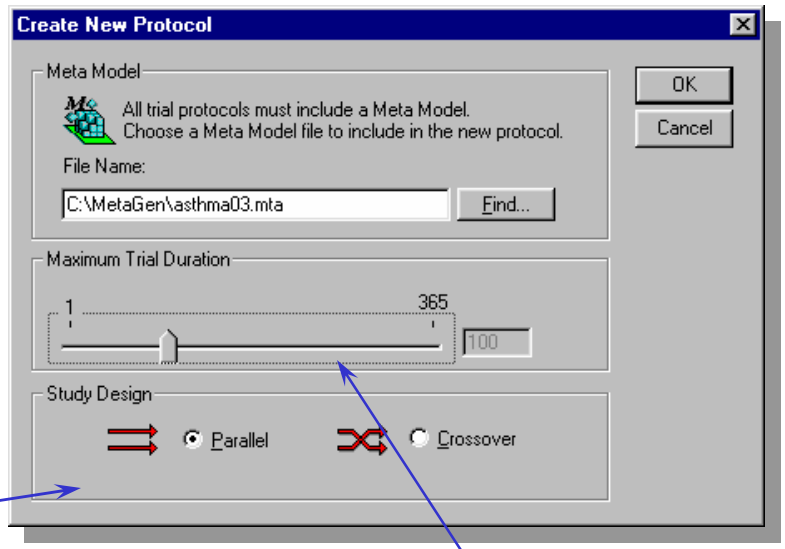
Example: Nocturnal asthma

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

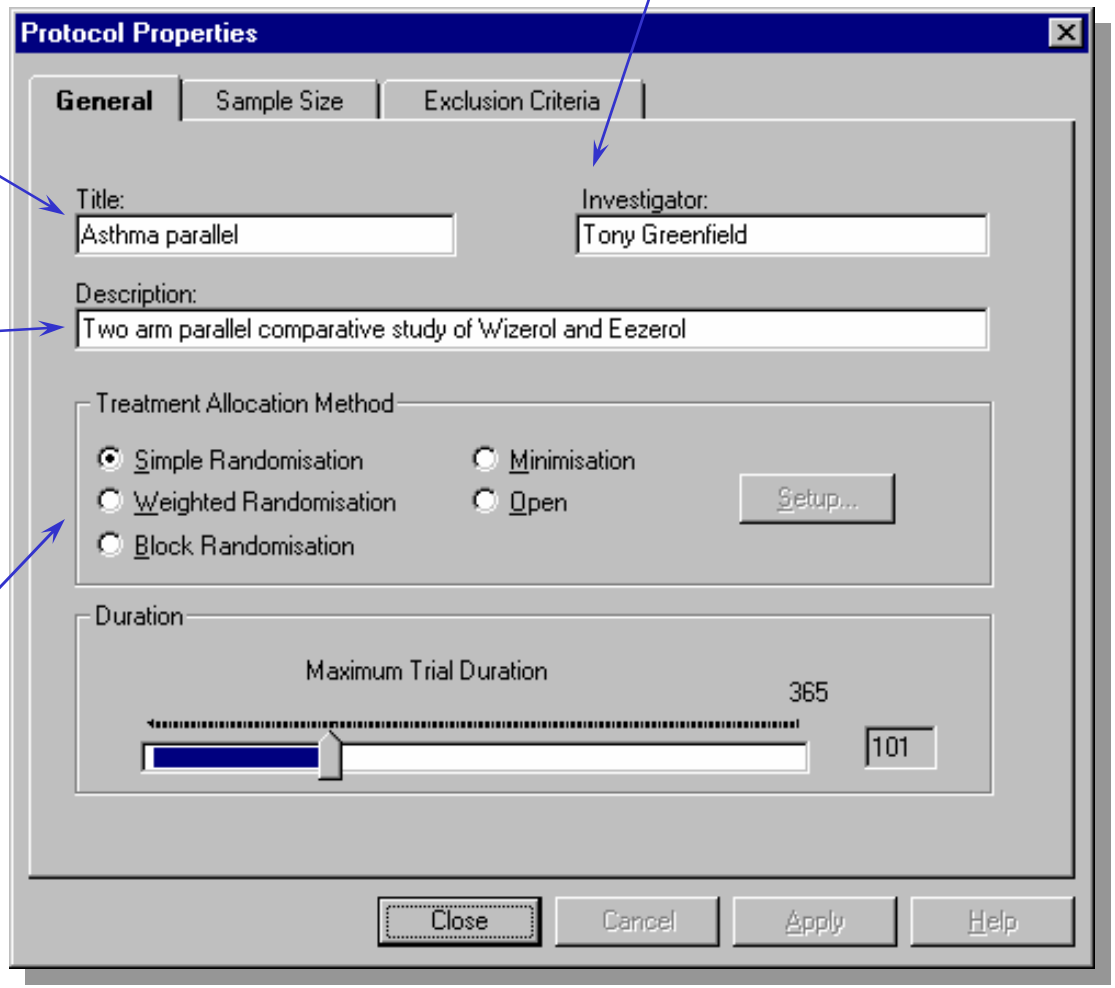
Enter

a title

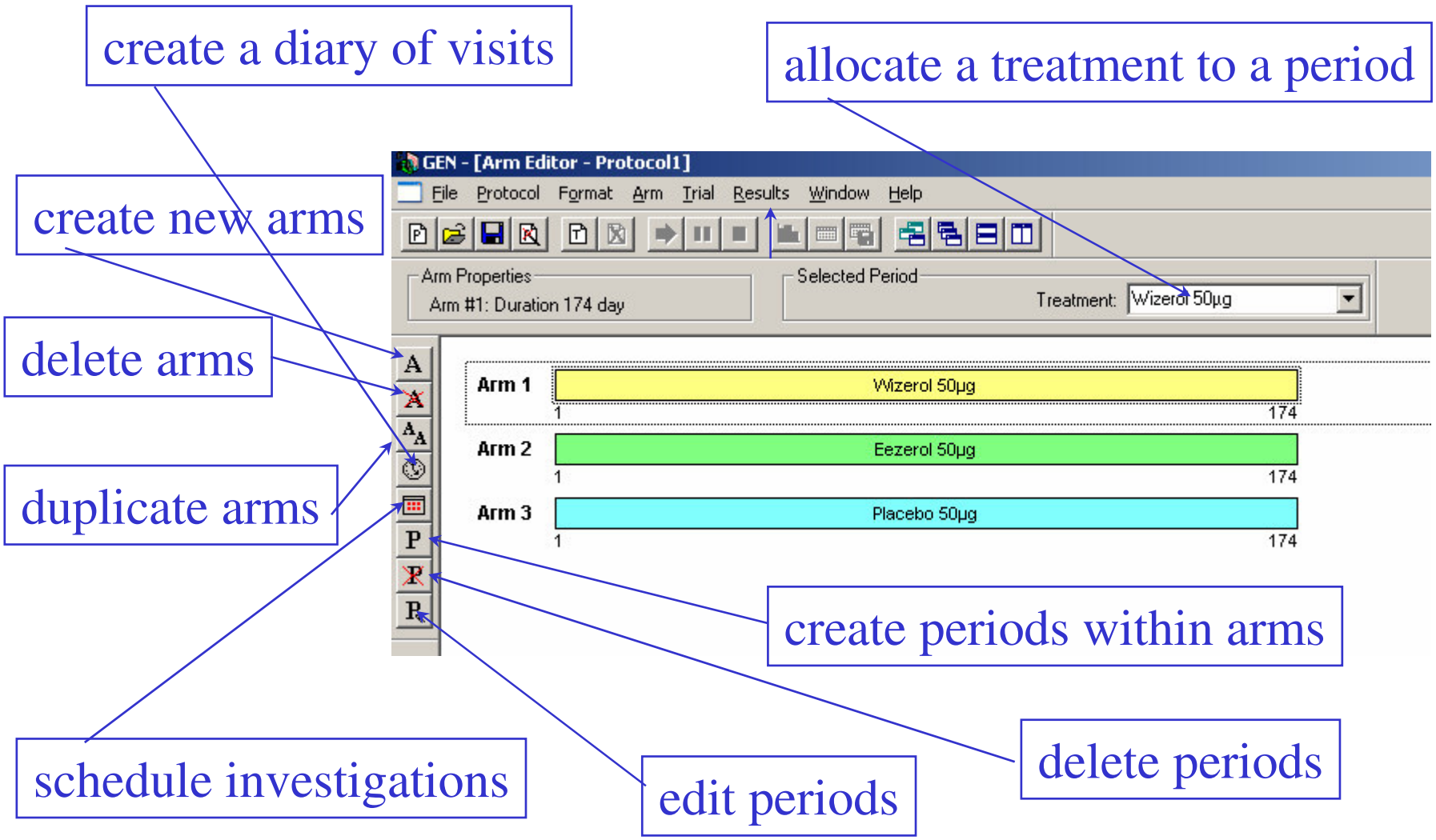
investigator name

a description

specify the treatment allocation method

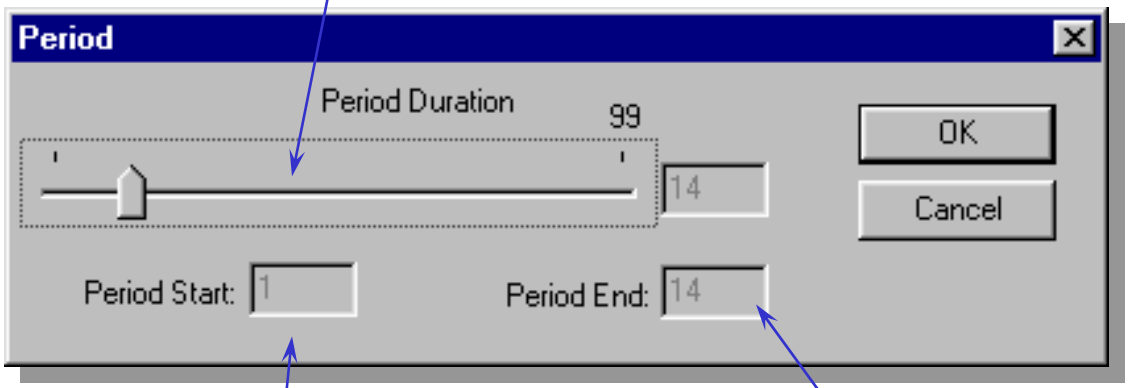


The **arm designer** allows you to:



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

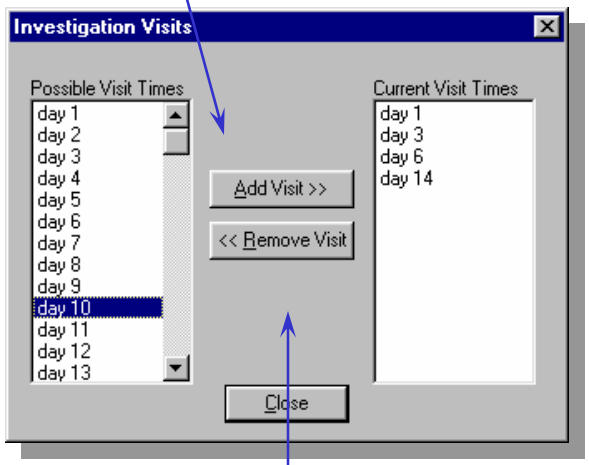
its duration



period start

period end

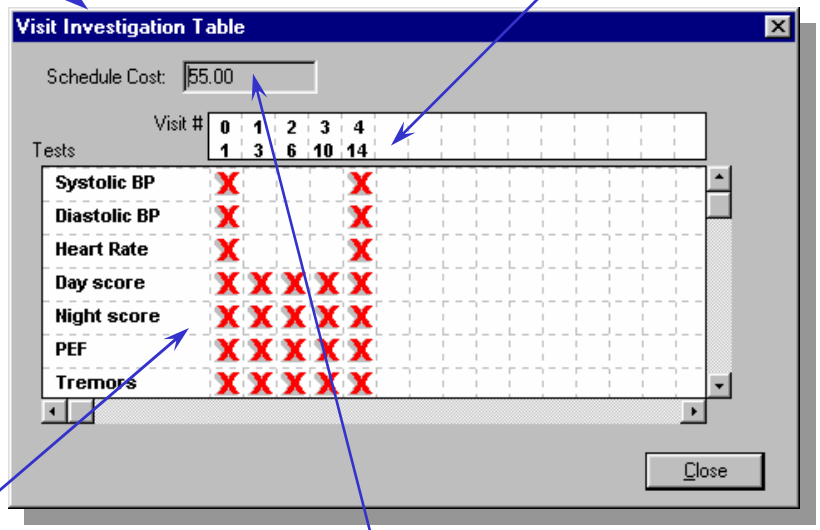
A **diary of visits** is created
by moving possible times
to the list of current visit times



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

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

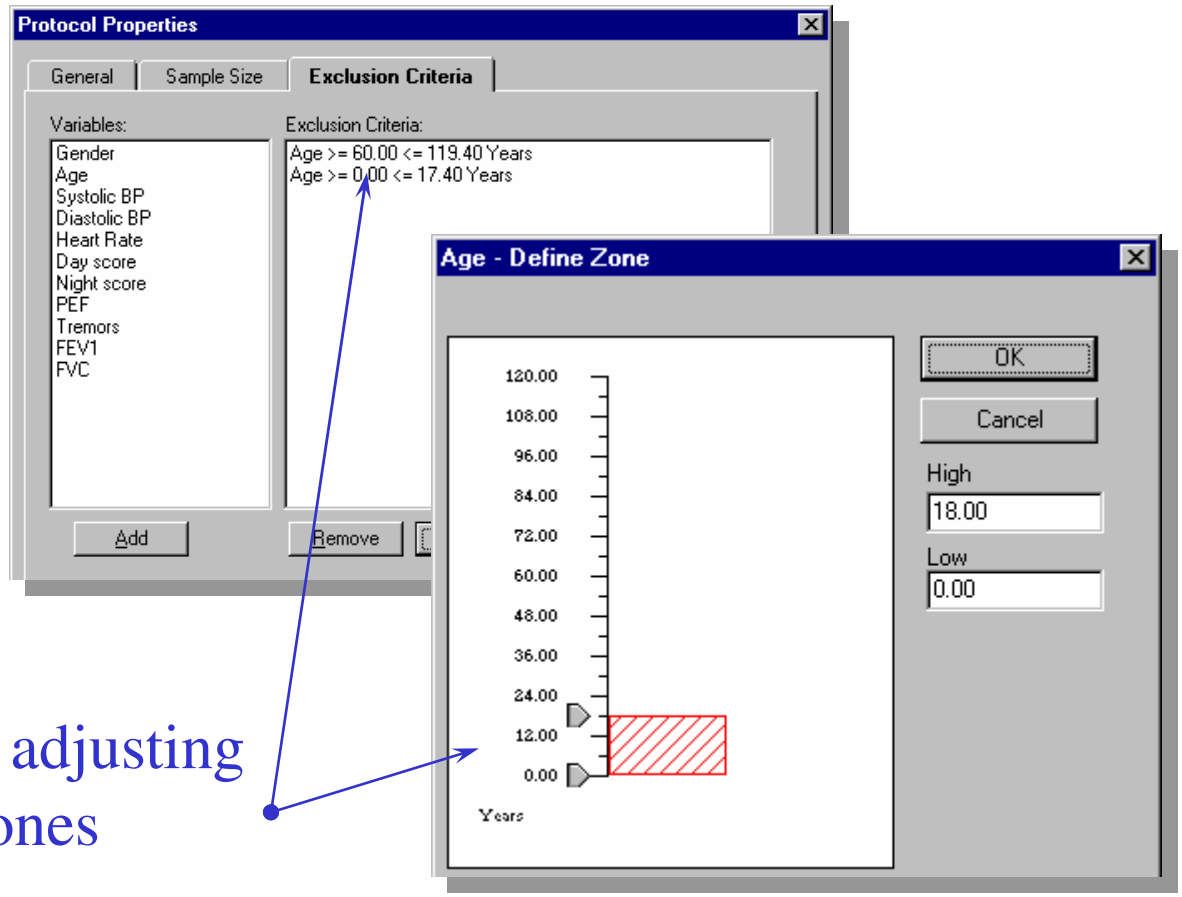
Exclusion criteria can be defined using

population variables

or

response variables

and graphically adjusting the exclusion zones



Sample size depends on

end point variable

standard deviation

clinically significant difference

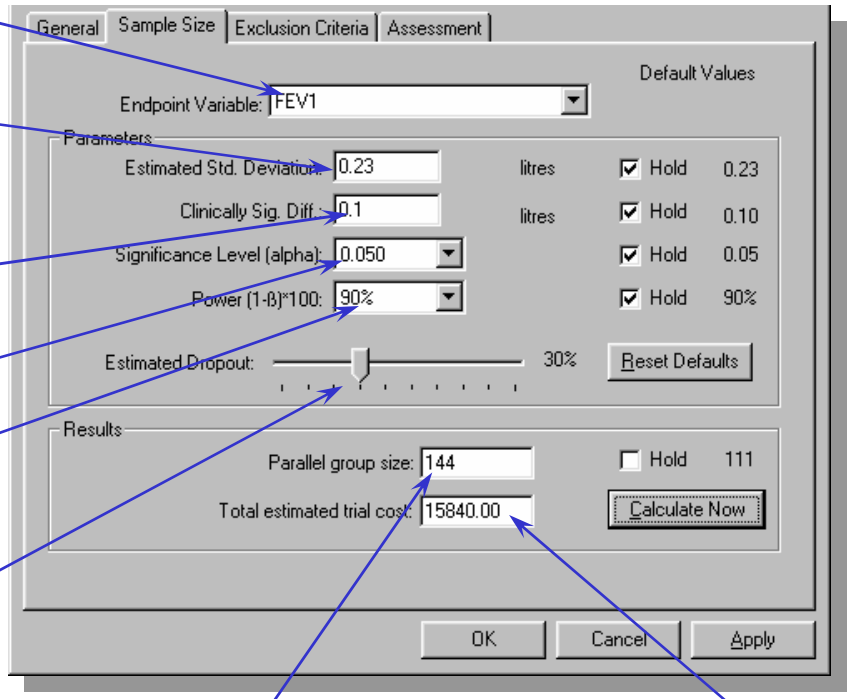
alpha value

power

allowance for drop outs

sample size

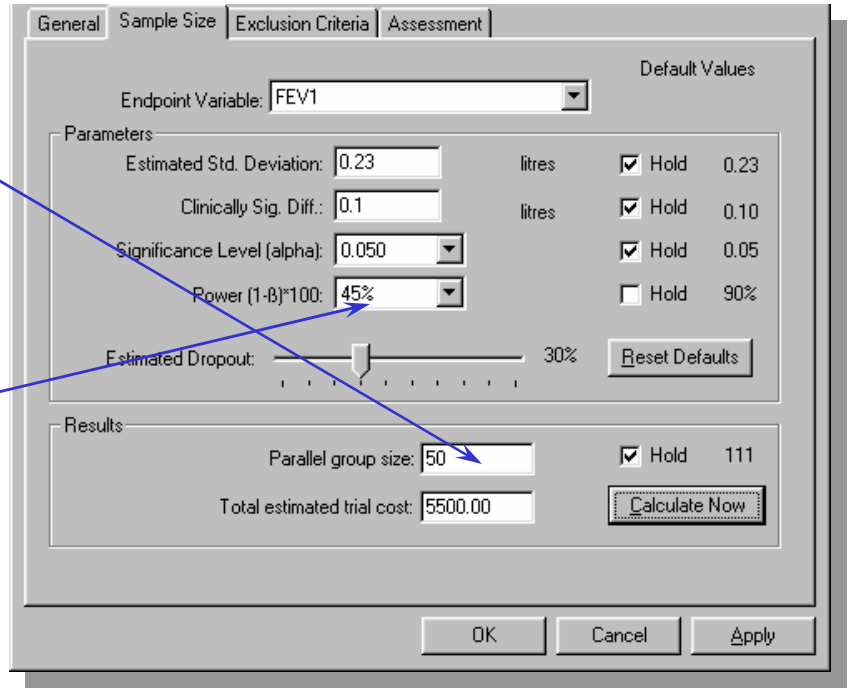
estimated **trial cost**



Every parameter can be estimated in terms of the others

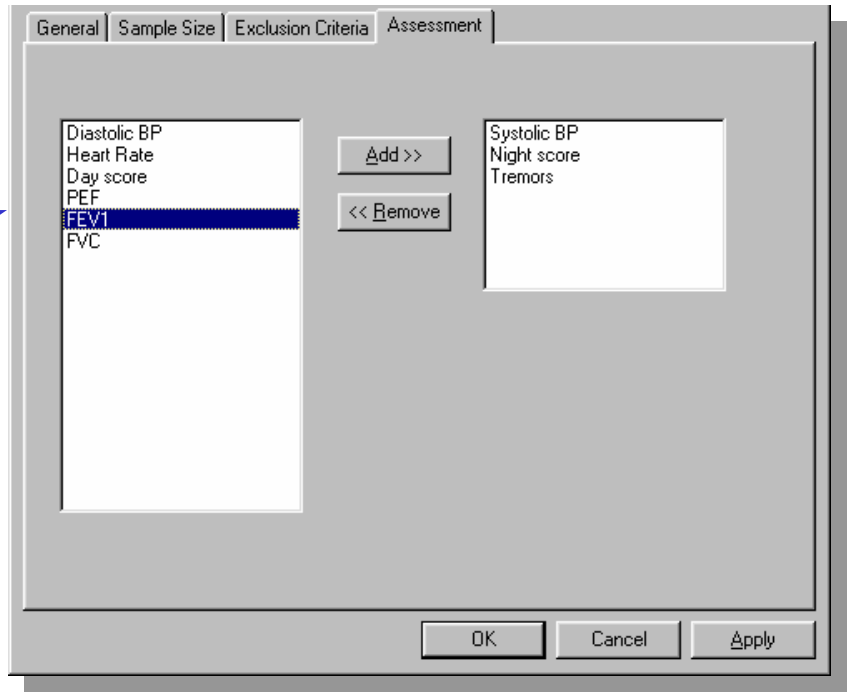
Set the **sample size** too low

and the **power** drops appallingly



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

Select variables for assessment tests

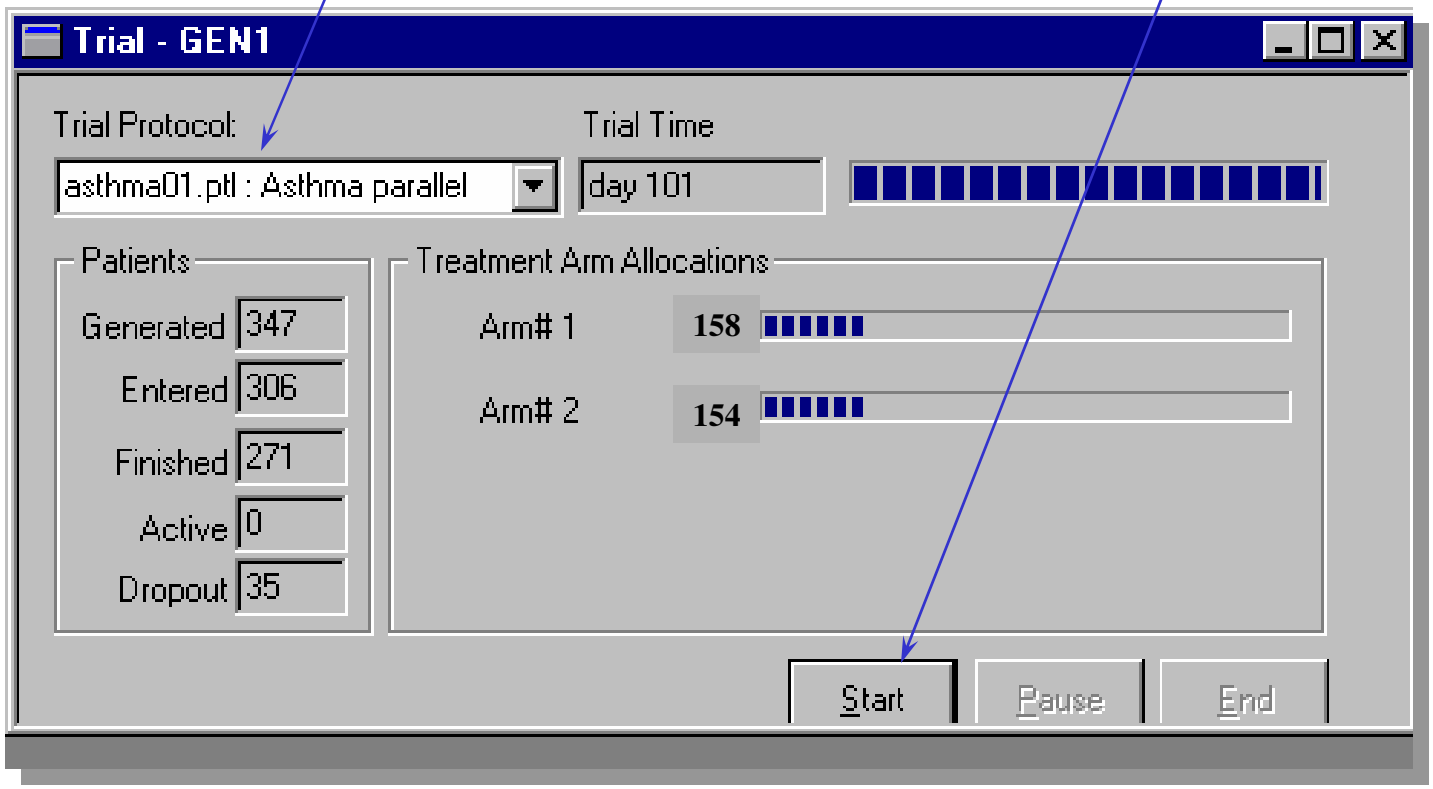


Warning:

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



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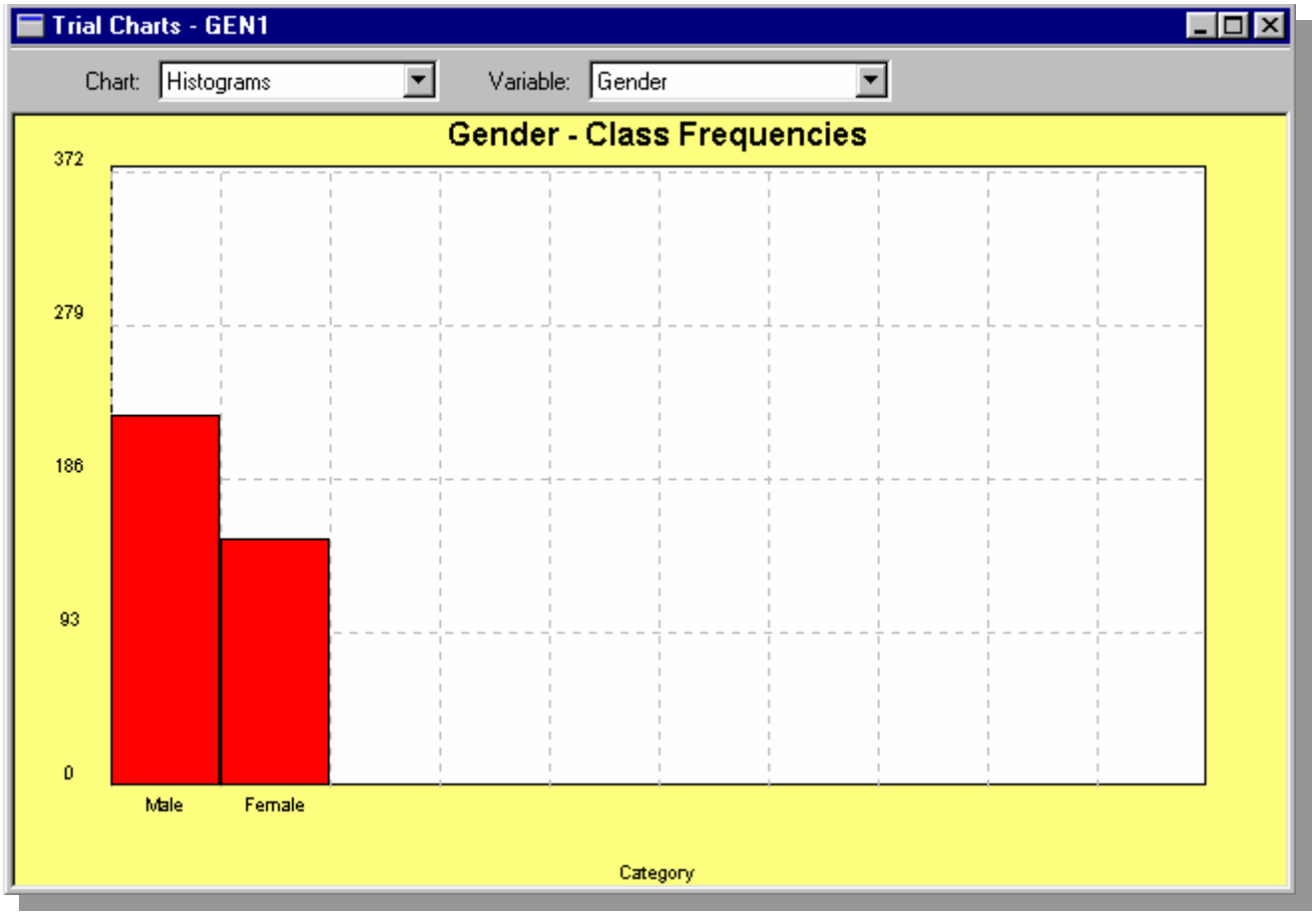
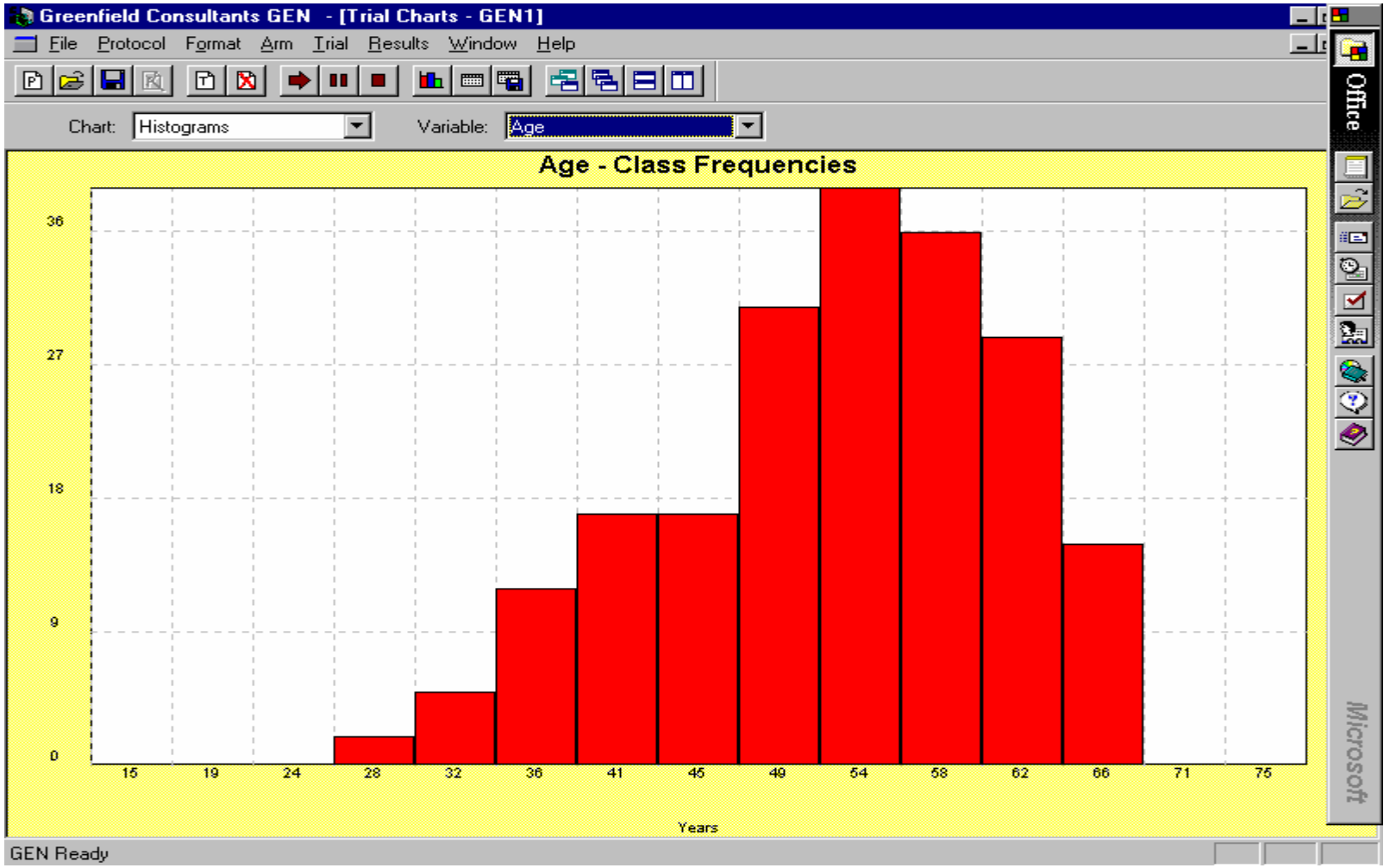
Histograms:

Gender of patients entered into trial

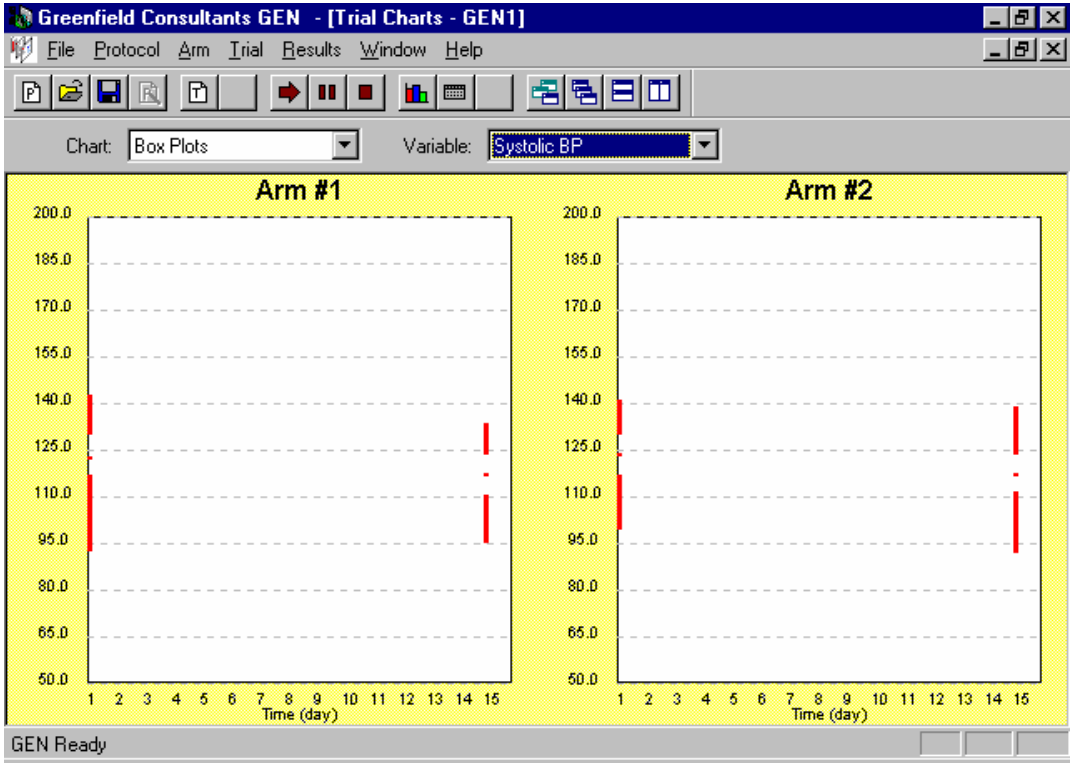


Histograms:

Ages of patients entered into trial



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



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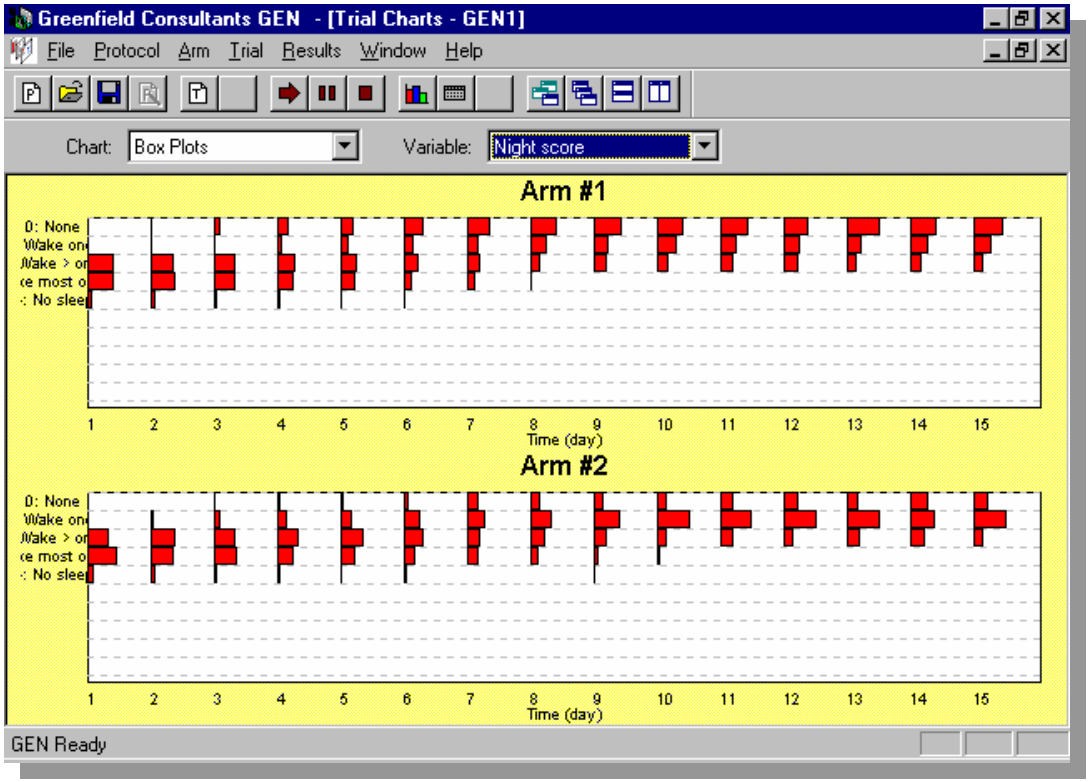
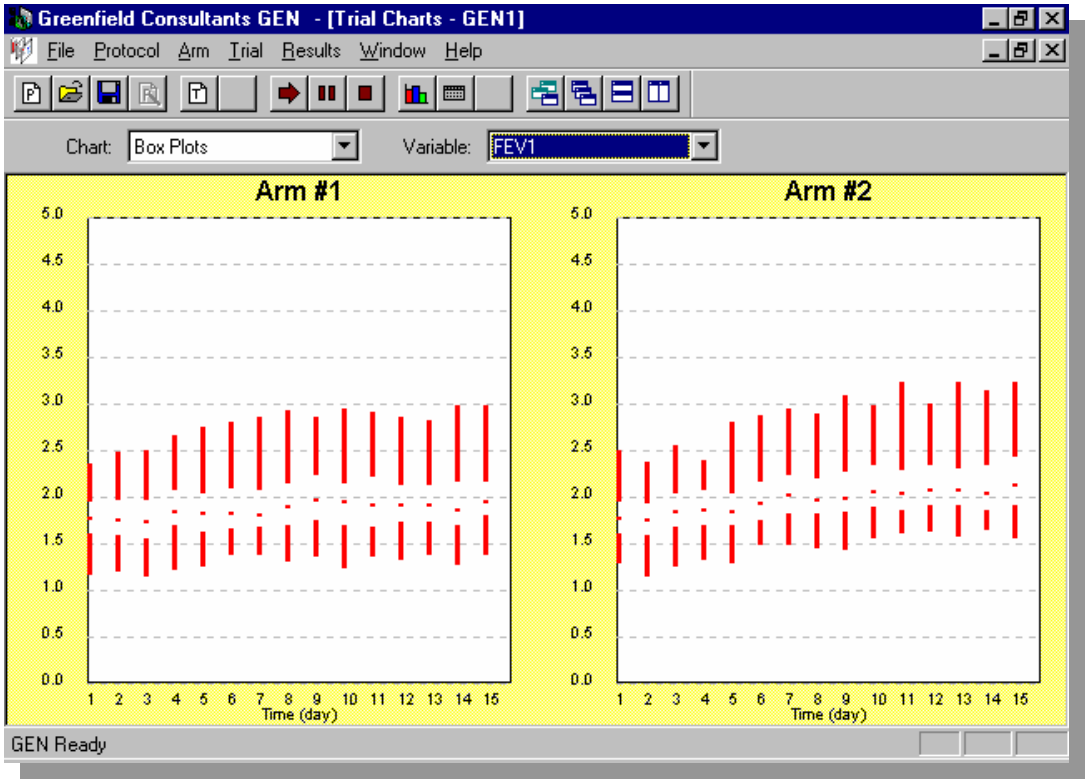
Sample distributions of **night score** in diary records for both treatments

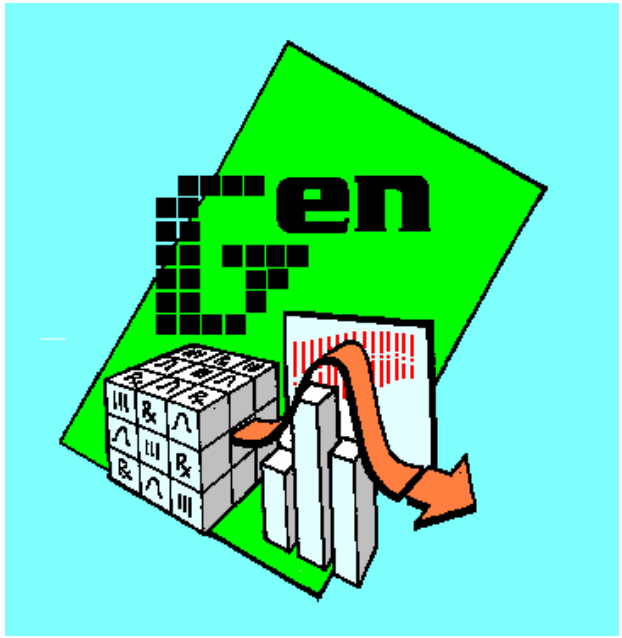


Sample distributions of **FEV1** in diary records for both treatments



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

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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
```

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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

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Asthma trial results

Data								
In/Out	Arm#		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

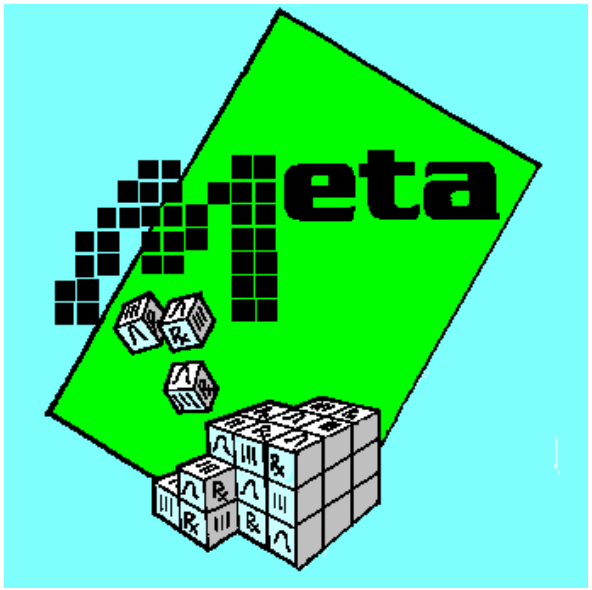
Assessments of significant difference

FEV1

Wizerol 50µg v Eezerol 50µg – No significant difference

Wizerol 50µg v Placebo 50µg – Significant difference

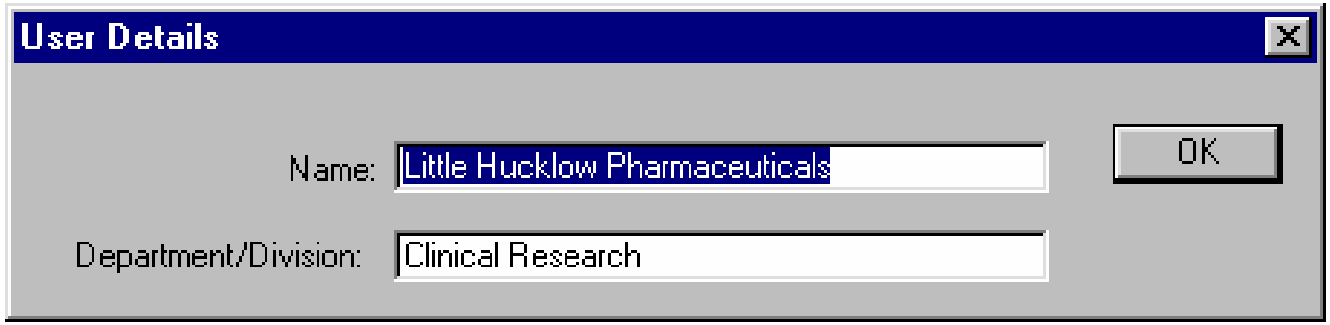
Eezerol 50µg v Placebo 50µg – Significant difference



META is used to specify a model for study:

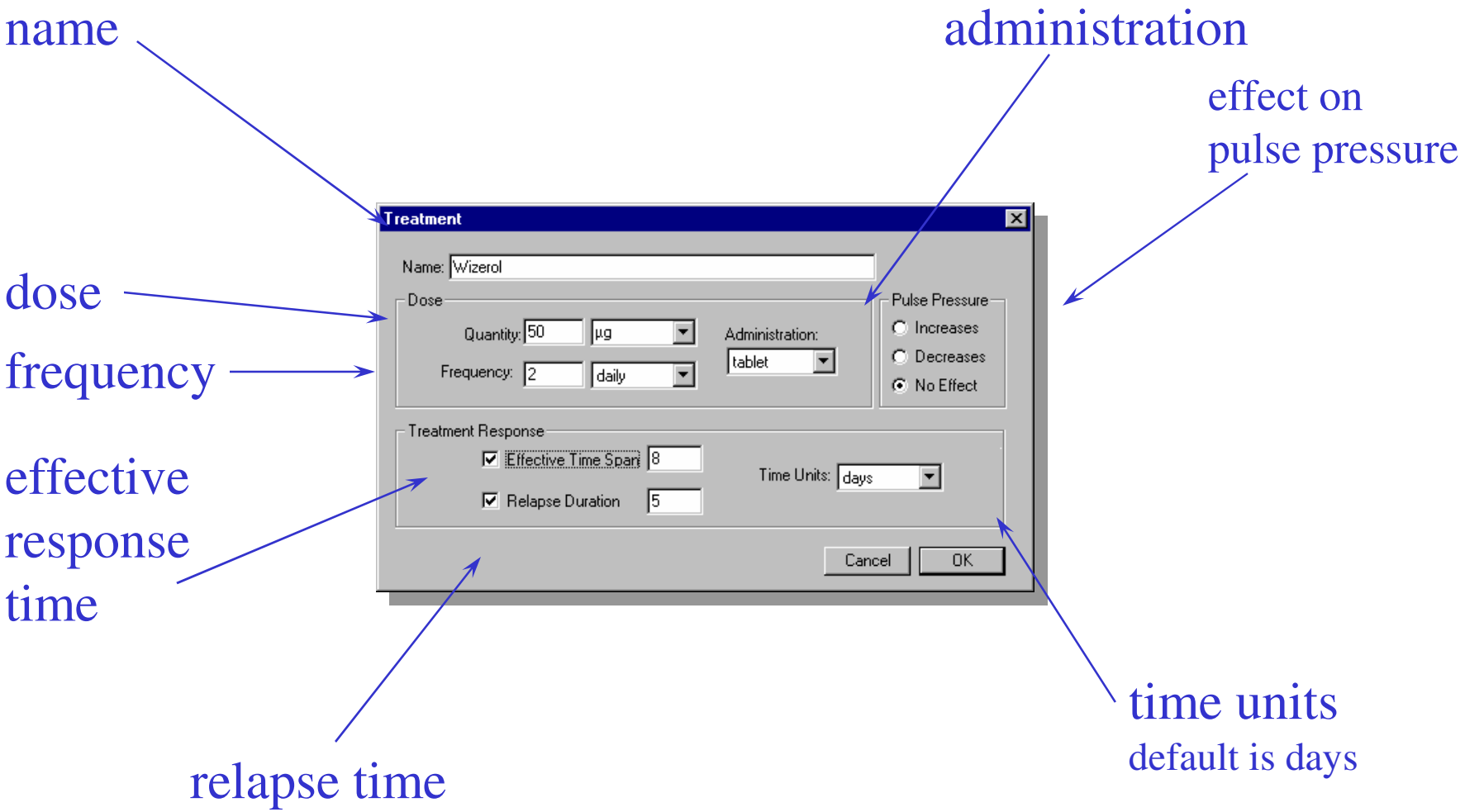
- treatments
- population variables
- response variables
- patient presentation and drop out rates

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



These will appear at the top of every report.

Each new treatment is entered with



There is no limit to

the number of treatments:

all those you enter are candidates

for inclusion in protocols

created in Gen

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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

Condition :
Nocturnal Asthma

Minimum presence of symptoms :
28 days

Creator:
Tony Greenfield

Test of proof:
night score >=2 in 3/7 days

Date :
Monday, September 25, 1995

Treatments

Wizerol 50µg 2 daily

Administration:
tablet

Pulse pressure:
No effect

Effective response time:
8 days

Relapse time:
5 days

Eezerol 50µg 2 daily

Administration:
tablet

Pulse pressure:
Decrease

Effective response time:
10 days

Relapse time:
7 days

Placebo 50µg 2 daily

Administration:
tablet

Pulse pressure:
No effect

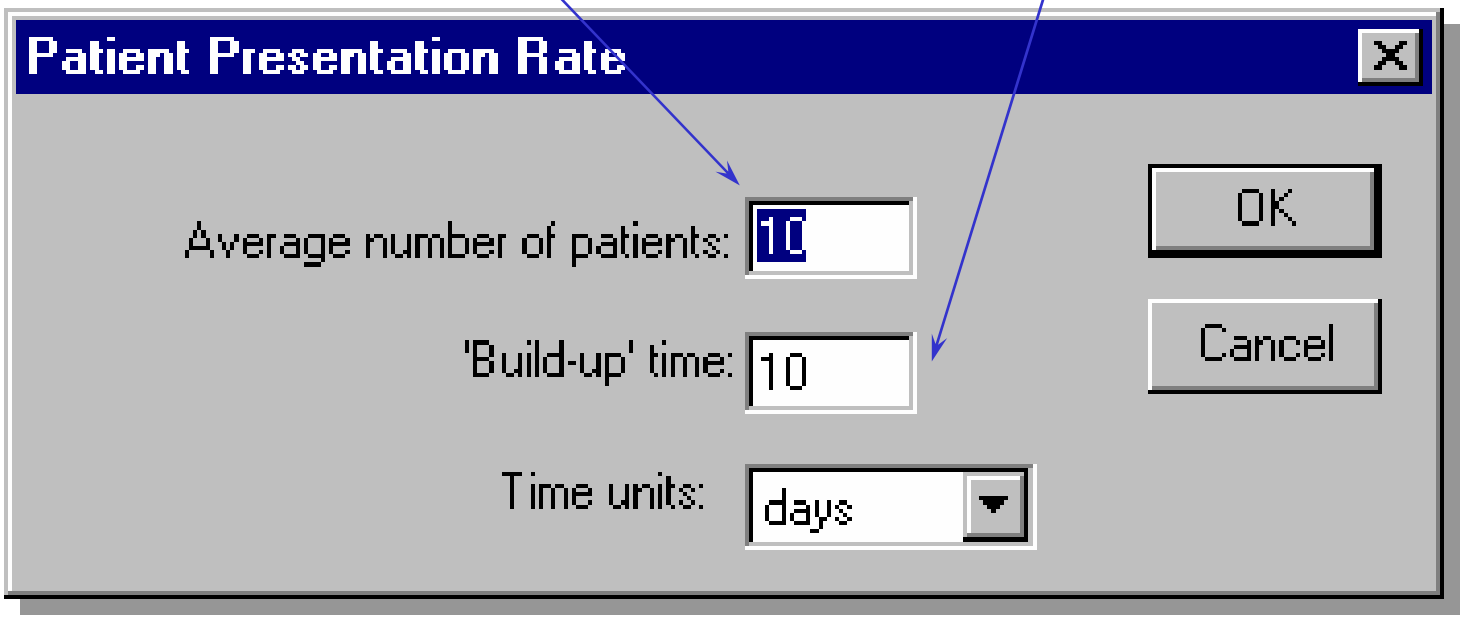
Effective response time:
5 days

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

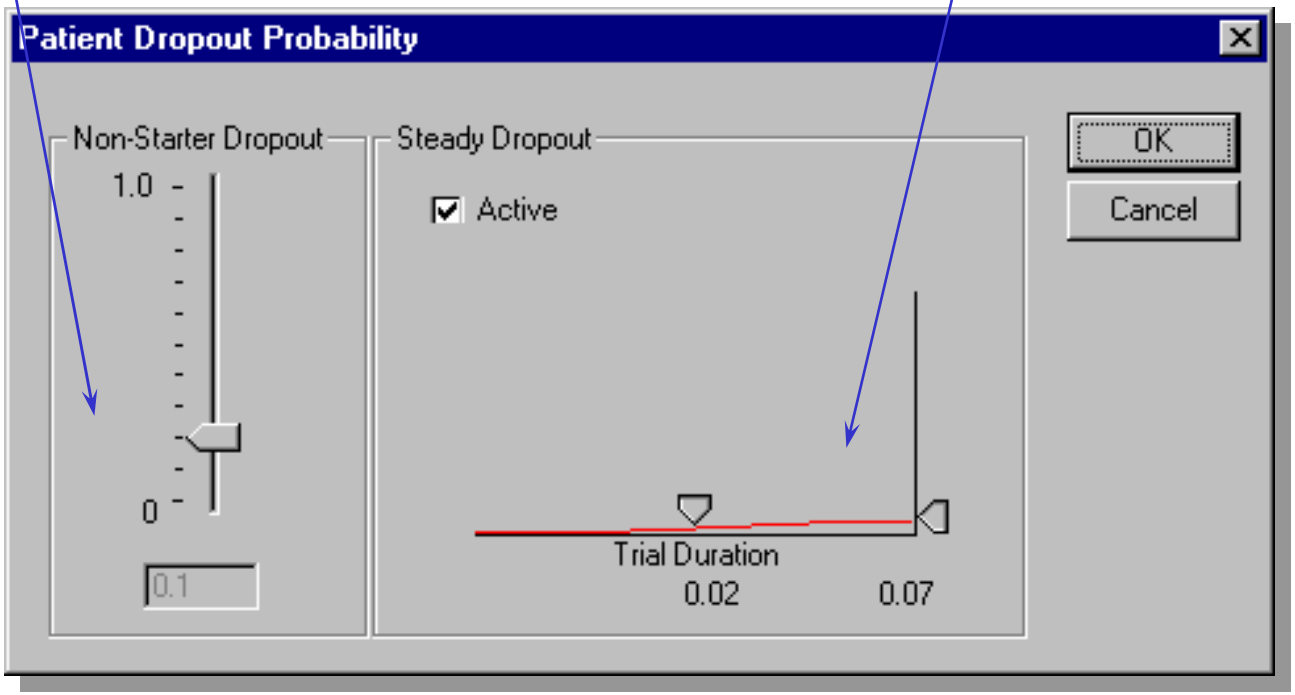


note that this is the **average** rate

Enter patient drop out rates during the trial

Some patients entered into the trial will fail to start

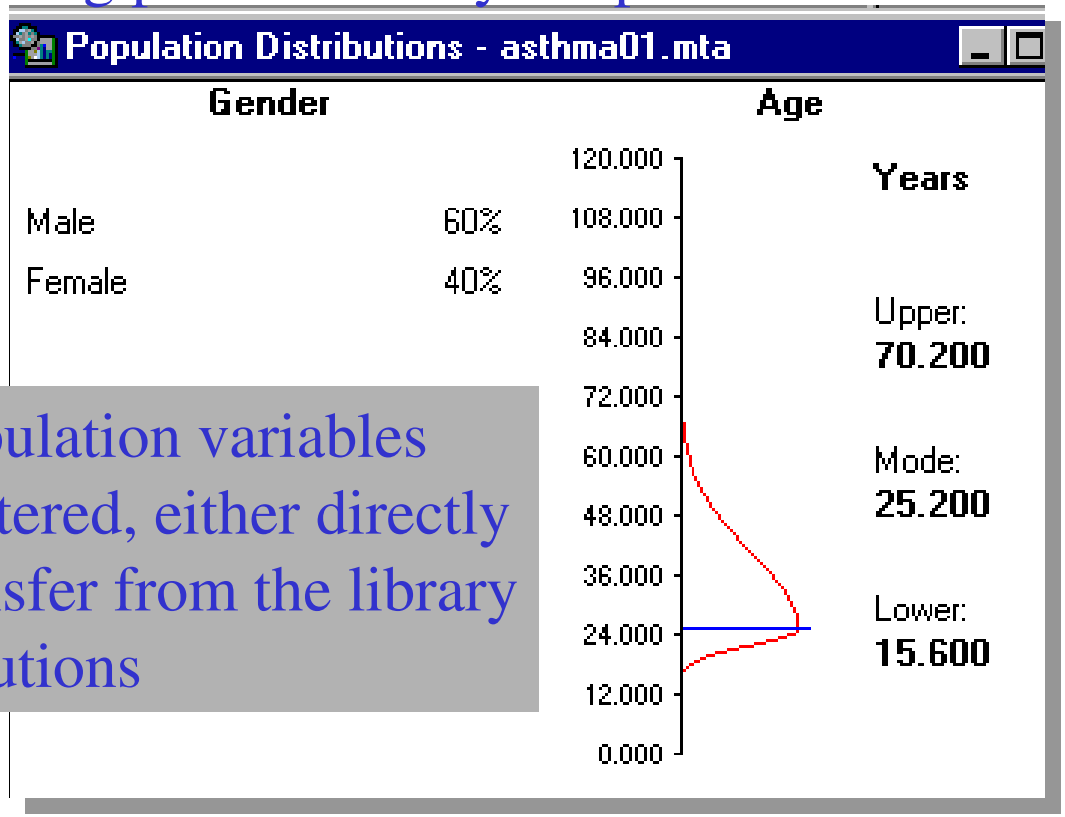
Others will drop out during the trial for no particular reason



Values are changed by mouse control of the sliders

Two standard population distributions are gender and age

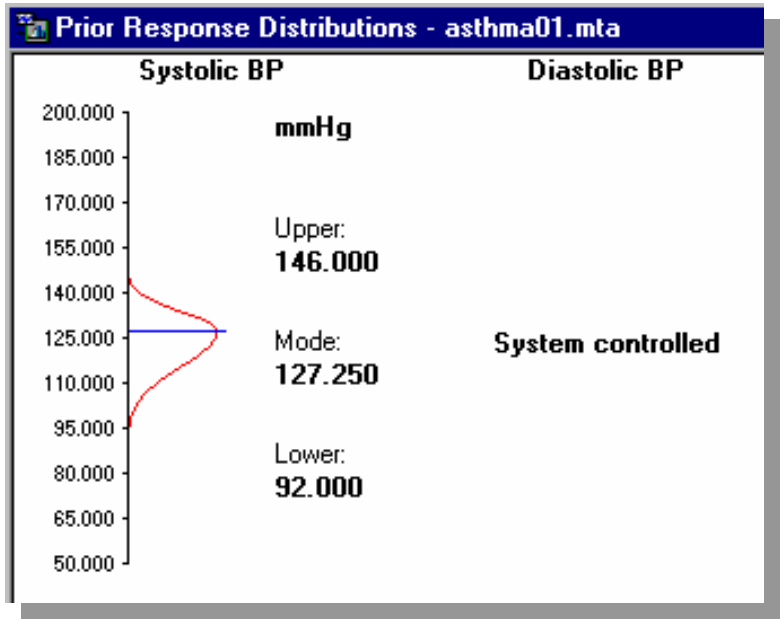
These can be adjusted to match your expectations of presenting patients . . . by simple mouse controls



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

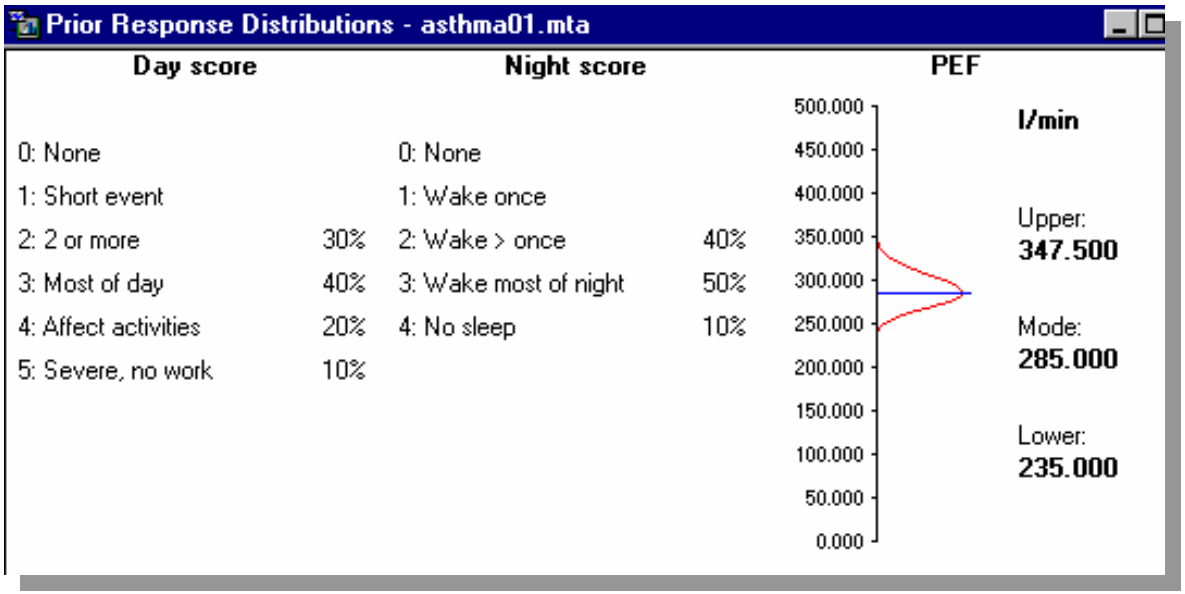


Diastolic blood pressure is system controlled: related to systolic by **pulse pressure**, in turn controlled by age and gender

More response variables can be entered,

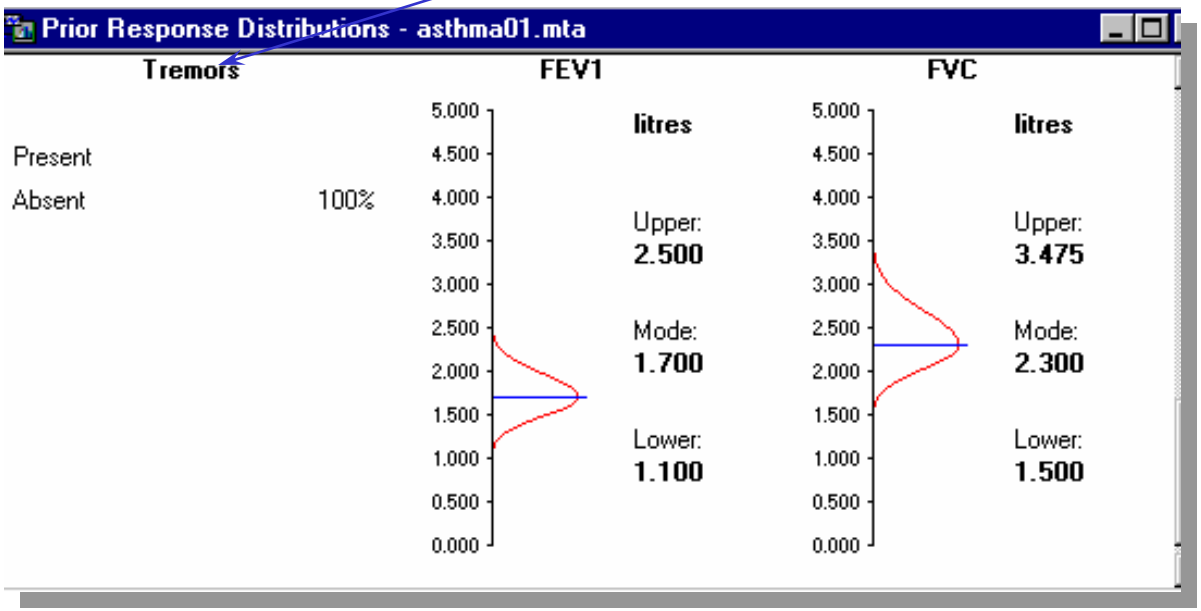
either **directly**

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

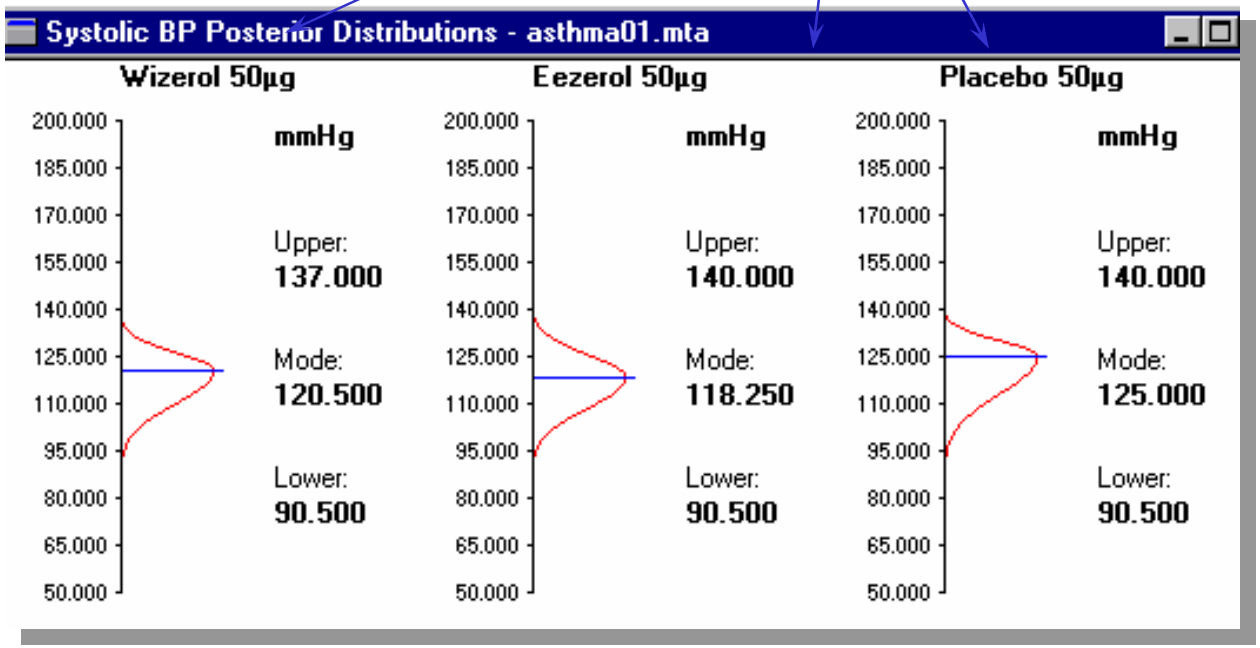


There is no limit to the number of variables that can be entered

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

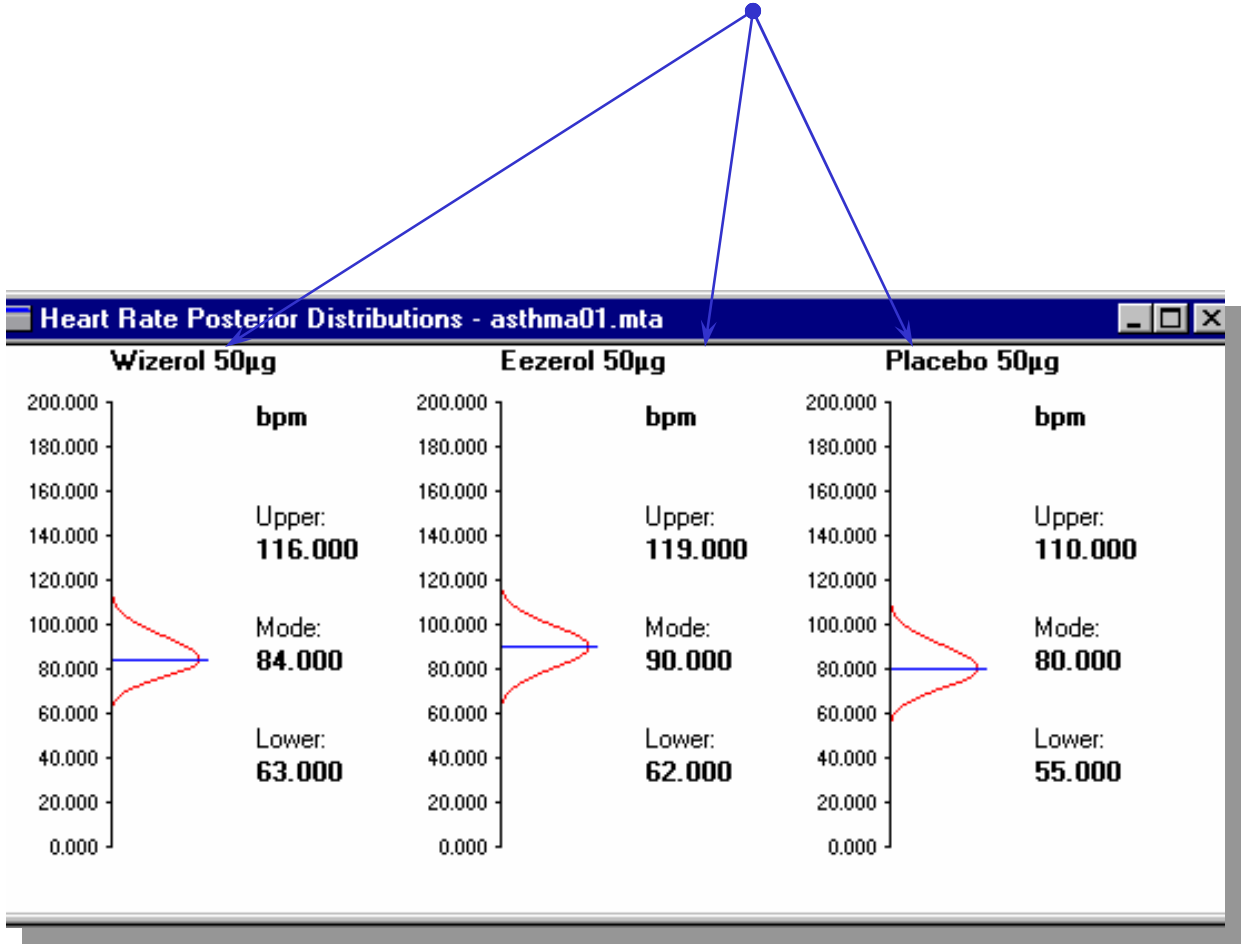


Treatment effects are shown as the **posterior distributions** of response variables one for each treatment

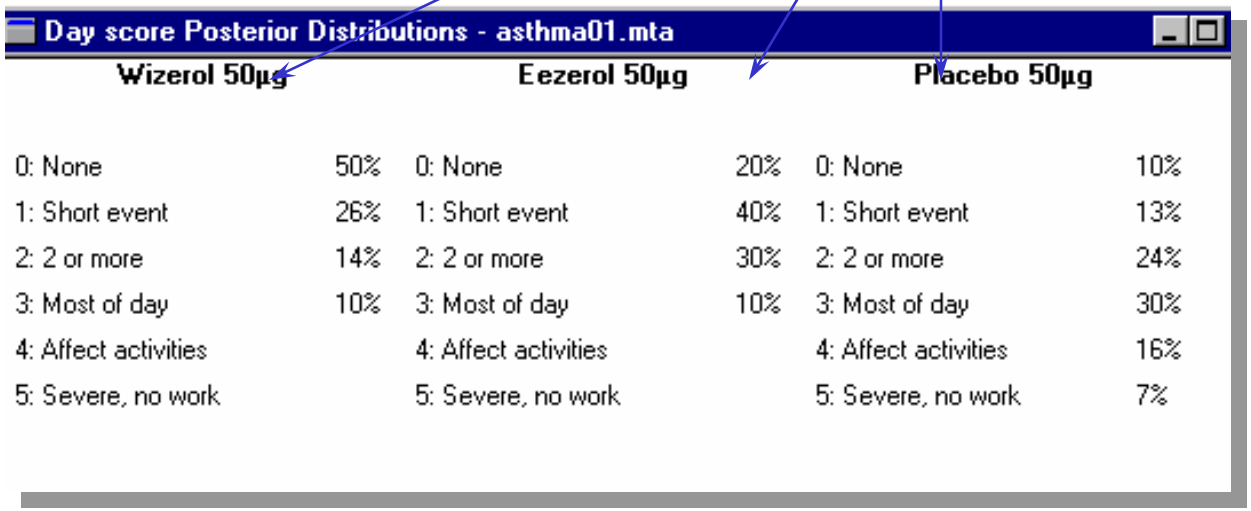


They are adjusted easily by mouse control

The posterior distributions for **heart rate** . . .



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



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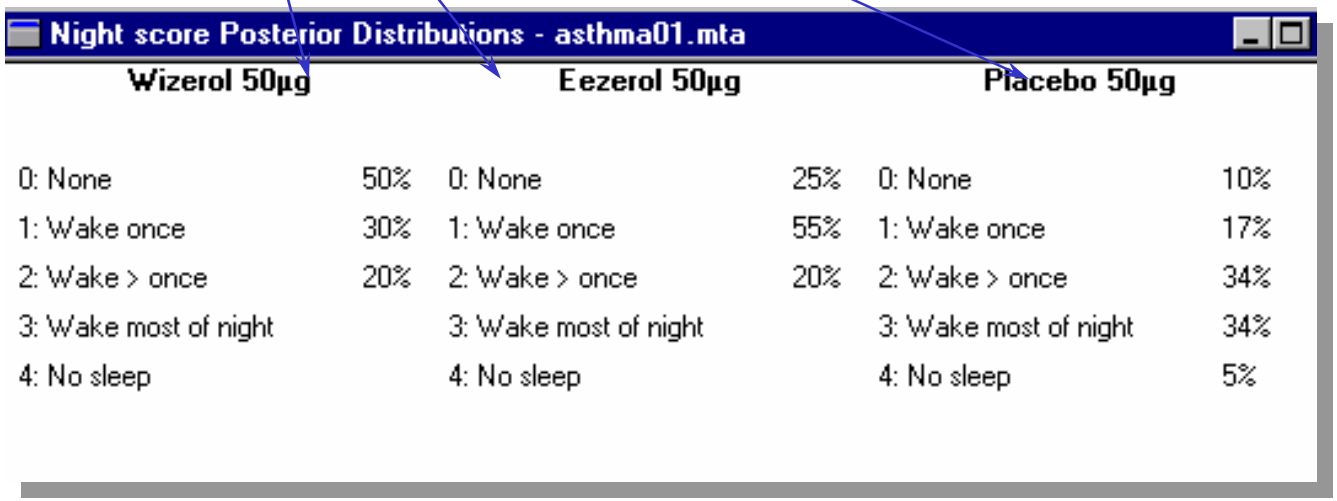
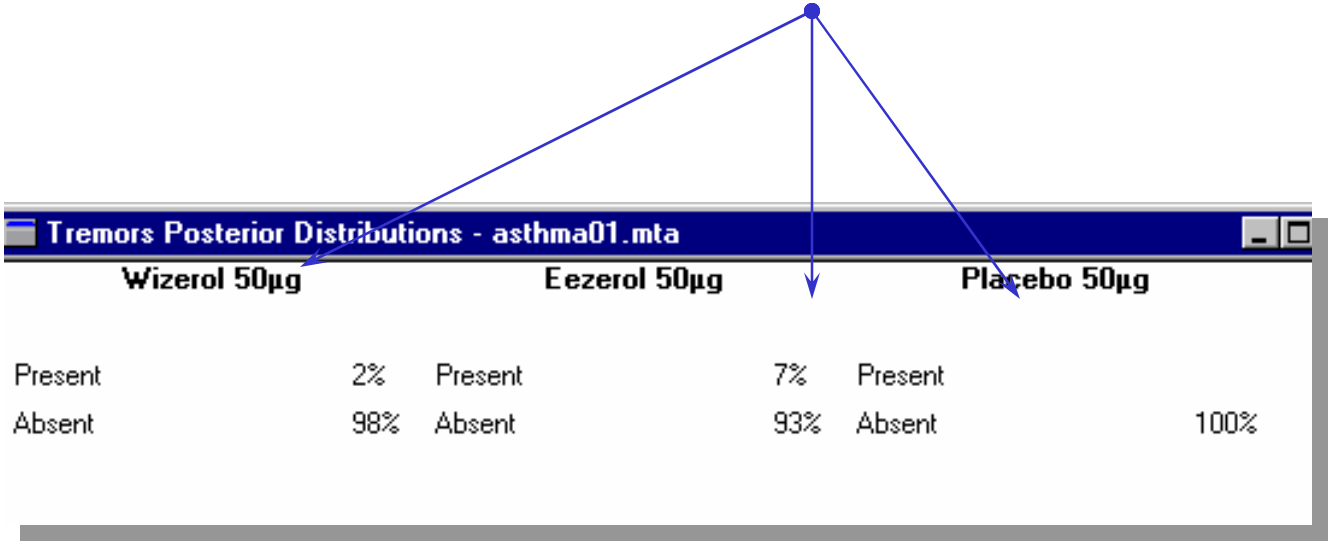
and **night score**

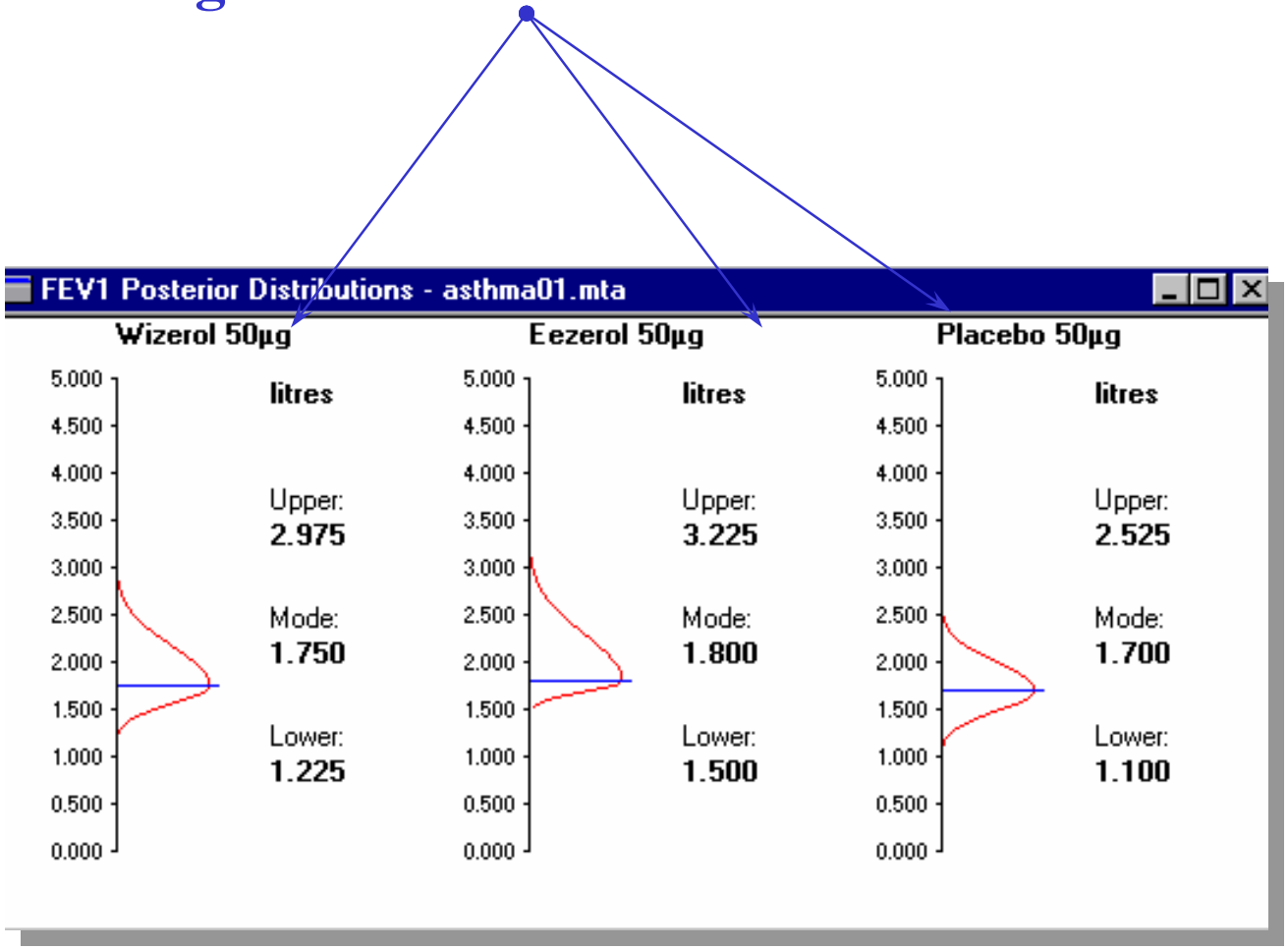


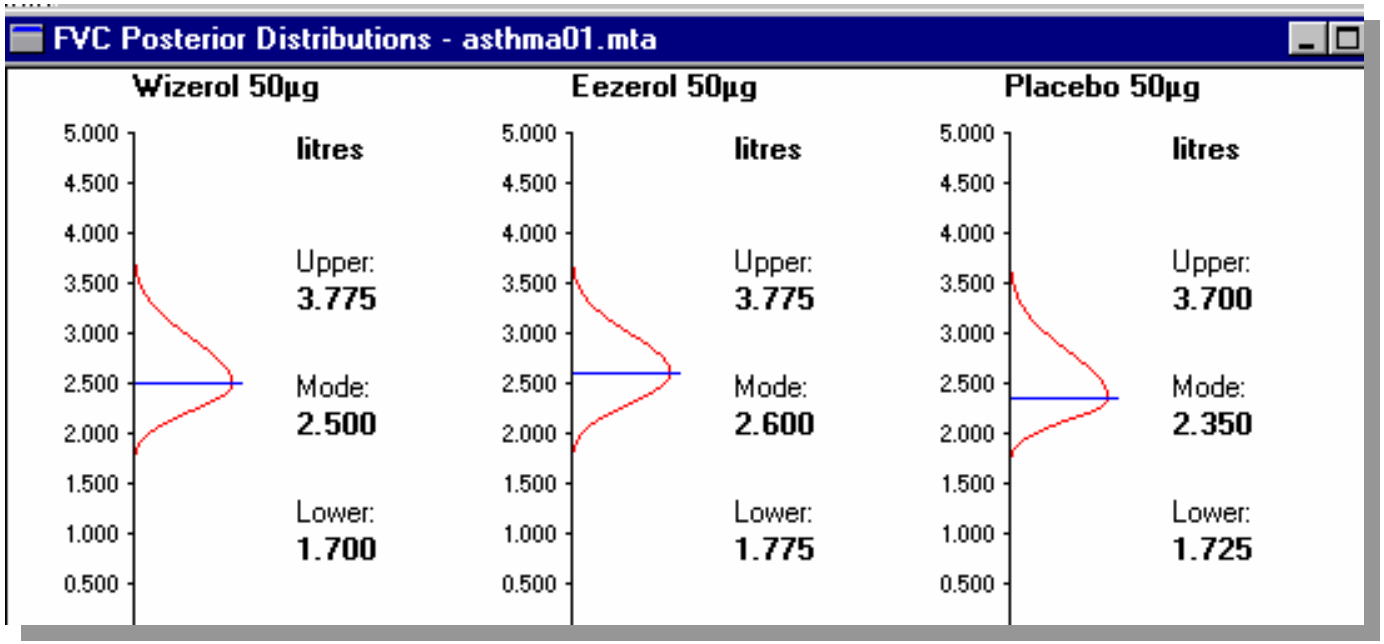
There are small differences between the posterior distributions of the side effect: **tremors**



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**

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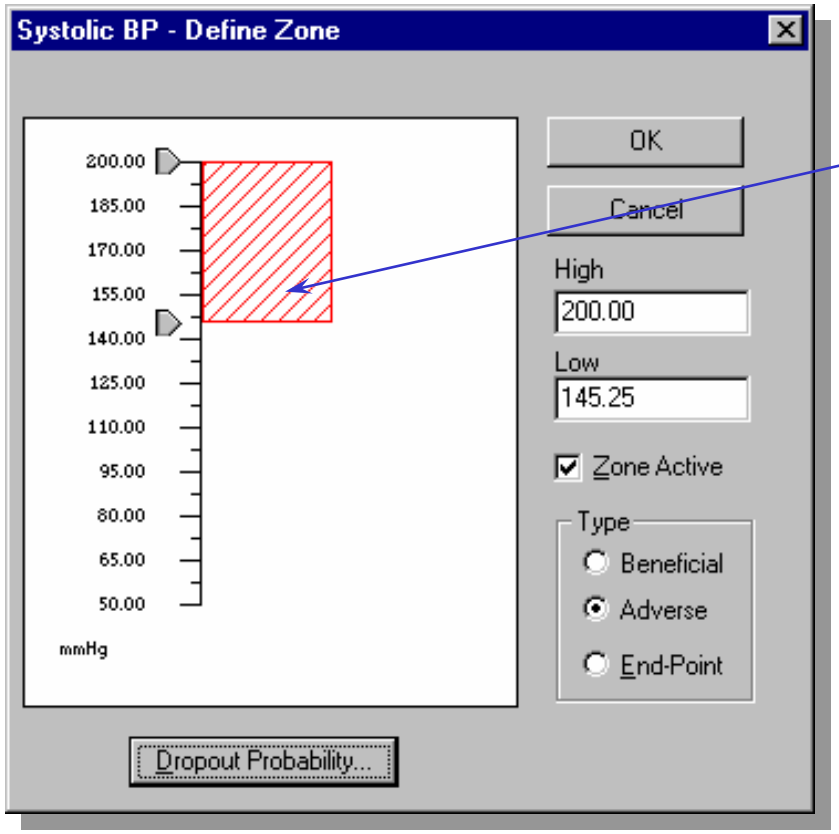
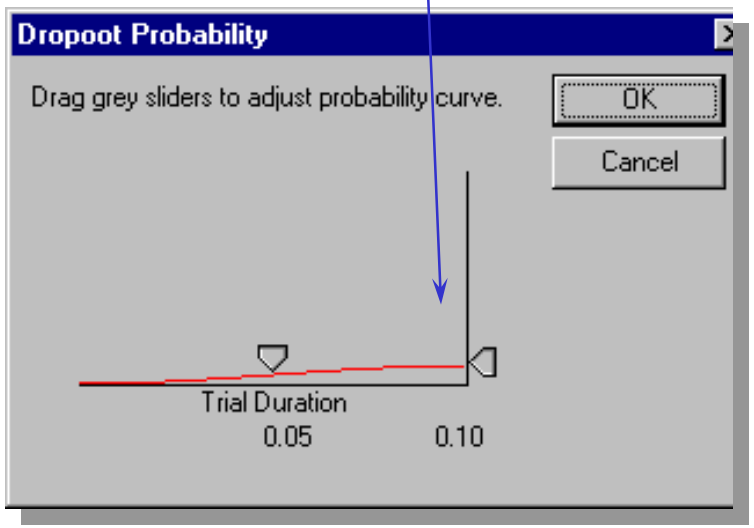
Some patients may drop out because they don't feel well

Such an adverse effect may be high blood pressure

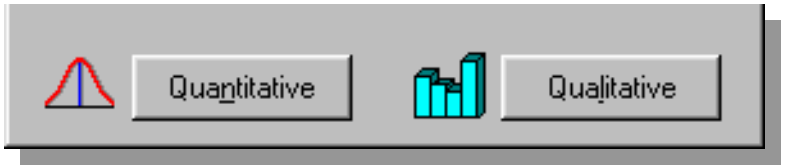
Estimate the probability that they will drop out





Investigation costs

can be entered when distributions are entered

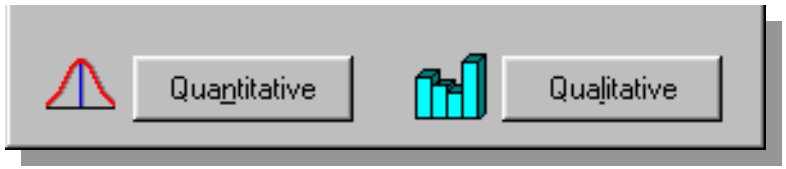


or they can be entered by transfer from the

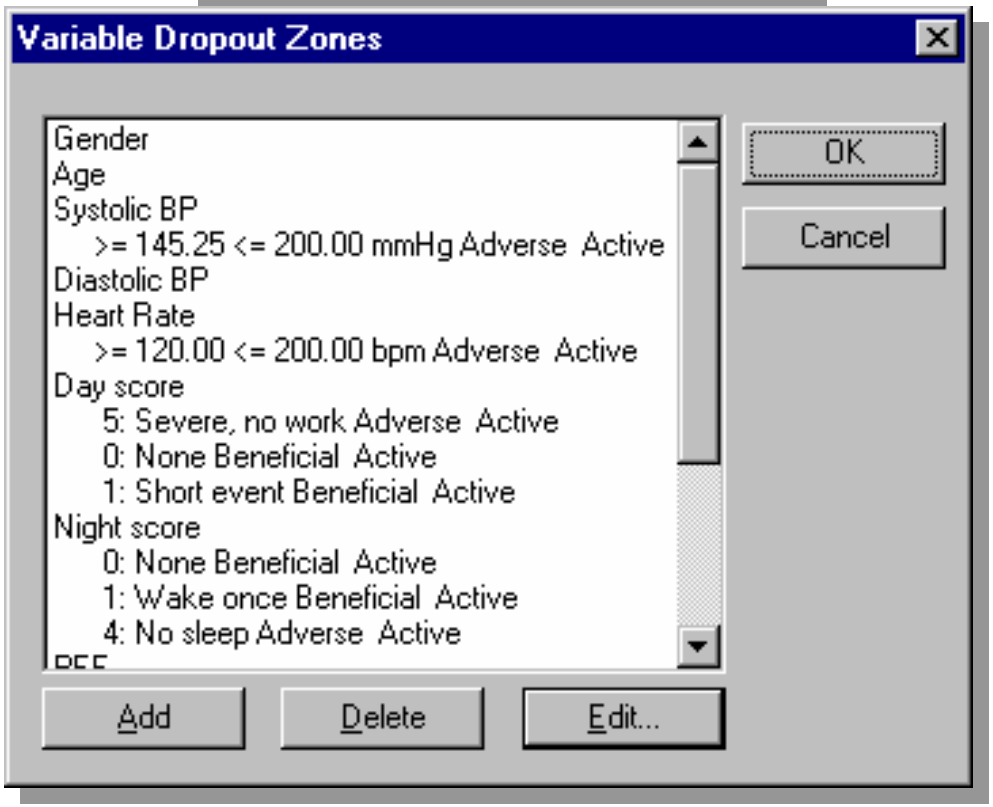
Drop out zones

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

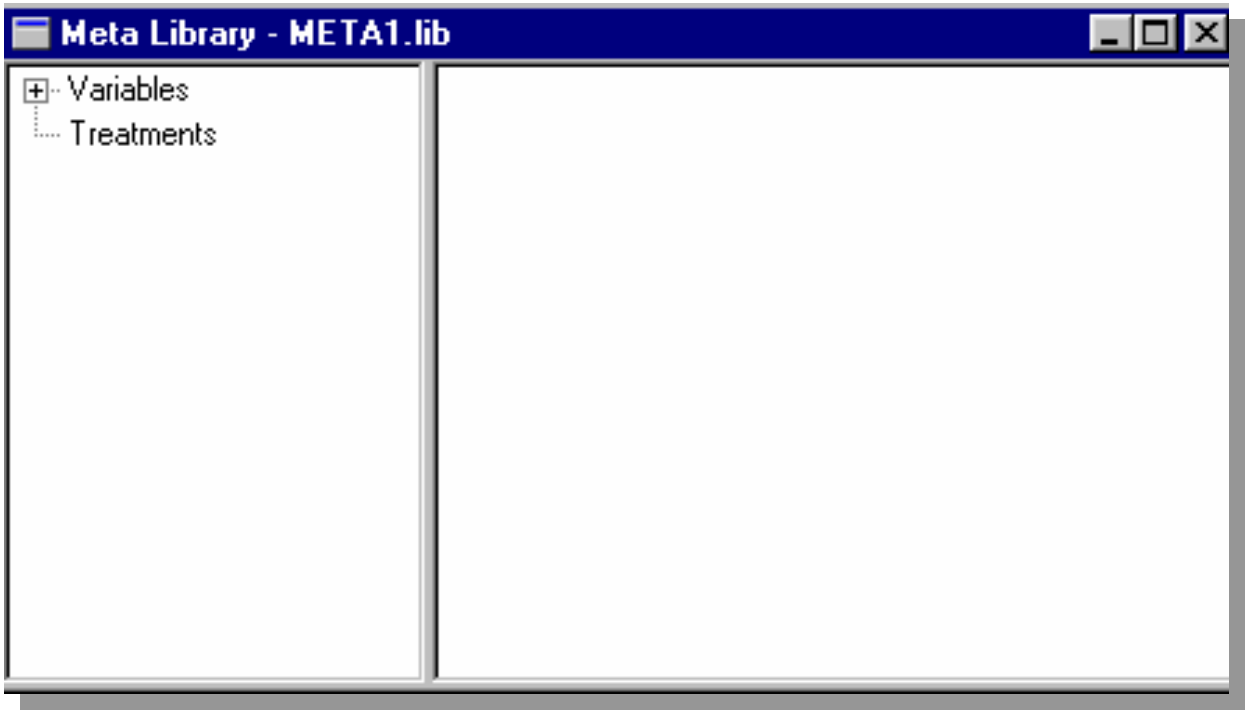
of **treatments**, **distributions**, and **costs**

The first level of categories in the library are

variables

and

treatments

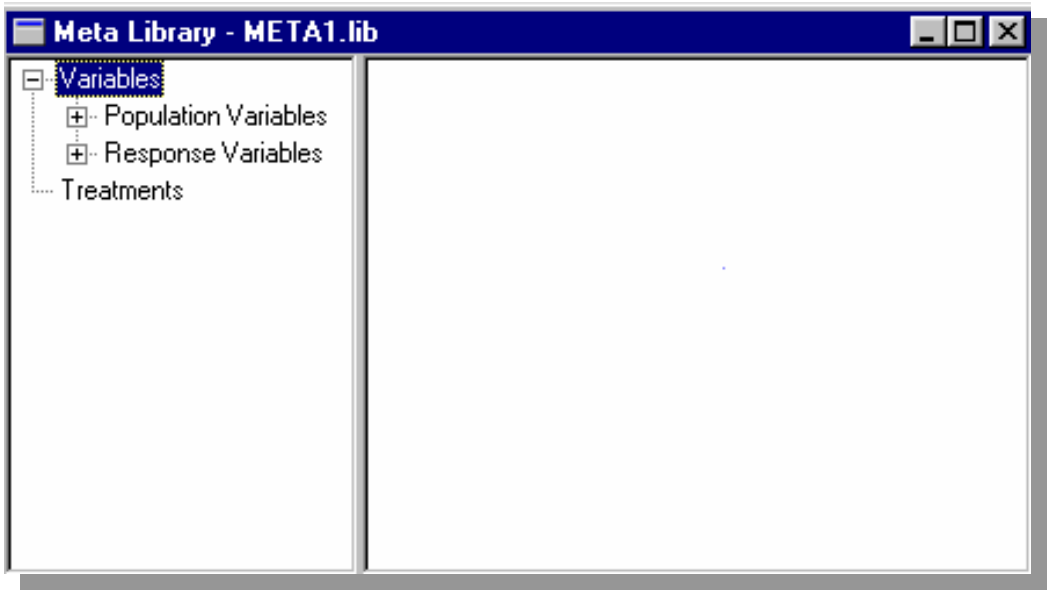


Variables are classed as

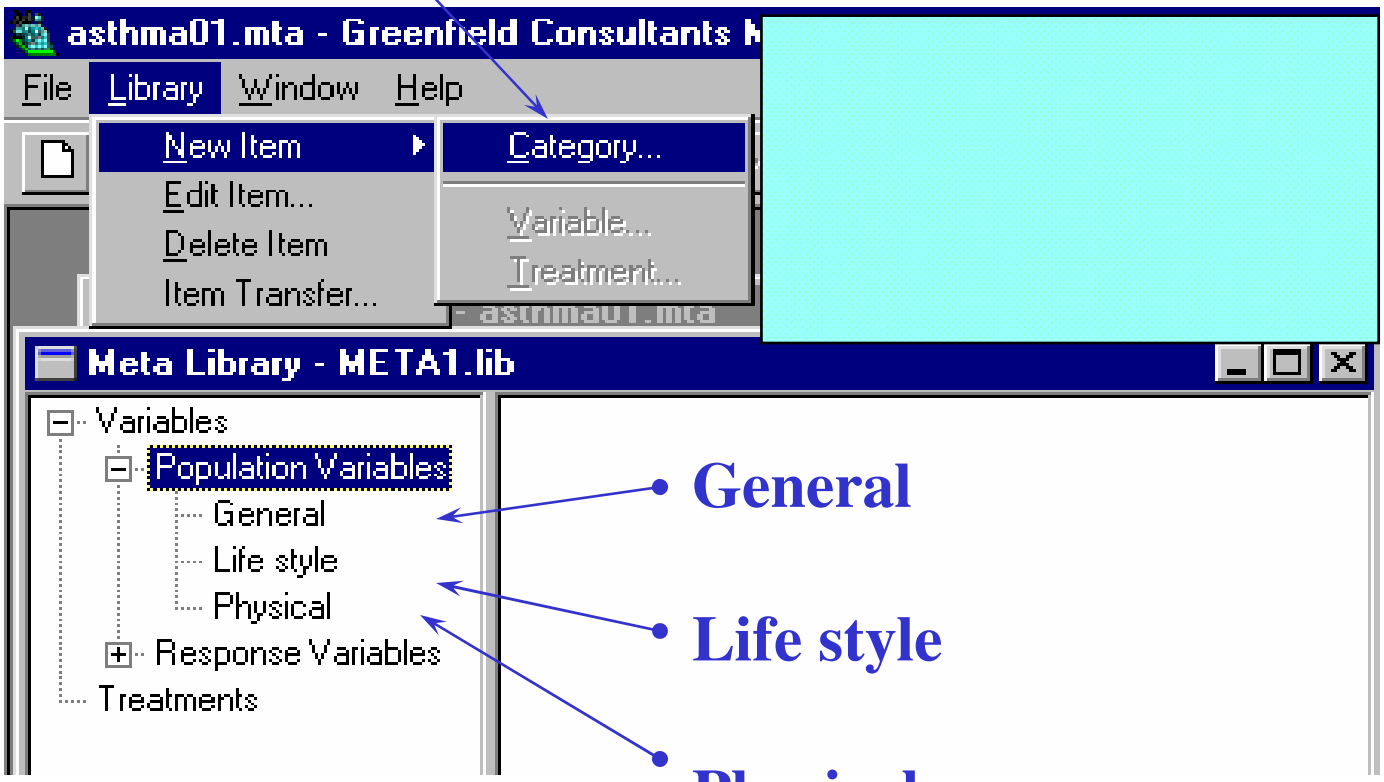
population variables

and

response variables



you can add **categories**



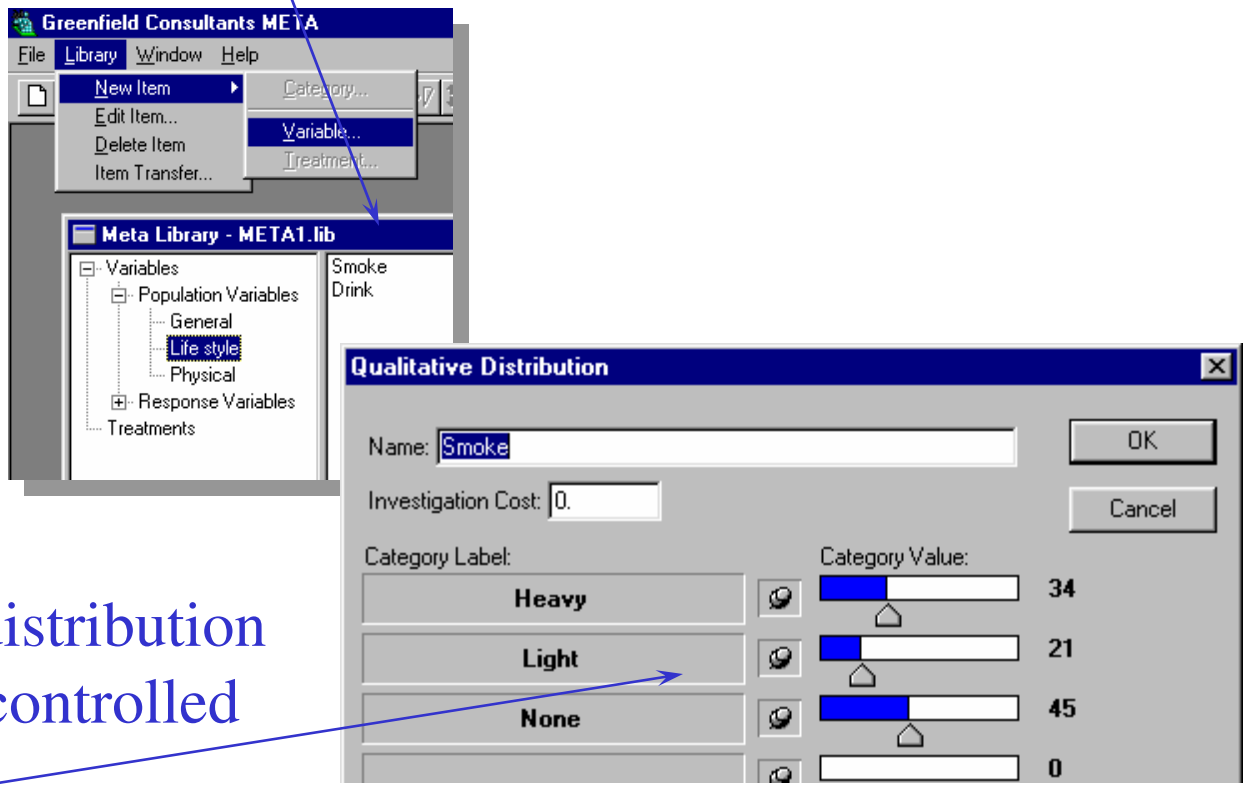
such as

General

Life style

Physical

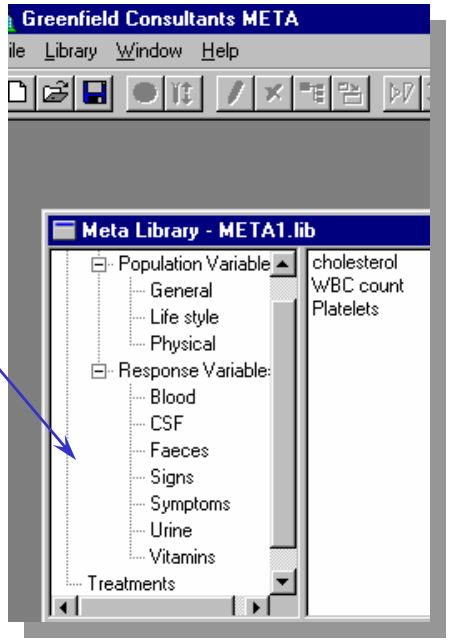
Add a population variable



and enter its distribution using mouse controlled sliders

Create categories of response variables

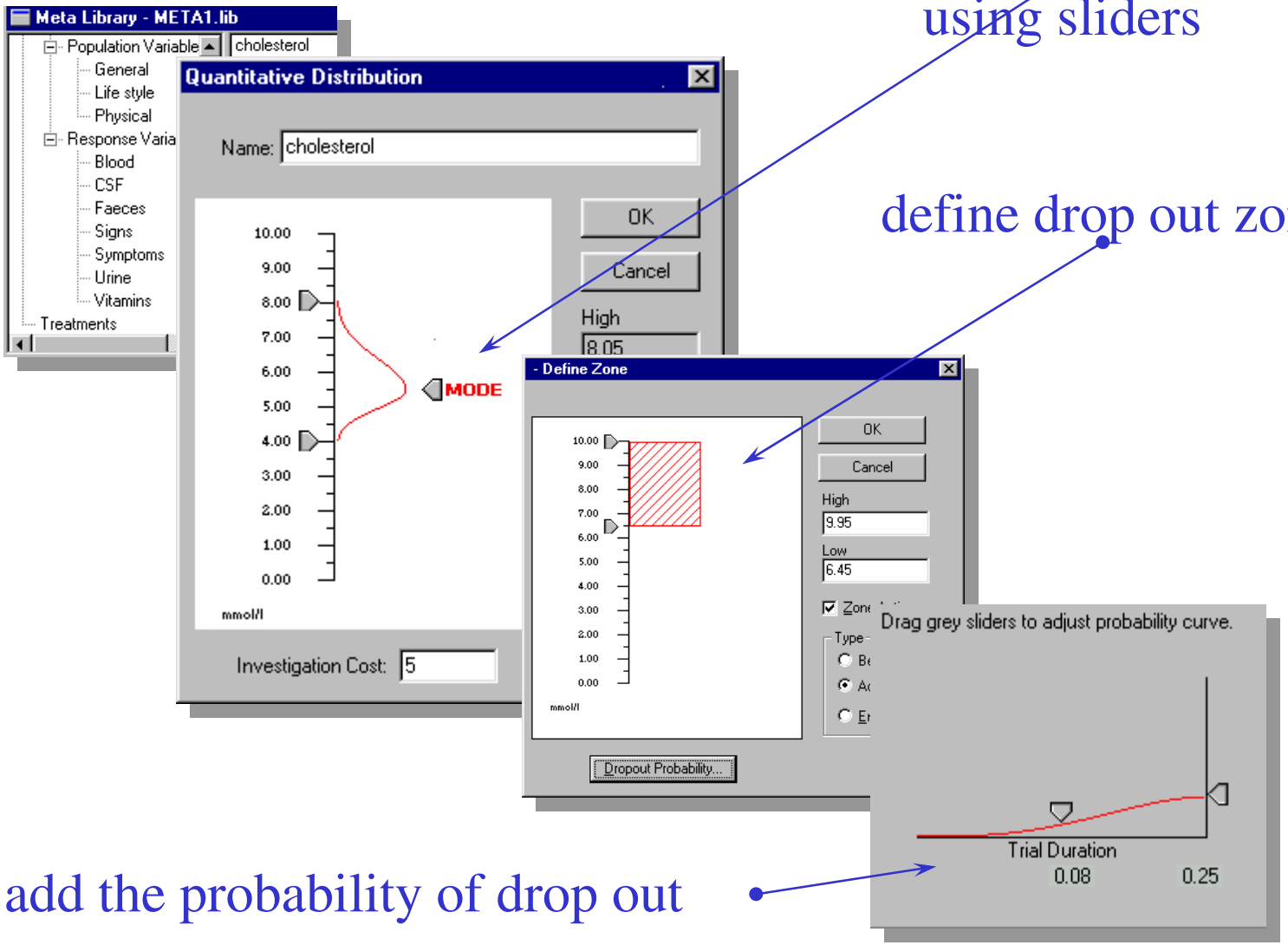
Blood
CSF
Faeces
Signs
Symptoms
Urine
Vitamins



Introduce variables in the category of **blood**

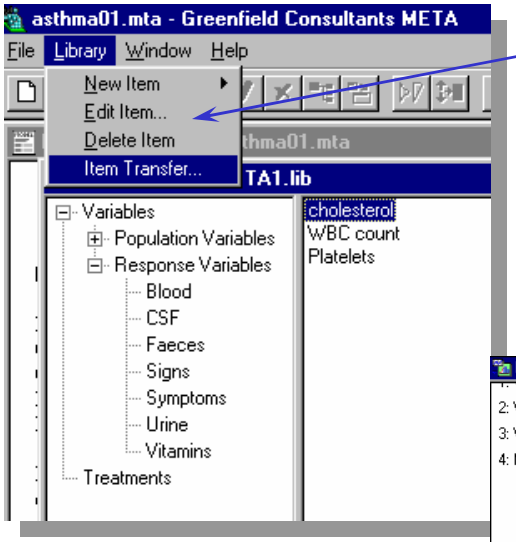
specify the distribution of cholesterol using sliders

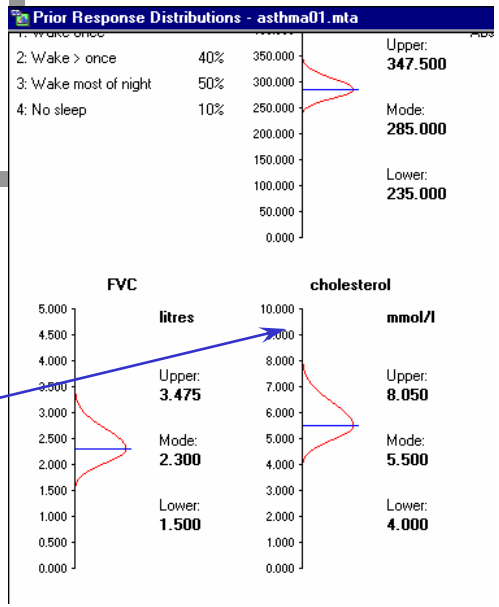
define drop out zones



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