

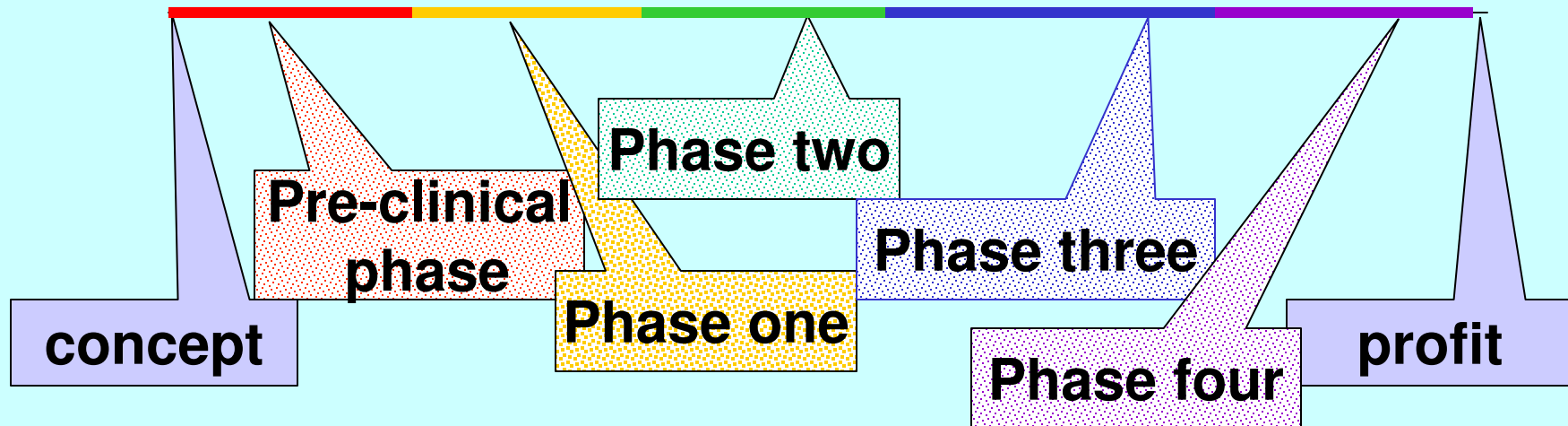
introduction
to
Statistical aspects of

clinical trials

New Clinical Entity (NCE)

In vitro: combinatorial chemistry; pharmacogenetics; effects
Phase one studies: safety, toxicity, drug-drug interactions; identify
Phase two studies: efficacy, dose response, pharmacokinetics, toxicity, drug-drug interactions; identify
Phase three studies: efficacy, dose response, pharmacokinetics, toxicity, drug-drug interactions; identify
Phase four studies: efficacy, dose response, pharmacokinetics, toxicity, drug-drug interactions; identify
surrogate markers.

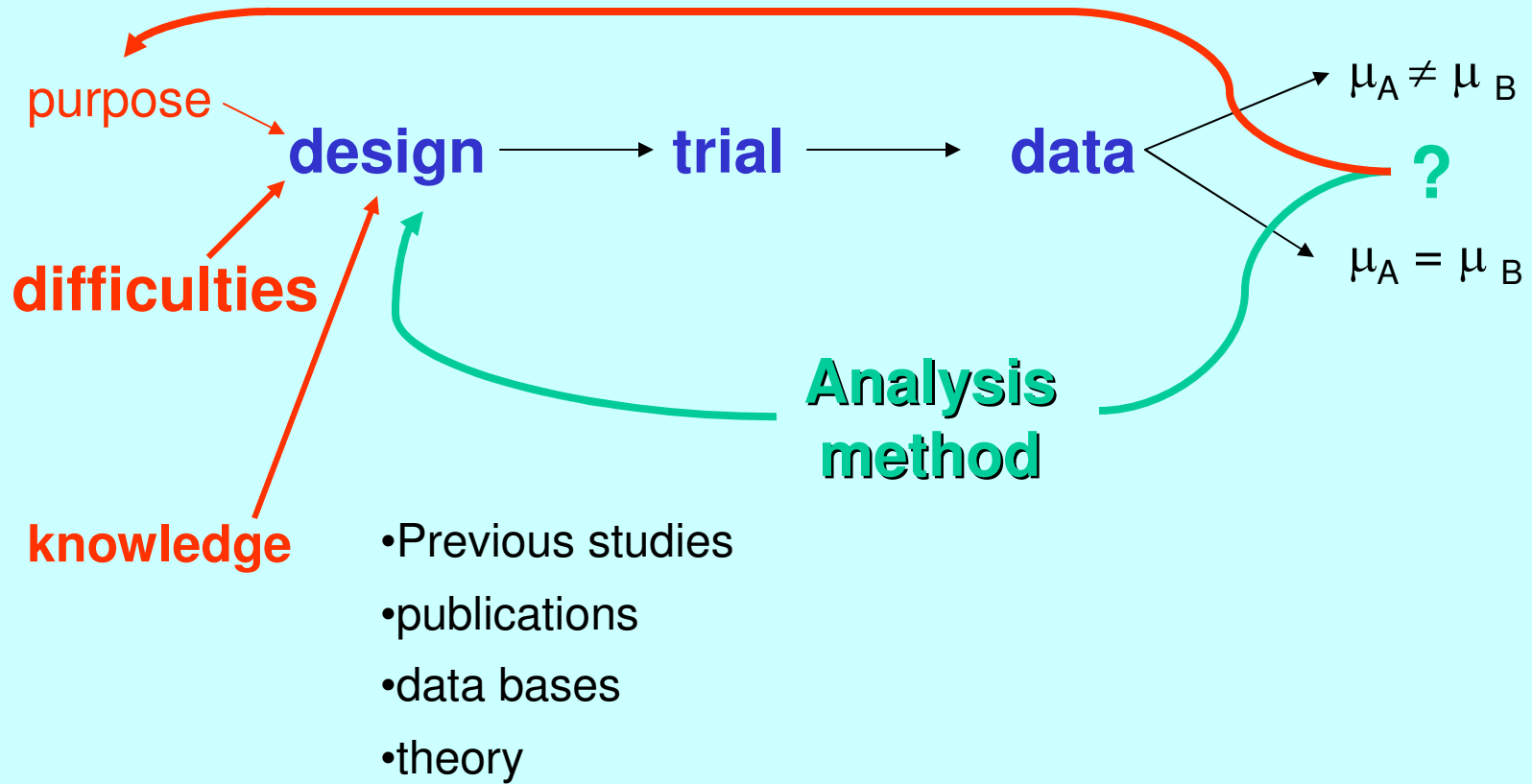
10 to 20 years 



Clinical trials

To determine whether or not there are differences between the effects of treatments

Treatments A and B



Difficulties and ethics:

- Patients
 - availability
 - inclusion and exclusion criteria
 - willingness to participate
 - presentation rates
 - compliance
 - how many?
- Data
 - measures of effects
 - adverse effects
 - influence of other factors
 - random variation of effects between people
 - bias
 - allocation bias
 - assessment bias
 - analysis
- Cost

Assume

everything else controlled except for

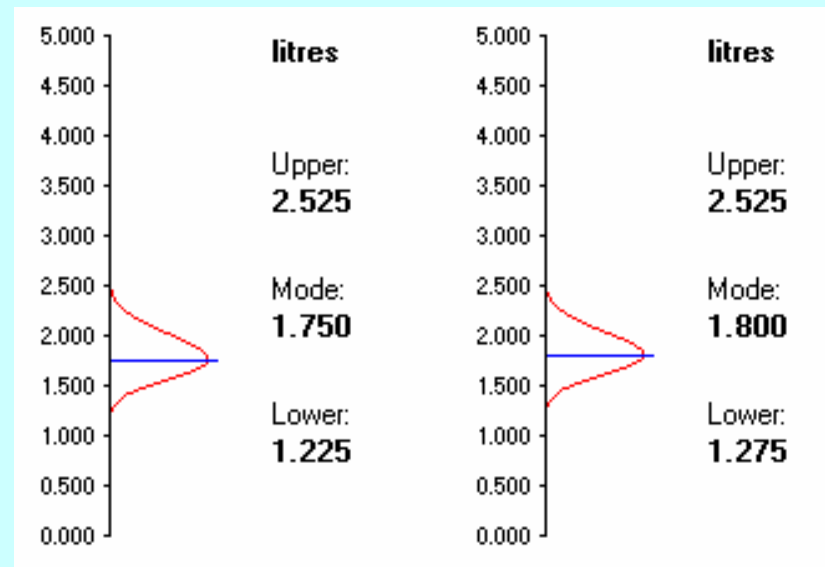
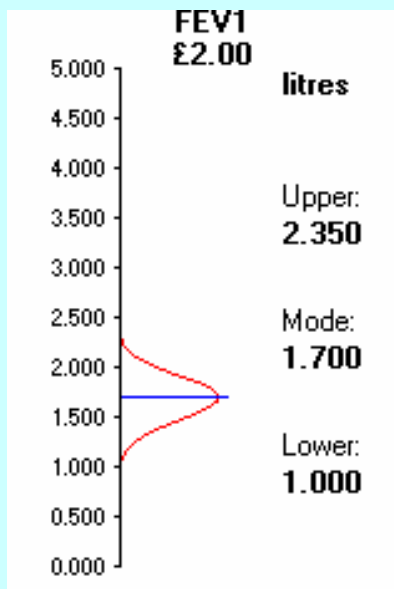
random variation of effects between people

Consider:

- a single continuous quantitative variable and its presentation distribution
- random allocation of patients to two treatments
- posterior (after treatment) distributions:
are they the same or different for the two treatments, as measured by their means and standard deviations?

FEV1:

- prior (presenting) distribution:
 - mean = 1.70
 - sd = 0.30
- posterior (after treatment) distributions:
 - treatment A mean = 1.75
 - treatment B mean = 1.80



Two approaches to analysis:

1. Compare means of the two posterior distributions.
2. Compare the means of the changes for all the patients in the two treatment arms.

Statistical tests are needed for these comparisons

Statistical tests help us to decide how many patients will be needed

Form of a test statistic:

$$\frac{\textit{What you want to test}}{\textit{Variability of what you want to test}}$$

Need to understand:

- Probability distributions, means and standard deviations
- Means and standard deviations of sums of variables
- Sampling distributions of means, standard errors of means
- Central limit theorem

Is treatment A better than treatment B?

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

If treatment A is better than treatment B . . .

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Why did these eight recover?

Were they younger, stronger, or in a better condition than those who did not recover?

If treatment A is better than treatment B . . .

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Why didn't these three recover?

Were they older, more feeble, or in a worse condition than those who did?

Perhaps treatment A is not better than treatment B? So . . .

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Could there have been an allocation bias?

Perhaps treatment A is not better than treatment B? So . . .

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Could there have been an assessment bias?

Perhaps treatment A is not better than treatment B? So . . .

	<i>Treatment A</i>	<i>Treatment B</i>	<i>total</i>
Recovered	17	8	25
No better	3	12	15
total	20	20	40

Could the results have occurred by chance?

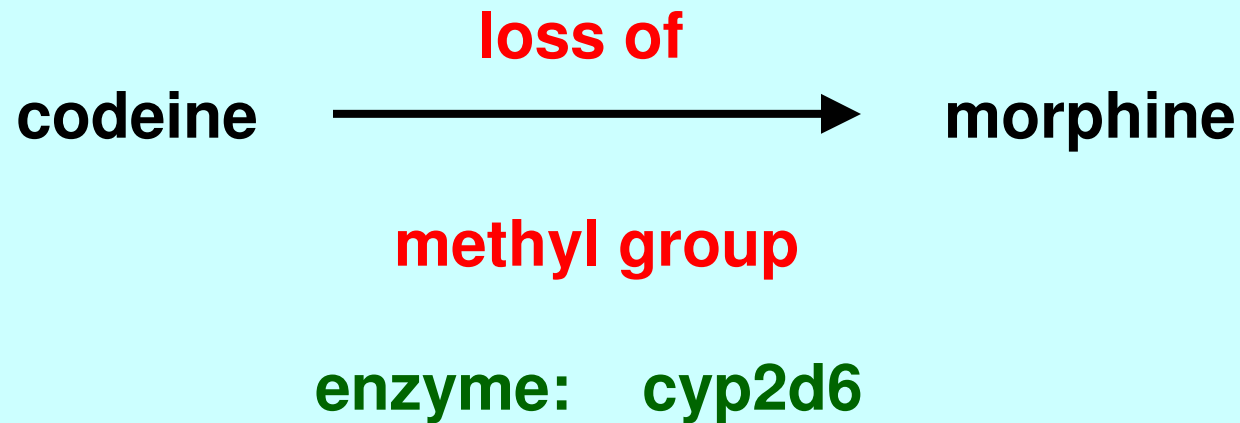
Pharmacogenetics:

How differences in genes can influence responses to drugs

Example of pharmacogenetics

	codeine		placebo	
	<i>Treatment A</i>		<i>Treatment B</i>	<i>total</i>
Recovered	17		8	25
No better	3		12	15
total	20		20	40

Perhaps these 3 cannot respond to codeine



Gene encoding cyp2d6 is on chromosome 22

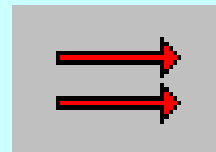
It is altered in ten percent of people

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

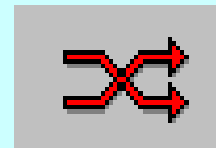
- **response to each treatment**
- **influence of other factors such as age, gender or life style**
- **number of patients**
- **how patients are selected for the trial**
- **how patients are allocated to treatments**
- **type of trial: parallel or crossover**
- **compliance of patients to treatments**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

Type of trial:

- **Parallel**

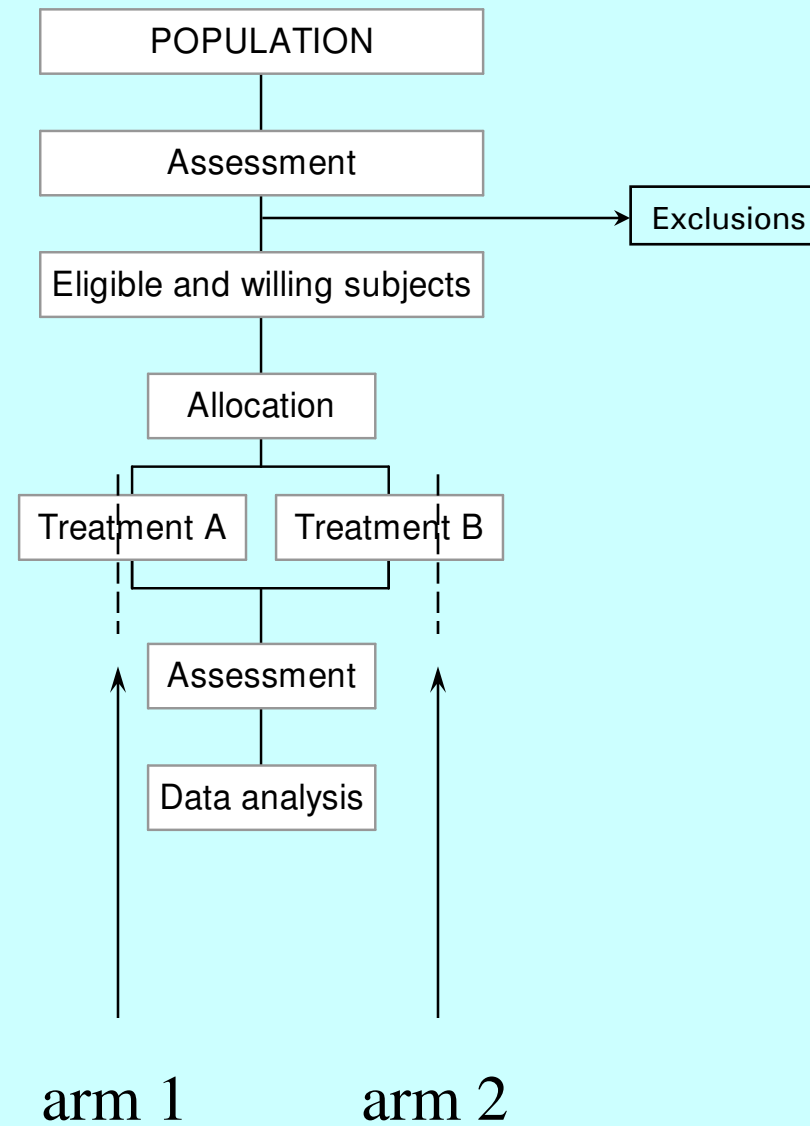
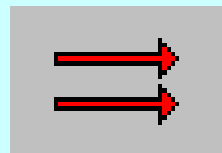


- **Cross-over**

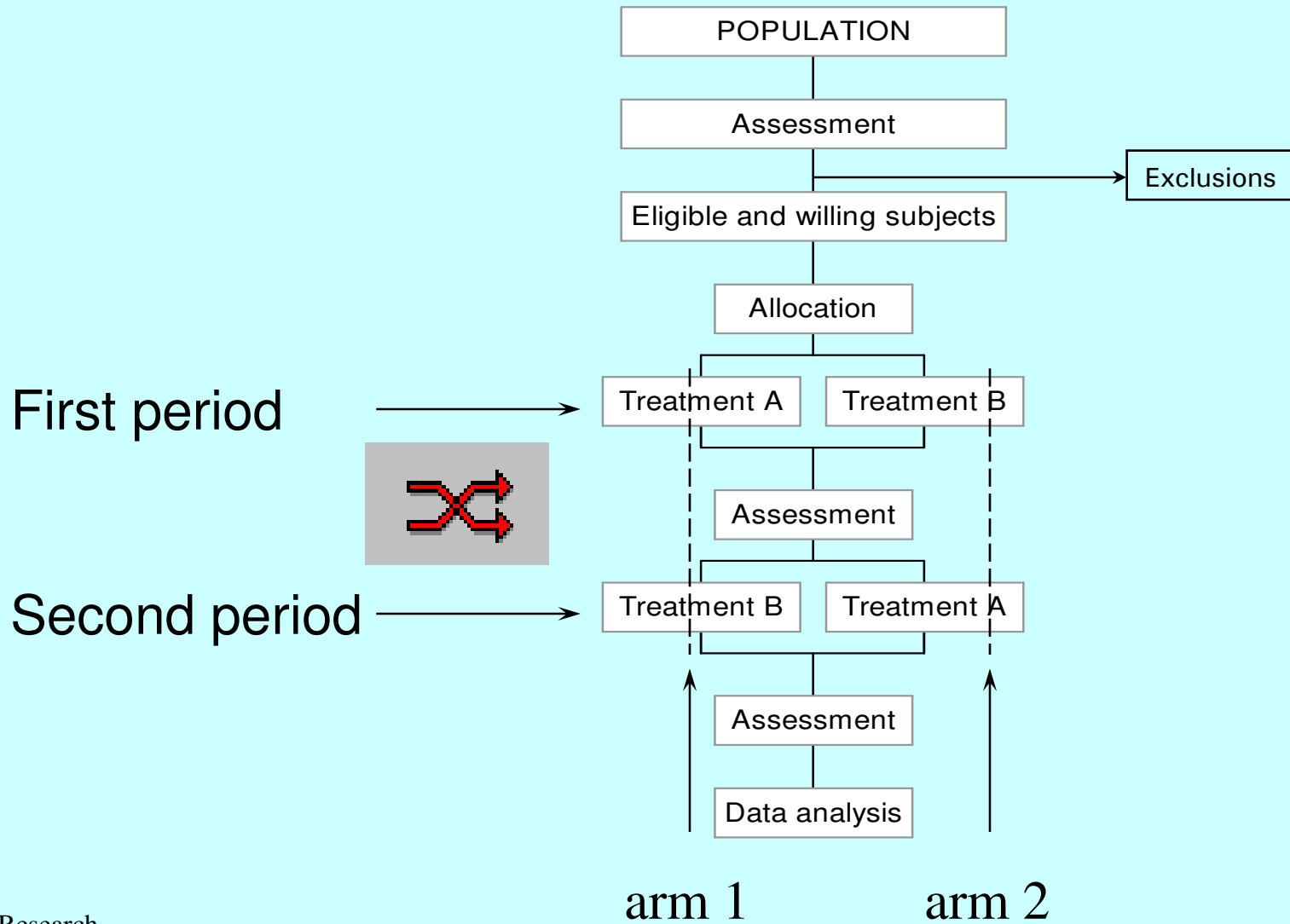


- Sequential
- Group sequential
- Factorial

Parallel Designs



Two-period Cross-over designs



Allocation

Random

- Simple randomisation
- Weighted randomisation
- Block randomisation
- Sequential randomisation

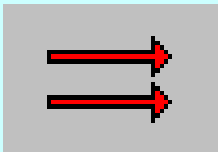
Semi-random

- Minimisation

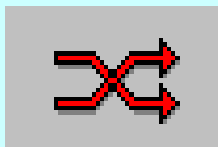
Non-random

- Open

Sample size **number of patients in a trial**



based either on **independent samples t -test**
or on **comparison of proportions**



based either on a **paired t -test**
or on **comparison of paired proportions**

Sample size

number of patients in a trial

alpha value: probability of a type one error :
of rejecting the null hypothesis
when it is actually true **0.05 or 0.01**

power: probability **(80% or 90%)** of getting
a statistically significant difference
if the true difference between treatments
is of a given size
(clinically significant difference)

adjust for expected *dropouts*

Exclusions:

patients presenting with the condition being studied must be assessed for suitable inclusion:

they may be excluded if, for example:

- over-weight
- over or under age
- pregnant
- exhibiting what may be an adverse response
- on interacting medication

Exclusion must be decided *before* allocation to treatment

Intention to treat

After a patient has been entered into a trial,
after allocation to treatment,
that patient's data **must** be included in the analysis
even if the patient has dropped out of the trial
before completion of treatment
or if there are any missing values.

If 'intention to treat' analysis is being applied,
missing values of a variable after drop out
will be replaced by the last values recorded.

