Trials: clinical, controlled, randomised

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Agenda for today

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What is a clinical trial?

Why is randomisation so important?

How do we analyse clinical trials?

What are key ethical issues in clinical trials?

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A clinical trial is a

scientific way of testing a clinical question

Clinical trials are set up to test the benefit of a new treatment.

Phase I	**studies of tolerability and toxicity**
Phase II	**studies of efficacy**
Phase III	**comparison of a new treatment against the standard treatment**
Phase IV	**post marketing surveillance; adverse reactions; long term effects**

May want to assess:

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Treatments

Supportive care

Devices

Screening programmes

Information

Diagnostic tests

Biomarkers

Need to compare with control group

Lessons from history

1. James Lind & Scurvy:

In 1747 he took 12 patients with scurvy and split them into 6 groups of 2 patients:

Cyder, Elixer Vitriol, Vinegar, Sea Water, Oranges & Lemons and Nutmeg.

“Their cases were as similar as I could have them…….....
They lay together in one place……..and I had one diet common to them all……..”

“ ….the most sudden and visible good effects were perceived from the oranges & lemons”.

Lessons from history

2. Gold Therapy for Tuberculosis – popular in 1920s and 30s

Peters & Short (1935) found that controls had better improvement.

	Treated	Historical control
	1930-1934	1925-1929
Number	492	490
% improved	27%	36%

"The examination of our statistics has been a painful shock, we were convinced treatment was valuable; many of the cases did extremely well. But one tends to forget many cases previously did extremely well……..".

Lessons from history

3. Natural history of disease and vaccine therapy

Vaccine therapy was a popular form of treatment in early 1900's for many chronic inflammatory disease.

However controlled trials were unable to demonstrate vaccine was better than placebo; e.g. rheumatoid arthritis, Sidel & Adams (1940)

Treatment	No.	% improved
Vaccine	25	68
Saline	33	72

Lessons from history

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- Collect data – don't just rely on anecdotal evidence

- The need for controls
  - -Natural history of disease
  - -Placebo effect

- Avoid bias – groups should be comparable except for the treatment

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Fundamental principles in comparing treatment groups

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•Differences in outcomes between treatment groups may be due to:

-Treatment effect

-Bias

-Chance

•Groups must be alike in all important aspects except for the treatments under evaluation (possible bias)

•Large enough sample (limit chance imbalances)

The best way to create a CONTROL group similar to the TREATMENT group in all respects (known and unknown):

Randomisation

Randomised Clinical Trials

Therapies allocated by a chance mechanism

Neither patient nor physician know in advance which therapy will be assigned

Advantages

1. Eliminate selection bias
2. Balance prognostic factors
3. Validity of statistical tests

Neural Tube Defects
Peri-Conceptual Multivitamin Treatment

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RESULTS FROM TWO TRIALS

	Multi-vitamin	Control
Total number of births	**397**	**493**
Number of neural defects	**3**	**23**
% with neural tube defects	**0.8%**	**4.7%**

P<0.0003; one-sided test.

Note: control group included more women from high risk areas and women who had opted not to have the vitamins.

Dilemma

- The poor design of the study meant that the results were difficult to interpret
- Comparisons of this kind can lead to proven to belief in unproven treatments
- Difficult to repeat trial

Sir Austin Bradford Hill, 1948, 1st properly designed RCT assessing streptomycin for tuberculosis in 107 patients.

S= streptomycin+bed-rest vs C=bed-rest alone

	S	C	
No.Patients	55	52	
X-ray improvement	28 (51%)	4 (8%)	P<0.001
Deaths	4 (7%)	14 (27%)	P<0.001

Definitions:

- A controlled clinical trial is a prospective study comparing effect(s) and value of an intervention against a control in human subjects
- A randomised clinical trial (RCT) is a controlled clinical trial where the therapies are allocated by a chance mechanism
- An uncontrolled clinical trial involves no control group

Classifying clinical trials by design

- Uncontrolled
- Historical controls
- Current non-randomised controlled
- Randomised controlled

Improved Design Reduces bias

Concept of statistical inference

Analysed data are results in a selected sample. We use these results to infer how all the population would behave.

Pop.	⟶	Protocol Trt patients	⟶	Observed Results	⟶	extrapolate

Estimate treatment effect (beware bias).
Variability of estimate due to sampling from population.
Goal: control bias and reduce variability.

Random allocation

We want groups to differ only in treatment they receive

Random allocation

- gives equal chance of receiving each treatment
- in long run leads to groups that are likely to be similar in characteristics *by chance*
- reduces selection bias if patients enter trial before randomisation
- is used in other experimental settings

The placebo effect

"Even if the therapy is irrelevant to the patient's condition, the patient's attitude to his or her illness, and indeed the illness itself, may be improved by ***a feeling that something is being done about it****"*

Source: Pocock SJ. *Clinical Trials. A Practical Approach.* Chichester: John Wiley and Sons, 1983

Comparing with ‘no treatment’

A difference between

- ‘new treatment’ group and
- ‘no treatment’ group

could be due to

- true treatment effect
- placebo effect as one group is receiving care

Blinding 'strengthens' randomisation

'Blind' trials

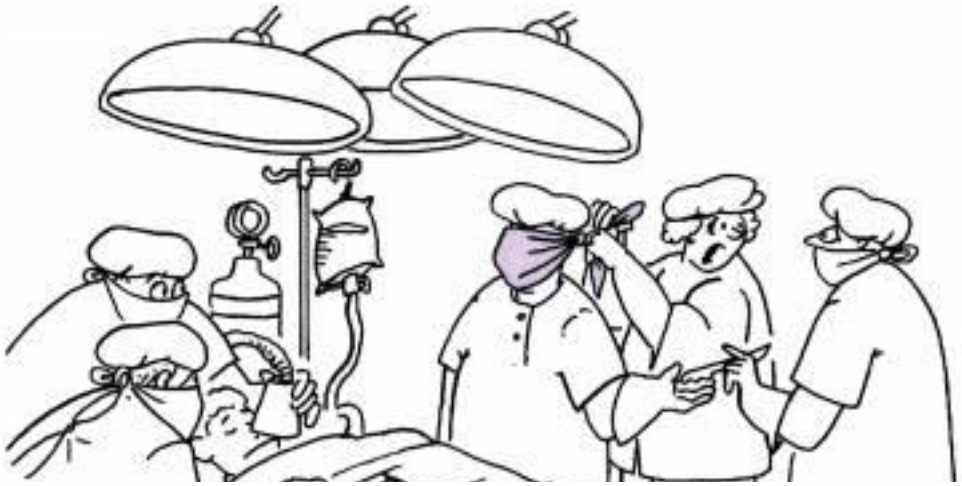
- Single blind – one of patient, clinician, assessor does not know the treatment allocation *(usually patient)*
- Double blind – two or more of patient, clinician, assessor does not know the treatment allocation *(usually patient + clinician/assessor)*

Aims to remove differential placebo effect that could bias comparison between treatments

Example of Blinding

- make treatments appear identical in taste, appearance, texture, dosage regime etc.
- Compare active drug with a ***placebo***

  (inert substance identical in appearance, taste, texture etc.)
- Use a designated pharmacy to label identical containers with code numbers



Are you sure this is what's meant by a double-blind trial?

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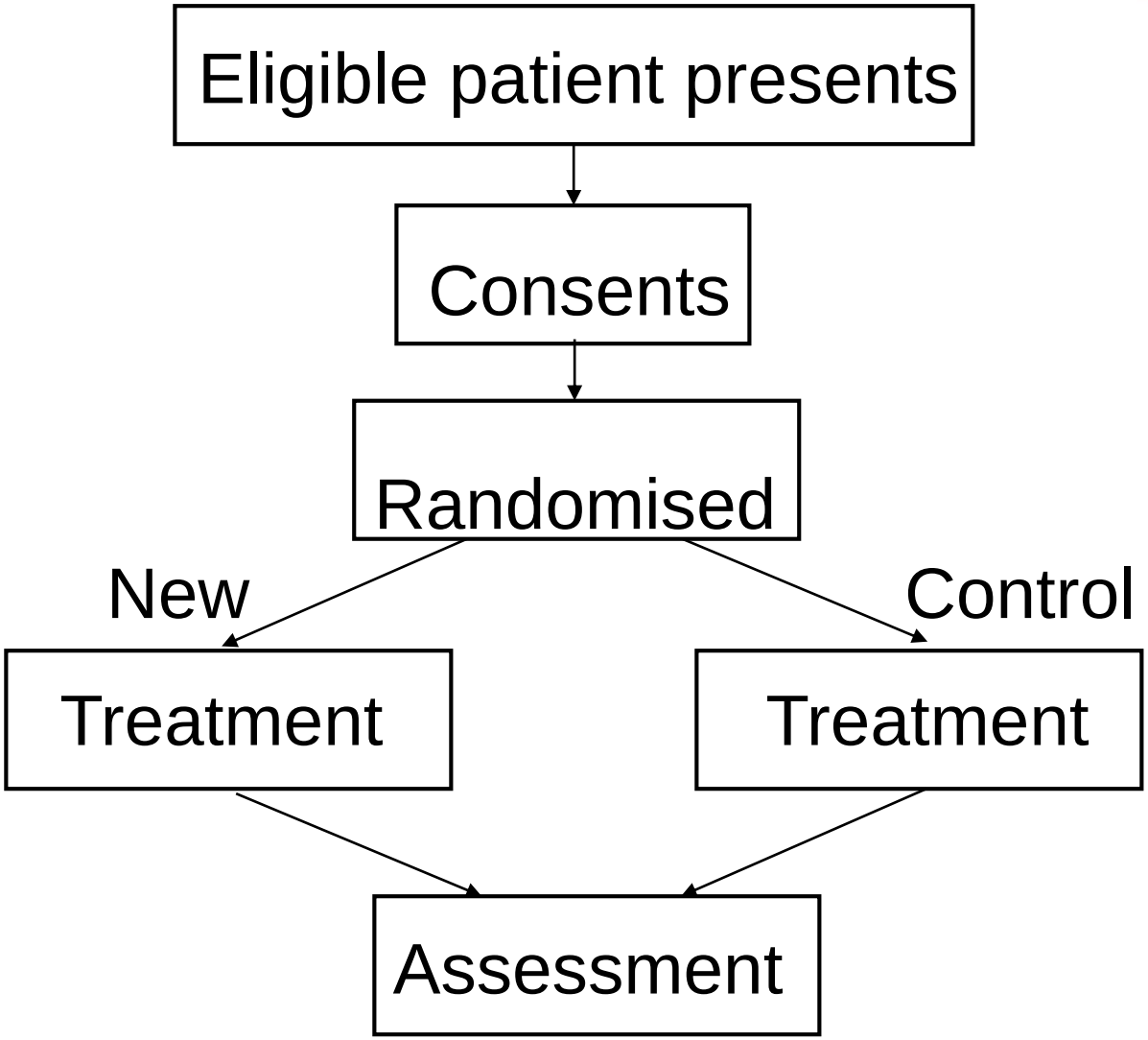
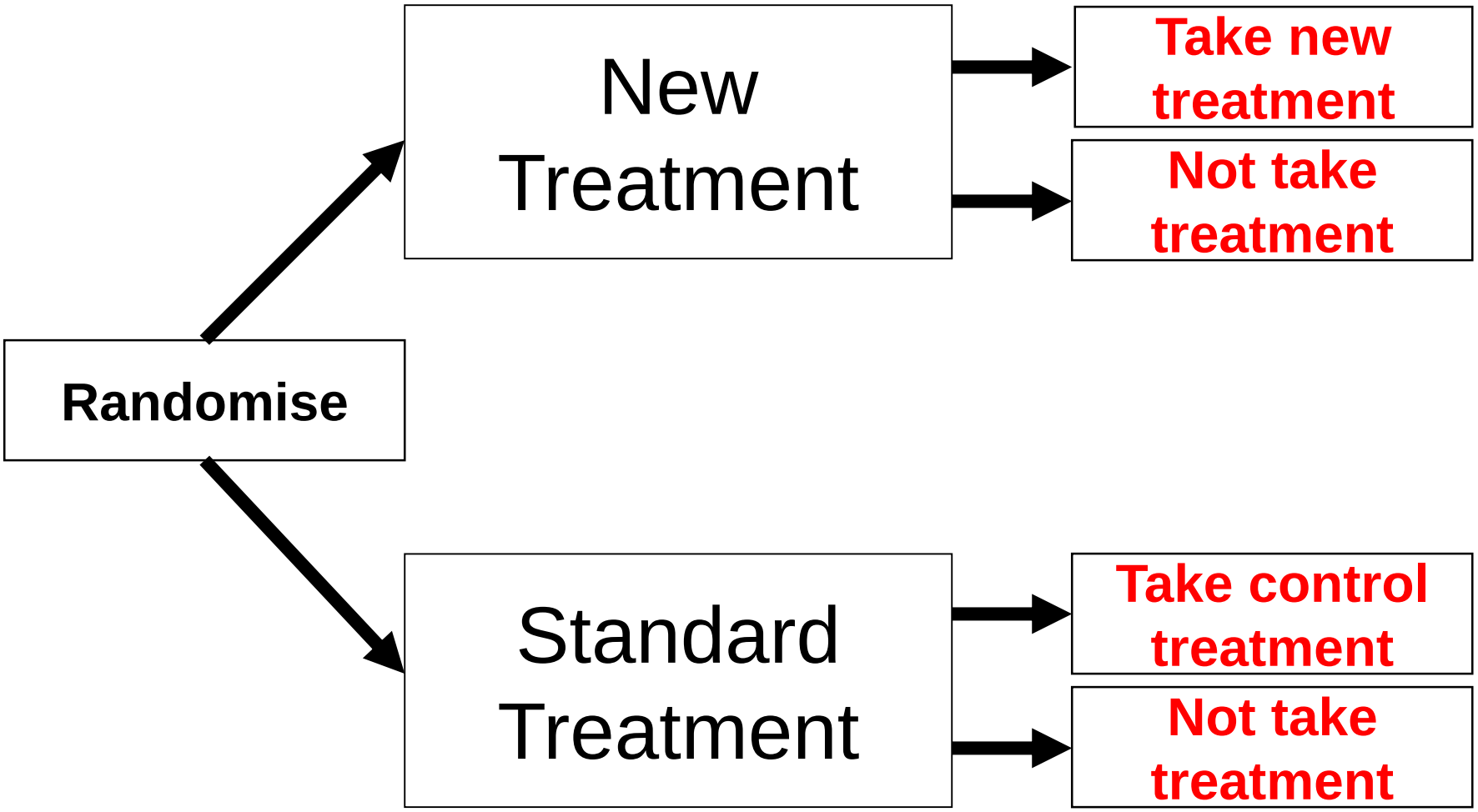
Conduct of the trial



Clinical Trial



Is the ‘new treatment’ better than the ‘standard’?

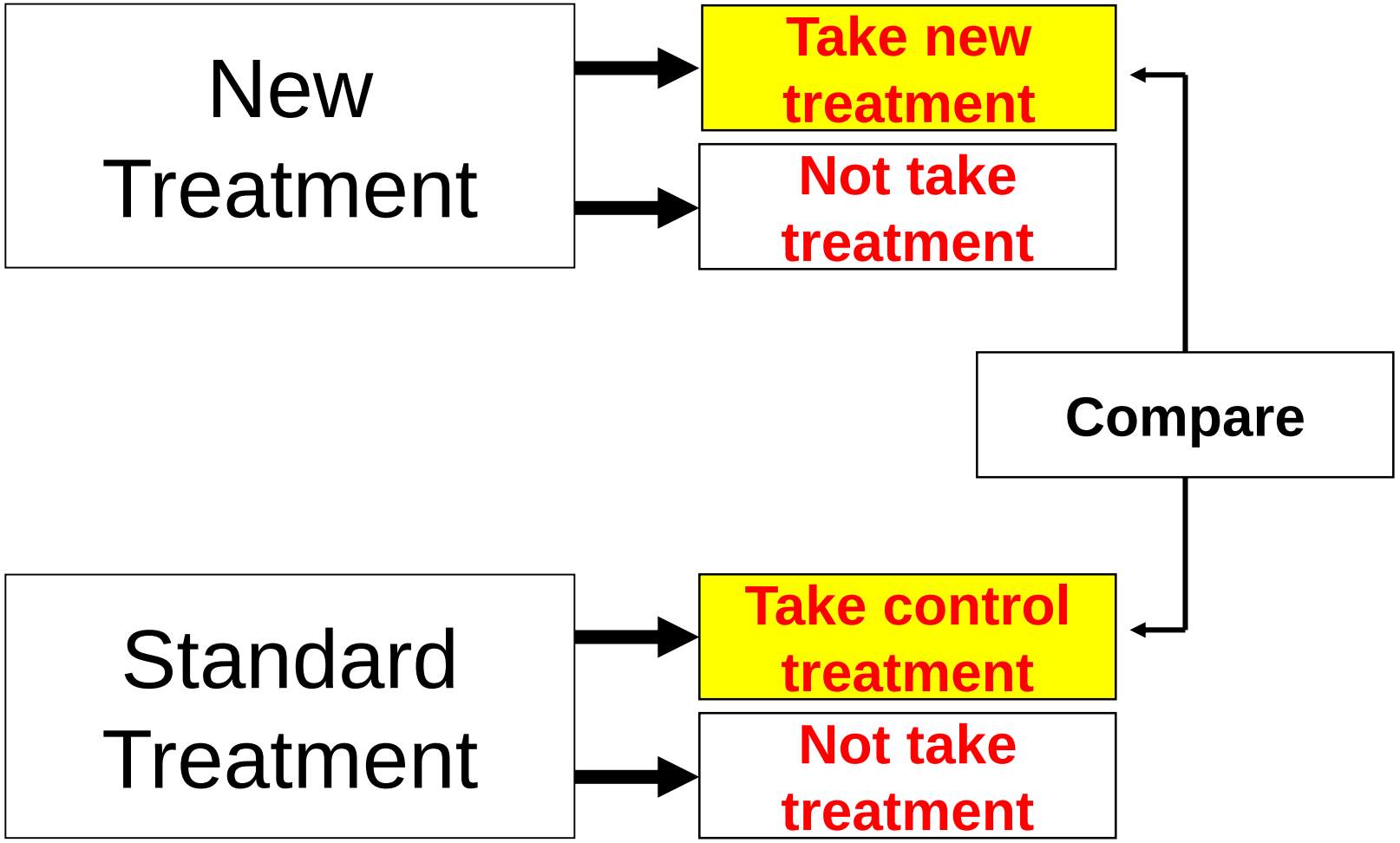
Two different interpretations:

- Is the ***physiological action*** of the new treatment better than the standard treatment?

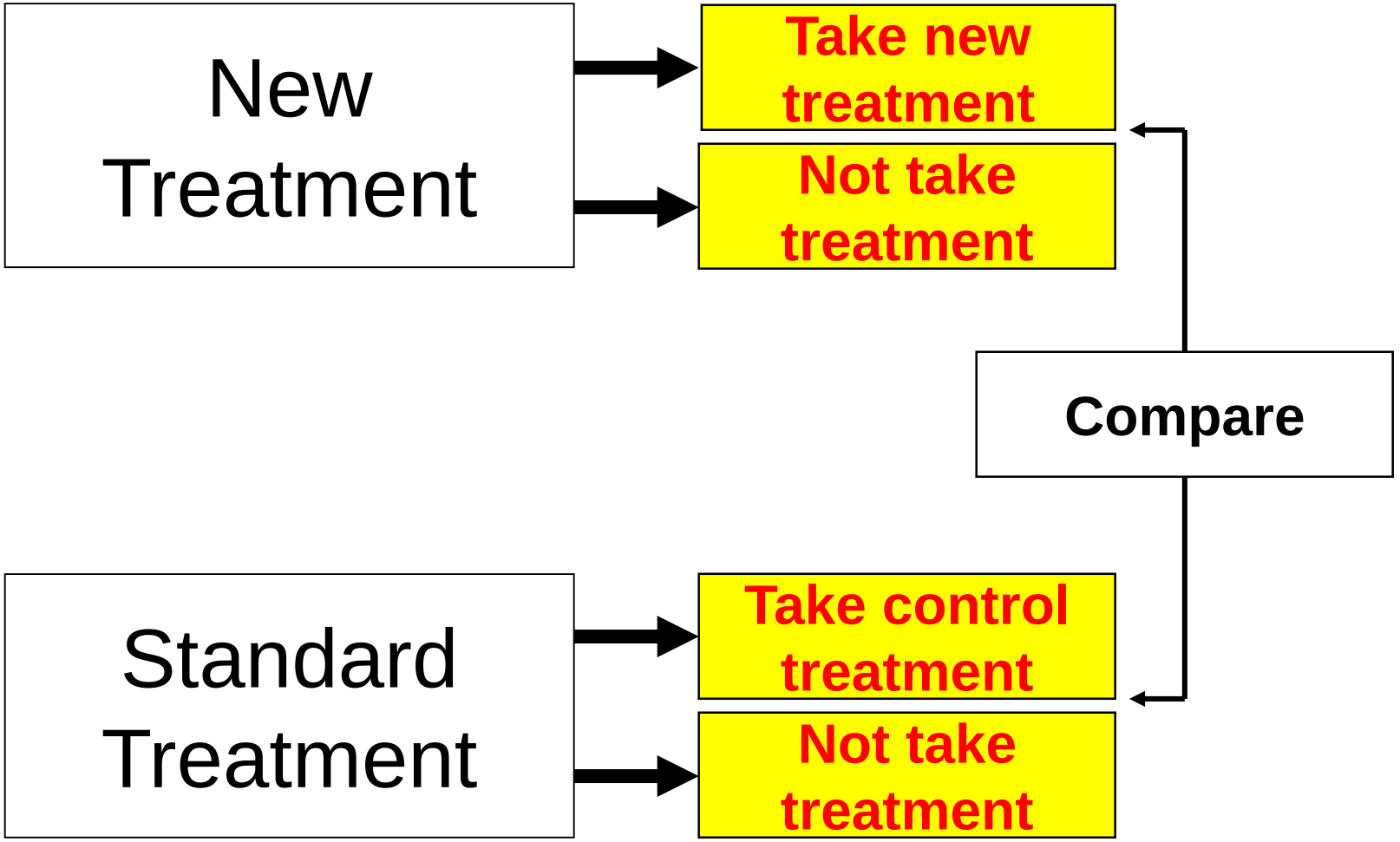
  OR

- Is the new treatment better than the standard treatment ***in routine clinical practice***?

Explanatory trial:
'As-treated' analysis



Pragmatic trial:
'Intention-to-treat' analysis



‘As-Treated’ vs. ‘Intention-to-Treat’

- ‘As-Treated’ analyses tend to give larger sizes of effect
- ‘Intention-to-Treat’ analyses tend to give smaller effect sizes and reflect effect in clinical practice

Definitive clinical trials should normally be analysed on an ‘Intention-to-Treat’ basis

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Ethical dilemma

Clinician should provide best treatment for each individual patient

Scientific integrity requires treatment chosen randomly

Can these requirements be reconciled?

Clinical Equipoise

Clinical equipoise: reasonable uncertainty about which treatment (including non-treatment) is better

Randomisation does not deny any patient the best treatment

"The only qualification is ignorance"

Informed Consent

It should be explained

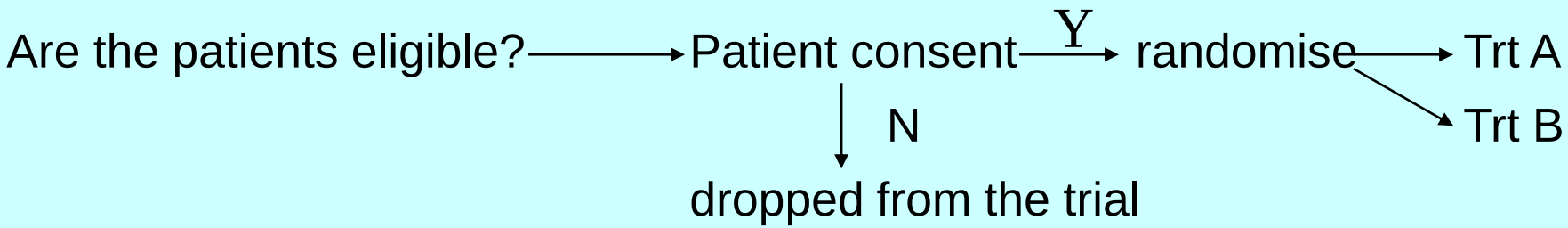
- that the patient is invited to be in a trial
- what the alternative treatments are (including known side effects)
- that treatment will be allocated at random
- that patients may withdraw at any time

Information should be given

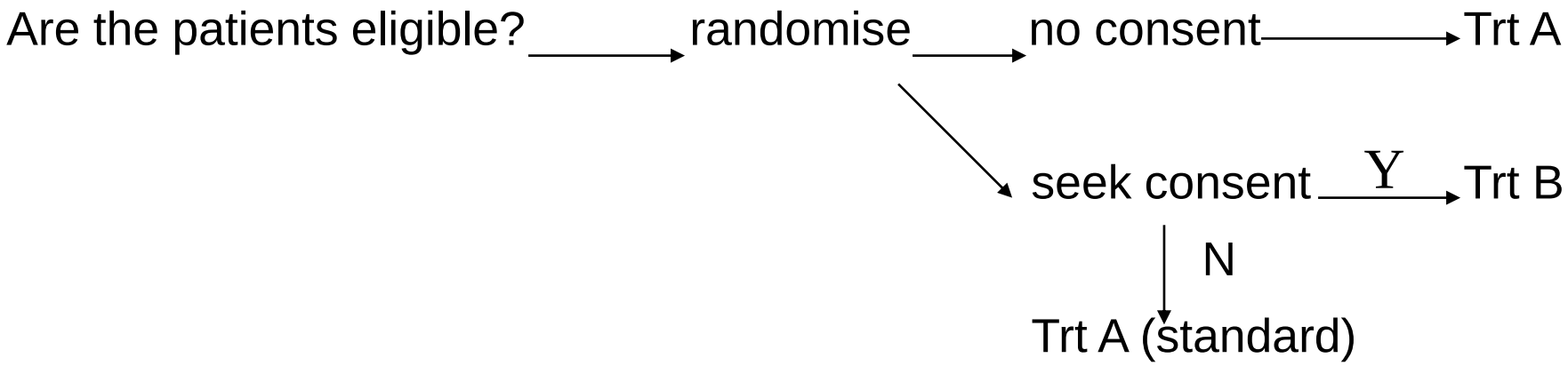
- verbally and in writing with ‘cooling off’ time
- by a knowledgeable informant

The Zelen method

Standard randomisation:



The Zelen method:



Key Points

- Clinical trial is a fair, controlled (comparative), reproducible experimental study
- Randomised: to minimise allocation bias and confounding
- Blinded: to minimise non-treatment effects and measurement bias
- Normally analysed on an ‘intention-to-treat’ basis
- In equipoise and with informed consent
- **PPI: make sure trial acceptable to patients**