MSc/BSc Programmes in International and Global Health
Epidemiology and Statistics
Week 8:

The Rise and Fall of HRT

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The "Hierarchy of Evidence"

See *e.g.* Greenhalgh, *How to Read a Paper*

- Syntheses of results from a number of clinical trials
- Clinical trials
- Cohort studies
- Case-control studies
- Cross-sectional surveys

} **observational** studies

- Case reports

What are **clinical trials**, and why are they at the top?

Definition of a Clinical Trial

Any research project that **prospectively assigns human subjects to intervention or concurrent comparison or control groups** to study the cause-and-effect relationship between a medical intervention and a health outcome

(from the Uniform Requirements for Manuscripts Submitted to Medical Journals, International Committee of Medical Journal Editors)

In particular, trials employ a number of measures designed to eliminate possible sources of bias

Motivating Example: Postmenopausal Oestrogen and Coronary Heart Disease

- A large cohort study of postmenopausal women (Stampfer *et al*) found an association between taking oestrogen and a reduced rate of coronary heart disease
- However, a clinical trial of oestrogen therapy in postmenopausal women (Women's Health Initiative) concluded that oestrogen did not prevent coronary heart disease

A (Very) Brief History of the Clinical Trial

James Lind, A Treatise of the Scurvy (1753)

Lind took 12 sailors with scurvy and divided them into 6 pairs, with each pair getting a different treatment:

- 1 quart of cider
- 25 drops of sulphuric acid
- 6 spoonfuls of vinegar
- ½ pint of seawater
- 2 oranges and one lemon
- spicy paste and barley water

A (Very) Brief History of the Clinical Trial

Johannes Fibiger, treatment of diphtheria (1898)

Investigated subcutaneous injections of diphtheria serum as a treatment for diphtheria

As a **control**, he looked at the effect of routine treatment – one of the first **controlled clinical trials**

As each new patient was recruited, he alternated between using serum and routine care

– *i.e.* controls were **concurrent** (to allow for seasonal variation in outcomes) as opposed to **historical**

A (Very) Brief History of the Clinical Trial

MRC streptomycin for tuberculosis trial (1948)

Used concurrent controls

Patients were randomly allocated either to streptomycin or a placebo control
– considered to be the first **randomised controlled trial**

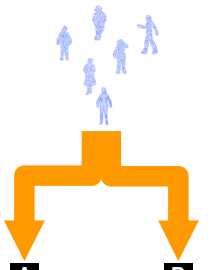
Describing the Research Question: PICO

P	Population	Where and how are participants recruited? What are the inclusion and exclusion criteria?
I	Intervention	What is the active intervention? It should be described in enough detail to allow another researcher to replicate it
C	Comparison	What is the control? This might be an established treatment or 'routine care', or else a placebo, sham, or inactive control
O	Outcome	How and when will outcome be assessed?

Women's Health Initiative Trial: PICO

Among postmenopausal women aged 50-79 years, does a daily pill containing 0.625mg of conjugated equine oestrogens and 2.5mg of medroxyprogesterone acetate reduce the risk of subsequent coronary heart disease (nonfatal myocardial infarction or CHD death) compared with a daily placebo pill?

Allocating to treatments



Oestrogen + Progestin

Placebo

Randomisation

Simple randomisation – essentially tossing a coin for each:

A
B
B
A
A
A
A
B
A
A
B
A

Randomisation

Block randomisation – *e.g.* blocks of 6:

A
B
B
A
A
B

Each block of 6 contains exactly 3 A's & 3 B's, but randomly arranged

A
B
A
B
B
A

Block randomisation ensures roughly equal numbers in each group

Randomisation

Stratified block randomisation – *e.g.* stratified by age:

50-64	65-79
A	B
B	B
B	B
A	A
A	A
B	A
A	B
B	A
A	A
B	B
B	A
A	B

Stratified block randomisation ensures the age distribution is similar in each group

Randomisation

Minimisation

- allocates successive participants so that treatment groups are evenly balanced on a number of characteristics
- each allocation depends on the previous allocations
- a random element is usually also included

Details are not covered in this course

Why randomise?

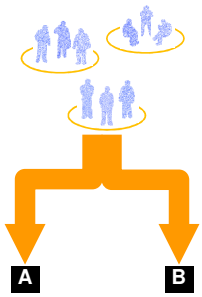
- Random allocation ensures treatment and control groups are sampled from the same population
- It also helps to ensure **allocation concealment**
  - trial staff do not know the next allocation
  - thus it cannot influence their choice of the next participant (which could introduce bias)

How is Randomisation Implemented?

The 1948 MRC streptomycin trial used allocations prepared in advance and put into a sequence of **sealed envelopes**

Contemporary trials use more sophisticated methods, *e.g.* telephone/internet-based randomisation services
– helps to guarantee allocation concealment

Randomising in clusters



A cluster is *e.g.* patients attending the same general practice

Why randomise in clusters?

- A treatment given to one individual in a cluster could spread to others – **contamination**
- The treatment may be delivered to groups rather than to individuals

Blinding

Blinding or **masking** refers to steps taken, once treatment has begun, to conceal the group a participant has been allocated to, in order to eliminate potential sources of bias

Blinding

Traditional terminology:

Single-blind: participants are blinded, but not trial staff

Double-blind: participants and trial staff are blinded

In fact you should consider whether it's possible to blind a number of different groups, *e.g.*

- participants
- staff providing care to participants
- staff assessing outcomes for the trial
- staff who will analyse outcomes from the trial

But remember – somebody needs to know!

Brief History of Blinding the Participants

Benjamin Franklin, investigation of mesmerism (1784)

Franklin literally blindfolded participants, whereupon they were unable to say when and where the "mesmeric energy" was being directed

Placebos as metaphorical blindfolds

Waclaw Sobieranski (1895): used bread pills and saline solutions to control for "autosuggestion"

W.H.R. Rivers (1906): used "control mixtures which have usually been wholly indistinguishable from those containing the active substance"

Randomisation and Blinding in the WHI Trial

"The randomisation procedure was developed at the WHI Clinical Coordinating Centre and implemented locally through a distributed study database, using a randomised permuted block algorithm, stratified by clinical centre site and age group. All study medication bottles had a unique bottle number and bar code to allow for blinded dispensing."

Accounting for all Participants in a Trial

Planning sample size

Researchers have an ethical responsibility to plan the number of participants in a trial:

- if too many, then people are exposed unnecessarily to medical research
- if too few, then their participation is unlikely to lead to useful results

– see later

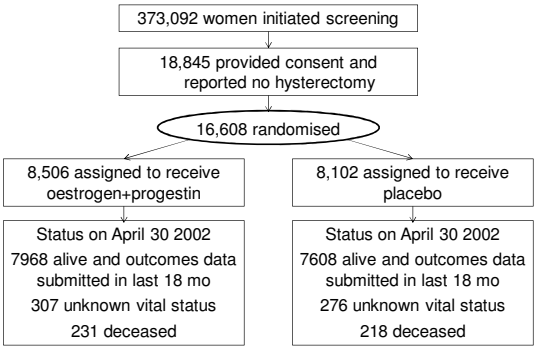
Accounting for all Participants in a Trial

Reporting sample size at different points in the trial

The CONSORT statement *(see seminar)* recommends a flow-chart showing numbers of participants in different treatment groups, including numbers at the point of

- enrolment
- treatment allocation
- follow-up
- analysis

CONSORT flow-chart for WHI Trial



Accounting for all Participants in a Trial

Accounting for all participants in the analysis

What if some participants do not comply with their treatment or change treatment?

- **Intention-to-treat** analysis: all participants analysed according to the group they were originally allocated to
- **Per-protocol** analysis: analysis includes only those participants who received the treatment as allocated

Results from the WHI Trial

"We calculated the relative risk associated with hormone use, defined as the incidence rate of cardiovascular disease among hormone users divided by the corresponding rate among women who had never used hormones."

Terminology:

relative risk

incidence rate ratio

hazard ratio

Results from the WHI Trial

Coronary Heart Disease

Estimate of effect of treatment compared with control – here it is a **ratio** (*i.e.* a value of 1 would indicate no difference)

Confidence interval – range of plausible values for the hazard ratio

Hazard ratio 1.29 (95% confidence interval 0.85–1.97)

P>0.05

P-value – P<0.05 would indicate evidence of a treatment effect

Results from the WHI Trial

Coronary Heart Disease

Hazard ratio 1.29 (95 confidence interval 0.85 – 1.97)

P>0.05

Results from the Cohort Study

Coronary Heart Disease

Hazard ratio 0.51 (95 confidence interval 0.37 – 0.70)

P<0.0001

Statistical and Clinical Significance

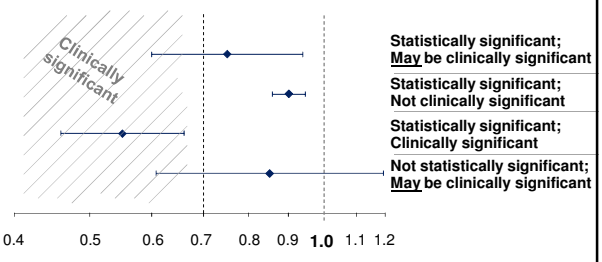
Statistical significance

- P-value is low
- Confidence interval for ratio excludes 1
  (or confidence interval for difference excludes 0)

But is this always **clinically significant**?

– *i.e.* is the effect important from a patient or clinician perspective?

Statistical and Clinical Significance



Using Significance to Justify Sample Size

To meet the ethical responsibility of planning sample size, researchers calculate the **power** of the trial

- Power is the probability of the trial producing evidence of the form P<0.05, assuming that there really is a clinically significant effect of the treatment
- The smaller the effect you're looking for, the lower the power
- You can increase power by increasing the sample size
- By convention, power should be at least 80%

Ethical Frameworks for Running Trials

These emphasise the protection of the human rights of participants in medical research – in particular that they should give **informed consent**

Ethical Frameworks for Running Trials

1947 – Nuremburg Code established in response to revelations at the Nuremburg Trials that unethical research was carried out in Nazi Germany

1964 – Declaration of Helsinki, a statement of ethical principals developed by the World Medical Association

1997 – ICH (International Conference on Harmonisation) Guidelines on Good Clinical Practice

2001 – EU Directive on Clinical Trials

2004 – UK legislation for drug trials: Medicines for Human Use (Clinical Trials) Regulations; Human Tissue Act

Coverage of Ethics in Journal Articles

Most journals now require statements concerning

- Patient consent – whether and how it was obtained
- Registration – the trial was registered in a public trials registry before recruitment started
  – among other things this shows that a protocol was followed
- Ethical approval – obtained from an ethics committee/ Institutional Review Board

Trial Monitoring

What happens if results start to accrue before the trial has finished?

e.g.

- outcome assessed at the end of a follow-up period that is short relative to the period of recruitment
- outcomes assessed continuously over time, such as CHD incidence in WHI trial

Trial Monitoring

Is it OK to stop the trial early?

concerns:

- going against the protocol
- validity of conclusions

reasons for stopping:

- concerns about safety
- treatment seems effective – want to give it to everybody
- treatment seems ineffective – want to stop wasting people's time

Who Makes the Decision to Stop a Trial?

DSMB – Data Safety & Monitoring Board /
DMC – Data Monitoring Committee

- independent of the trial
- they may access unblinded interim data
- they can recommend to the sponsor that the trial be stopped
- remit of the DSMB/DMC is established in a charter drawn up before recruitment begins
- not required for every trial

Placing Trials in the Hierarchy of Evidence

Remember:

- A poorly conducted trial may be less persuasive than a well-conducted cohort study
- A trial may be unethical to carry out
- Trials are not appropriate for every research question