RCTs

MRCPsych Academic Day 19.09.2019

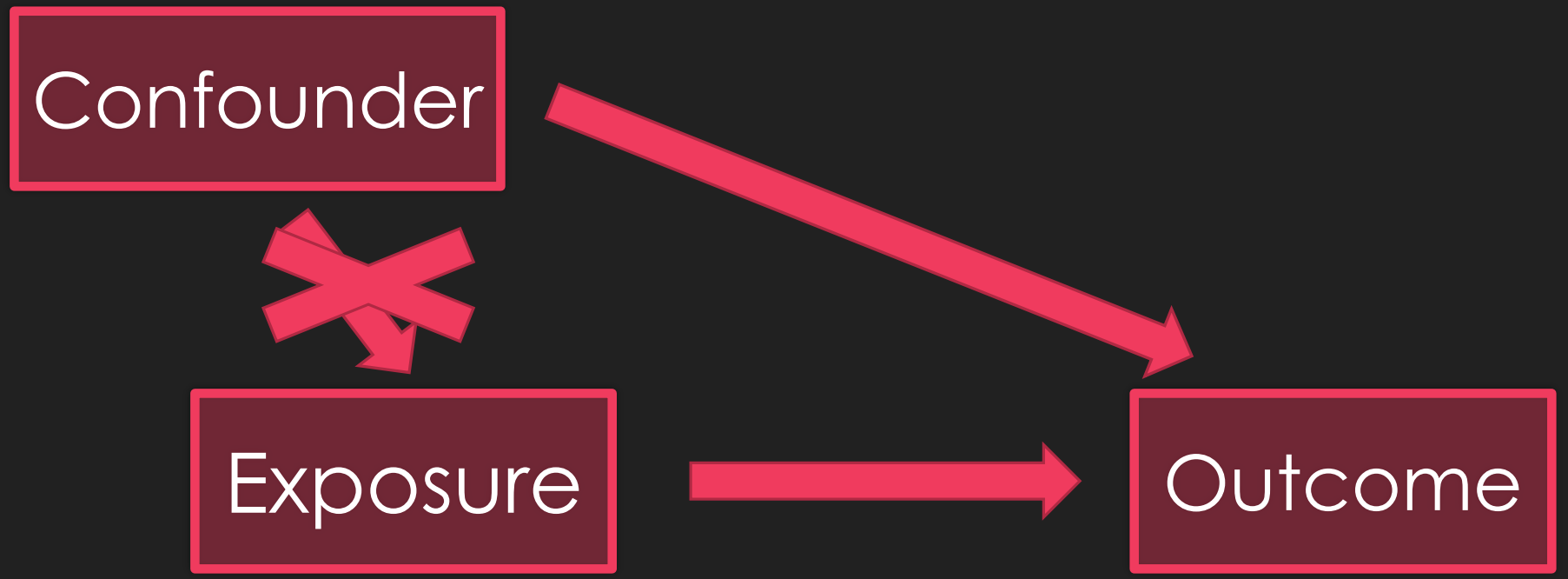
Randomized Controlled Trials

- An intervention (e.g. medication, psychological therapy, surgery) is given to some people within a selected group of people and not to other members of the same sample.
- An assessment of how much incident disease/recovery or level of a health outcome has been altered by the intervention is carried out.
- Seen as the 'gold standard' research design (for treatments) as you have control over the factor you wish to test & produces more **internally valid** results than observational studies.
- Evidence from intervention studies are powerful, especially if well randomised, controlled and blinded.

Why randomize?

- Randomization (if done properly) prevents anything **confounding** the relationship between exposure and outcome.
- This is because **nothing predicts exposure**, and if nothing predicts exposure then nothing can be a confounder

Confounding



Methods of Randomization

- Simple – a series of random numbers is allocated as treatment A or B. Each participant is allocated a number and receives the corresponding treatment.
- Stratification – the participants are divided into groups based on important characteristics. A set number of patients is randomized to each option from within those groups.
- Minimization (aka adaptive stratification)- an algorithm is used which assesses covariate imbalance then assigns new treatment probabilities to individuals based on their covariates

Methods of Randomisation

- Stratification is often thought to prevent a problem with covariate imbalance affecting causal inference.
- It actually is for **reducing error** and therefore increasing statistical power.
- Stratification is more important in smaller trials because of this.
- The more important the prognostic variable the more important stratification on it becomes.
- It also can make sure you have enough participants with a certain characteristic for any sub-group analyses you want to do.

Methods of Randomisation

- Cluster – a group is randomly allocated to the treatment (eg by ward, classroom, GP surgery etc.)
  - Simply more appropriate for some interventions
  - Less power per participant (individuals are not **independent**) but easier to recruit more participants

Methods of Randomisation

- Block – participants are allocated to a trial arm in blocks eg 4 at a time to treatment A then 4 to treatment B, then 4 to A and so on.
  - This has the advantage of keeping balance between trial arms.
  - It can reduce blinding
  - It can introduce bias if there is a reason for people with similar characteristics to present for treatment at the same time.

Doing an RCT

- A hypothesis must be formulated first
- Chose type of study design that will efficiently supply information to either support or refute the hypothesis
- Things to consider in choosing study design:
  - State of knowledge
  - Frequency of exposure and disease
  - Expected strength of association between the two
  - Practical and ethical problems

Doing an RCT

- Sample size calculation: Can be done manually or with computer software
- Sample size calculation is a vital part of the planning of a trial, and is carried out to reduce the chances of making Type I and Type II errors in any given situation.
- How to do a sample size calculation is not on the syllabus so you should not be asked to do this.

Doing an RCT

- Research proposal is written
- Ethical approval is sought
- Eligibility criteria are set (Inclusion and exclusion criteria)
- Eligible people will give informed consent to participate
- Recruitment of study participants
- Randomised methods are used to assign people to different study branches

Doing an RCT

- Treatment and comparison group are monitored for outcomes under study.
- During follow-up, investigators maintain contact with participants through periodic visits, phone calls, or letters.
- Effort is made to keep dropouts and loss to follow-up to a minimum during follow-up visits.
- During analysis; intention to treat analysis is the classical approach used i.e. everyone allocated to the treatment group is included in the analysis (whether they received the Tx or not) to preserve the baseline comparability and ensure generalisability of the study

A Note on Intention to Treat (ITT)

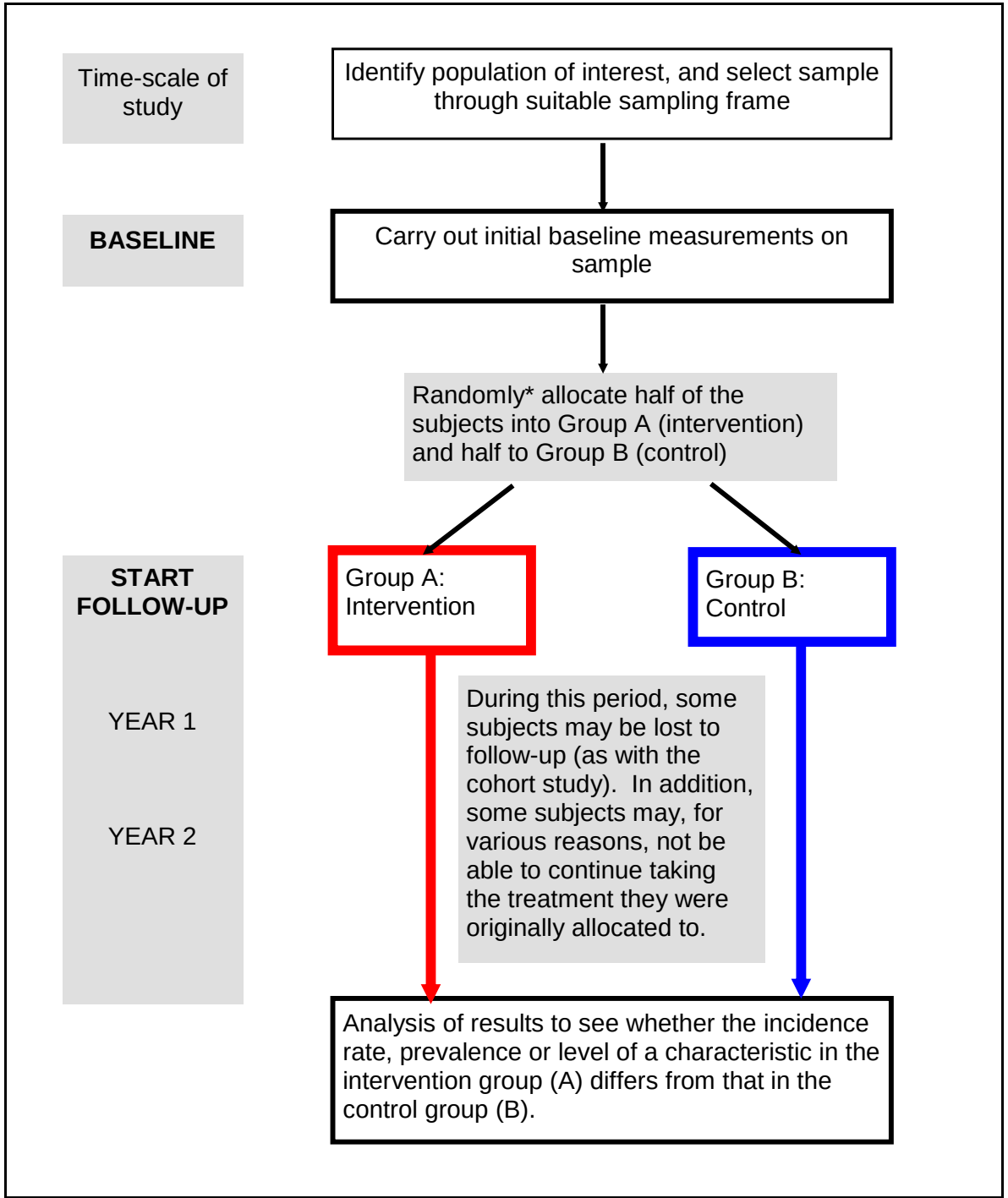
- ITT is used because participants don't drop out of a study at random.
- Non-random dropout can cause bias, usually towards a greater treatment effect because non-responders are more likely to drop-out.
- So ITT is a **conservative** method of analysis.
- This means that it biases the results towards the null hypothesis.
- There are newer methods which get around this problem but they are not yet widely adopted and you don't need to know about them.

Blinding AKA Allocation Concealmeant

- Single-blind study: Study participants not aware if receiving tx or not
- Double-blind study: Both study participants and investigators administering the tx not aware if receiving tx or not
- Triple-blind study: Study participants, investigators administering tx, and investigators monitoring the effect of treatment are not aware if receiving tx or not

Doing an RCT

- Blinding participants equalises the placebo effect across trial arms. Not always easy or even possible to do eg. psychological interventions or cancer chemotherapy
  - This can be very intricate as the colour, shape, smell, taste, pretty much anything about the treatment can influence the results!
- More important the more subjective the outcome
- Blinding investigators giving treatment reduces bias in assessments of patient condition or their other medical management.
- Blinding assessors or analysers prevents massaging the results to favour one group via various means.


Time-scale of study
Identify population of interest, and select sample through suitable sampling frame
BASELINE
Carry out initial baseline measurements on sample
Randomly* allocate half of the subjects into Group A (intervention) and half to Group B (control)
START FOLLOW-UP
Group A: Intervention
Group B: Control
YEAR 1
YEAR 2
During this period, some subjects may be lost to follow-up (as with the cohort study). In addition, some subjects may, for various reasons, not be able to continue taking the treatment they were originally allocated to.
Analysis of results to see whether the incidence rate, prevalence or level of a characteristic in the intervention group (A) differs from that in the control group (B).

RCT planning task

RCTs

Intervention	Type of Randomization	Control / Placebo Group	Blinding
Drug or Vaccine			
Surgical Operation			
Psychological Treatment			
Health Promotion Initiative			

RCTs

Intervention	Type of Randomization	Control / Placebo Group	Blinding
Drug or Vaccine	Simple random or Stratified	Placebo pill / injection or alternative treatment	Triple Blinding usually possible
Surgical Operation	Block, simple random or stratified	Sham surgery or non-surgical alternative	Blinding of patients if sham surgery, blinding of assessors
Psychological Treatment	Simple random or Stratified	Alternative therapy, non-directed contact, TAU	Blinding of assessors and analysts only
Health Promotion Initiative	Cluster	Control areas with no initiative	Blinding of analysts or assessors may be possible

Thank you

Questions?