Session 1

Randomised Controlled Trials

Introduction – Study Design

- We often wish to investigate the efficacy of new treatments and interventions on patient outcomes
- In this session, we shall consider a study design commonly used to answer such questions – Randomised Controlled Trials
- Session 2 will consider when it is appropriate to use other types of studies (observational studies)

Outline of Session

- The need for a control group and randomisation
- Types of RCT study design
- Important features of well performed RCTs
- The CONSORT statement
- The benefits and limitations of RCTs

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Example – the need for a control group

- A study assessed the effect of thyroxine sodium on new clinic patients with hypothyroidism. 139 patients were treated and followed-up
- 22% of patients had improvement or resolution of symptoms and the mean number of clinical features of disease decreased from 13.3 to 3.0 ($p<0.0001$)

Skinner; J Nutr Environ Med; 2000; 10(2); 115-124

The need for a control group

- Conditions may improve with time, and this improvement cannot necessarily be attributed to treatment
- 'Hawthorn effect': observation that patients in clinical trials generally do better than similar patients on same treatment (closer monitoring, clear treatment plan, enthusiastic team, etc.)
- Therefore, a control group gives us the opportunity to see 'what would have happened without the new intervention'

Example – the need for randomisation

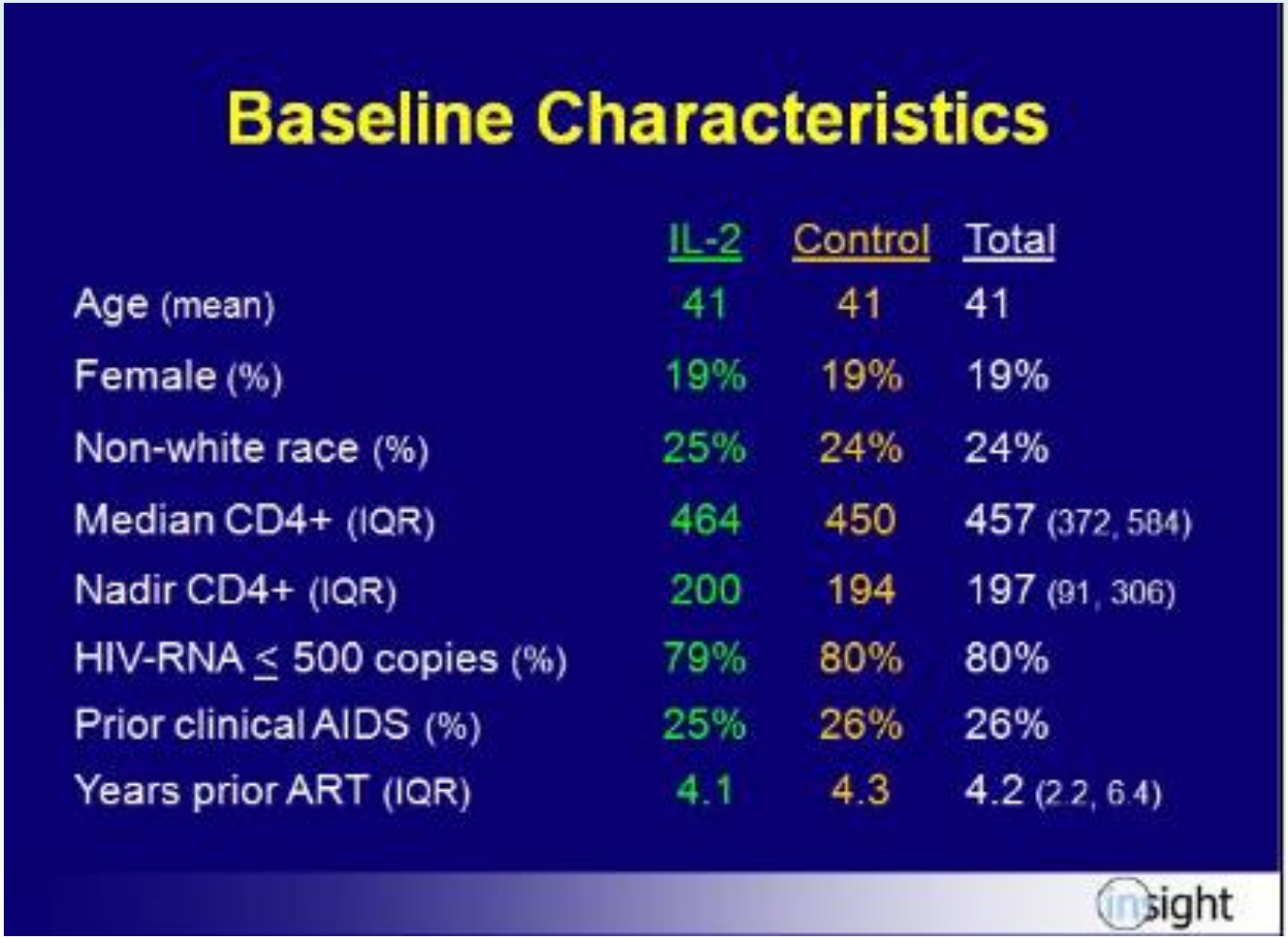
- Aim: To evaluate the outcome (rate of post-operative complications) of caesarean delivery performed by assistant medical officers with that performed by specialists in obstetrics and gynaecology
- Method: Outcome of 958 caesarean sections performed by assistant medical officers compared with 113 performed by specialists
- Outcome: No differences were observed

Pereira; Br J Obs Gynae; 1996; 103(6); 508-12

The need for randomisation

- Patient allocation to new intervention or control groups is determined purely by chance
- Thus, any differences between the different arms of the trial are due to chance alone
- This includes both known and unknown factors
- Thus, provided individuals are treated similarly during the study period, any differences in outcome between the two groups can be attributed to the intervention

Example - Baseline characteristics



ESPRIT Study Group; CROI 2009; 90aLB

Randomised Controlled Trials (RCTs)

- Experimental, longitudinal, prospective
- Randomised – ensures that treatment groups are similar at start of trial; any differences are due to chance only
- Controlled – control group allows us to conclude that any improvement in outcome is due to the test treatment rather than some other factor
- Comparison is usually between a new regimen/intervention and an existing standard of care or placebo

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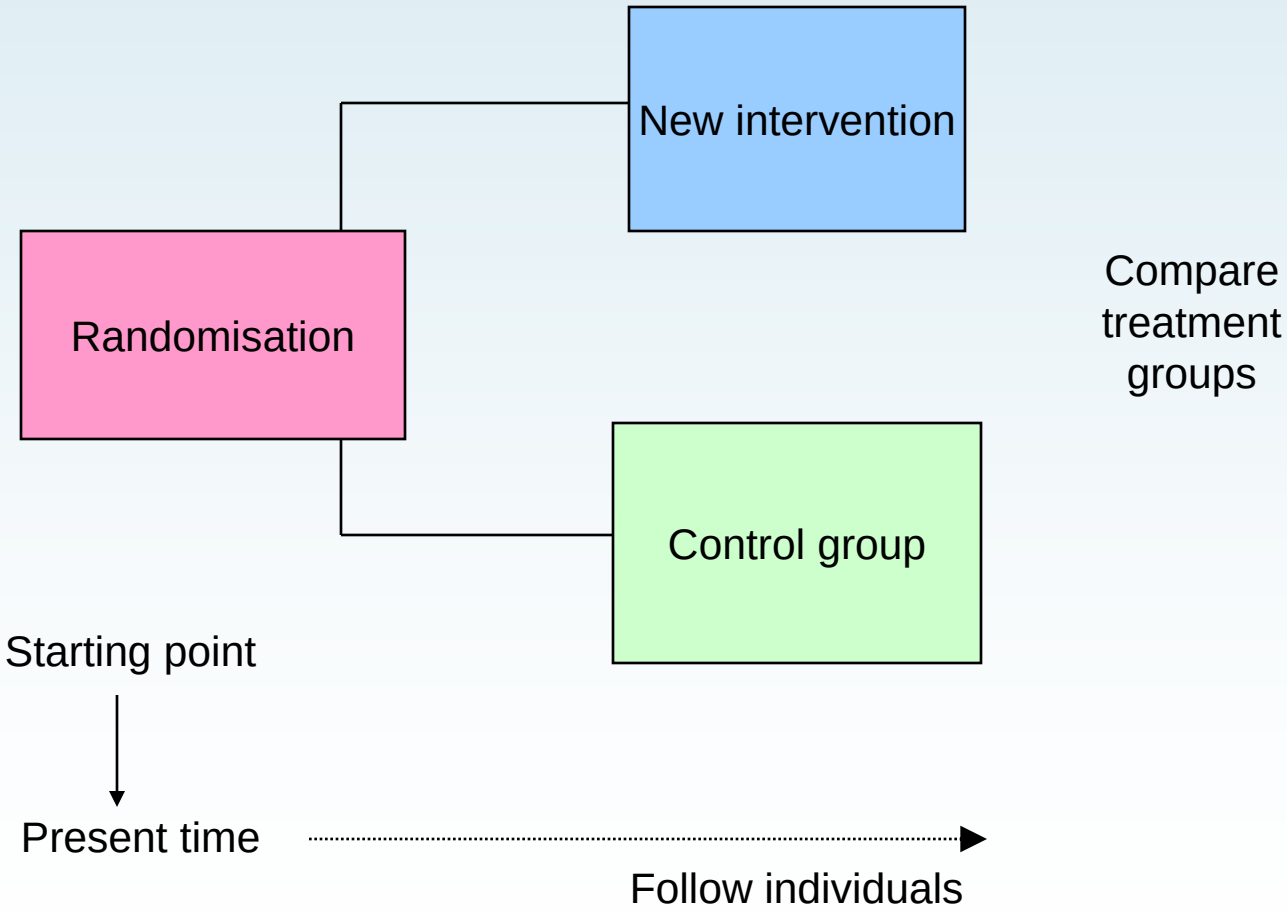
Types of RCTs

- Parallel group: each patient is randomised to receive only one of the two different strategies
- Crossover trial: each patient receives first one treatment strategy then the other, but the treatment order is randomised
- Cluster randomised: each 'cluster' of patients (GP surgeries, outpatient clinics) randomised to receive one of the two different treatment strategies

Parallel design trials



Example – Parallel Group trial

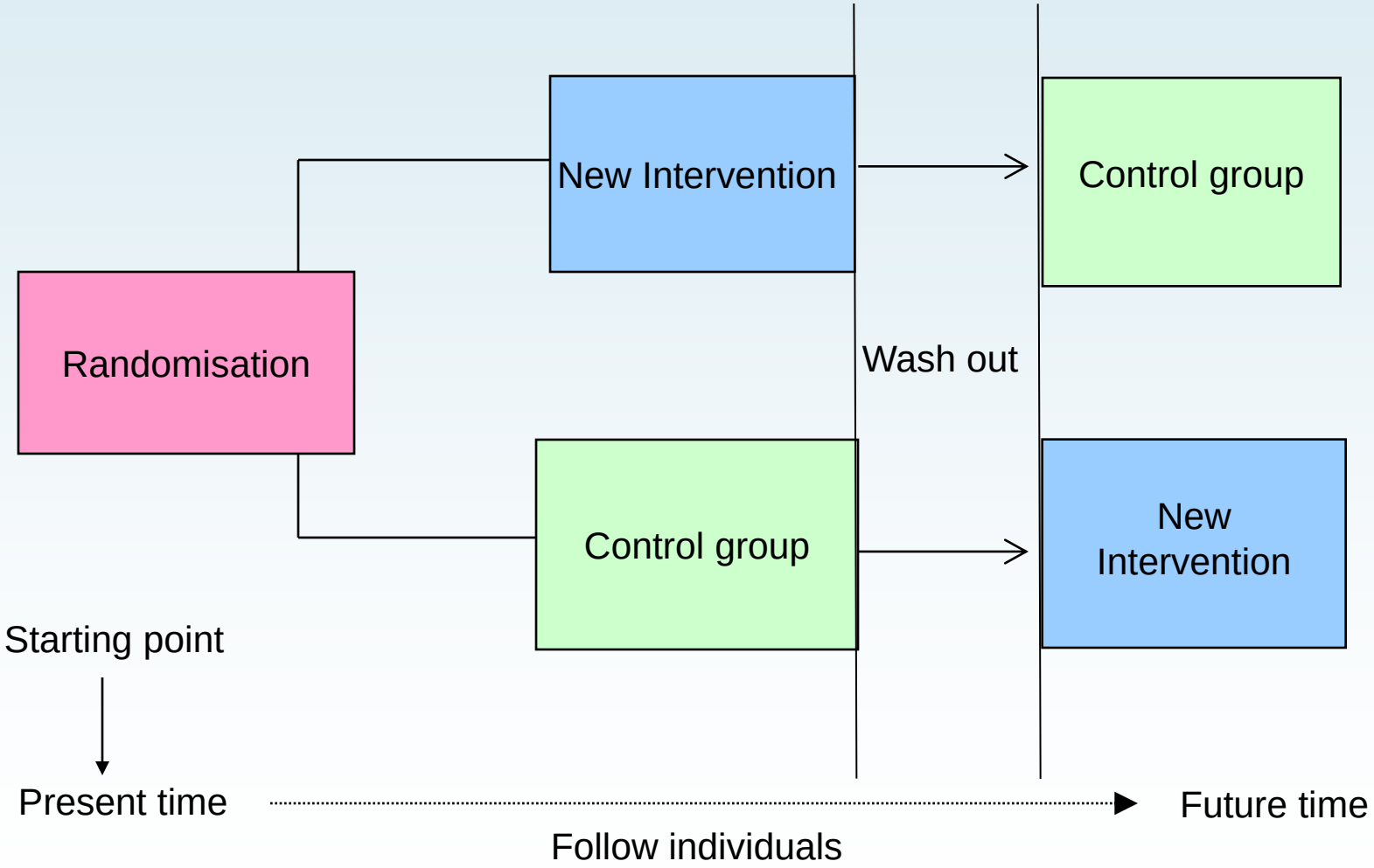
- Trial evaluating effect of dietary advice (DA) alone versus dietary advice plus pravastatin on cholesterol among HIV patients on PI-based regimens
- Randomised to:
  - Dietary advice alone

  OR

  - Dietary advice plus pravastatin
- Endpoints: change in total cholesterol from baseline to week 12

Moyle; AIDS; 2001; 15(12); 1503-1508

Cross-over trials



Example – Crossover trial

- Safety and acceptability of Reality condom for MSM
- Sero-concordant couples randomised to:
  - Reality condoms for 6 weeks, followed by latex condoms for 6 weeks

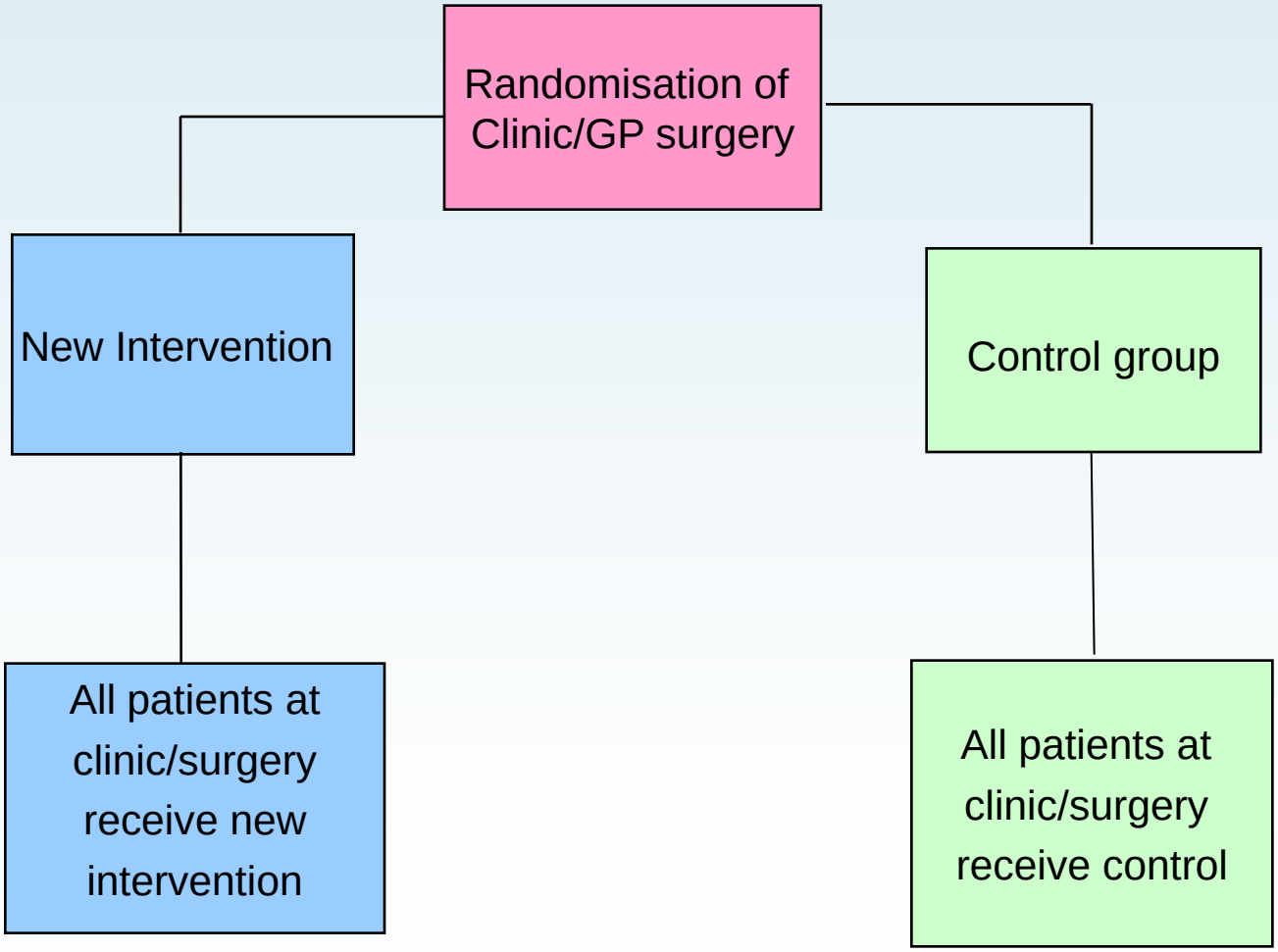
  OR
  - Latex condoms for 6 weeks, followed by Reality condoms for 6 weeks
- Endpoints: frequency of slippage with removal, pain or discomfort on use, rectal bleeding, willingness to use in future

Renzi; AIDS; 2003; 17; 727-731

Crossover trial

- Crossover trials are particularly useful for short term outcomes in chronic conditions
- The treatment must be one that does not permanently alter the disease or condition under study
- The main limitation of a crossover trial is that the effect of the first treatment administered may carry over and alter subsequent responses

Cluster randomised trials



Example – Cluster randomised trial

- Two strategies for voluntary HIV counselling and testing at the workplace, Zimbabwe
- 22 businesses were randomised to:
  - Intensive VCT: counselling and rapid testing available on site

  OR
  - Standard VCT: pre-paid vouchers for an external provider
- Endpoints: 3146 HIV-negative individuals were assessed for HIV incidence in each study arm

Corbett; AIDS; 2007; 21; 483-489

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Trial populations

- Explicit and objective inclusion and exclusion criteria are required for any RCT
- Narrow and restrictive inclusion criteria can allow us to focus on people most likely to benefit from treatment, and reduce variability in the outcome
- However, we want the included participants to be representative as far as possible of those who may receive treatment in the future

Example – Trial populations

- Does the addition of interleukin 2 to a combination ART regimen result in a reduction in new opportunistic infections and death

- Study population: HIV-positive men who have sex with men attending a large teaching hospital in London, UK

- Results of study may not be generalisable to all HIV-positive individuals

Example – Trial populations

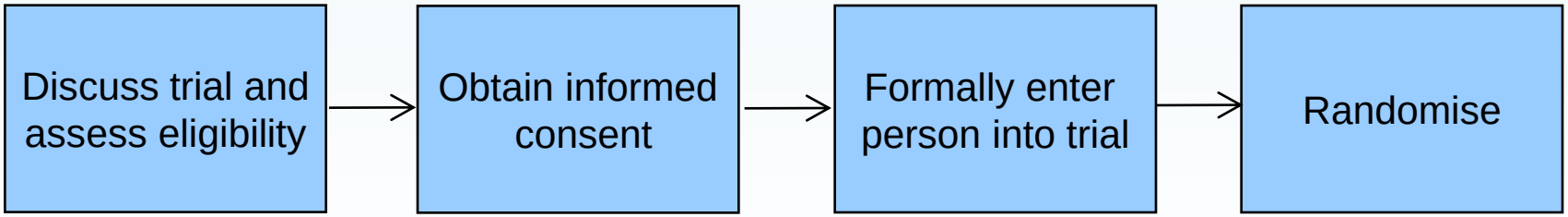
- Does the addition of interleukin 2 to a combination ART regimen result in a reduction in new opportunistic infections and death

- Inclusion criteria: liver function tests, kidney function tests and lipids within normal ranges

- Results of study may not be generalisable to all HIV-positive individuals

Treatment allocation

- A person's treatment allocation should not be known before they are entered into a trial
- If there is no concealment of treatment allocation, this may influence the decision to recruit, leading to imbalances



Blinding

- Bias can occur if a patient, treatment team, assessor are aware of treatment allocation
  - Patient: psychological effect, adherence to treatment
  - Clinical team: treatment modifications, additional treatments, intensity of examination
  - Assessor: recording of responses to treatment and adverse events
- The extent of the bias may depend on the intervention and the nature of the outcome measure

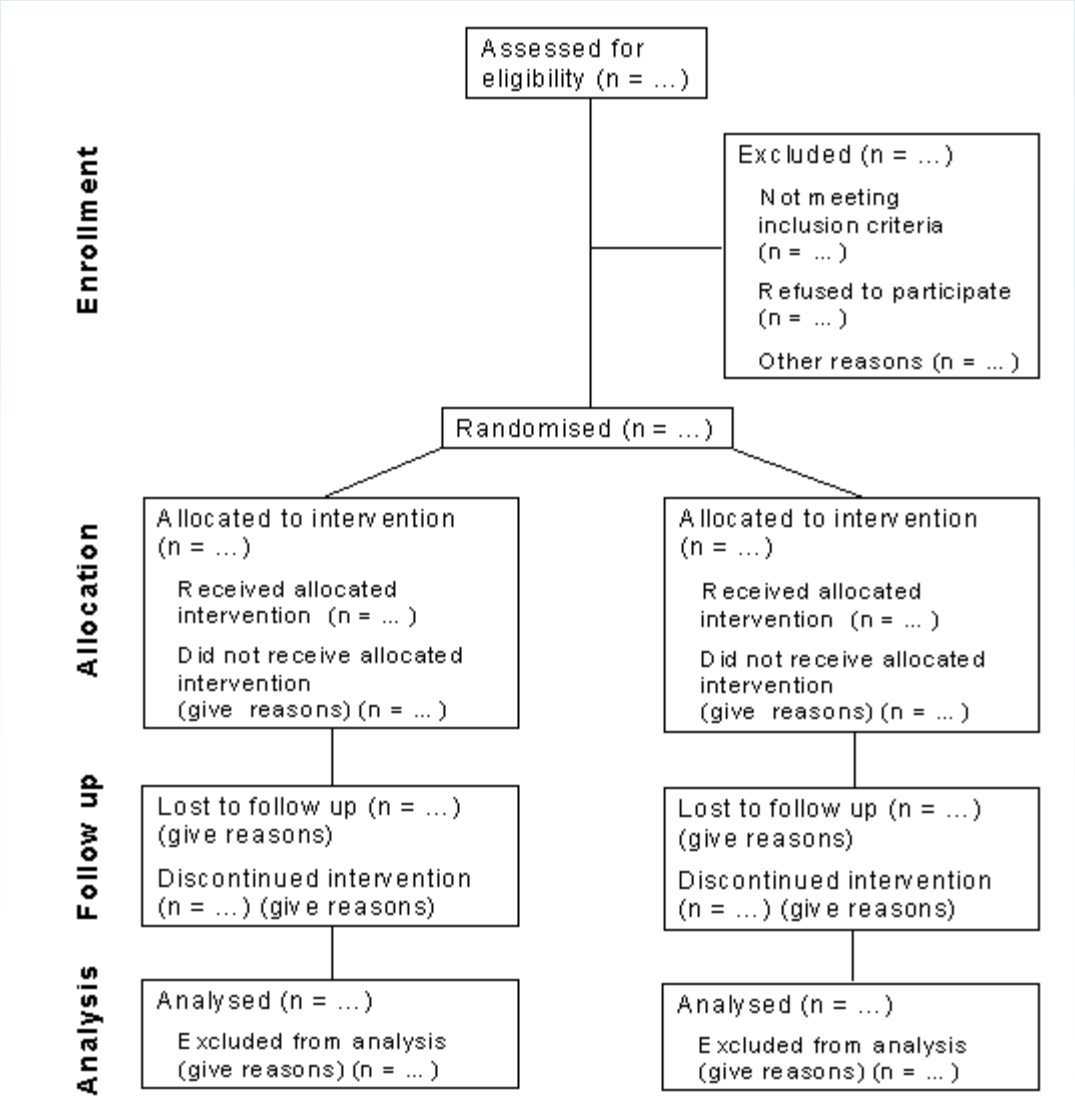
Blinding

- Blinding is not always possible, but in most trials some element can be introduced
- Double-blind: neither patient nor clinical team know which treatment patient is receiving
- Single-blind: only patient does not know which treatment s/he is receiving
- Blinding is particularly important for subjective endpoints

Loss to follow-up

- The validity of trial results are dependent on complete follow-up of randomised patients
- All patients who were randomised should be accounted for when the results are reported
- Ideally, all patients who were assessed for eligibility should be accounted for, as this may impact on the generalisability of the trial
- Intent-to-treat approaches should be used to account for missing data (See Session 3)

CONSORT flow diagram



Determining the study sample size (1)

- Sample size is an important component of study design because we require:
  - Large enough numbers to ensure we are likely to be able to detect a difference between treatment arms should one exist
  - Small enough that we are not unnecessarily exposing individuals to inferior treatments and not wasting resources
- We can then use published formulae to calculate the required sample size – these are widely available

Determining the study sample size (2)

- For superiority trials, we require information on:
  - Expected response in the control arm
  - The minimum clinically meaningful difference we wish to be able to detect
  - Type I error (probability of incorrectly concluding there is a difference between the two groups when truly none exists) – typically 5%
  - Power (probability of detecting a difference between groups if one exists) – typically 70-90%
  - For continuous outcomes - a measure of variability in the response (e.g. standard deviation)

Primary Endpoint

- Defined in advance (essential for power calculations)
- Should address the 'primary aim' of the trial
- Should have a good chance of discriminating between the different treatment arms
- Should have clinical/biological relevance
- Should be appropriate for the population included in the trial
- Should be mindful of regulatory requirements

Example: Primary Endpoint

- ESPRIT Study
- Aim: To investigate whether CD4 count increases seen with IL-2 result in a lower rate of clinical progression amongst patients taking ART with CD4 counts>300 cells/mm3
- Primary Endpoint: Opportunistic Disease (OI) or death

ESPRIT Study Group; CROI 2009; 90aLB

Secondary Endpoint

- All clinical trial protocols should state one (sometimes two) primary endpoint
- Main conclusions should be based on the results from this endpoint
- Pre-defined secondary endpoints can also provide supportive data

Example: Secondary Endpoints

- ESPRIT Study
- Aim: To investigate whether CD4 count increases seen with IL-2 result in a lower rate of clinical progression amongst patients taking ART with CD4 counts>300 cells/mm^3
- Primary Endpoint: Opportunistic Disease (OI) or death
- Secondary Endpoints: Death, Grade 4 clinical adverse events, Serious non-AIDS events

ESPRIT Study Group; CROI 2009; 90aLB

Trial endpoints in HIV

- RCTs in the HIV setting can use a number of different primary endpoints
  - Clinical: AIDS event, death, serious non-AIDS event
  - Immunological: CD4 count>500 cells/mm^3, change in CD4 count
  - Virological: change in VL, time to VL<50 copies/ml
  - Other: Treatment switches, adherence, quality of life
  - Composite: Time to loss of virologic response (TLOVR)
- Each has advantages and disadvantages, and we should take these into consideration when we interpret the study results

How do we account for missing data?

- Missing=Failure analysis (M=F):
  - Those lost to follow-up are considered as virological failures from that time point onwards
  - Those with missing study visits are considered as virological failures at that time point
- Missing=Excluded analysis (M=E):
  - Those lost to follow-up are excluded from analyses from that time point onwards
  - Those with missing study visits are excluded from analyses at that time point

How do we account for treatment changes?

- Intent-to-treat analysis (ITT): all individuals are included in analysis
  - Switch=Failure (S=F): individuals who make drug changes are considered as virological failures
  - Switch=Ignored (S=I): drug changes are ignored; patients are categorised according to virological response
- On treatment analysis (OT): only individuals who complete the study and adhere to the protocol are included
  - Also known as per-protocol analysis

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Where to go for guidance

- The Consolidated Standards of Reporting Trials (CONSORT) Group was set up to ensure transparency in the reporting of RCTs
- Their main output is the CONSORT Statement which is an 'evidence based, minimum set of recommendations for reporting RCTs'
- It includes a checklist and flow diagram, which can be very helpful both for conducting and appraising RCTs
- www.consort-statement.org

CONSORT

- The CONSORT statement is a checklist for reporting and appraising RCTs
  - www.consort-statement.org

Table. **Checklist of Items To Include When Reporting a Randomized Trial**

Paper Section and Topic	Item Number	Descriptor	Reported on Page Number
Title and abstract	1	How participants were allocated to interventions (e.g., "random allocation," "randomized," or "randomly assigned").	
Introduction			
Background	2	Scientific background and explanation of rationale.	
Methods			
Participants	3	Eligibility criteria for participants and the settings and locations where the data were collected.	
Interventions	4	Precise details of the interventions intended for each group and how and when they were actually administered.	
Objectives	5	Specific objectives and hypotheses.	
Outcomes	6	Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors).	

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Benefits and Limitations of RCTs

- RCTs are the ‘gold standard’ method to investigate the effects new treatments and interventions
- This is because randomisation and blinding enables us to obtain an unbiased estimate of how well the new treatment works compared to the standard of care treatment
- However, RCTs also have a number of limitations, which will be discussed in Session 2