

## **Session 3**

# **Randomised Controlled Trials**

# Introduction – Study Design

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- 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 4 will consider when it is appropriate to use other types of studies (observational studies)

# Outline of Session

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- 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

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- 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 ( $p < 0.0001$ )

# The need for a control group

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- 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

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- 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

# The need for randomisation

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- 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

**Table 1.** Characteristics of the Patients at Baseline.\*

Characteristic	Immediate-Initiation Group (N = 2326)	Deferred-Initiation Group (N = 2359)	All Patients (N = 4685)
Median age (IQR) — yr	36 (29–44)	36 (29–44)	36 (29–44)
Female sex — no. (%)	624 (26.8)	633 (26.8)	1,257 (26.8)
Race or ethnic group — no. (%)†			
Asian	198 (8.5)	190 (8.1)	388 (8.3)
Black	702 (30.2)	708 (30.0)	1,410 (30.1)
Latino or Hispanic	320 (13.8)	318 (13.5)	638 (13.6)
White	1,015 (43.6)	1,071 (45.4)	2,086 (44.5)
Other	91 (3.9)	72 (3.1)	163 (3.5)
Geographical region — no. (%)			
Africa	499 (21.5)	501 (21.2)	1,000 (21.3)
Asia	179 (7.7)	177 (7.5)	356 (7.6)

# Randomised Controlled Trials (RCTs)

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- Experimental, longitudinal, prospective
- **R**andomised – ensures that treatment groups are similar at start of trial; any differences are due to chance only
- **C**ontrolled – 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

# Outline of Session

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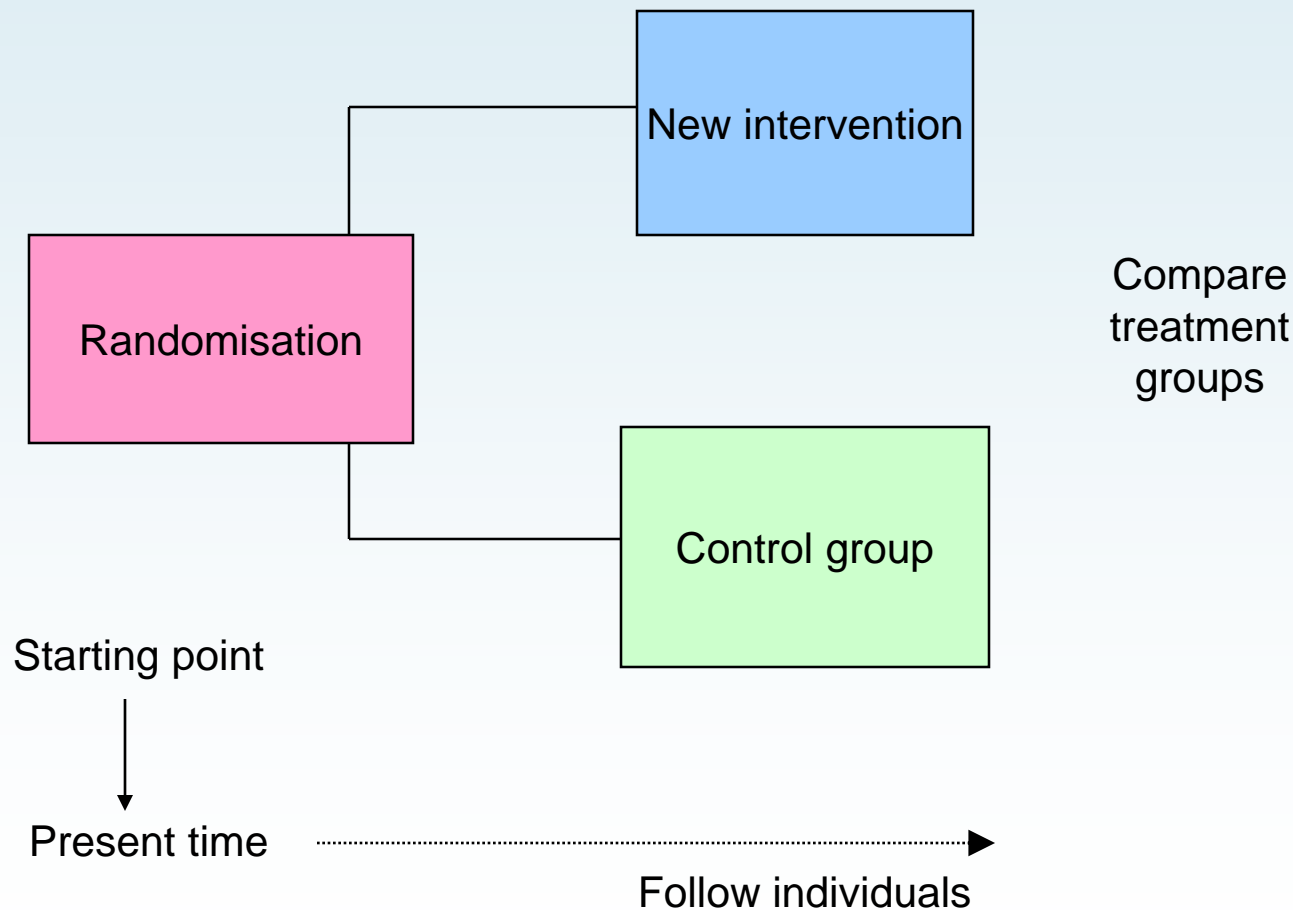
- The need for a control group and randomisation
- **Types of RCT study design**
- Important features of well performed RCTs
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# Types of RCTs

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- **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

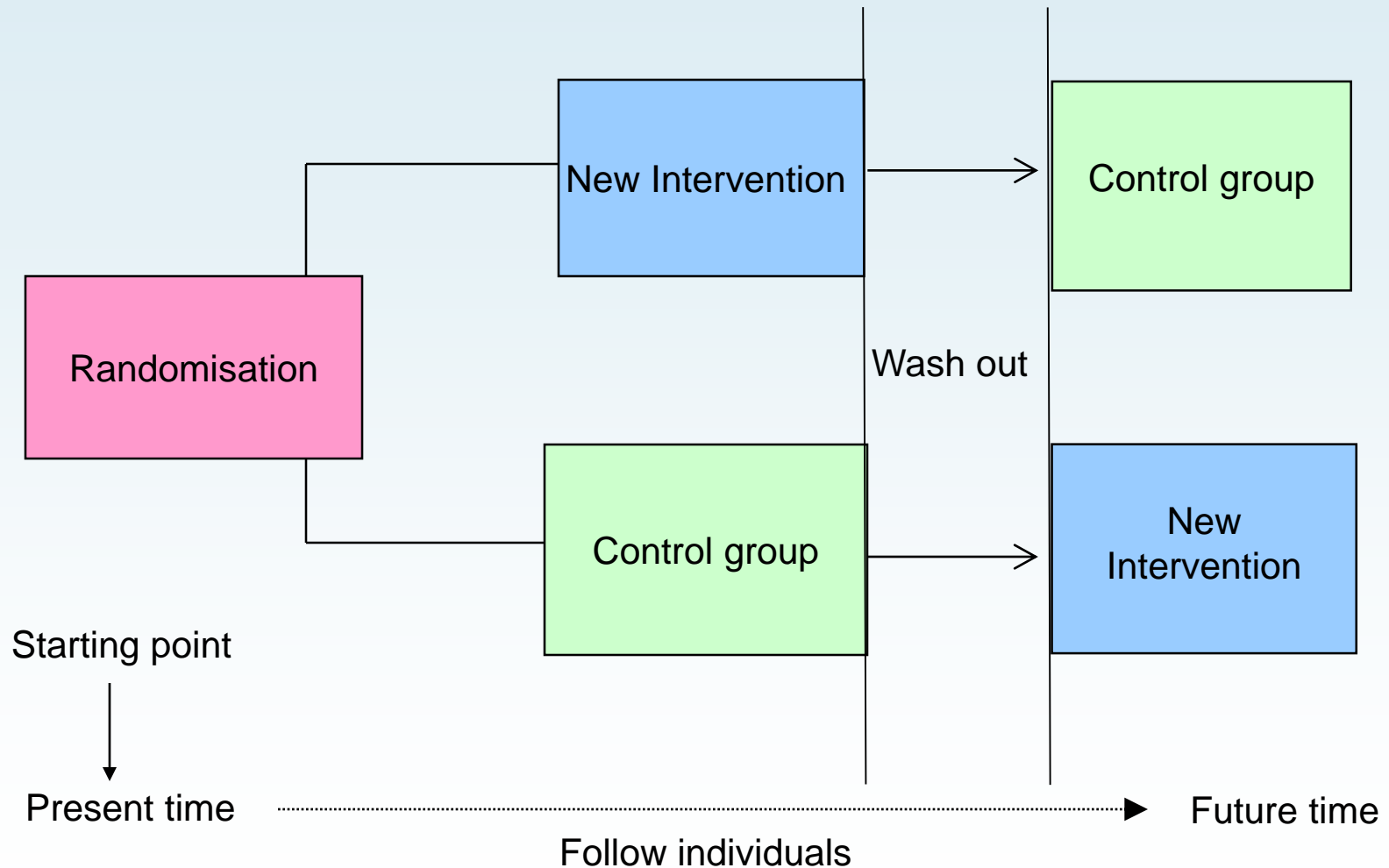


## Example – Parallel Group trial

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- Trial evaluating when to start ART among HIV-positive individuals who are ART-naïve with CD4 count  $>500$  cells/mm<sup>3</sup>
- Randomised to:
  - Initiate ART immediately following randomisation
  - OR
  - Defer ART until CD4 count declines  $<350$  cells/mm<sup>3</sup> or AIDS develops
- Endpoints: Serious AIDS, death from AIDS, serious non-AIDS and death not attributable to AIDS

# Cross-over trials



## Example – Crossover trial

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



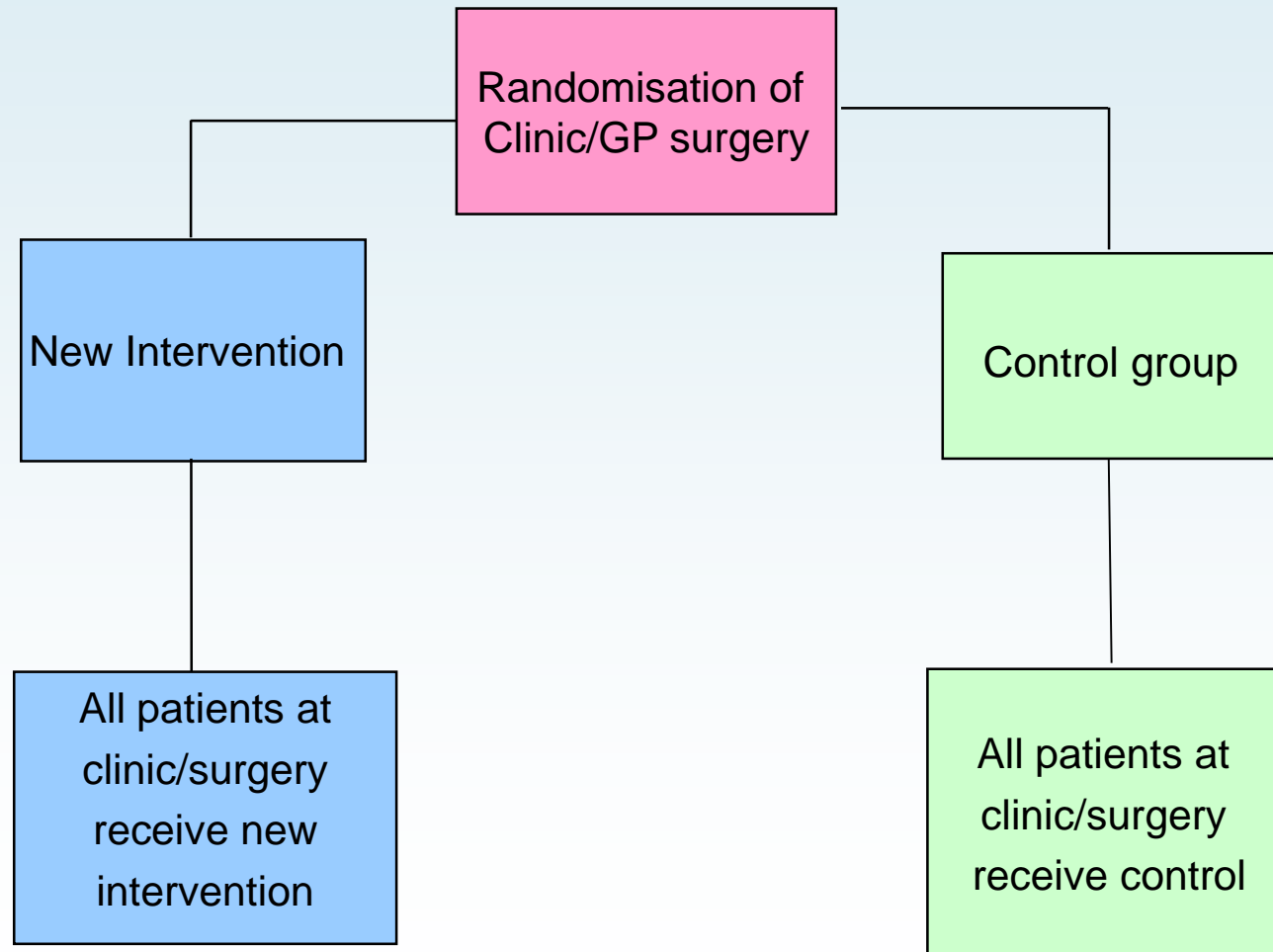
# Crossover trial

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- 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

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## Example – Cluster randomised trial

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- RCT of malaria prevention in Gambia
- 70 villages were randomised to:
  - Long lasting insecticidal nets (LLIN)OR
  - LLIN + indoor residual spraying
- Endpoints:
  - incidence of clinical malaria assessed by passive case detection in >7,000 children
  - number of *Anopheles gambiae* sensu lato mosquitoes collected per light trap per night

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# Trial populations

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- 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

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- Does immediate ART result in a reduction in new AIDS events, non-AIDS events and death compared to deferred ART?
- Study population: HIV-positive men who have sex with men attending a large teaching hospital in London, UK
- Generalisable to all HIV-positive individuals ?

## Example – Trial populations

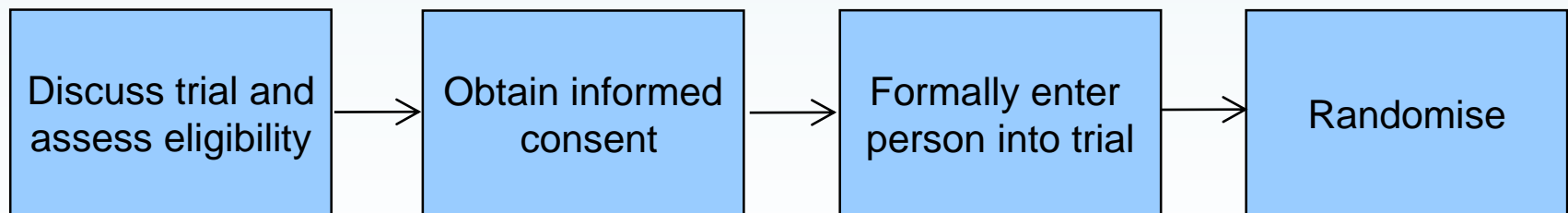
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- Does immediate ART result in a reduction in new AIDS events, non-AIDS events and death compared to deferred ART?
- Inclusion criteria: age  $\geq 18$  years, Karnofsky performance score  $\geq 80$ , no previous AIDS, no previous serious non-AIDS, not currently pregnant or breast feeding
- Generalisable to all HIV-positive individuals?

# Treatment allocation

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- 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

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- 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

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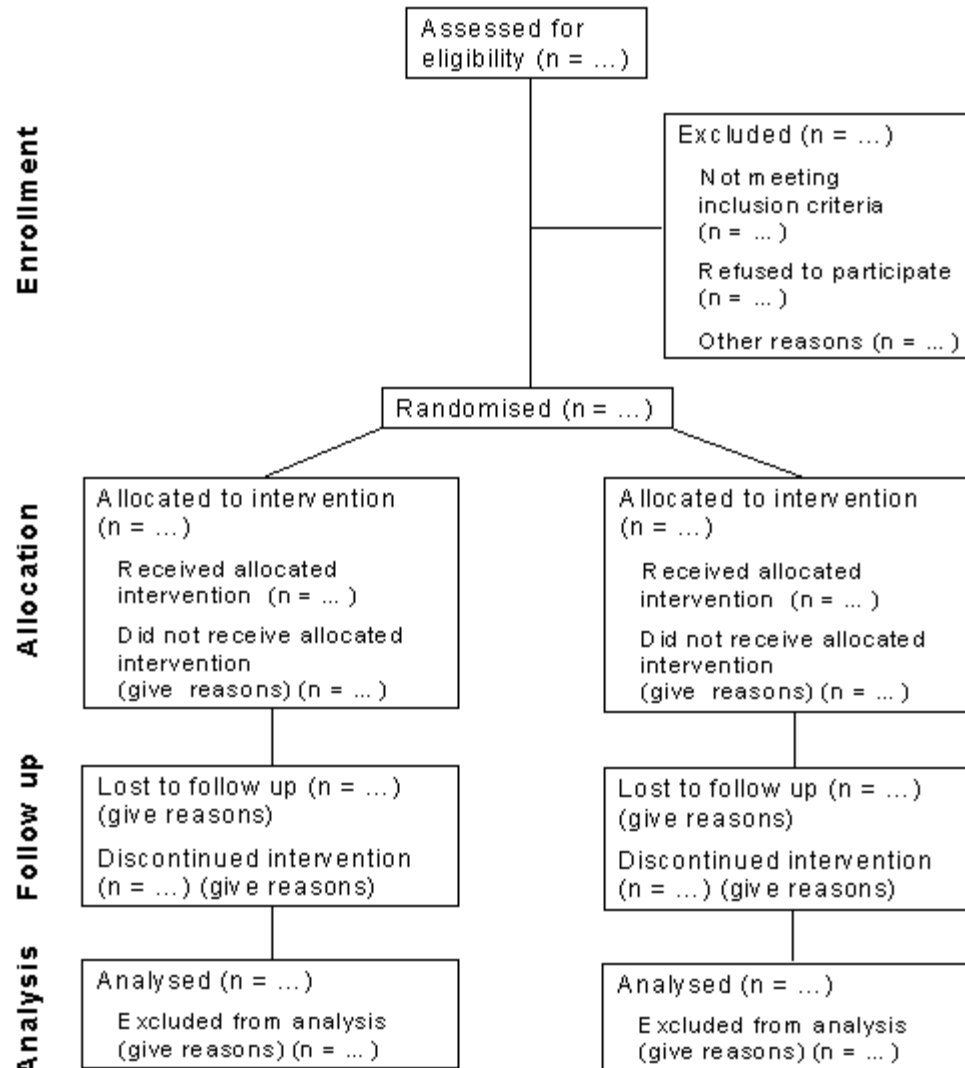
- Blinding is not always possible, but in most trials some element can be introduced
- **Double-blind:** neither patient nor clinical team know which treatment patient is receiving
- **Single-blind:** only patient does not know which treatment s/he is receiving
- Blinding is particularly important for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

# Loss to follow-up

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- 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

# CONSORT flow diagram



# Determining the study sample size

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- 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
- See session 6

# Primary Endpoint

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- 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 in START

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- Primary Endpoint (Composite outcome):
  - Serious AIDS-related event\* or death from AIDS
  - Serious non-AIDS-related event~ or any death not attributable to AIDS

\*1993 CDC definition excluding non-fatal HSV and oesophageal candidiasis and including Hodgkin's lymphoma);

~ CVD (MI, stroke or coronary revascularisation), ESRD (starting dialysis or transplantation, decompensated liver disease, NADC (excluding basal-cell or squamous-cell skin cancer)

# Secondary Endpoint

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- 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 in START

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- Primary Endpoint (Composite outcome):
  - Serious AIDS-related event\* or death from AIDS
  - Serious non-AIDS-related event~ or any death not attributable to AIDS
- Secondary Endpoints:
  - Major components of primary endpoint
  - Serious AIDS-related events
  - Serious non-AIDS-related events
  - Death from any cause
  - Grade 4 events
  - Unscheduled hospitalizations for reasons other than AIDS

# Trial endpoints in HIV

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- RCTs in the HIV setting can use a number of different primary endpoints
  - **Clinical:** AIDS event, death, serious non-AIDS event
  - **Immunological:**  $CD4 > 500$  cells/mm<sup>3</sup>, change in CD4
  - **Virological:** snapshot, 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?

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- 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?

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- **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

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- 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](http://www.consort-statement.org)

# CONSORT

- The CONSORT checklist for reporting and appraising RCTs

*Table.* CONSORT 2010 Checklist of Information to Include When Reporting a Randomized Trial\*

Section/Topic	Item Number	Checklist Item	Reported on Page Number
Title and abstract	1a	Identification as a randomized trial in the title	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance, see CONSORT for abstracts [21, 31])	
<b>Introduction</b>			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
<b>Methods</b>			
Trial design	3a	Description of trial design (such as parallel, factorial), including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined prespecified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	

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# Benefits and Limitations of RCTs

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- 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 4