Mini lecture:
Conducting and managing randomised controlled trials (RCTs)

Conflict of Interests

No conflict of interests to declare.

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
- The following session 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
- Important features of well performed RCTs
- The CONSORT statement

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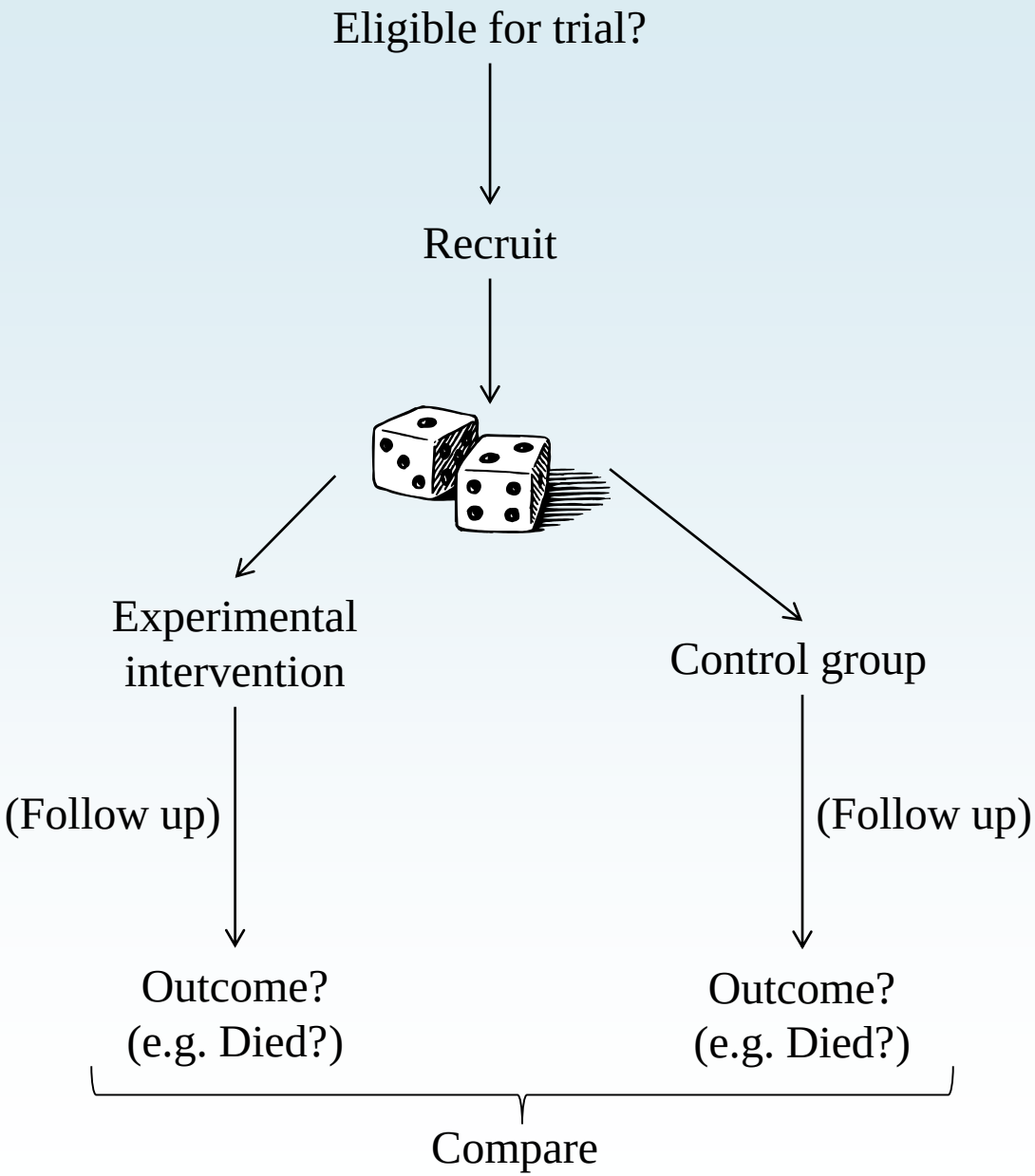
Eligible for trial?
Recruit
Experimental intervention
Control group
(Follow up)
(Follow up)
Outcome? (e.g. Died?)
Outcome? (e.g. Died?)
Compare

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

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)

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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 immediate ART result in a reduction in new AIDS events, non-AIDS events and death compared to deferred ART?

- Inclusion criteria: age ≥18 years, Karnofsky performance score ≥ 80, no previous AIDS, no previous serious non-AIDS, not currently pregnant or breast feeding

- Generalisable to all HIV-positive individuals?

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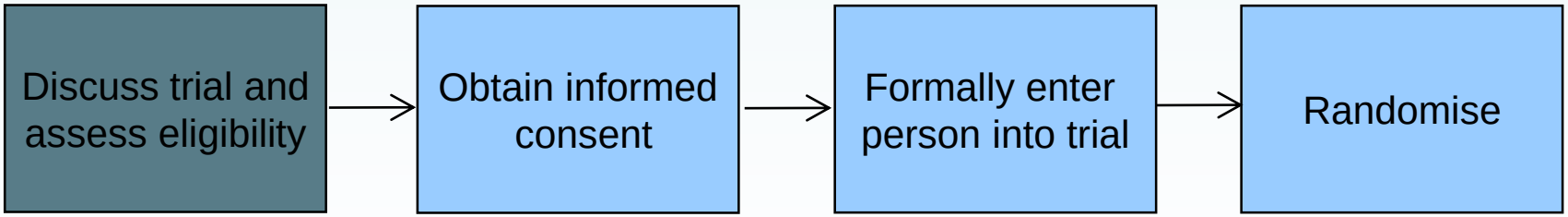
Treatment allocation

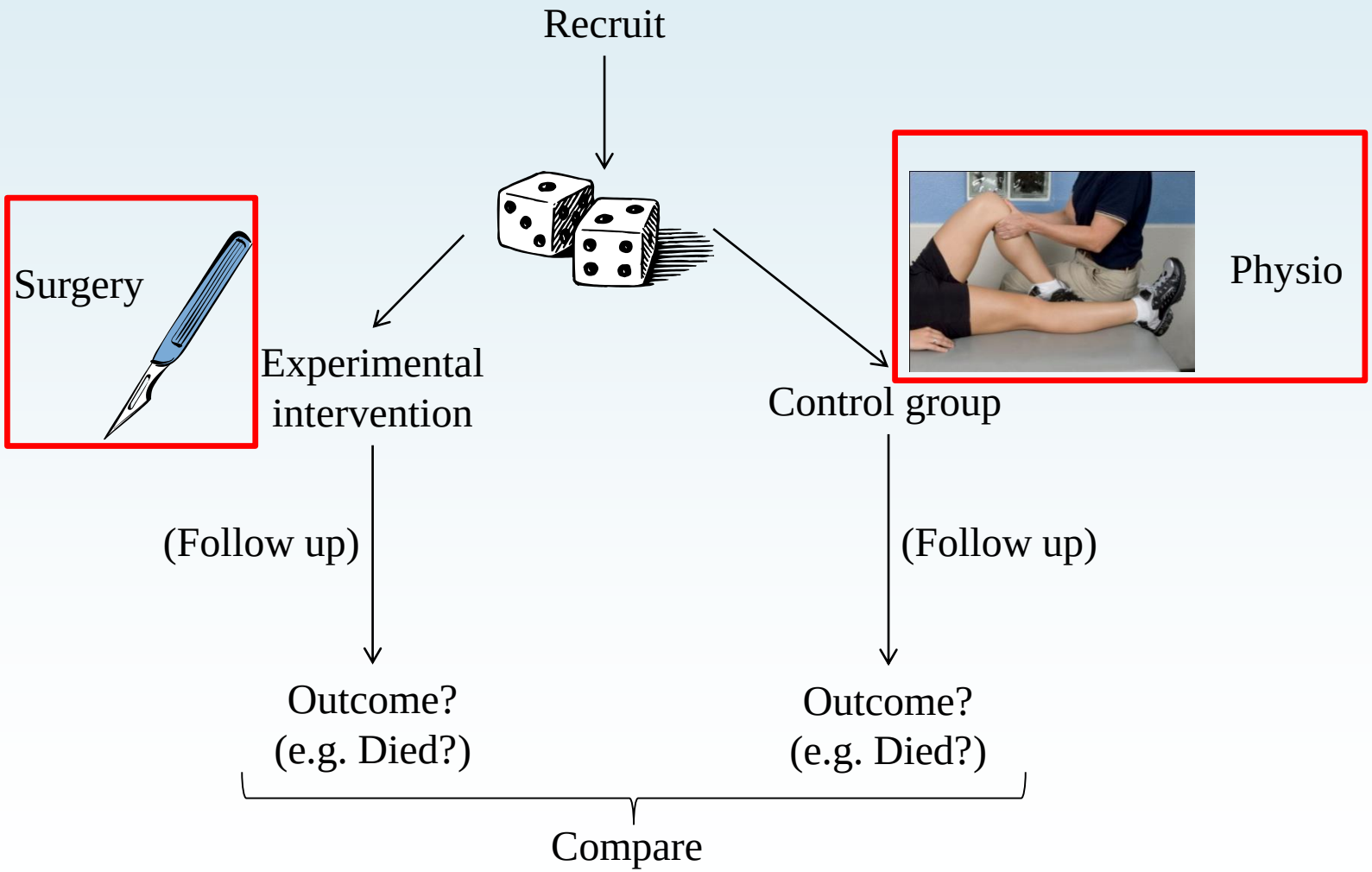
- A person's treatment allocation should not be known before they are entered into a trial
- If there is no concealment of treatment allocation, this may influence the decision to recruit, leading to imbalances



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 not always an option!



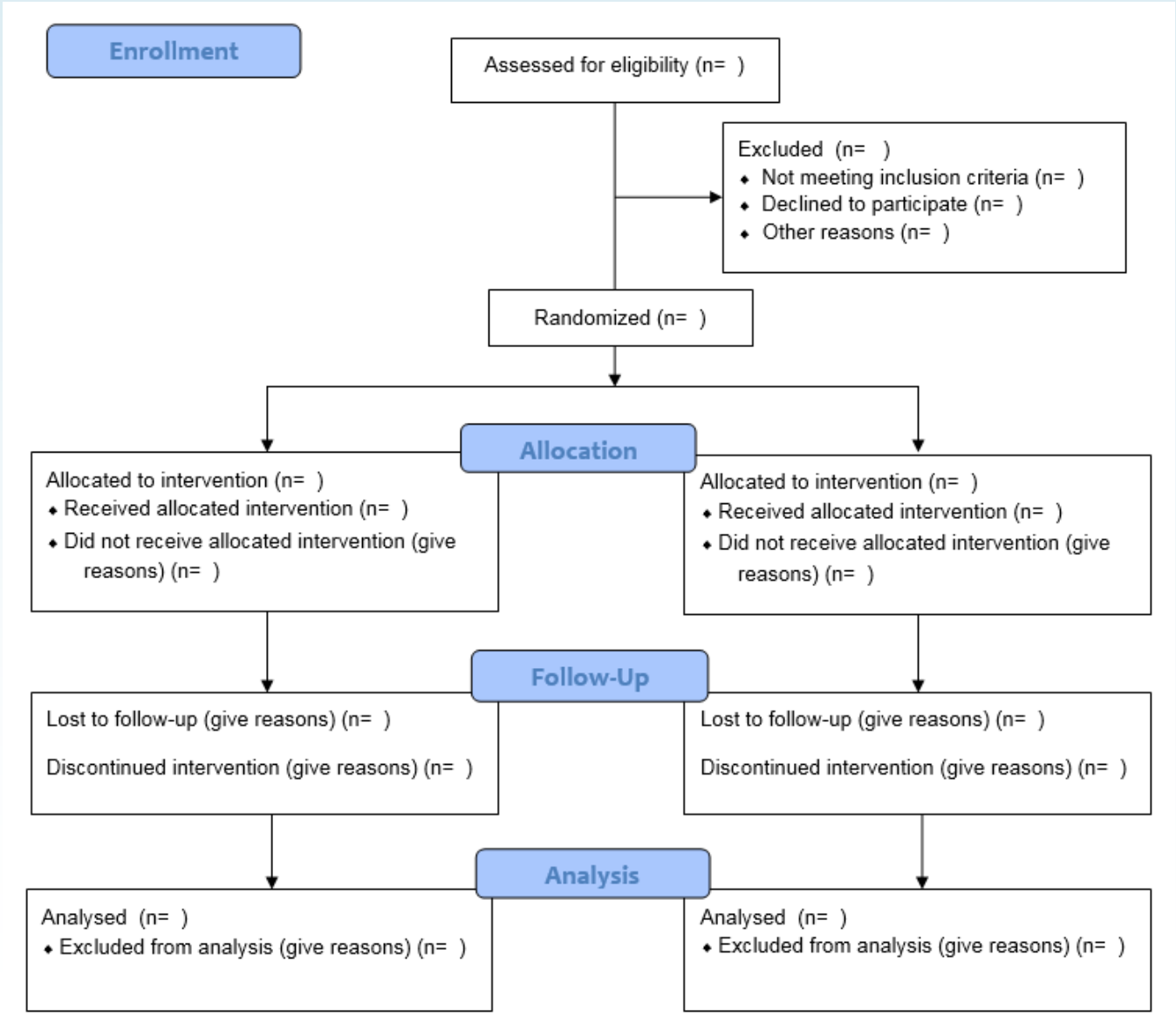
Blinding

- 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

CONSORT 2010 flow diagram



http://www.consort-statement.org/

Study Endpoints

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

Example: Primary and Secondary

- 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

*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)

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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 flow diagram and a checklist, which can be very helpful both for conducting and appraising RCTs
- 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])	
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	
	2b	Specific objectives or hypotheses	
Methods			
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	