Session 2: What study design should I choose?
There are many different approaches that we can use to answer a specific research question

Each study design has pros and cons that must be considered when identifying the optimal design to address a specific question

In this session we will consider the most commonly used study designs and will assess their advantages and disadvantages
Hierarchy of evidence

- RCT
- Cohort study
- Case-control study
- Cross-sectional study
- Case series/case note review
- ‘Expert’ opinion

BEST QUALITY EVIDENCE

WORST QUALITY EVIDENCE
Outline of Session

- RCTs – why do they top the evidence hierarchy?
- Different types of RCT
- Key features of well performed RCTs
- What are the limitations of RCTs?
- Cohort studies
- Case-control studies
- Other study designs – cross-sectional and ecologic studies
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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’ in a trial setting.
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
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.
Randomised Controlled Trials (RCTs)

- **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

- Randomisation
- New intervention
- Control group

Compare treatment groups

Starting point

Present time

Follow individuals
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

- Randomisation
- New Intervention
- Control group
- Wash out
- New Intervention
- Control group

Starting point
Present time
Follow individuals
Future time
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

Randomisation of Clinic/GP surgery

New Intervention
- All patients at clinic/surgery receive new intervention

Control group
- All patients at clinic/surgery receive control
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
  - 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
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)
Determining the study sample size

- 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
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
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](http://www.consort-statement.org)
The CONSORT statement is a checklist for reporting and appraising RCTs
- www.consort-statement.org

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<tr>
<th>Paper Section and Topic</th>
<th>Item Number</th>
<th>Descriptor</th>
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<tbody>
<tr>
<td>Title and abstract</td>
<td>1</td>
<td>How participants were allocated to interventions (e.g., “random allocation,” “randomized,” or “randomly assigned”).</td>
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<td>2</td>
<td>Scientific background and explanation of rationale.</td>
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<td>Introduction Background</td>
<td>3</td>
<td>Eligibility criteria for participants and the settings and locations where the data were collected.</td>
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<tr>
<td>Methods</td>
<td>4</td>
<td>Precise details of the interventions intended for each group and how and when they were actually administered.</td>
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<tr>
<td>Participants</td>
<td>5</td>
<td>Specific objectives and hypotheses.</td>
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<tr>
<td>Interventions</td>
<td>6</td>
<td>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).</td>
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RCTs may have some limitations

1. RCTs are only possible where there is an ‘intervention’ that people are willing to be randomised to
RCTs may have some limitations

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Examples...

- Impact of smoking and/or alcohol consumption on response to HAART
- Impact of co-infection with TB on HIV progression rates
RCTs may have some limitations

2. Patients in RCTs may not be representative of the clinic population, and follow-up of patients may differ to that in clinic – thus, outcomes may differ from what would normally be expected
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Examples...

- Patients may be selected on the basis of their likely adherence to treatment
- Patients may attend clinic more frequently – outcomes may be detected sooner
- Monitoring may be more intensive
RCTs may have some limitations

3. RCTs may be short (48 weeks) and may focus on two or three main treatment comparisons.
RCTs may have some limitations

4. RCTs may concentrate on short-term surrogate marker endpoints rather than long-term clinical events
4. RCTs may concentrate on short-term surrogate marker endpoints rather than long-term clinical events

Example...

- Early studies of IL-2 treatment in HIV infection focussed on CD4 endpoints only
Experimental / observational studies

- In an experimental study (e.g. an RCT) the investigator intervenes in the care of the patient in a pre-planned way and records the outcome.
- In an observational study, the investigator does not intervene in the care of the patient, but simply records outcomes when they occur.
- Common observational studies: cohort studies, case-control studies, cross-sectional studies.
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Cohort studies

- Follow a group of individuals over time to assess the incidence of a disease (or some other outcome)
- Are used to describe the effect of exposure to one or more factors of interest (potential risk factors) on the incidence of the outcome
- Can be prospective or retrospective/historical
Cohort studies

Disease-free

Exposed to factor
- Develop disease
- Do not develop disease

Not exposed to factor
- Develop disease
- Do not develop disease

Starting point
- Present time

Follow individuals
- Future time
Cohort Studies

- Advantages
  - Can assess temporal relationships between exposure and disease
  - Can make some attempt to assess cause and effect (although RCTs are preferable)
  - Can sometimes be more representative of clinic population

- Disadvantages
  - If disease is rare then cohort may need to be large and follow-up long
  - May be problem with loss to follow up
  - Cannot rule out presence of unmeasured confounding
Bias due to confounding

- Occurs when a spurious association arises due to a failure to fully adjust for factors related to both the risk factor and outcome.
Bias due to confounding

- Occurs when a spurious association arises due to a failure to fully adjust for factors related to both the risk factor and outcome.
Traditional interval cohort

- Patients often seen at a study site (often different to their place of care) on regular occasions for ‘study visits’ (e.g. 6-monthly)
- Participants may complete questionnaire on their health since last visit, treatments received, etc.
- Laboratory tests performed at pre-defined time intervals – this information is unlikely to be available at intervening times or when an event occurs, unless this coincides with a study visit
- Patients must give consent to participate
Traditional interval cohort - example

- The Multicenter AIDS Cohort Study (MACS)
- HIV+ve and HIV-ve individuals from 4 centres in Baltimore, Chicago, Los Angeles and Pittsburgh
- Participants recruited from 1984-1985 (n=4954), 1987-1991 (n=668) and 2001-2003 (n=1351)
- Visits are bi-annual – at each visit, participants undergo a detailed interview, physical examination, quality of life assessment and collection of blood for concomitant laboratory testing and storage
Observational databases

- Utilise data that are already routinely collected as part of patient’s medical care
- Patient does not have to attend for a particular study visit or fill in any questionnaires
- Laboratory testing will be performed according to clinical needs – will be more frequently monitored if patient is ill or requires investigation
- Some data items may be difficult to collect if not part of routine care
- May or may not require patient consent, depending on local regulations in country
Observational databases - example

- The UK Collaborative HIV Cohort (CHIC) Study
- All HIV+ve individuals who have attended one of 11 UK clinical centres at least once between 1996 and 2012
- Median (inter-quartile range) time between consecutive CD4 counts: 95 (71-137) days
- Current dataset includes information on >47,000 patients
- Median (range) duration of follow-up: around 4 years (1 day – 20+ years) years
## Distinction between the two types of cohort

<table>
<thead>
<tr>
<th></th>
<th>Traditional cohort</th>
<th>Observational database</th>
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<tbody>
<tr>
<td><strong>Study visits</strong></td>
<td>At regular defined intervals</td>
<td>As and when patient attends for care</td>
</tr>
<tr>
<td><strong>Data entry</strong></td>
<td>Often form-based</td>
<td>Often electronic transfer of data</td>
</tr>
<tr>
<td><strong>Representative?</strong></td>
<td>May not be – patients must give consent</td>
<td>Often includes all patients – therefore representative</td>
</tr>
<tr>
<td><strong>Loss to follow-up</strong></td>
<td>May be substantial, but can be determined</td>
<td>May be difficult to assess as some patients attend infrequently</td>
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<tr>
<td><strong>Data quality</strong></td>
<td>Can introduce quality control measures</td>
<td>Difficult to regulate</td>
</tr>
<tr>
<td><strong>Data items collected</strong></td>
<td>Can determine at outset and change over time</td>
<td>May be difficult to influence</td>
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Choosing the optimal sample size

- The power of a cohort is largely determined by the number of events that occur; this can be increased either by increasing the size of the cohort or by lengthening the period of follow-up.
- Whilst large cohorts may sometimes be desirable, the real value of many cohorts is provided by their length of follow-up and detailed data collection.
Examples

- Royal Free Haemophilia HIV cohort
  - 111 men with haemophilia infected with HIV between 1979 and 1985; over the 25 years of the study, the cohort published >100 papers in peer-reviewed journals, including many that were highly influential at the time

- The D:A:D Study
  - Using existing data, it was estimated that 100 incident myocardial infarction (MI) cases would be required to detect a doubling in the risk of MI in those receiving cART; the investigators calculated that they would require 30,000 PYFU to achieve this
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Case-control studies

- Retrospective studies in which a group of patients with a disease (cases) are compared to a group of patients without the disease (controls)
- Aim is to see whether exposure to any factor has occurred more or less frequently in the past in cases than in controls
- Cases and controls may often be matched on basic demographic information (e.g. sex and age) to make the two groups as similar as possible
Case-control studies

Exposed to factor

Disease (cases)

Not exposed to factor

Exposed to factor

No disease (controls)

Not exposed to factor

Compare cases and controls

Starting point

Past time

Trace individuals
Case control studies

- **Advantages**
  - Relatively cheap, quick and easy to carry out
  - No loss-to follow up
  - Particularly suitable for rare events

- **Disadvantages**
  - Potential for recall bias
  - Timing of events cannot be reliably established
  - Cannot assess incidence (proportion with disease is fixed as part of the study design)
Recall bias

- Tendency of cases to ‘recall’ information (particularly relating to exposure) differently to cases
- Can lead to apparent association between outcome and exposure, even if the association does not exist
- Example: cigarette smoking and lung cancer
General points

- Retrospective, so reliant on recorded data (which may contain inaccuracies and be subject to missing data)
- Care should always be taken to ensure that the timing of events (e.g. exposures, outcome) is captured accurately
- As with cohort studies, criteria for selection of cases/controls (e.g. outcome) and exposures should be standardised, precise and unambiguous
Selection of cases

- Criteria for selection may include clinical definitions (e.g. CDC AIDS definition), laboratory or histological classifications

- Must decide whether the study will include only incident cases (i.e. new cases identified in population during study period) or prevalent cases (cases who had already been diagnosed at the study of the study period)
Selection of controls

- Controls should be drawn from the same population as cases
- May include 1 (1:1) or >1 (n:1) control per case, but little to be gained from >4 controls per case
- Controls may be people using the same hospital as cases (hospital controls) – if so, care should be taken to ensure that they don’t have another condition that is also related to the exposure
- Use of friends/relatives/neighbours of cases may give cases of similar socio-economic background
Matching in case-control studies

- Cases and controls may often be matched on a small number of factors associated with both the exposure and outcome (e.g. sex, age)
- Matching may help to minimise effects of confounding and may increase study power
- However, it may be impractical to match patients on many factors and special analytical methods may be required if matching is used
- If a factor has been used in matching, then it is not possible to evaluate its association with the outcome
Risk factors for thrombocytopenia in HIV-infected persons attending one of two HIV clinics in New York

Cases: patients with platelet count <100x10^9/L persisting for >3 consecutive months; cases could be incident or prevalent (n=73)

Controls: patients with at least one outpatient record but no thrombocytopenia (n=73)

Cases were matched 1:1 by age (+5 years), sex and first appointment (+6 months)

Marks KM et al; JAIDS 2009; 52: 595-599.
Nested case-control studies

- A case-control study may often be nested within a larger cohort or RCT
- This provides a means of studying associations between novel biomarkers and disease outcome, particularly if these are expensive to measure
- Alternatively, may be useful if additional detailed information is required which cannot be collected through standard data collection mechanism
- Example: nested case-control study in SMART trial, measured lipoprotein particles in 248 patients with a CVD event (cases) and 480 matched controls
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Cross-sectional studies

- Carried out at a single point in time
- Often used to assess the prevalence of a condition, to describe the current situation or to assess attitudes and beliefs
- Whilst relatively cheap and quick to perform, it is not possible to estimate the incidence of disease, only the prevalence
Ecologic studies

• Epidemiological study where unit of observation is a community, country or group of individuals

• Aim to assess whether a summary measure of outcome (e.g. mortality rate) at community level is associated with other community-level factors

• E.g. association between national mortality rates and country-specific nutritional indices

• Ecologic studies particularly vulnerable to the ecological fallacy
Density of drinking establishments and HIV prevalence, Namibia

- **Hypotheses:**
  - **Primary:** density of drinking establishments is positively associated with HIV prevalence
  - **Secondary:** areas with higher incidences of unregistered shebeens will have higher HIV prevalence compared to those with higher densities of other drinking establishments

- **N=9** socially and ethnically diverse neighbourhoods in Luderitz, Namibia

- Density of drinking establishments, registered/unregistered shebeens and bottle stores calculated for each neighbourhood; HIV prevalence by neighbourhood abstracted from medical records

Nichols BE *et al.* AIDS Behav 2012;16: 829-834
Density of drinking establishments and HIV prevalence, Namibia

Nichols BE et al. AIDS Behav 2012;16: 829-834
Which study design?

- Largely an issue of resources, although it is possible to use a combination of approaches.
- Important to consider whether the data collected using a particular design will be able to answer the question of interest.
- Can often be a compromise between costs and the amount and type of data that can be collected.
- Ultimately it is important to be aware of, and transparent about, the limitations of each study design.
Where to go for guidance?

- Similar to CONSORT but provides guidance on reporting of observational studies
- Provides a checklist for reporting studies, as well as educational material
- Recommendations limited to 3 main designs of observational studies
  - Cohort
  - Case-control
  - Cross-sectional studies
- www.strobe-statement.org
Summary

- Whilst RCTs are perceived to provide the highest quality evidence when assessing associations, they may sometimes suffer from limitations which make them inappropriate for use when addressing certain questions.

- In these situations, observational studies may provide useful information.

- However, observational studies are always subject to bias and must be designed, managed, and interpreted with caution so as to minimise this.