Mini lecture:
Conducting and managing observational studies

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- Gilead Sciences
- ViiV Healthcare
- Janssen-Cilag
Outline of Session

- The limitations of RCTs
- Designing a cohort study
- Designing a case-control study
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- Designing a cohort study
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Limitations of RCTs

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

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.
3. RCTs may be short (48/96 weeks) and may focus on two or three main treatment comparisons
Limitations of RCTs

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
Outline of Session

• The limitations of RCTs
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• Designing a case-control study
Reminder – Cohort Studies

Starting point → Present time → Follow individuals → Future time

Disease-free

Exposed to factor
  - Develop disease
  - Do not develop disease

Not exposed to factor
  - Develop disease
  - Do not develop disease
Basic study design issues

- Important to have a clear objective for the study and to design accordingly
- Ensure that sample size will be sufficient to address at least one key hypothesis
- Participants included in cohort should be representative of the population to which the results will be generalised
Ways of following individuals

• Failure to ascertain all disease events can result in under-estimation of event rates

• Can also lead to bias in comparisons between exposure levels

• Nationally recorded registers/databases
  - Death certificates
  - Disease registers, e.g. cancer registry
  - (In UK) NHS electronic information systems e.g. hospital episode statistics, GP databases
  - Office of national statistics (ONS)

• Other efforts to contact people (e.g. phone call, letter)
Key outcome variables

- Ideal outcome should address the primary aim of the study, have biological/clinical relevance and be appropriate for the population studied

- Should be ascertainable on all cohort participants (including those lost-to-follow-up)
Toxicity outcomes

- Cohorts may be the only study design that is able to capture data on long-term toxicities of HAART
- Toxicity outcomes may be based on clinical symptoms and/or laboratory data
- Need to be aware of possible biases when interpreting results from such studies:
  - Irregular/infrequent laboratory monitoring
  - Selective laboratory monitoring
  - Between-clinic assay variability
  - Clinic differences in monitoring policies
  - Bias due to confounding
What other data should be captured?

- Potential confounders (traditional definition):
  - Factors that are associated both with the exposure and outcome of interest
  - Failure to adjust for confounders may introduce bias, as they may lead to a spurious association between the exposure and outcome

- Effect modifiers:
  - Factors that modify the size of the association in one group compared to another
  - Provide important clinical information
  - Often referred to as a ‘statistical interaction’
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

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Alcohol consumption

Smoking → ? → Cardiovascular disease
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• The limitations of RCTs
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Reminder – Case-control studies

- Exposed to factor
  - Disease (cases)
  - No disease (controls)
  - Not exposed to factor

Compare cases and controls

Starting point

Past time

Trace individuals
General points

• Retrospective, so reliant on recorded data (which may contain inaccuracies and be subject to missing data)
• Useful for rare diseases and diseases with long latency periods
• Care should always be taken to ensure that the timing of events (e.g. exposures, outcome) is captured accurately
Selection of cases

- Develop a **case definition** to identify cases that is precise, objective and unambiguous

- This could include:
  - Histologically or laboratory confirmed diagnosis
  - Clinical diagnosis
  - Stages of disease (standardised e.g. CDC AIDS definition)

- Source of cases needs to be carefully considered
  - Population based or clinic based cases?
  - How complete is your source of cases?
  - Time lag between diagnosis and notification/ identification?
  - What about patients who may have moved or died?
Selection of controls

- Controls should be selected to be as similar to cases as possible except for the outcome of interest
  - Drawn from the same population
  - Fulfil the same eligibility criteria

- Aim is to provide estimate of “level of exposure” in those without outcome

- Should represent same population as cases are
  - General population (voting registries, random digit dialling etc)
  - Hospital/clinic based controls – care should be taken to ensure they don’t have another condition also related to the exposure
  - People related to the case – i.e. friends, relatives, neighbours
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

• But, 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
Recall bias

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

- Case-control study may often be nested within a larger cohort or RCT
- Provides a means of studying associations between novel biomarkers and disease outcome
- May also 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
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