Mini lecture 3:

Conducting and managing observational studies

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Conflict of interest

I have received funding for the membership of Data Safety and Monitoring Boards, Advisory Boards and for the preparation of educational materials from:

- 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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Limitations of RCTs

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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

Limitations of RCTs

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

Limitations of RCTs

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

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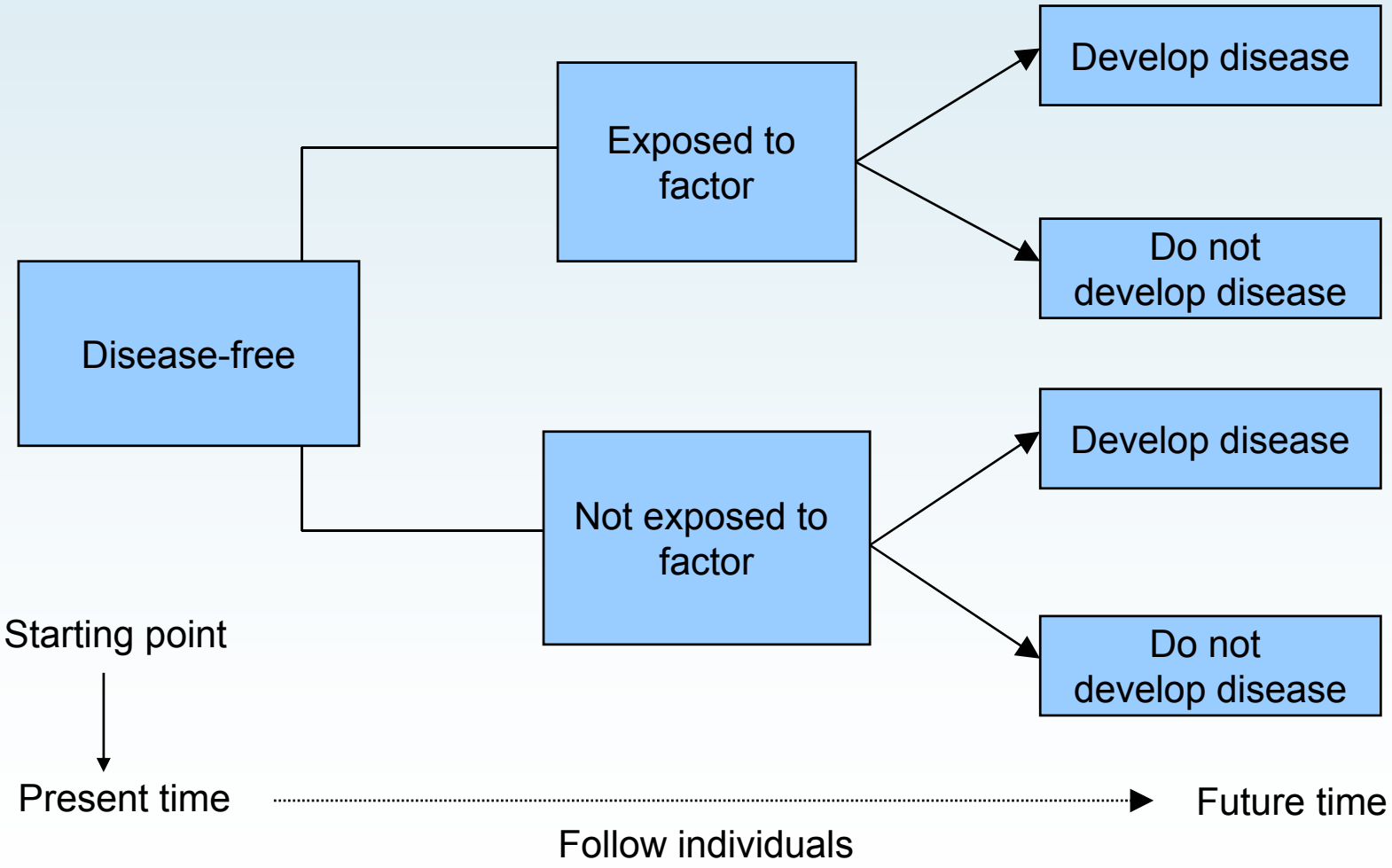
Reminder – Cohort Studies



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

Open vs Closed

- Closed/Fixed cohorts
  - New patients unable to join study
  - Participant population is fixed at baseline.
  - People can only exit study (withdrawal, death)
- Open/Dynamic cohorts
  - People move in and out of the study.
  - New patients able to join

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 under go a detailed interview, physical examination, quality of life assessment and collection of blood for concomitant laboratory testing and storage

Observational databases

- Utilise data routinely collected as part of patient's medical care
- Patient does not attend for a particular study visit
- Laboratory testing performed according to clinical need – will be more frequent 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
- Increasingly common with emergence of electronic record systems

Observational databases - example

- French Hospitals Database on HIV (FHDH)
- Hospital-based multicentre open cohort with inclusions since 1989
- Currently has information >120,000 patients (53% of French HIV+ population in care; representative in terms of geographical origin, sex, age)
- Standardized variables collected at each outpatient visit/hospital admission at which new clinical condition diagnosed, new treatment prescribed, laboratory test performed and/or at least every 6 months

Mary-Krause et al; Int J Epidemiol; 2014; 43(5): 1425-1436

Ways of following individuals

- Failure to ascertain all disease events, including due to loss to follow-up, 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

- An ideal outcome should address the primary aim of the study, have biological/clinical relevance and be appropriate for the population studied
- It should be ascertainable on all cohort participants (including those lost-to-follow-up)

Toxicity outcomes

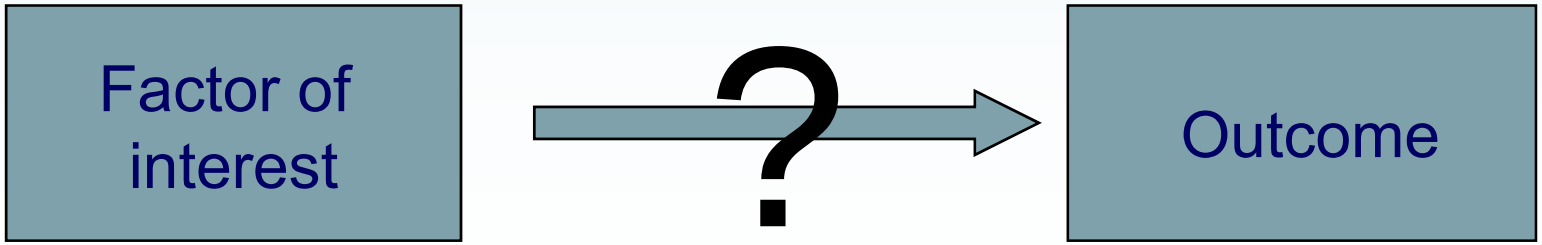
- Cohorts may be the only study design that is able to capture data on long-term toxicities of HAART
- Toxicity outcomes may be based on clinical symptoms and/or laboratory data
- Need to be aware of possible biases when interpreting results from such studies:
  - Irregular/infrequent laboratory monitoring
  - 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.



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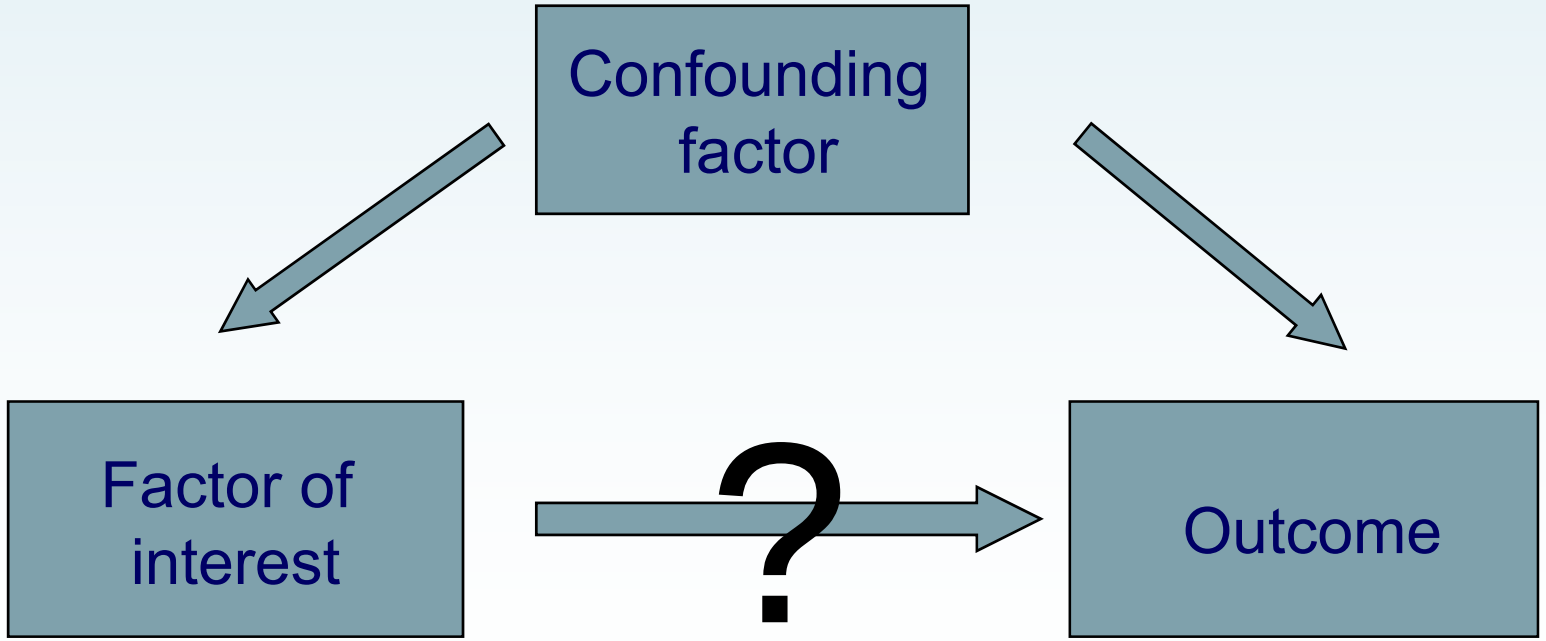

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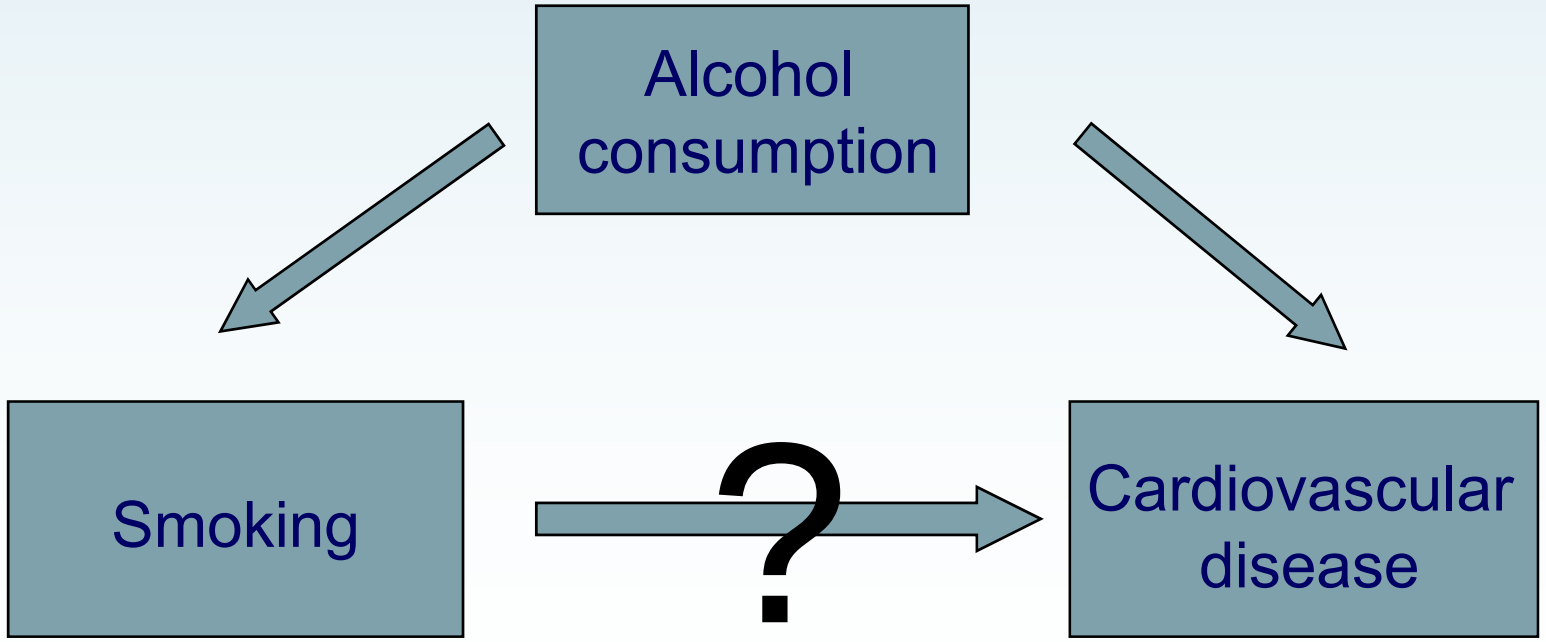

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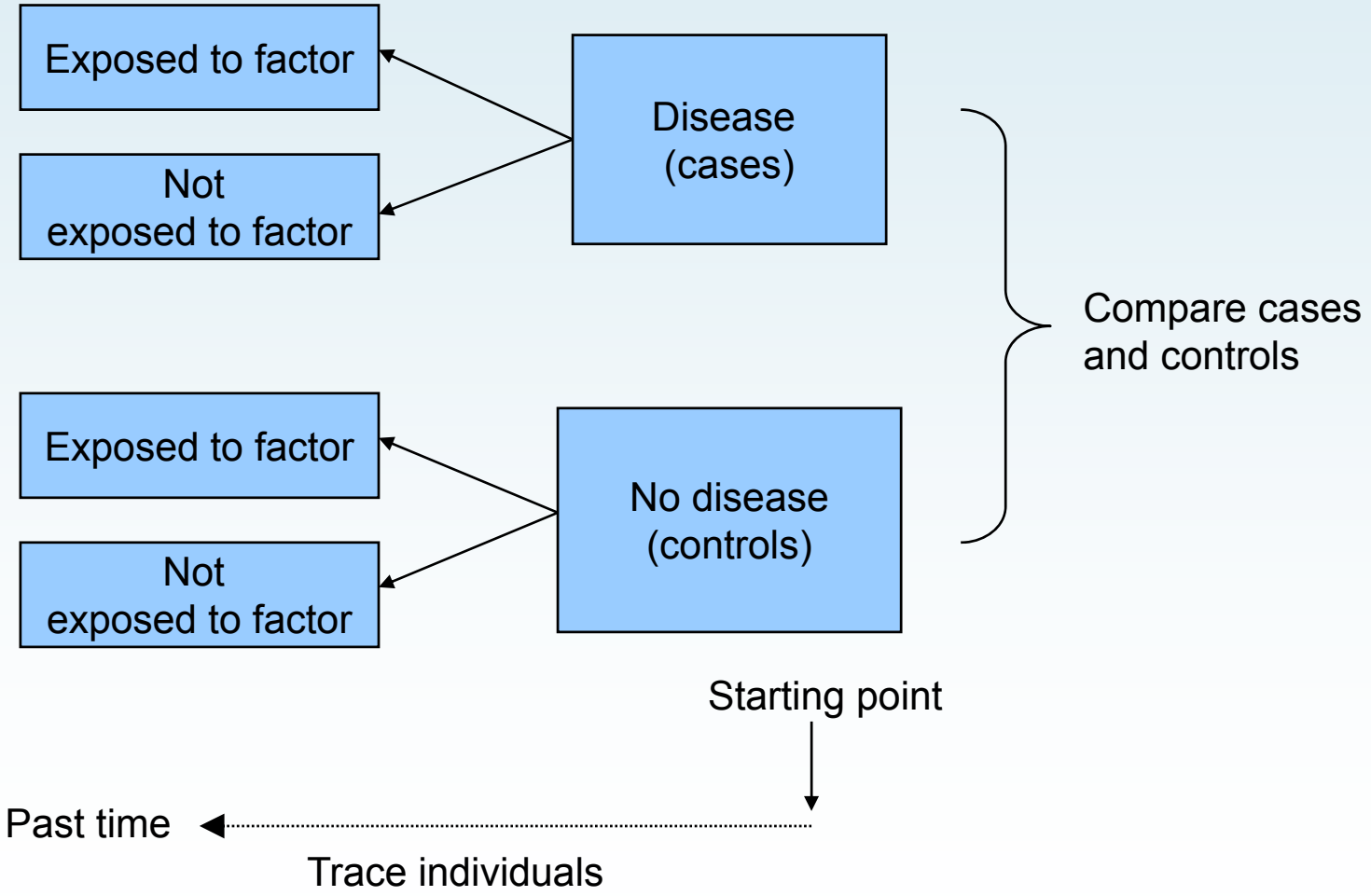
- Observational studies – their benefits and limitations
- Designing a cohort study
- Designing a case-control study

Reminder – Case-control studies



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?
  - Is there a 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
- Purpose is to provide an estimate of “level of exposure” in those without outcome
- Should represent population from which the cases are drawn
  - 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
- 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

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

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

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