Choosing the right study design

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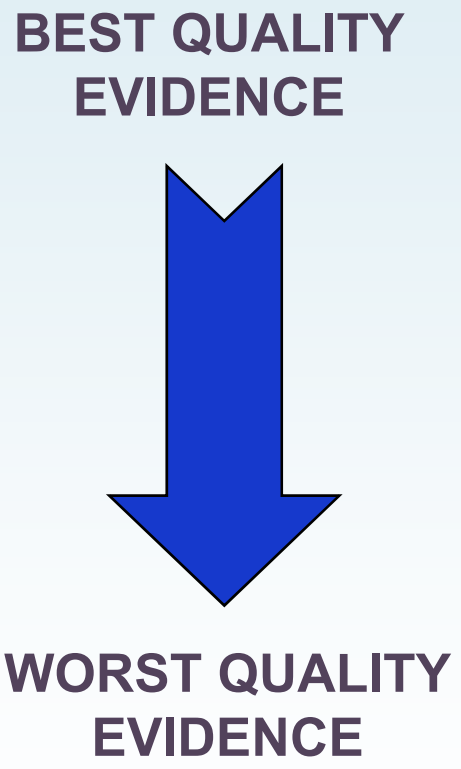
Conflicts of interest

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

Main types of study design

- Randomised controlled trial (RCT)
- Cohort study
- Case-control study
- Cross-sectional study
- Case series/case note review
- ‘Expert’ opinion



Experimental vs. Observational

Experimental study

Investigator **intervenes** in the care of the patient in a **pre-planned, experimental way** and records the outcome

Observational study

Investigator does not intervene in the care of a patient in any way, other than what is routine clinical care; investigator simply **records** what happens

Cross-sectional vs. Longitudinal

Cross-sectional study

Patients are studied at a **single time-point only** (e.g. patients are surveyed on a single day, patients are interviewed at the start of therapy)

Longitudinal study

Patients are followed over a **period of time** (days, months, years…)

Assessing causality (Bradford Hill criteria)

- Cause should precede effect
- Association should be plausible (i.e. biologically sensible)
- Results from different studies should be consistent
- Association should be strong
- Should be a dose-response relationship between the cause and effect
- Removal of cause should reduce risk of the effect

Incidence vs. prevalence

Incidence: proportion of patients **without the event of interest** who **develop the event** over the study period

- Can only estimate from a longitudinal study
- Must exclude those who have the event at start of study from the calculation

Prevalence: proportion of **all patients in study** who have the event **at a particular point in time**

- Can estimate prevalence from longitudinal or cross-sectional studies
- Generally include all patients in calculation

Randomised controlled trials (RCTs)

- **Experimental** and **longitudinal**
- **Comparative** – comparison of two or more treatment strategies (e.g. new regimen vs. existing regimen)
- Control group allows us to conclude that any improvement in outcome is due to the test treatment rather than some other factor
- Where no existing regimen exists, control group may consist of untreated patients (usually receive a **placebo**)

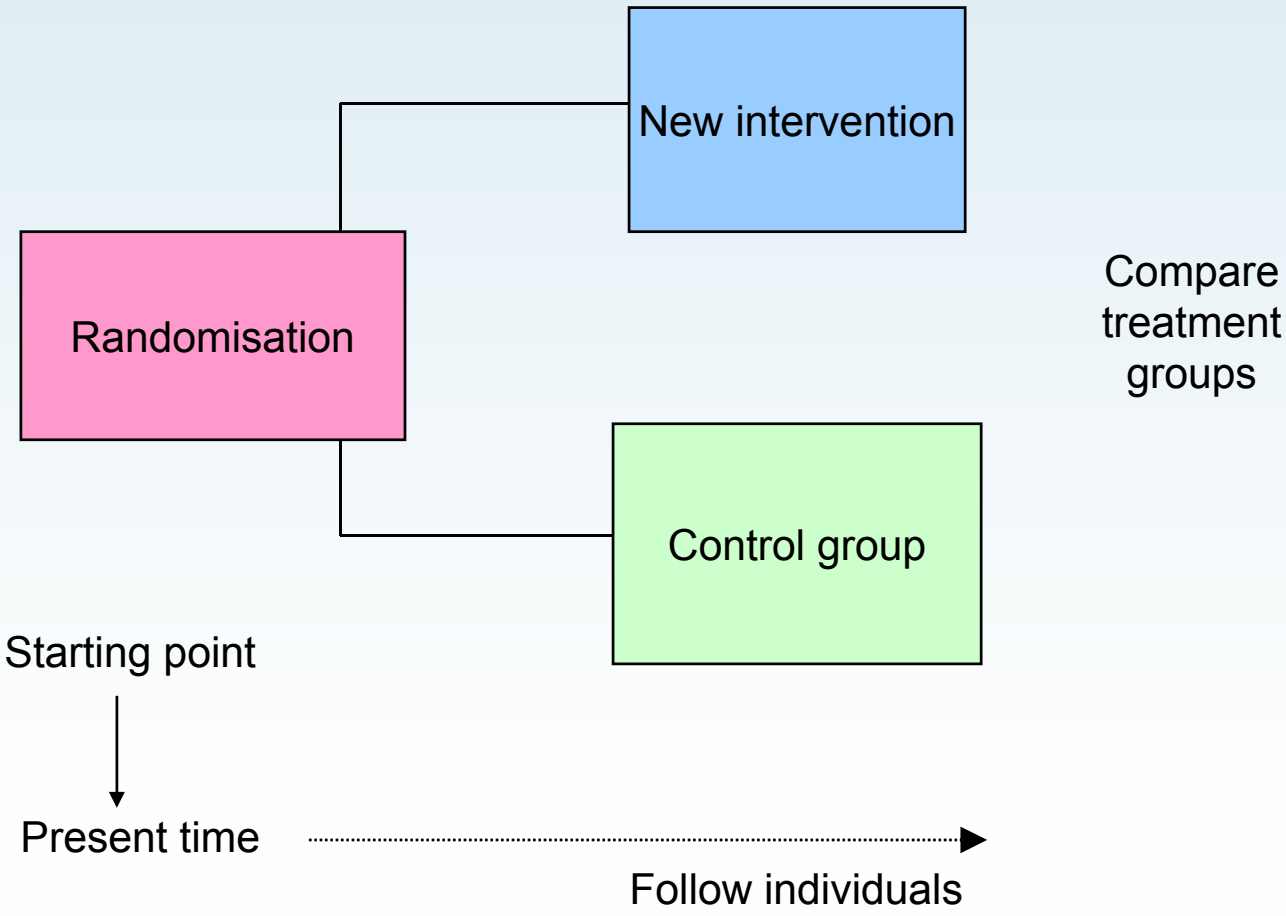
Randomised controlled trials (RCTs)

- Subjects allocated to treatment groups by process known as **randomisation**
- Ensures that treatment groups are similar at start of trial; any differences are due to chance only
- Randomisation is most important feature of a RCT and is why RCTs are perceived to be the gold-standard approach to obtaining evidence of a treatment effect
- If you can randomise you should – however, randomisation is not always possible or feasible

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



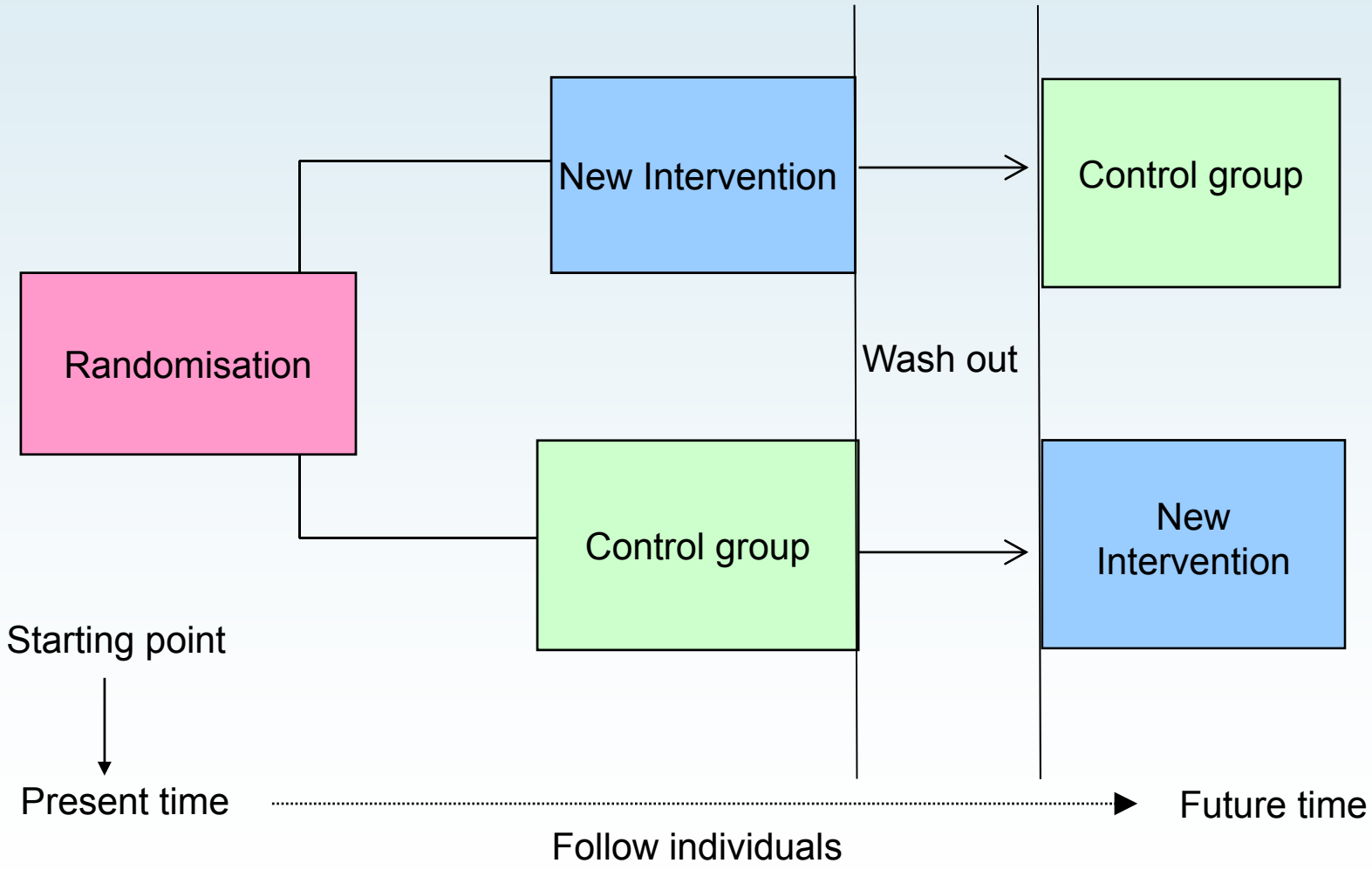
Example – Parallel Group trial

- Trial evaluating when to start ART among HIV-positive individuals who are ART-naïve with CD4 count >500 cells/mm^3
- Randomised to:
  - Initiate ART immediately following randomisation

  OR
  - Defer ART until CD4 count is <350 cells/mm^3 or AIDS develops
- Endpoints: Serious AIDS, death from AIDS, serious non-AIDS and death not attributable to AIDS

INSIGHT START Study Group *N Eng J Med* 2015: **373**: 795-807.

Cross-over trials



Example – Crossover trial

- Safety and acceptability of Reality condom for MSM
- Sero-concordant couples randomised to:
  - Reality condoms for 6 weeks then latex condoms for 6 weeks

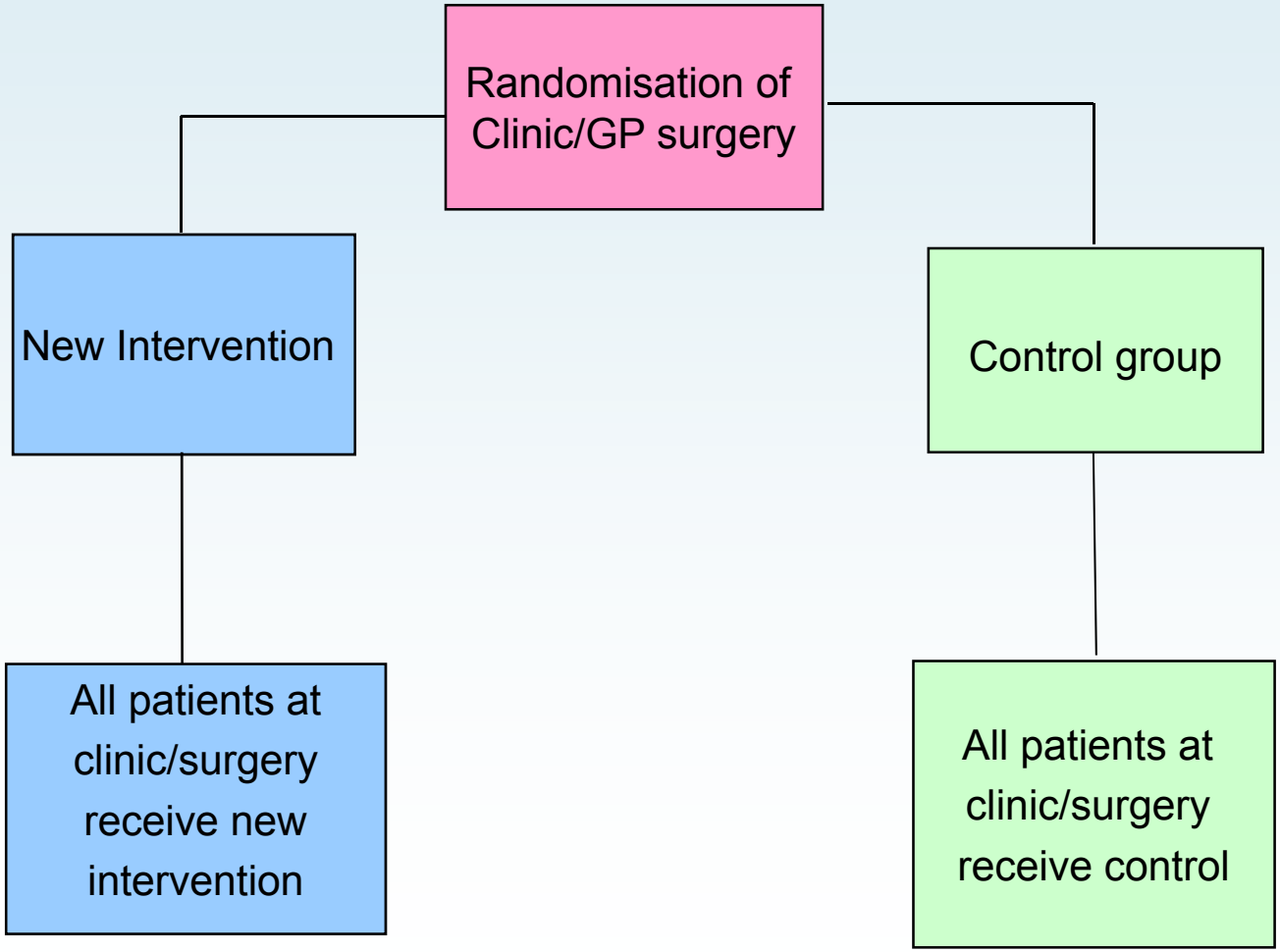
  OR
  - Latex condoms for 6 weeks then Reality condoms for 6 weeks
- Endpoints: frequency of slippage with removal, pain or discomfort on use, rectal bleeding, willingness to use in future

Renzi C *et al. AIDS* 2003; **17**: 727-31.

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



Example – Cluster randomised trial

- RCT of malaria prevention in Gambia
- 70 villages randomised to:
  - Long lasting insecticidal nets (LLIN)

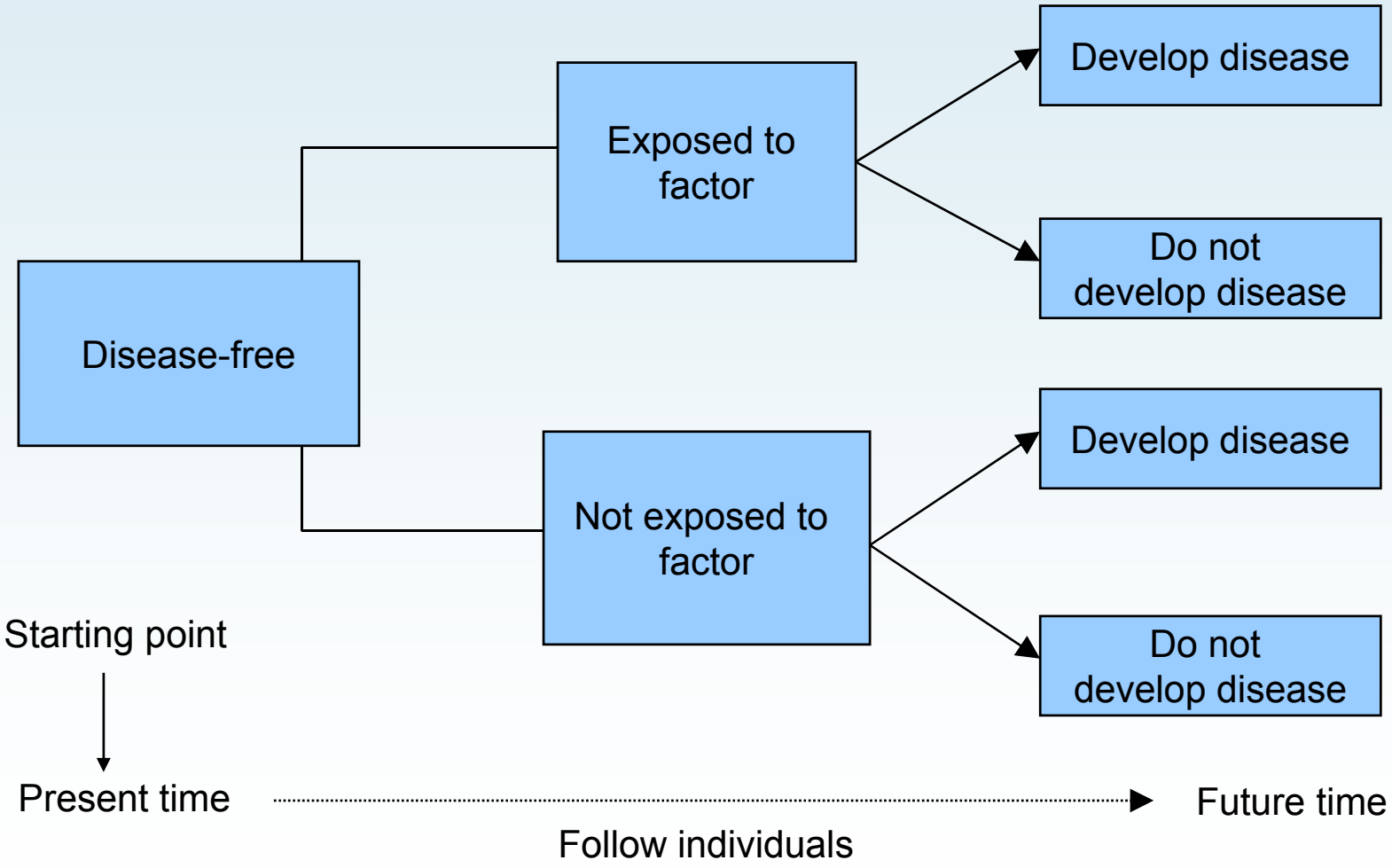
  OR
  - LLIN + indoor residual spraying
- Endpoints:
  - incidence of clinical malaria assessed by passive case detection in >7,000 children
  - number of *Anopheles gambiae* sensu lato mosquitoes collected per light trap per night

Pinder M *et al*. *Lancet* 2015; **385**: 1436-46.

Cohort studies

- **Observational** and **longitudinal**
- Follow a group of individuals over time to assess the **incidence** of a disease (or some other outcome)
- Can look at the effect of exposure to a number of factors of interest (potential risk factors) on the incidence of the outcome

Cohort studies



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 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
- Information on >120,000 patients (53% of French HIV+ population in care)
- Standardized variables collected at each outpatient visit/hospital admission (clinical conditions, treatments prescribed, laboratory tests) and/or at least every 6 months

Mary-Krause *et al*. *Int J Epidemiol* 2014; **43**: 1425-36.

Pros and cons of cohort studies

Advantages

- Can assess **temporal relationship** between exposure and disease (i.e. we know which event occurs first)
- Can make some attempt to assess cause and effect

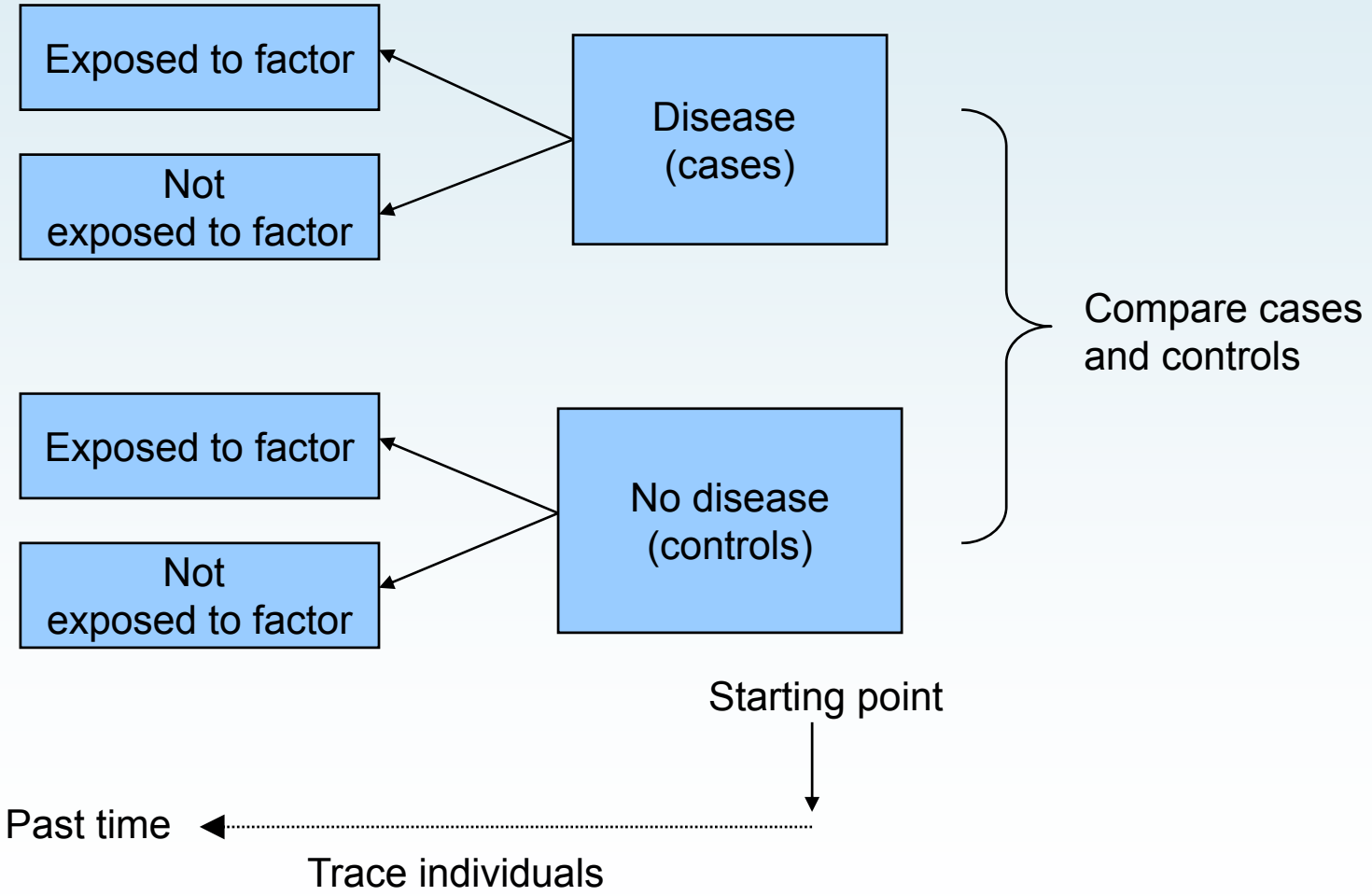
Disadvantages

- If the disease is rare then cohort may have to be very large and follow-up long (i.e. expensive)
- May be problem with **loss-to-follow-up**
- Potential for bias due to **confounding**

Case-control studies

- **Observational** and **longitudinal** (retrospective)
- Group of patients with a disease (cases) are compared to group of patients without the disease (controls)
- Aim: has exposure to any factor 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



Pros and cons of case-control studies

Advantages

- Relatively cheap, quick and easy to conduct
- No loss-to-follow-up
- Suitable for rare events

Disadvantages

- Potential for **recall bias**
- Timing of events cannot be reliably established – therefore more difficult to assess causality
- Cannot assess incidence (proportion with disease is fixed as part of the study design)

Predictive factors for HIV seroconversion

Cases: Persons attending a Spanish HIV unit who seroconverted to HIV >3 months after their first visit following a specific risk of HIV (n=69)

Controls: Persons attending same unit after a risk of HIV who did not seroconvert, matched by gender, birthdate and date (n=69)

Variables: Demographics, serostatus of partner, exposure risk, previous PEP and STI, PEP regimen, previous HIV testing and presence of STI at baseline

Conclusions: Being MSM, having had previous PEP, an HIV-positive sexual partner and previous STI were all predictive factors for HIV seroconversion

Leal L *et al*. *AIDS Res Hum Retroviruses* 2016; **32**: 1016-21.

Cross-sectional studies

- Carried out at a **single point in time** – no follow-up
- Often used to assess the prevalence of a condition, to describe the current situation or to assess attitudes and beliefs
- Advantages – relatively cheap and quick
- Disadvantages – not possible to estimate incidence of disease, but can assess prevalence

Alcohol use in HIV+ve persons

- Cross-sectional study: 2230 HIV+ve patients in 3 primary care clinics in Pretoria
  - - 25.1% reported hazardous or harmful drinking
  - - 2.0% had possible alcohol dependence
- In multivariable analyses, high-risk drinking associated with male gender, never being married, tobacco use, greater independence and more depressive symptoms
- Recommendation of routine screening for alcohol use and harm reduction interventions

Huis In't Veld D *et al.* *Int J STD AIDS* 2017; **28**: 651-9.

Case series / case-note review

- Fairly low form of evidence but can provide useful preliminary data
- Useful as a descriptive tool – i.e. to define the natural history of disease or to describe current practices
- No comparative element – therefore not possible to show a link between exposure and disease
- Usually retrospective – therefore potential for problems with historical data

Choosing an appropriate study design

- The hypotheses that can be tested in any study, particularly regarding ‘cause and effect’, will depend on the study design
- Some study designs may offer ‘benefits’ in terms of cost, time and administrative effort, but in general, studies that are quicker and cheaper to perform will provide weaker evidence
- Must have a clear idea of the hypotheses being tested before choosing the optimal study design

Research question

QUESTION:

Do elderly (>70 years), Irish, female patients with metabolic syndrome and first presentation of TIA who have standard, multi-specialist (endocrinology, cardiovascular, gerontology) care have higher one-year mortality compared to those receiving integrated (endocrinology, cardiovascular, gerontology) guideline-driven, single centre specialist care within a metabolic clinic?

Summary

- The hypotheses that can be tested in any study, particularly regarding ‘cause and effect’, will depend on the study design
- Some study designs may ‘offer’ benefits in terms of cost, time and administrative effort – these are likely to provide weaker evidence
- All studies involve the selection of a sample – if the sample is not representative, the results of the study may be biased