Choosing the right study design

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)

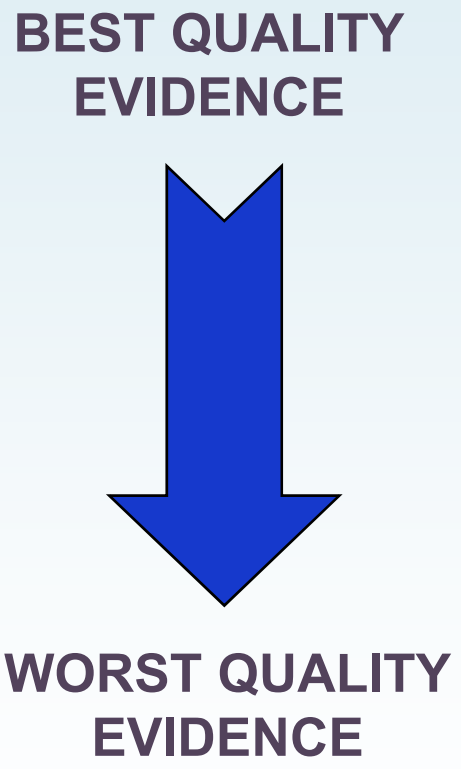
Cohort study

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**)

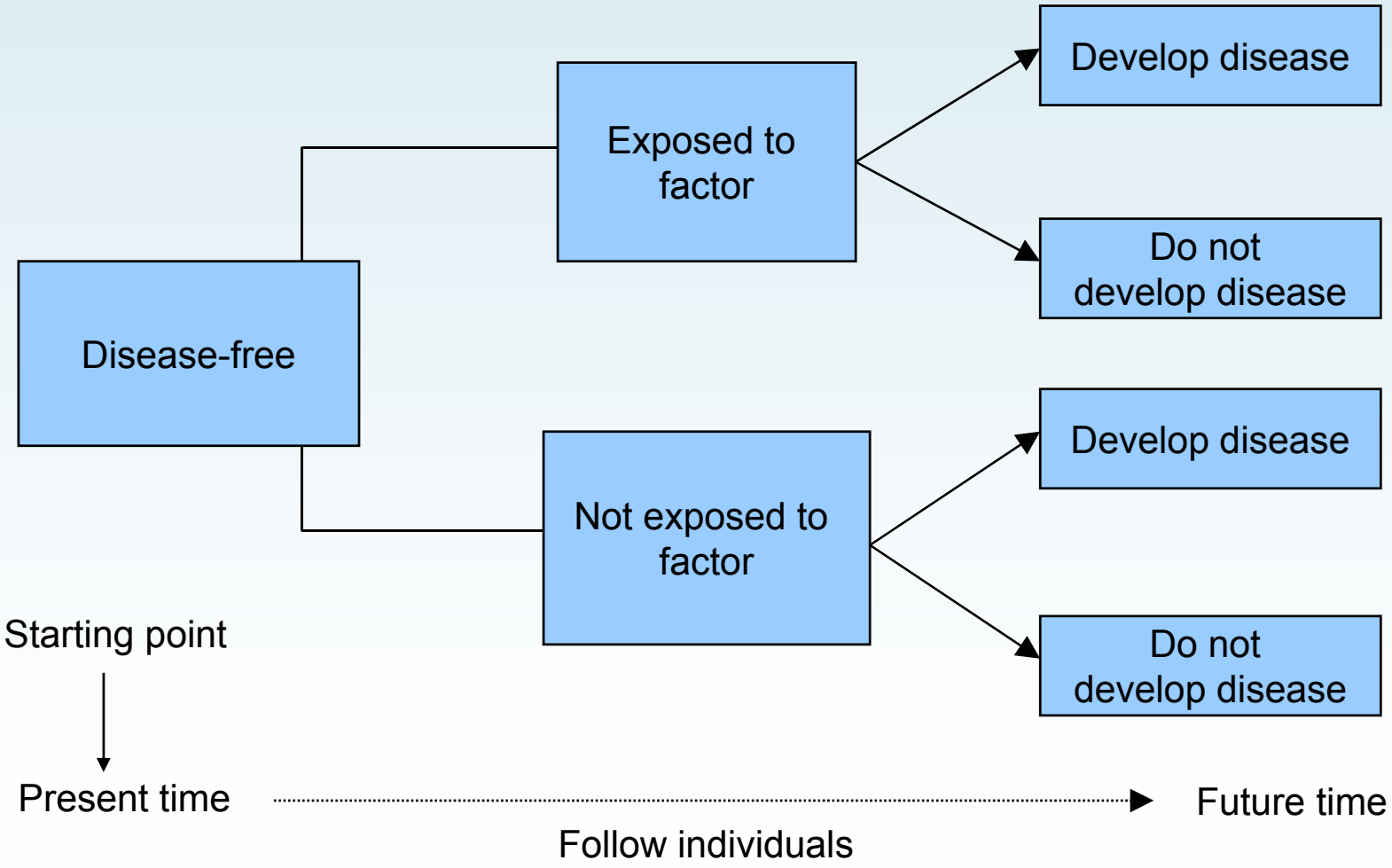
Randomised controlled trials (RCTs)

- 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

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



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**

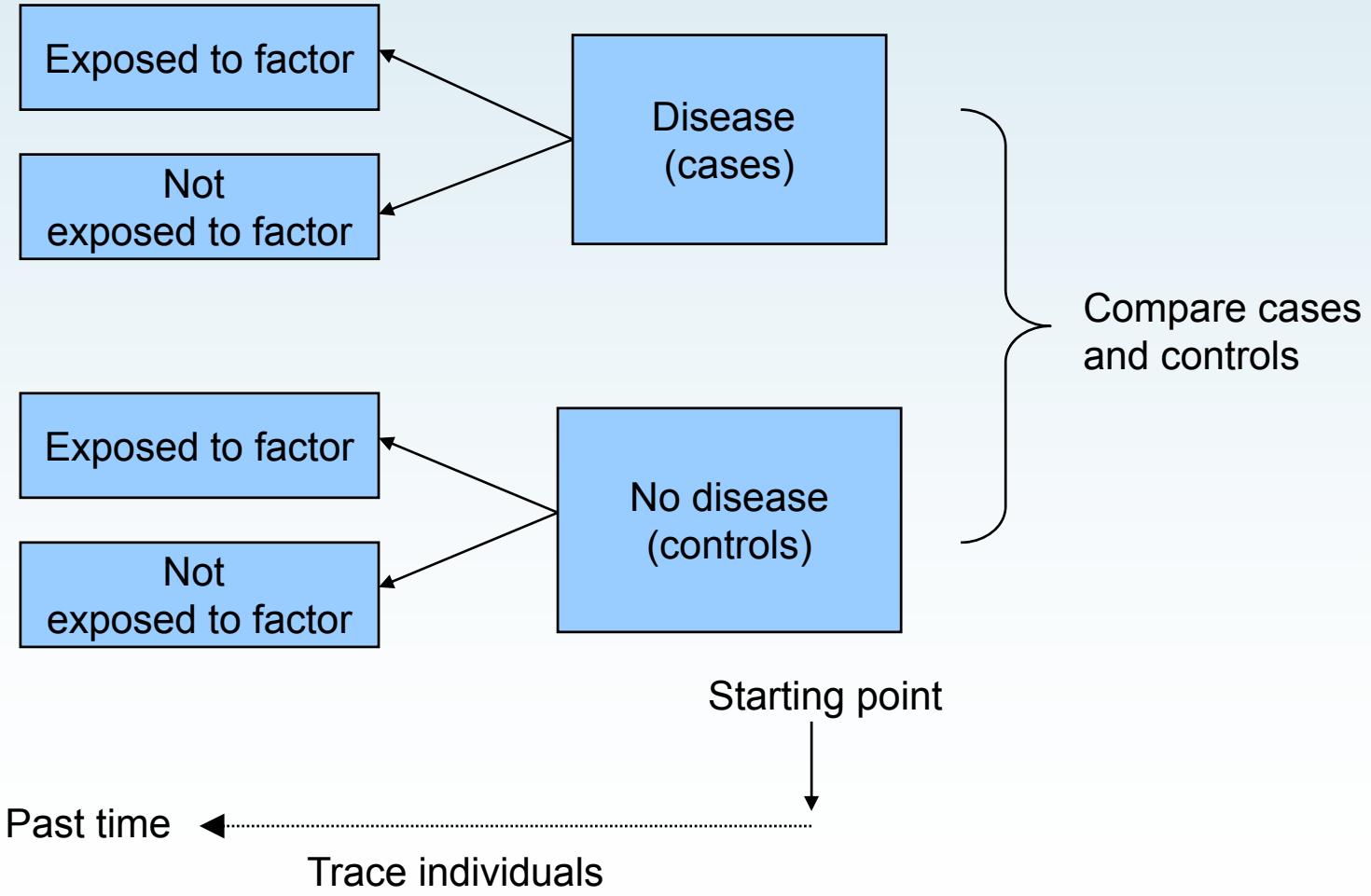
Example: Royal Free Hospital (RFH) Haemophilia Cohort

- 111 men with haemophilia registered at RFH Haemophilia Centre became infected with HIV between 1979 and 1985
- Men were followed for over 25 years to describe the natural history of HIV infection
- Information collected on demographics, clinical events, laboratory data and treatment information
- When follow-up ended (Dec 2005), 39 men remained alive and 28 were under follow-up at the hospital

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)

Example: 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); in press.

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

Example – Associations with high-risk alcohol use in HIV+ve persons in South Africa

- Cross-sectional study of 2230 HIV+ve patients in three 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, a higher level of independence and more depressive symptoms
- Authors recommend routine screening for alcohol use and harm reduction interventions, taking into account associated factors

Huis In't Veld D et al. Int J STD AIDS (2016); in press.

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

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