Why is research important?

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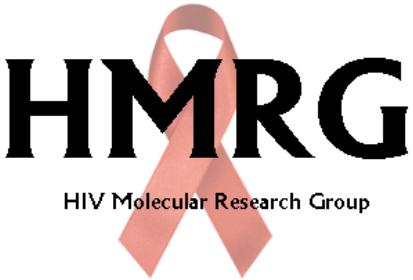

Scoil an Leighis agus Eolaíocht An Leighis UCD

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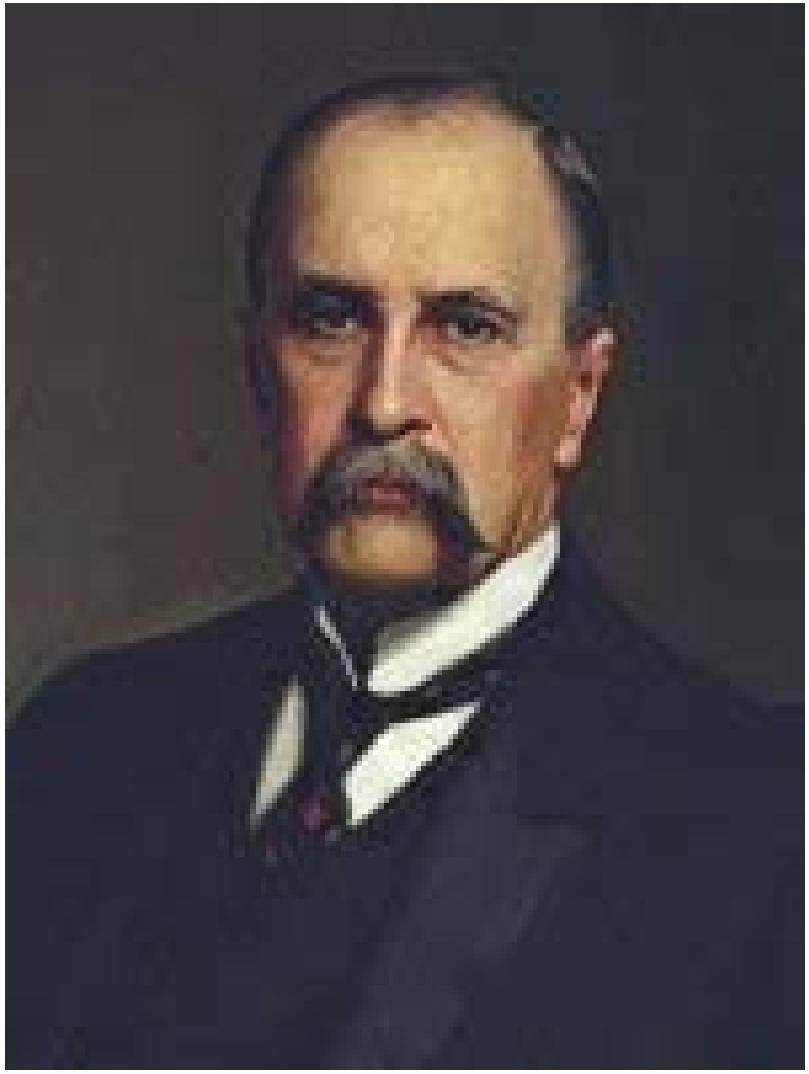
- Merck Sharpe & Dohme
- Health Research Board
- Wellcome Trust
- National Institutes of Health (US)
- European Union – Horizon 2020



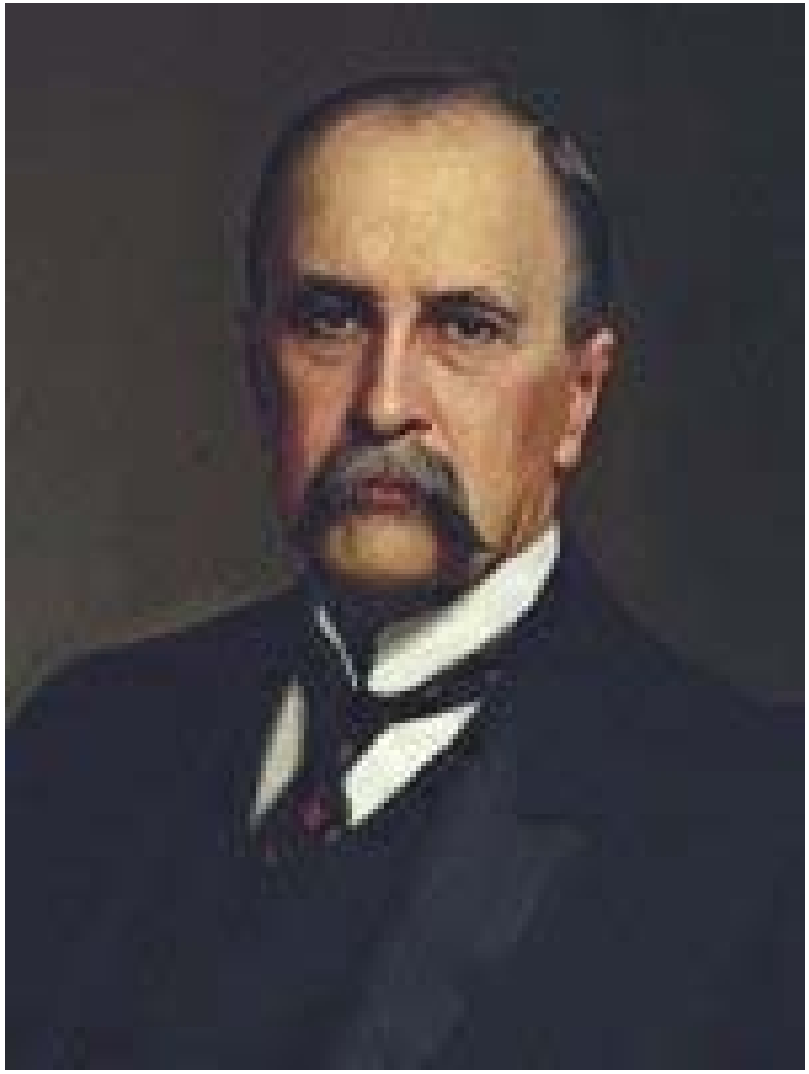
Sir William Osler

1849-1919

Founder of Johns Hopkins

Regius Professor of Medicine at Oxford

'Father of Modern Medicine'



‘The value of experience is not in seeing much but in seeing wisely’

William Osler

Why always ask why?

The practice of medicine is continually evolving

- New drugs, new indications, new drug consequences

The population is continually changing

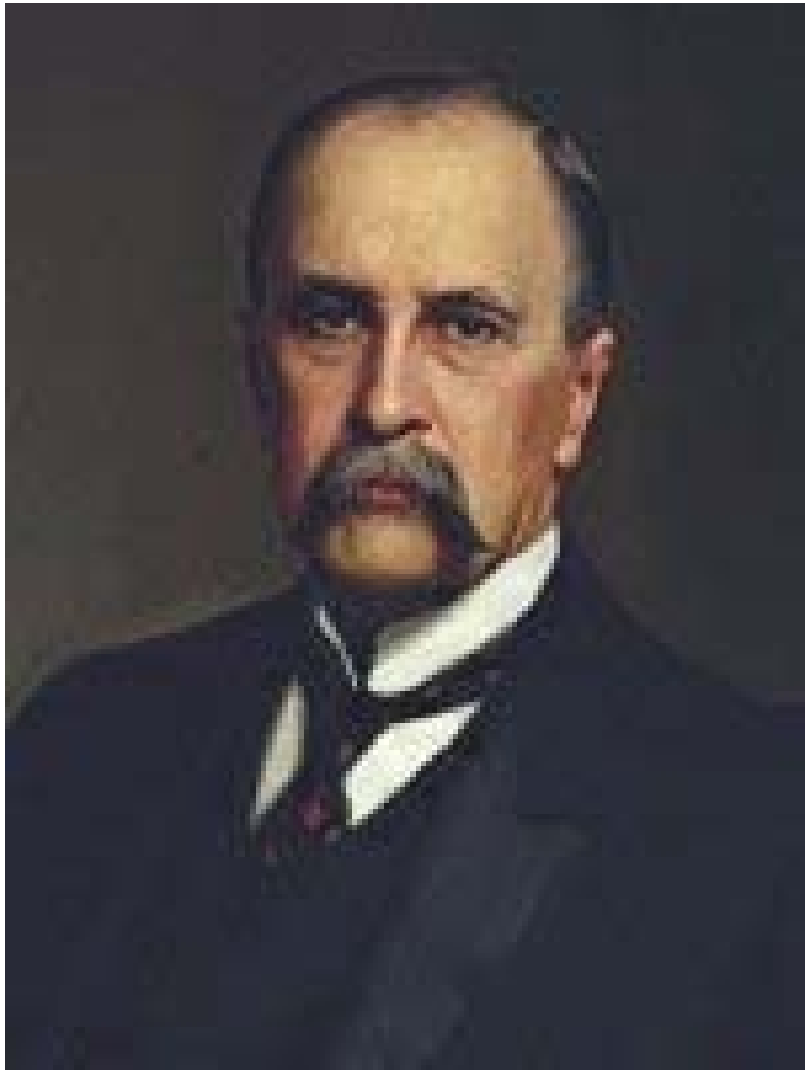
- Ageing, obesity, population shifts

Diseases continually evolving

- New manifestations as people age

ALWAYS BE VIGILENT!

KEEP AN OPEN MIND



‘The effective, most vitalizing work of the world is done between the ages of 25 and 40..’

William Osler

Research pathway for clinical discovery

Define / describe the clinical observation

↓

Model associations with the observation

↓

Elaborate associations into potential mechanisms

↓

Investigate mechanisms (in vitro / translational)

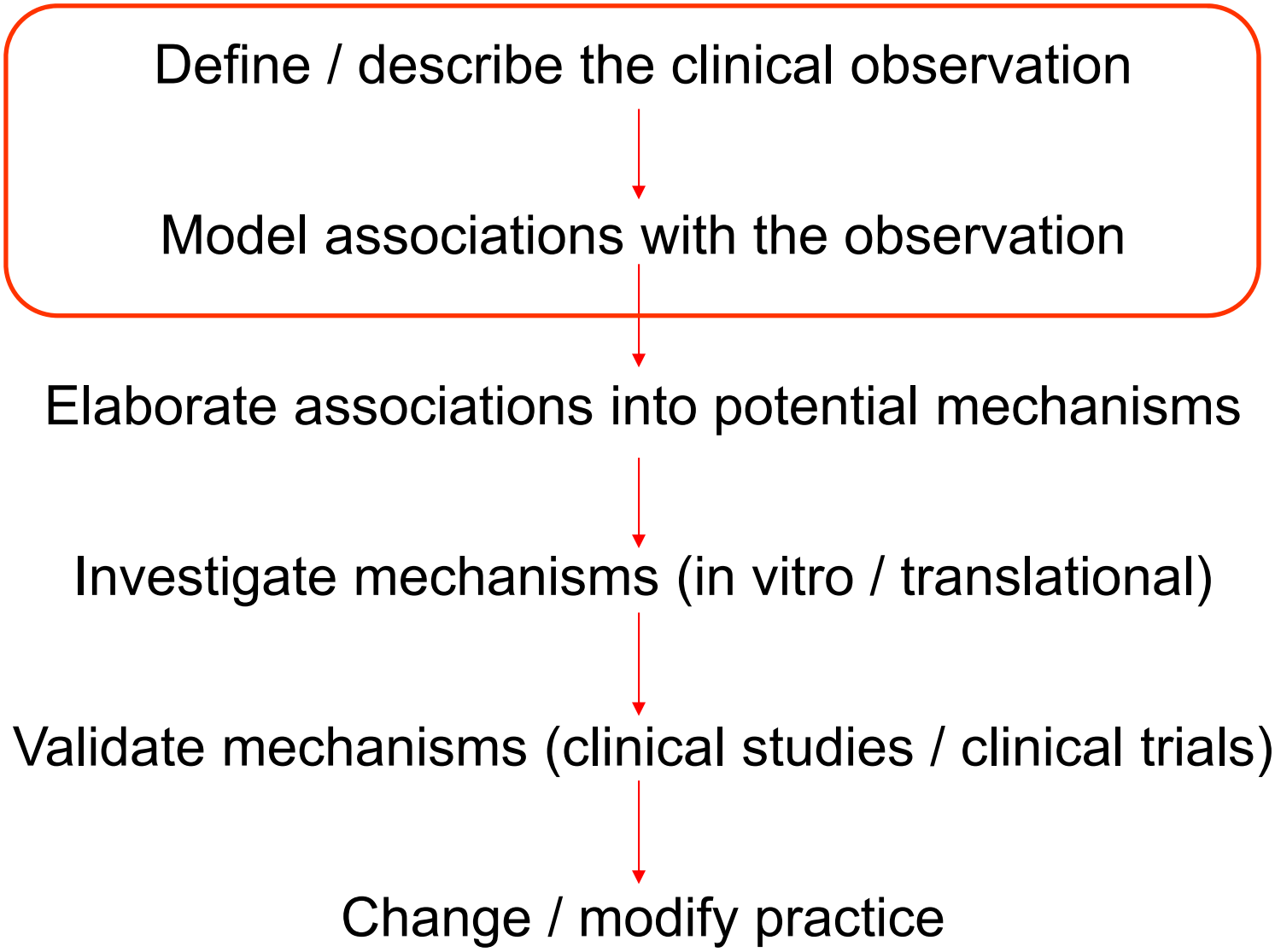
↓

Validate mechanisms (clinical studies / clinical trials)

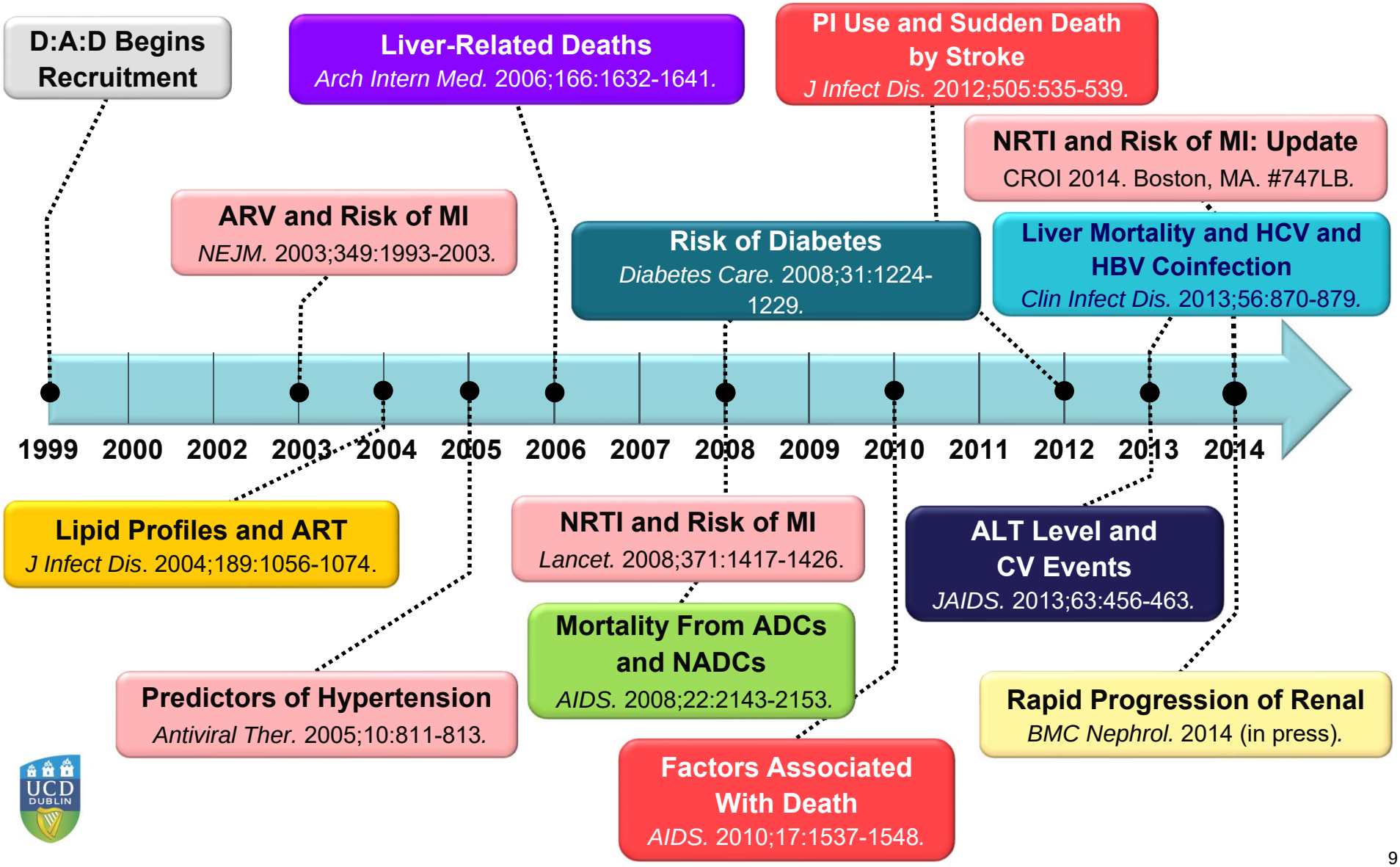
↓

Change / modify practice

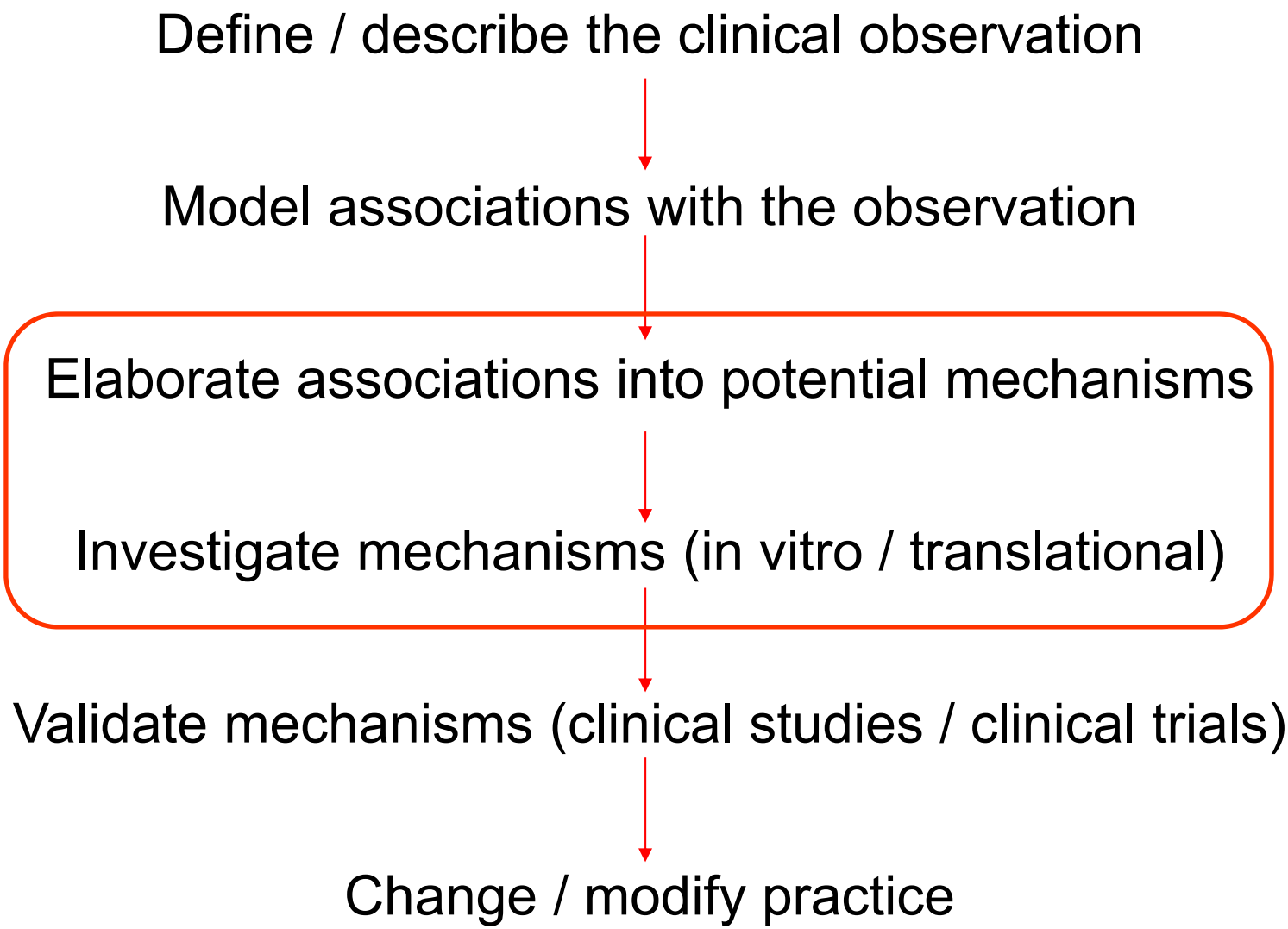
Research pathway for clinical discovery



The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study



Research pathway for clinical discovery

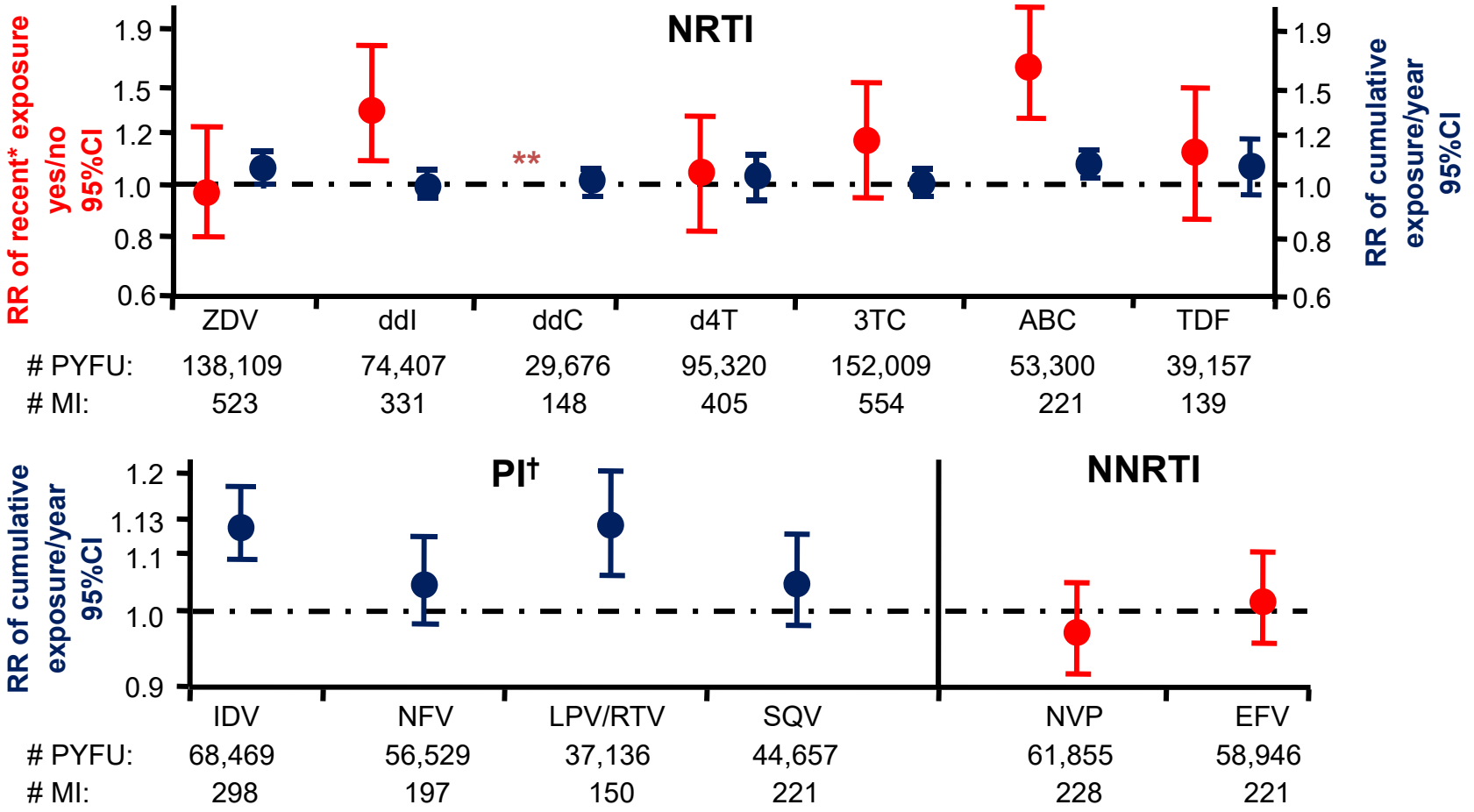


Translational research

- Most modern medical research is ‘translational’
- ‘From bench to bedside’ – vice versa!
- ‘Omics’ and bioinformatics
  - Genetics, genomics, proteomics, microbiome, epigenetics, functional assays
  - ‘Systems biology’
- Learn to collaborate and learn from your mistakes!
- *Helicobacter pylori*
  - Robin Warren
  - Barry Marshall

Cardiovascular events: Do drugs matter?

D.A.D: MI risk is associated with **recent** and/or **cumulative** exposure to specific NRTIs and PIs



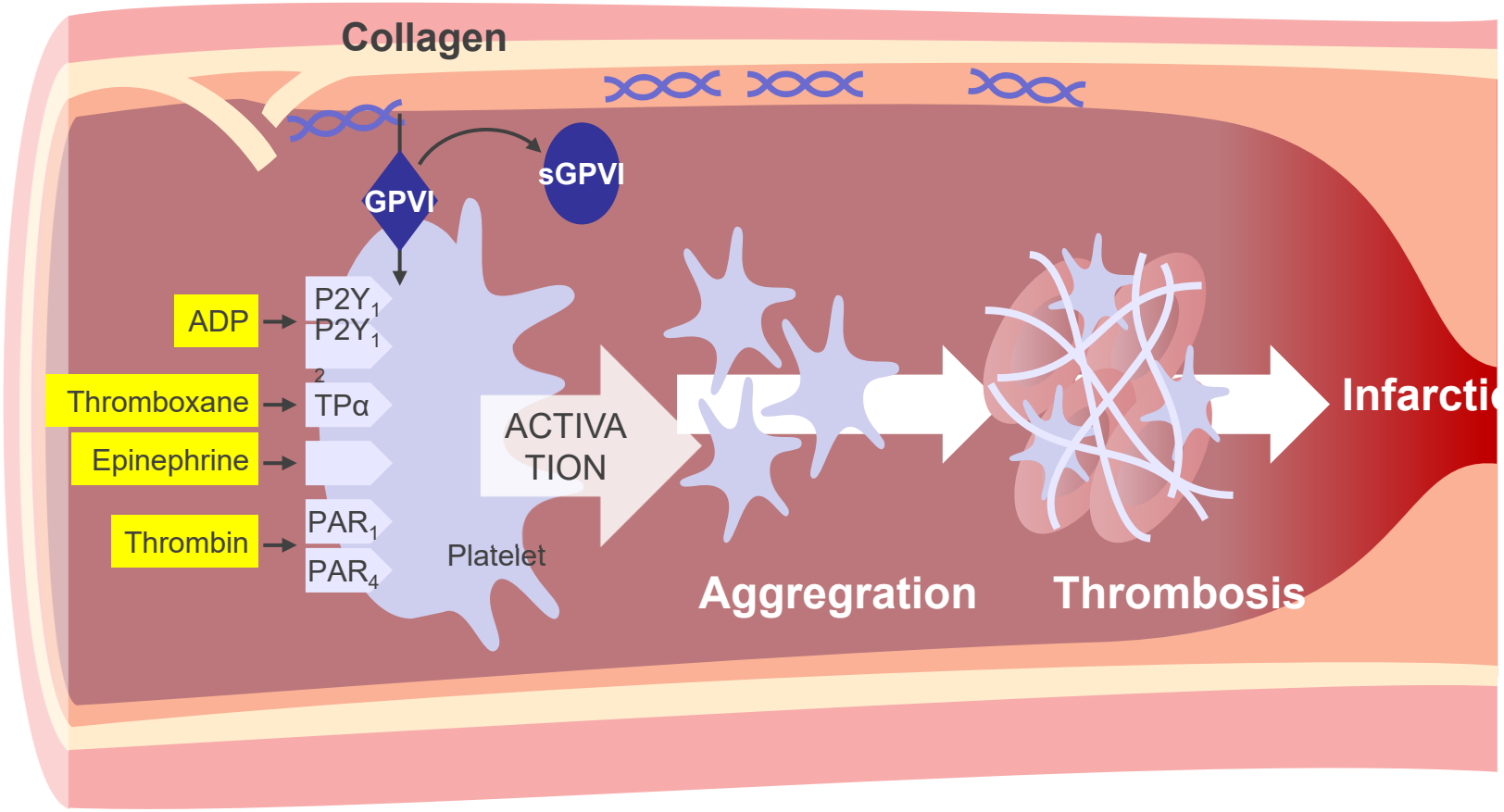
*Current or within past 6 months; †Approximate test for heterogeneity: p=0.02; **not shown due to low number of patients receiving ddC.
CVD=cardiovascular disease; MI=myocardial infarction; RR=relative risk; PYFU=patient years of follow up.

Adapted from Lundgren JD, et al. CROI 2009. Oral presentation 44LB.

Platelet activation and abacavir

Environmental Changes….

Liver	Inflammation (HIV)	Acute Coronary Syndrome



Switching from Lamivudine/Abacavir (3TC/ABC) to Emtricitabine/Tenofovir DF (FTC/TDF) Based Regimen (SWIFT)Study

Platelet Biology Sub-study

O'Halloran JA[1], Dunne E[2], Tinago W[1], Denieffe S[1], Kenny D[2], Mallon PWG[1]

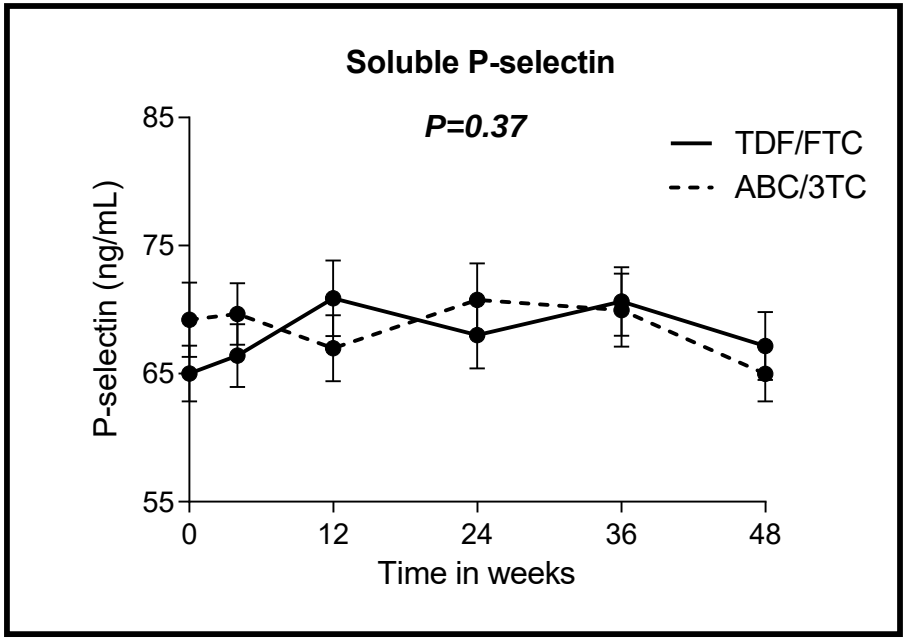
[1]HIV Molecular Research Group, School of Medicine and Medical Science, University College Dublin, Dublin, Ireland, [2] Cardiovascular Biology Group, Royal College of Surgeons in Ireland, Dublin, Ireland

RCSI

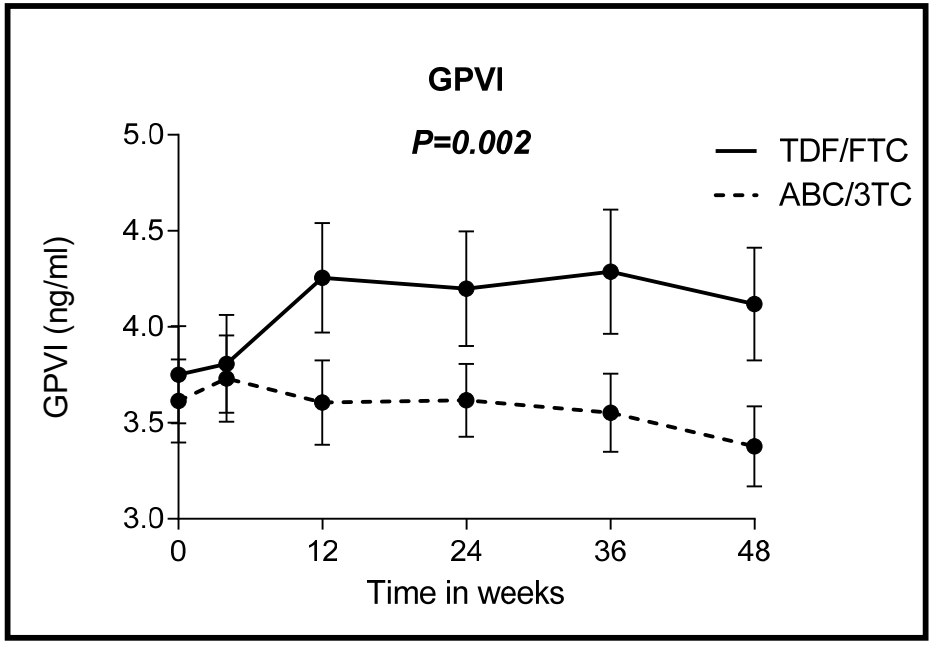
UCD DUBLIN

HMRG HIV Molecular Research Group

HIV and CVD – role of abacavir



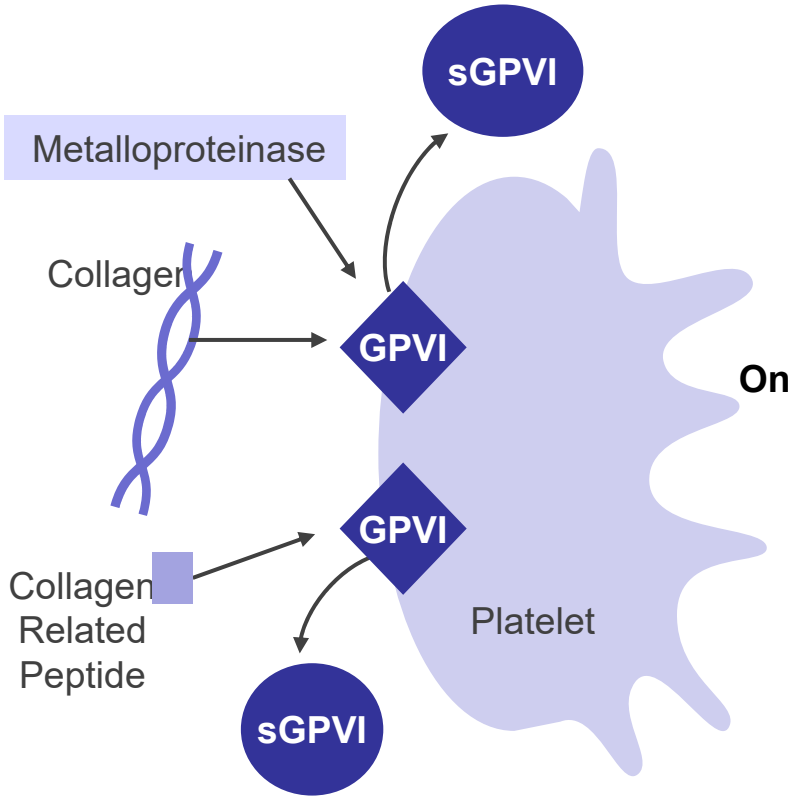
No between-group differences in sP-selectin from baseline to 48 weeks (p=0.37)



sGPVI increased to week 48 in those who switched to TDF/FTC (effect size +0.012 (95%CI 0.0041, 0.02), between group p=0.002.

O' Halloran J et al. AIDS 2018.

GPVI and CVD



Study 1717 - Phase 3, randomized, double-blind, active-controlled study

N=556
On ABC/3CTC

n=280 — **TAF/FTC QD** — Continue Third Agent

n=276 — **ABC/3TC QD** — Continue Third Agent

Week 0 — 12 — 48 — 96

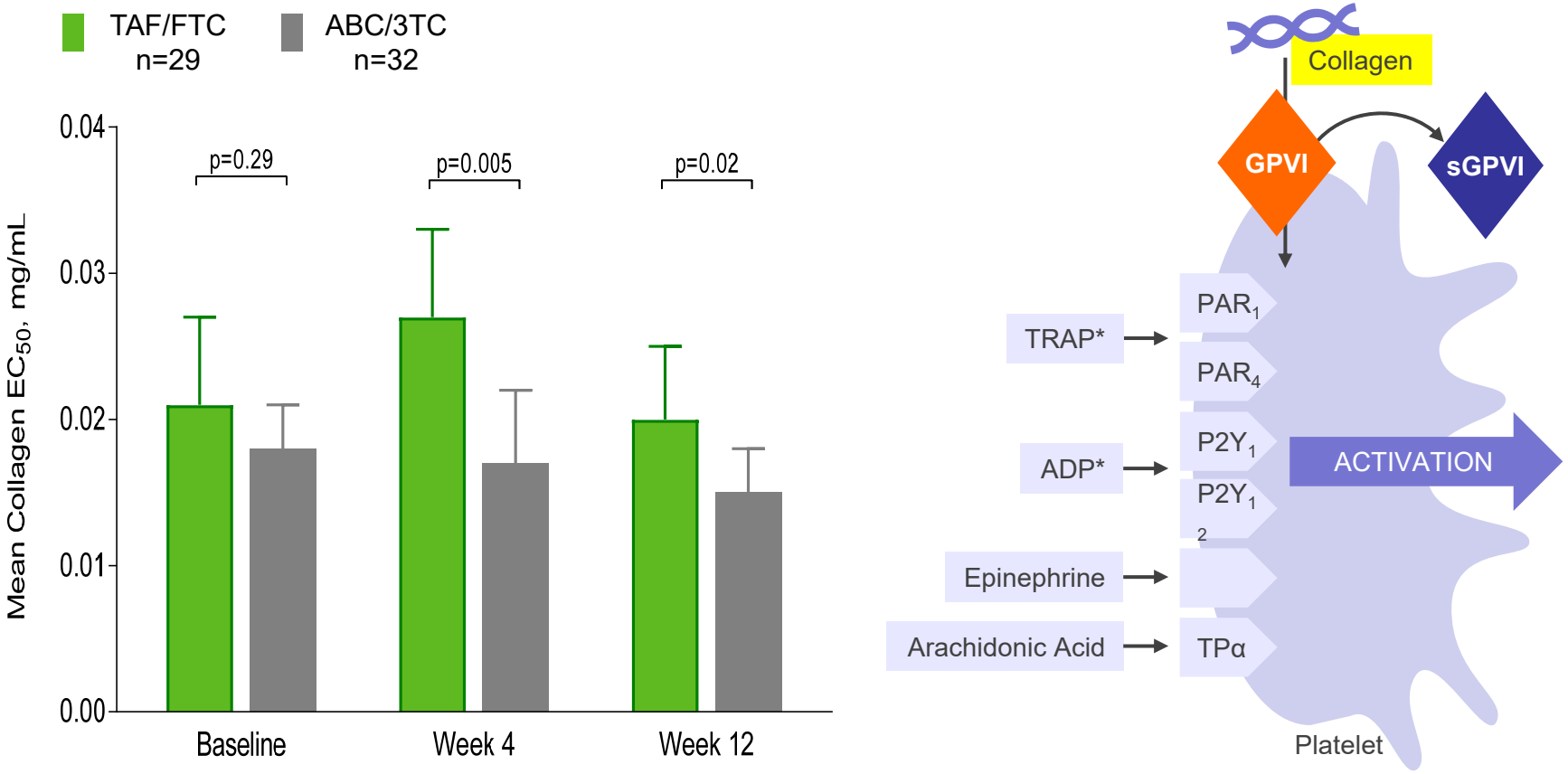
0 — 4 — 12

Platelet Substudy n=61

Sites in Dublin and London

Mallon PWG et al. CROI 2018.

Abacavir, GPVI and CVD

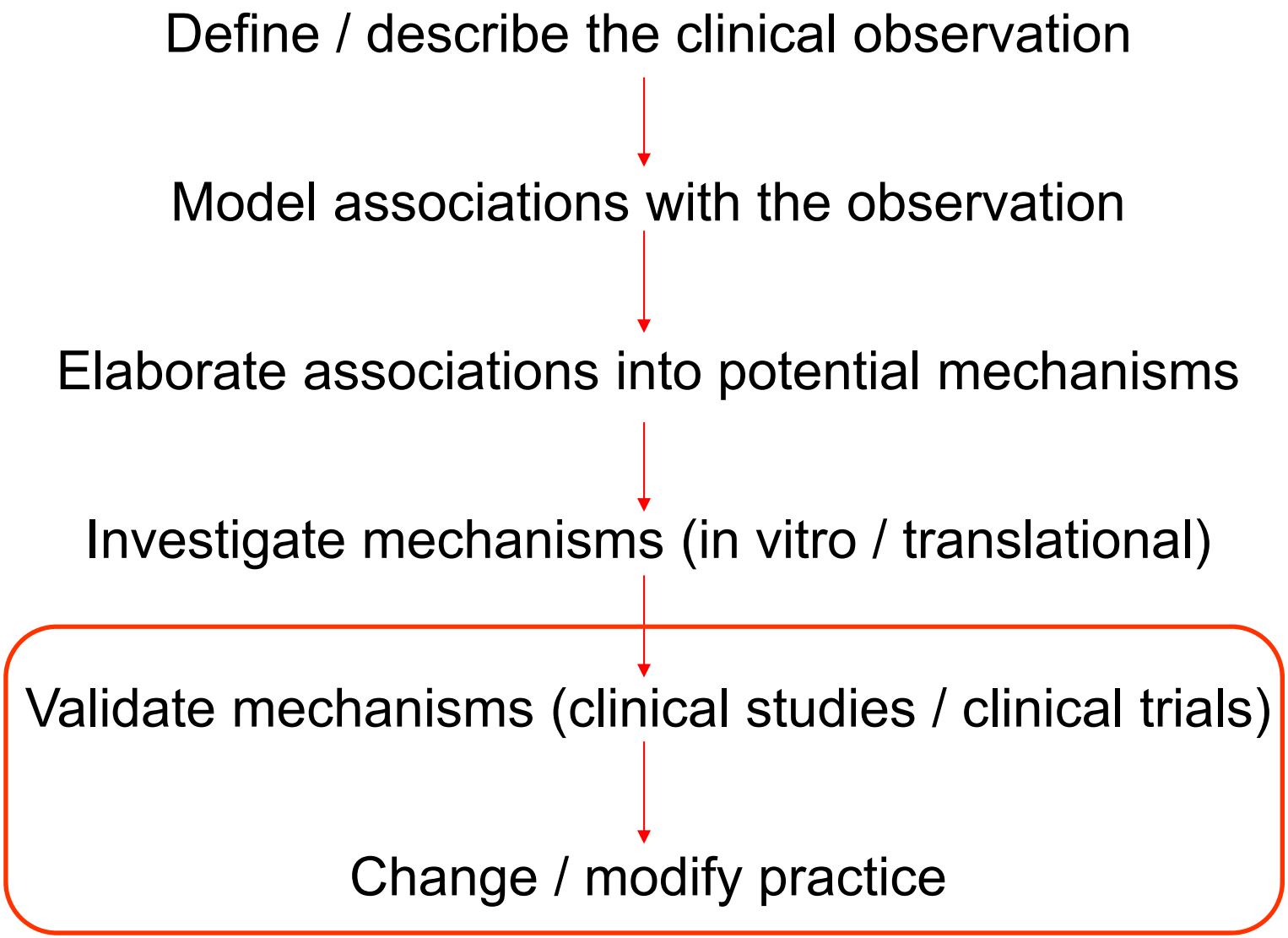


Higher collagen EC_{50} (i.e., less reactive platelets) in TAF/FTC group at both Weeks 4 and 12

Similar results seen with TRAP and ADP but not with Epinephrine or Arachidonic Acid

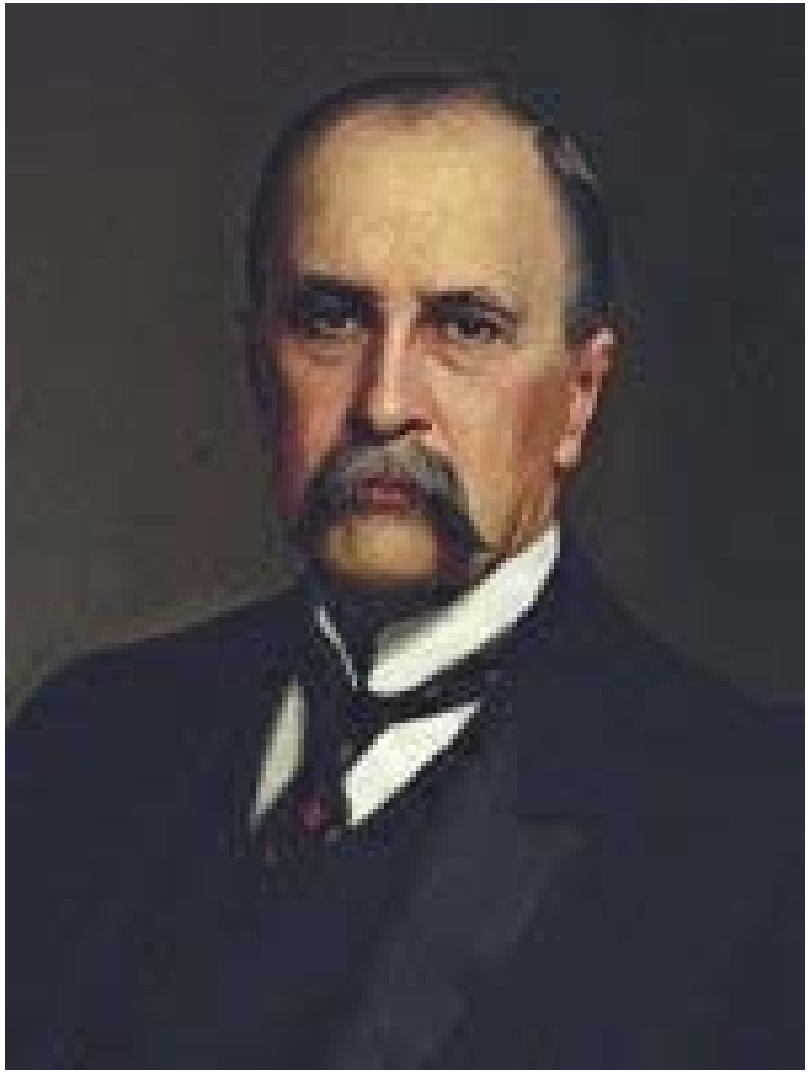
Mallon PWG et al. CROI 2018.

Research pathway for clinical discovery



Research pathway for clinical discovery

- Different research questions suit different parts of pathway:
  - Modelling – cohort studies
  - Mechanisms – in vitro / translational studies
  - Validate mechanisms – pilot clinical trials
- Different study designs suit different research questions
- A well thought research question forms the basis of a robust study



‘The best preparation for tomorrow is to do today’s work superbly well.’

William Osler

The research pathway…

Research Idea

↓

Study Concept

↓

Pilot Study (optional)

↓

Funding Proposal

↓

Study Protocol

↓

Analysis Plan

↓

Dissemination

(Presentation / Manuscript)

Pathway to researching a new therapy

Different research questions suit different parts of pathway:

- Modelling – Cohort studies
- Mechanisms – in vitro / translational studies
- Validate mechanisms – pilot clinical trials

Different study designs suit different research questions

A well thought research question forms the basis of a robust study

Identifying the research question…

It is important to have a clear question before starting to design your study

This will allow you to make the most appropriate decisions surrounding:

- The study population
- The choice of study design
- The method of collecting data
- The primary outcome of interest
- The main exposure/predictors of interest (if applicable)
- The number of patients to be recruited

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

Is this a clearly defined question?

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

Think about three main factors:

- the **population**
- the **intervention / exposure**
- the **outcome**

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The Population

How do we define ‘people’?

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The Population

How do we define 'people'?

- General population
- Specific disease populations
- Specific demographics; age, gender, ethnicity
- Use of specific therapies

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The Intervention / exposure

How do we define 'seeing more doctors'?

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The Intervention / exposure

How do we define 'seeing more doctors'?

- Different specialists / conditions
- Single vs multiple doctors within a clinic
- Same condition but different clinics

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The outcome:

How do we define ‘worse outcomes’?

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

The outcome:

How do we define 'worse outcomes'?

- Increase in CD4 count?
- Viral load suppression?
- Improvement in clinical outcome?
- Improvement in survival?
- Some other measure?

Identifying the question…example

QUESTION:

Do people who see more doctors end up with worse outcomes?

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?

Research questions and hypotheses:

START study

'..among asymptomatic participants with a CD4+ count greater than 500 cells/mm3, immediate use of ART that results in suppression of HIV RNA levels and increases in CD4+ cell counts and potentially other beneficial effects will delay the development of AIDS, non-AIDS, and death from any cause.'*

INSIGHT START Study Group. NEJM 2015;373(9):795-807

The research question should be…

Clear

Unambiguous

Measurable

Of clinical / biological relevance

Realistic within the resource setting

DON'T BE TOO FOCUSED.

The more focused the less the answer will mean to the wider patient population

Keeping it real!!

Study subjects should be representative of the population to which the results will be generalized - '*real world*'

The more detailed you make the research question the greater the risk that you will lose relevance

Balance study design to retain IMPACT!

What to do with your research question?

Make sure it hasn't already been answered!!

- Colleagues
- PubMED / Google

Design your research question

- Hypothesis, hypothesis, hypothesis……

Determine if you are able to answer the question

- Do you have the resources?
- Do you have the correct population?
- Do you have the time?

What to do with your research question?

DESIGN THE RIGHT STUDY TO ANSWER YOUR QUESTION

Choosing the right study design

Caroline Sabin

Professor of Medical Statistics and Epidemiology
Institute for Global Health

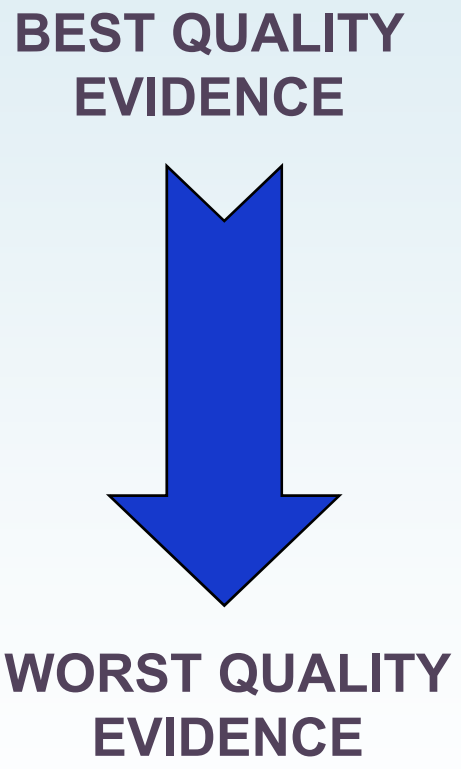
Conflicts of interest

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**)

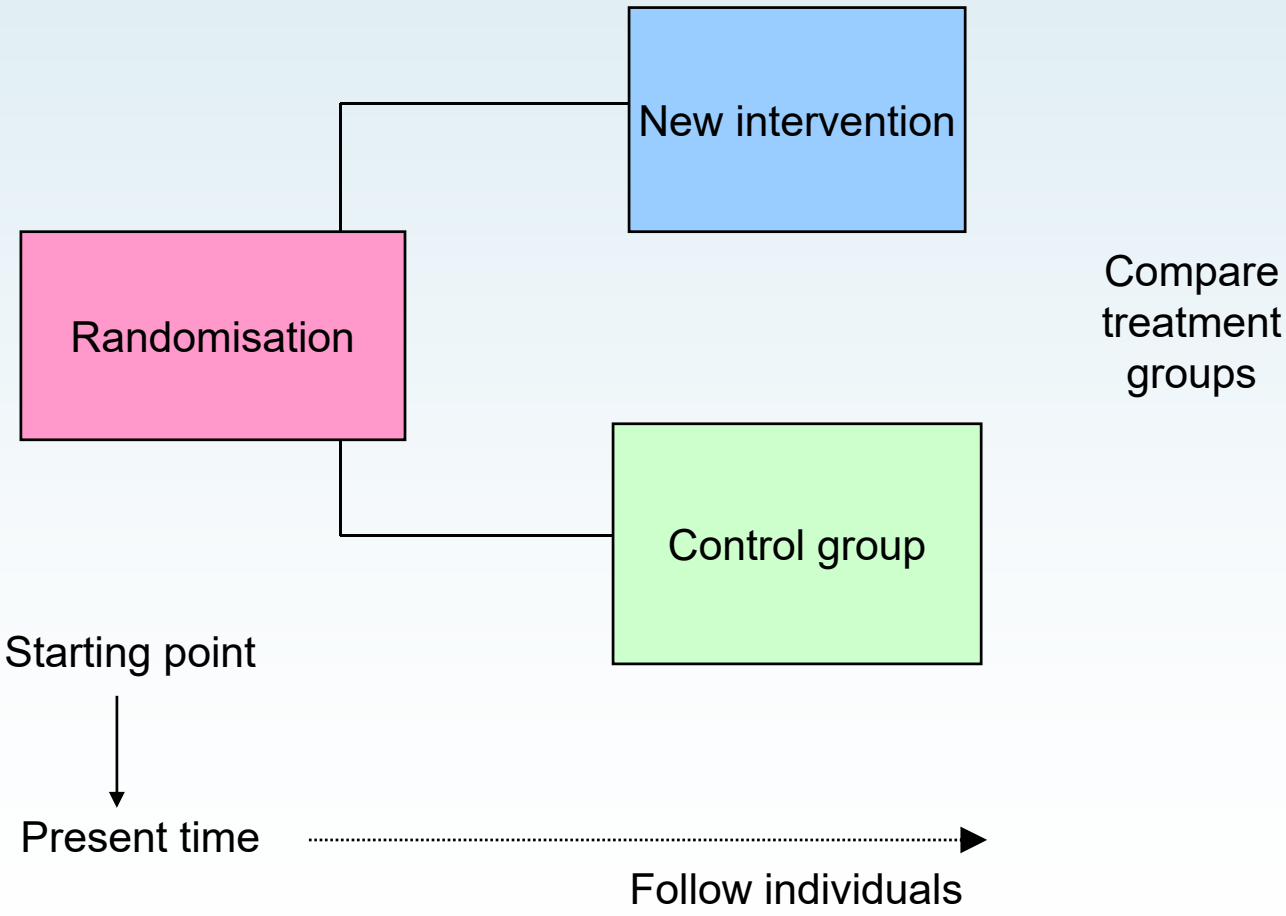
Randomised controlled trials (RCTs)

- 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



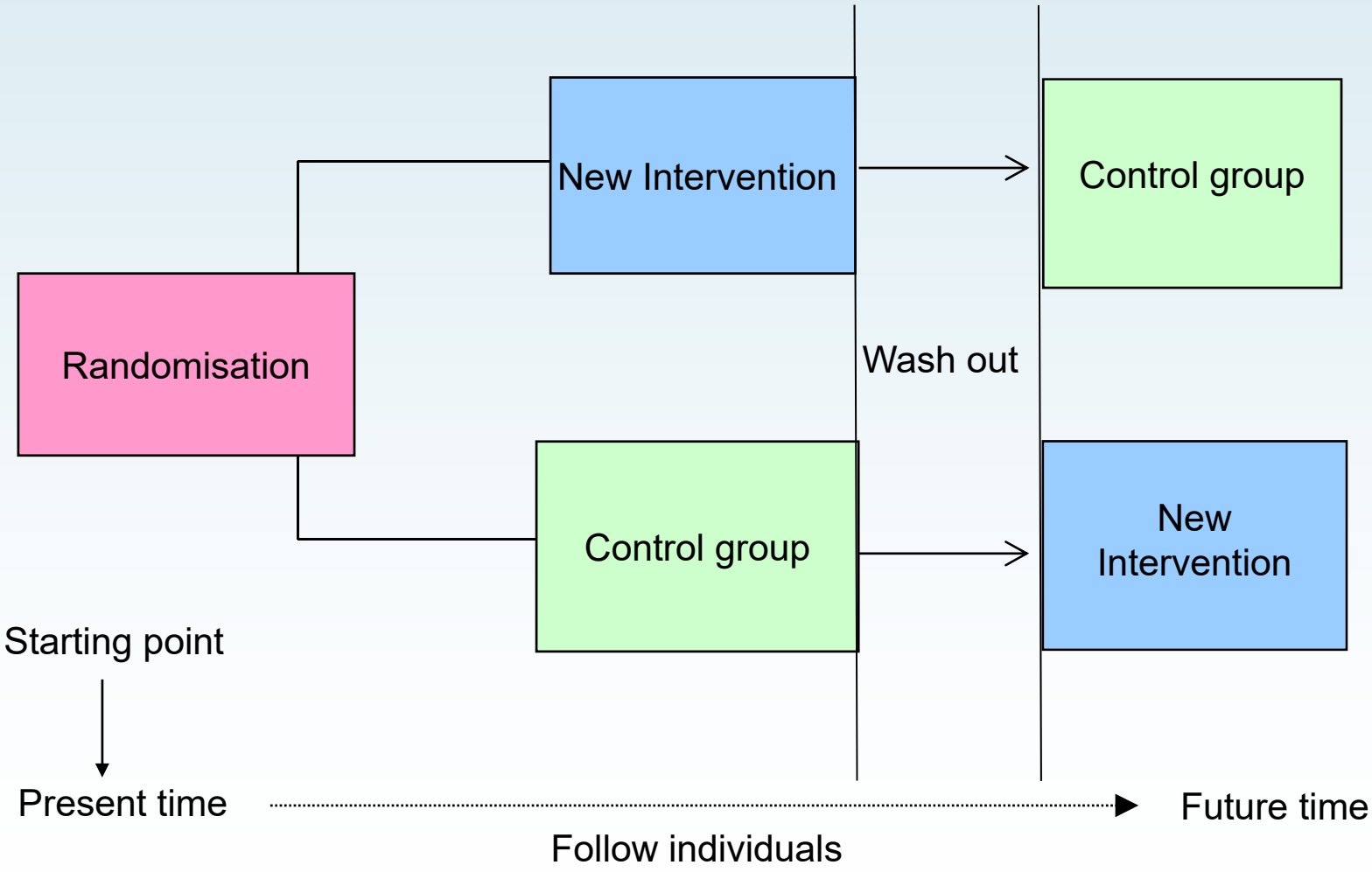
Example – Parallel Group trial

- 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

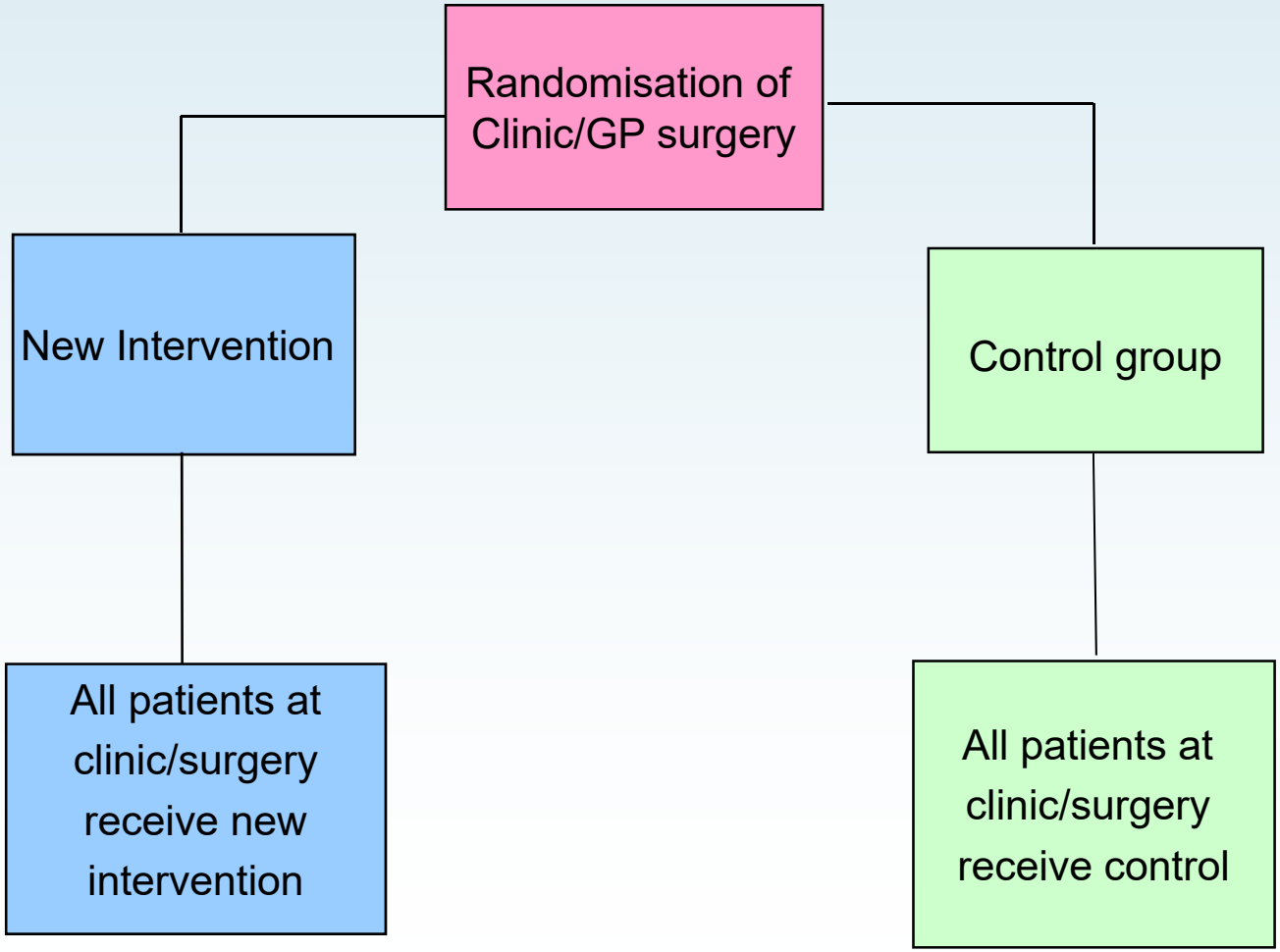
  OR
  - Latex condoms for 6 weeks then Reality condoms for 6 weeks
- Endpoints: frequency of slippage with removal, pain or discomfort on use, rectal bleeding, willingness to use in future

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)

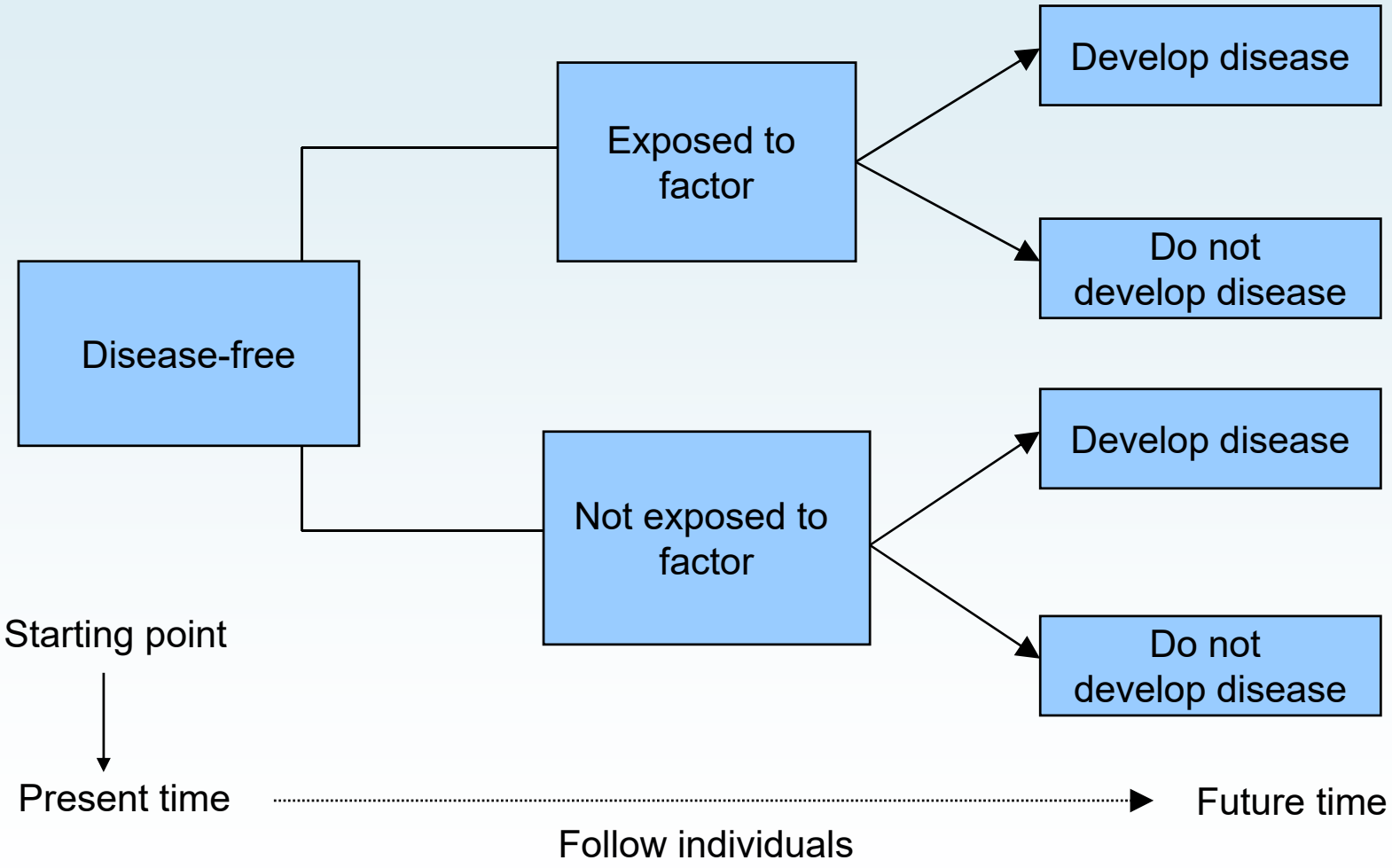
  OR
  - LLIN + indoor residual spraying
- Endpoints:
  - incidence of clinical malaria assessed by passive case detection in >7,000 children
  - number of *Anopheles gambiae* sensu lato mosquitoes collected per light trap per night

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

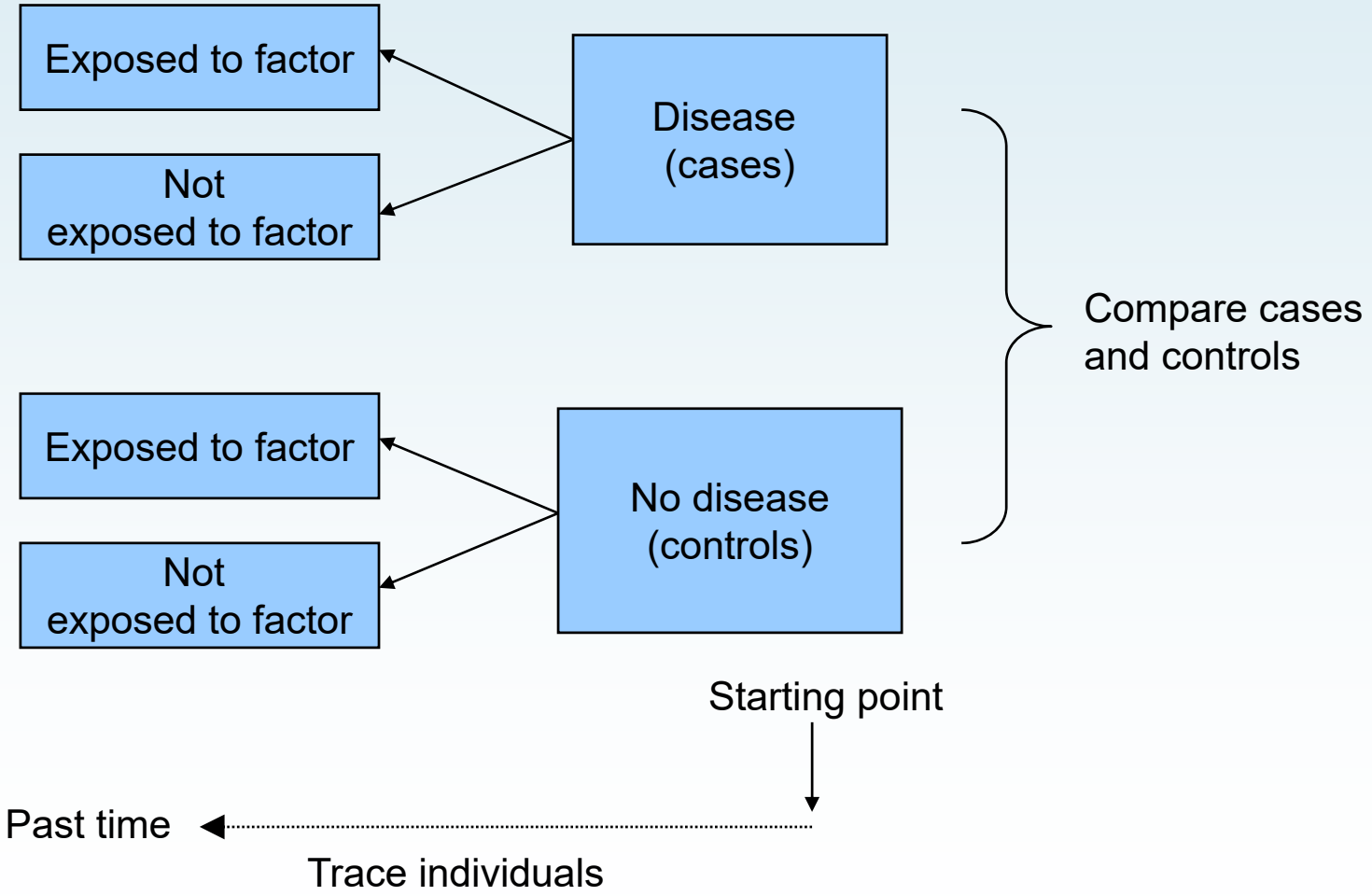
Disadvantages

- 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