UP-ART Training
Research Methods Part 1: Study Design

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Edith Milanzi

Friday 2nd July 2021

UP-ART training sessions

Session	Date/time	Overview of content to be covered
Research Methods Part 1: Study design	Friday 2nd July 12pm-2pm Uganda	What are randomised trials, cohorts, case control, cross sectional studies, and when to use each design
Research Methods Part 2: Introduction to Statistical Analysis I	Friday 9th July 12pm-2pm Uganda	Descriptive statistics, confidence intervals, hypothesis testing and p-values
Research Methods Part 3: Introduction to Statistical Analysis II	Friday 23rd July 12pm-2pm Uganda	Odds ratio/risk ratio/risk difference, survival analysis, incidence/prevalence, methodological issues in statistical analysis (such as bias and confounding)
Journal club	TBC	

UP-ART training sessions

Session	Date/time	Overview of content to be covered
Paediatric HIV Study coordination and governance; Safety studies and assessment	Tuesday 13th July 2pm-4.30pm Uganda	*Study coordination and governance:* Sharing experiences from the UK CHIPS study: running a clinical network, feedback of data to sites, dissemination of findings to patients/families. *Safety studies and assessment*: examples of pharmacovigilance studies conducted and their findings. Capturing safety data, including definitions, causality and severity.
Cohort collaborations, informing policy makers, modellers	TBC	

Aim of session

To outline the different study designs which are used in experimental and observational studies

- Strengths and weaknesses of different designs
- Which designs are most appropriate for answering different research questions
- How the different designs may complement each other

Outline

- Overview of study designs
- Experimental studies (clinical trials)

➢Activity

- Observational studies
  - Descriptive studies / case series
  - Cross sectional studies
  - (break!)
  - Case control studies
  - Cohort studies

➢Activity

- Selecting a study design

OVERVIEW OF STUDY DESIGNS

Experimental v observational

Experimental (Clinical Trials)

- Studies which evaluate a new treatment or intervention and compare outcomes in treated and untreated, or conventionally treated, group

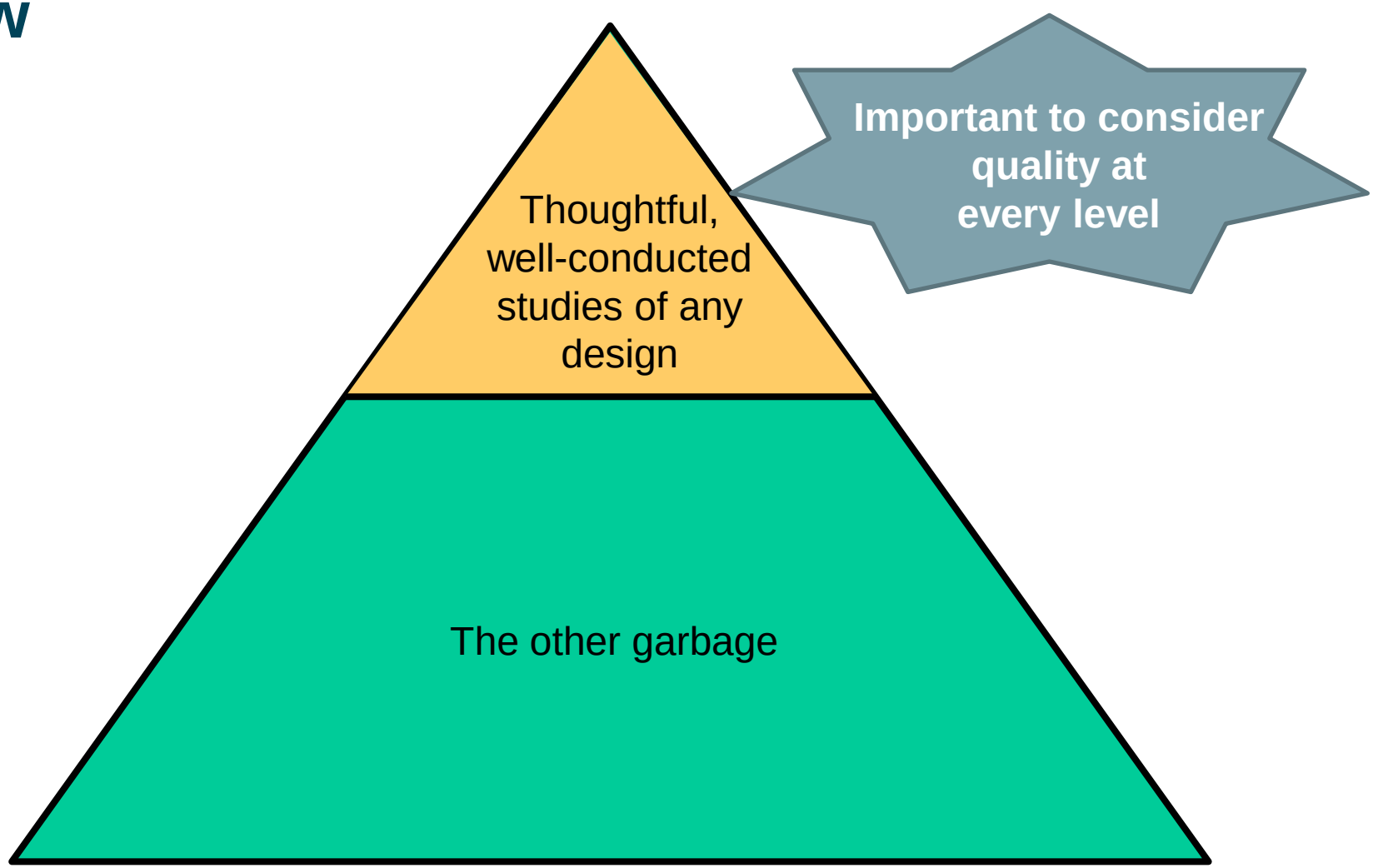
Observational

- Studies which involve careful recording of exposures, treatments and outcomes as they occur normally or routinely, with no study-specific intervention or treatment

Hierarchies of Research Design

www.cebm.net

Another view



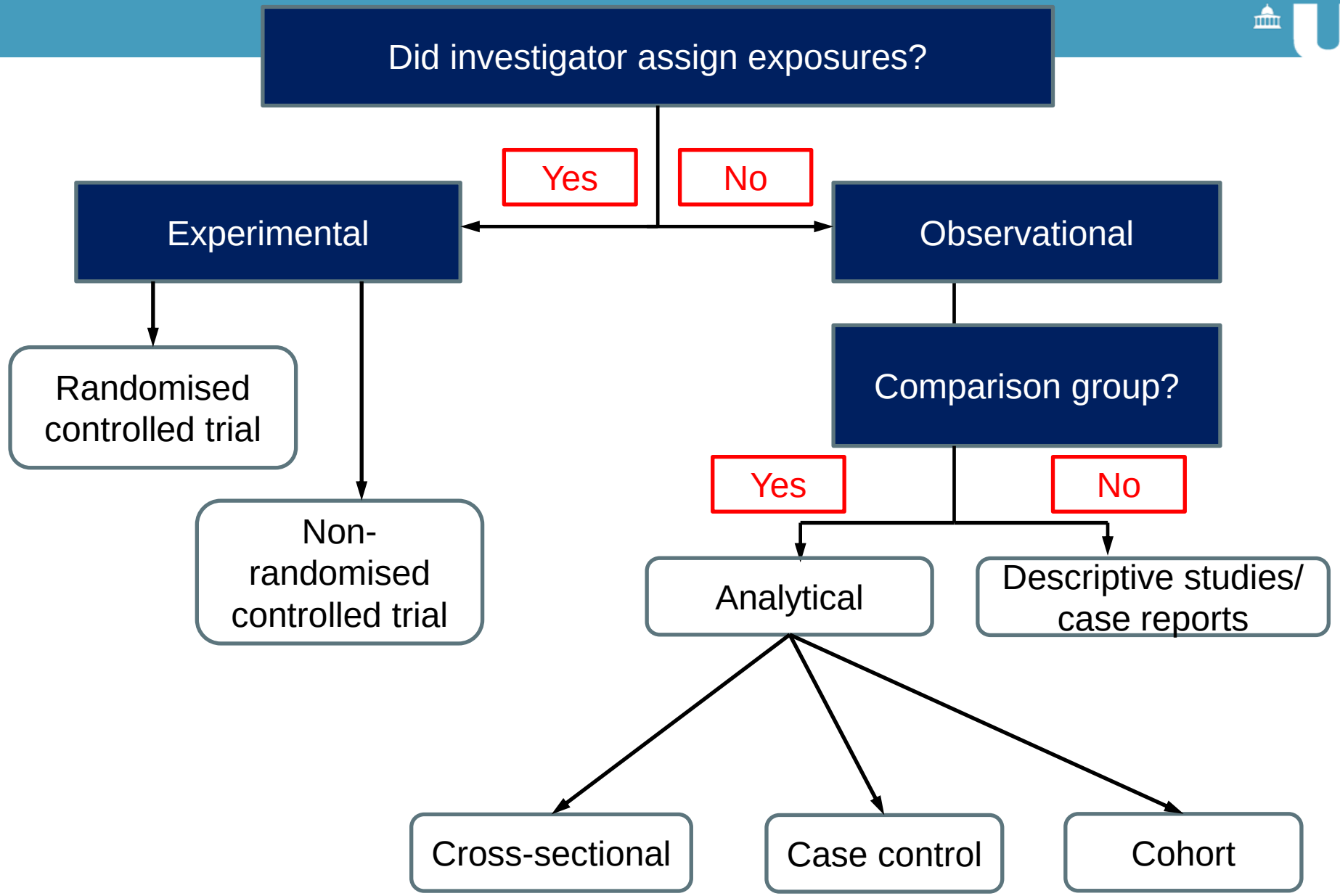
Based on Darren L Dahly, Twitter @statsepi

Why is high-quality research important?

- Provide **an evidence base** to inform treatment guidelines and improve patient care

4.3.5 Timing of ART for adults and children with TB	ART should be started in all TB patients living with HIV regardless of CD4 count (strong recommendation, high-quality evidence).[1] TB treatment should be initiated first, followed by ART as soon as possible within the first 8 weeks of treatment (strong recommendation, high-quality evidence).[2] HIV-positive TB patients with profound immunosuppression (e.g. CD4 counts less than 50 cells/mm^3) should receive ART within the first two weeks of initiating TB treatment.

WHO Consolidated HIV guidelines 2016



Adapted from Schulz and Grimes, The Lancet Handbook of Essential Concepts in Clinical Research

EXPERIMENTAL STUDIES/ CLINICAL TRIALS

Experimental v observational

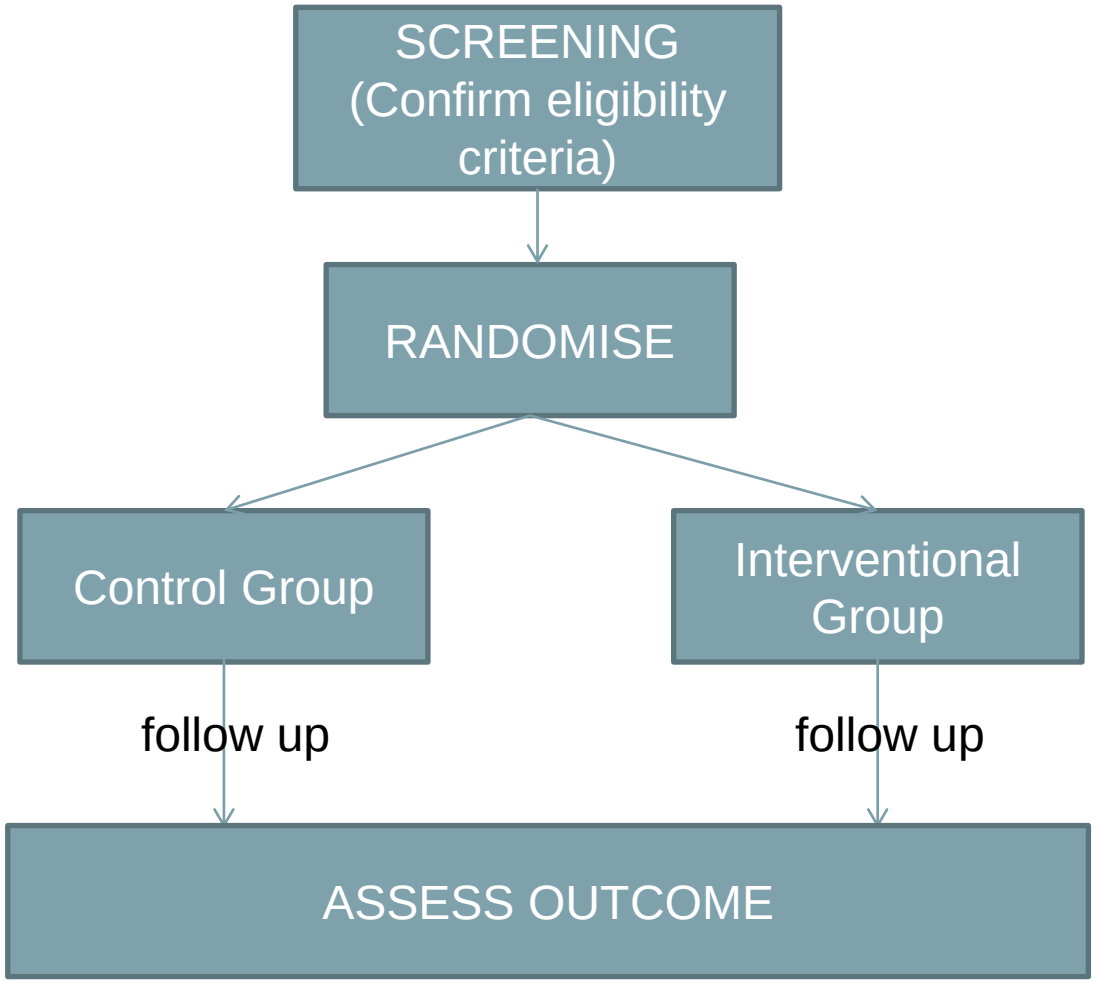
Experimental (Clinical Trials)

- Studies which evaluate a new treatment or intervention and compare outcomes in treated and untreated, or conventionally treated, group

Observational

- Studies which involve careful recording of exposures, treatments and outcomes as they occur normally or routinely, with no study-specific intervention or treatment

Design: Simple parallel RCT



Types of question

- Can answer different types of questions
  - **Treat** illnesses by testing new or existing medicine (treatment trial)
  - **Prevent** illnesses by testing a vaccine (prevention trial)
  - Detect or **diagnose** illnesses by testing a scan or blood test (diagnostic trial)
  - Find out how best to **manage** patients (strategy trial)

- Main question of interest in our trial = “primary outcome”
  - Look at other additional questions too = “secondary outcomes”
  - E.g. acceptability, quality of life, costs, cost-effectiveness

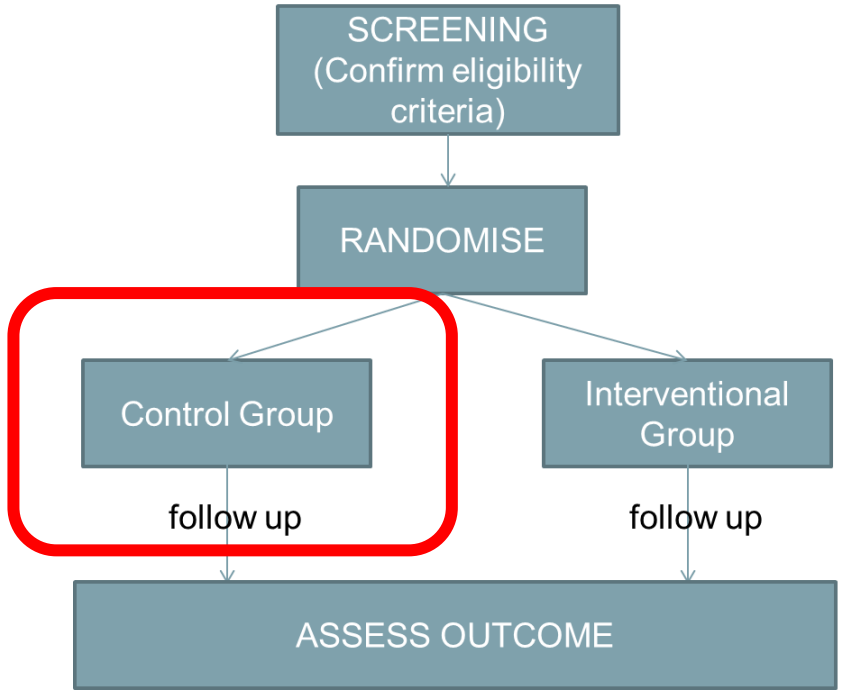
Features of a clinical trial

- Features of a ‘good’ clinical trial
  1) **Use of a control group**
  2) **Randomisation**
  3) **Blinding**
  4) **Sufficient sample size**

© Can Stock Photo - csp23725158

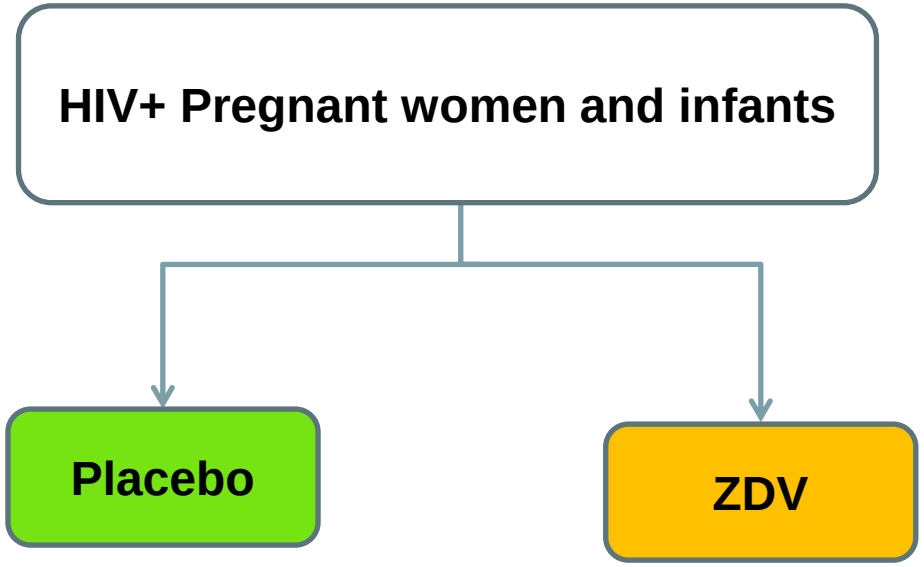
1) Control Group

- A comparator group of participants who **do not** receive the experimental intervention
- Important to determine if the new intervention works
- Control serves as **a standard or reference population**
- Should receive the **best current treatment/standard** of care or a **placebo if no existing treatment**

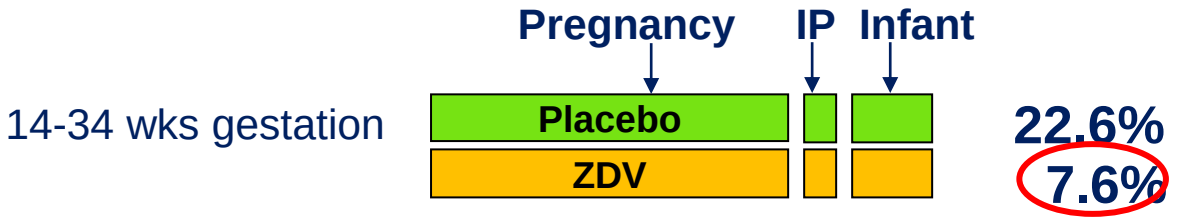


Parallel 2-arm trial: PACTG 076

Q: Can antiretrovirals reduce the risk of mother to child transmission of HIV?

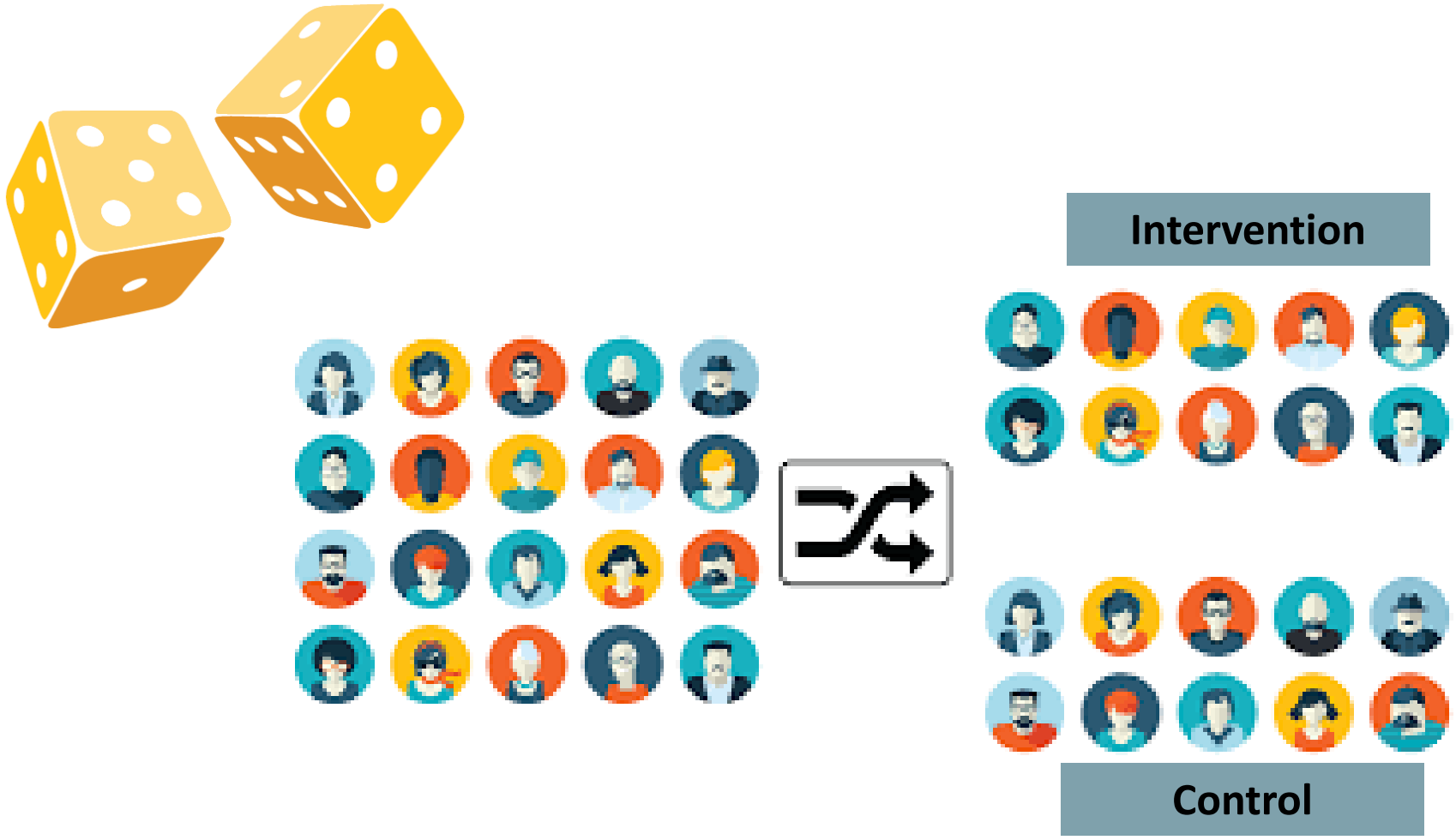


Non Breastfeeding mothers



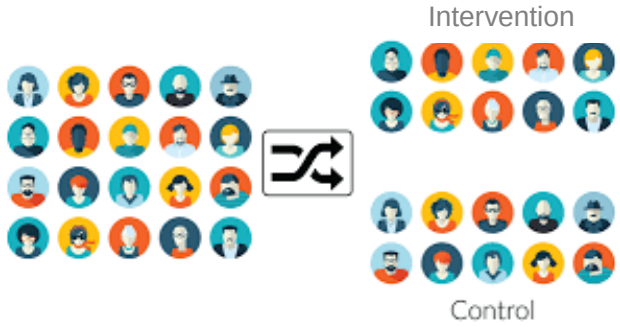
Sperling et al. *NEJM*,1996

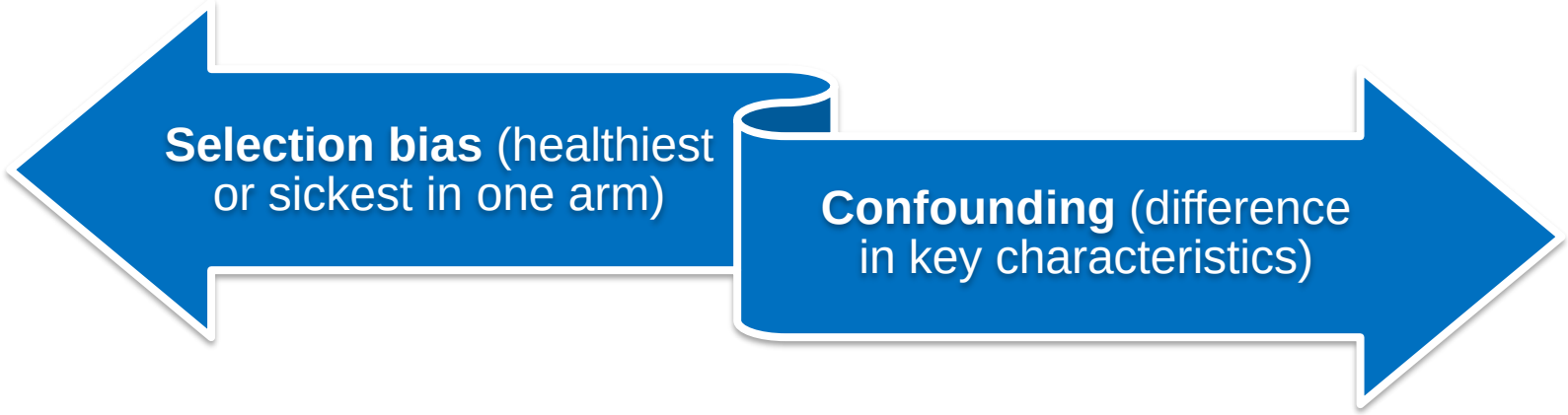
2) Randomisation: to minimise bias and confounding



What if we do NOT randomise?

- If doctors select the intervention?
- If participants select the intervention?





- Bias is: 'tendency of an estimate to **deviate from a true value**' → impact **validity and reliability** of the study findings. Important to **minimise bias**.

Successful randomisation: (i) Protect against selection bias,
(ii) minimise confounding of known and unknown prognostic factors;
(iii) randomised groups will have similar baseline characteristics

3) Blinding

- Allocation of treatment is **hidden from the study participants, doctors or those evaluating study outcomes**

- Helps to:
  - **Ensure no differences** in the way in which each group is **assessed or managed**
  - Minimises **information bias** (reporting/observer bias) - when one has a prior interest or belief that a treatment is better or worse than another

Blinding

- Not always possible or appropriate

Journal of Alzheimer's Disease 50 (2016) 443–453
DOI 10.3233/JAD-150817
IOS Press

Moderate-to-High Intensity Physical Exercise in Patients with Alzheimer's Disease: A Randomized Controlled Trial

Kristine Hoffmann[a], Nanna A. Sobol[b,c], Kristian S. Frederiksen[a], Nina Beyer
Karsten Vestergaard[d], Hans Brændgaard[e], Hanne Gottrup[e], Annette Lolk[f], L

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D.,
Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc.,

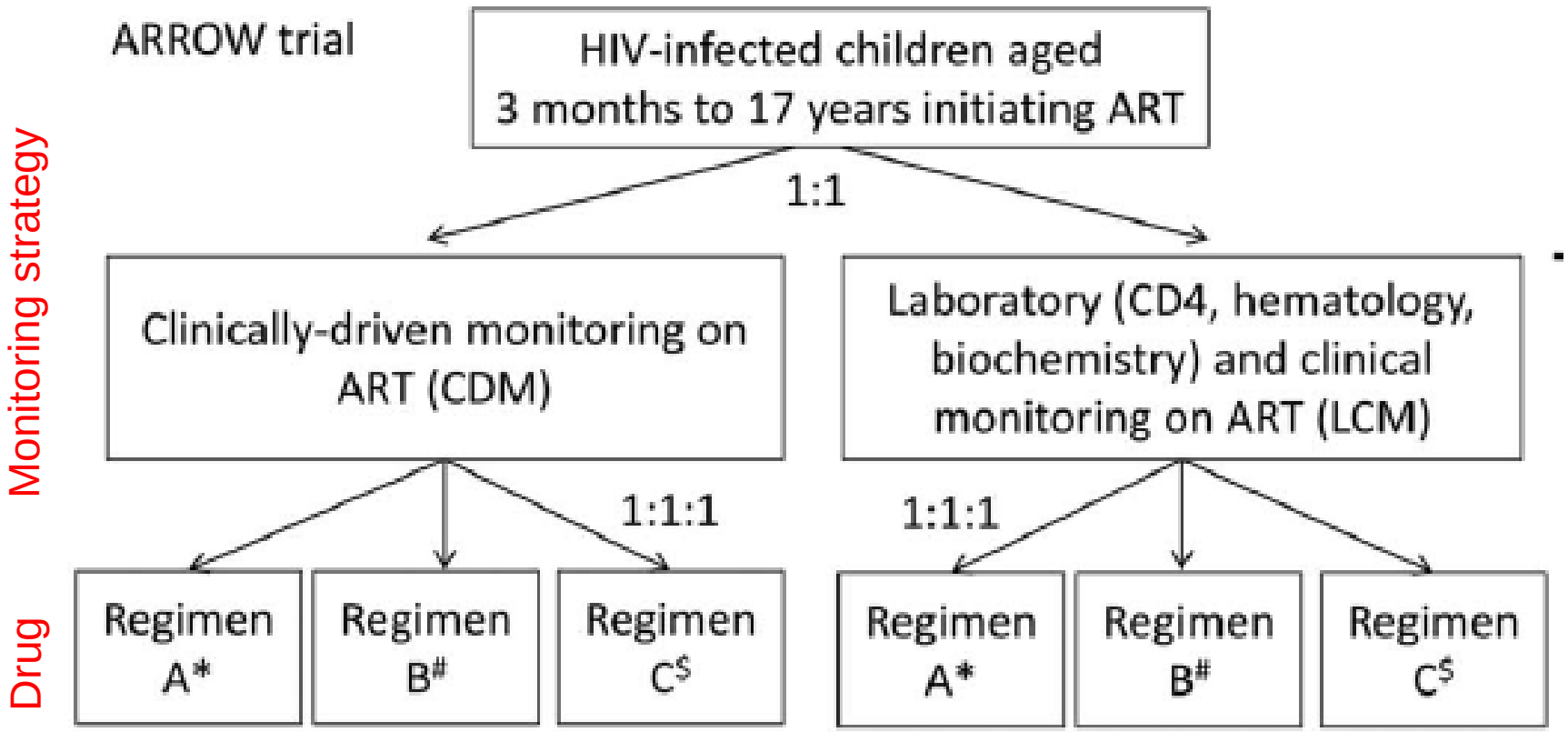
4) Large enough sample size

- Includes **enough people to answer the hypothesis**
- Trials that aren't large enough = lack the **statistical power** to detect clinically important differences between groups

Alternative types of clinical trial design

- Factorial design
- Cluster-randomised trial

Factorial design: test multiple hypotheses

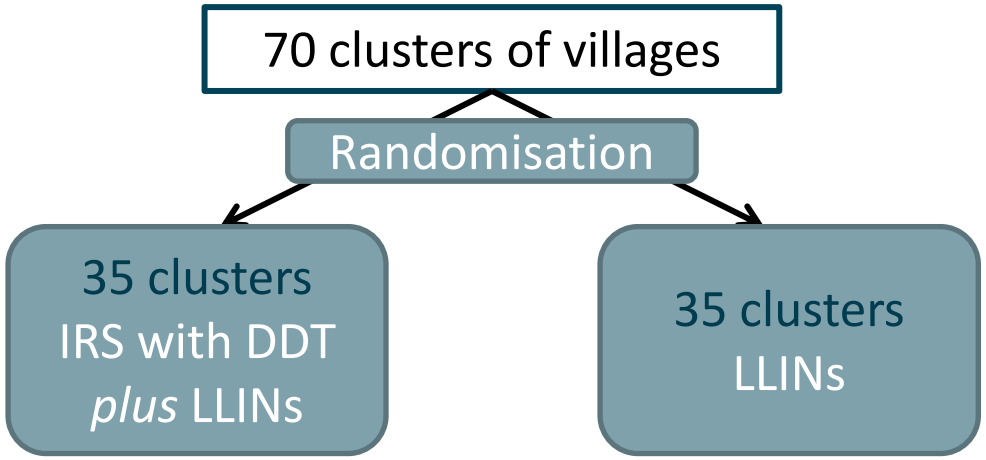


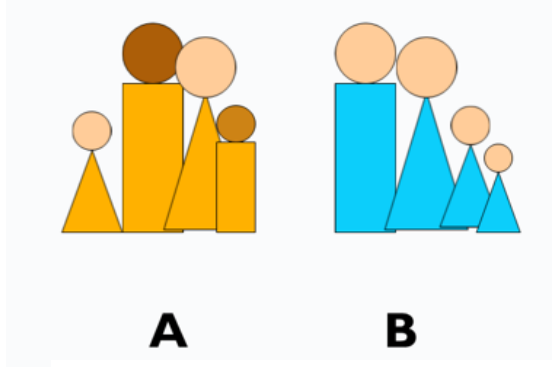
Ford et al. JAIDS 2018: 78 (S1)

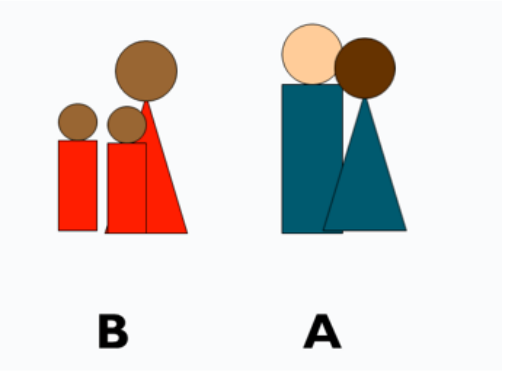
Cluster-randomised trials

Cluster-randomised trial of indoor residual spraying (IRS) with DDT to prevent malaria, the Gambia

- Intervention assigned to **groups** e.g. household, school, GP clinics or community







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

Strengths	Weaknesses
Can provide **strongest evidence for the effectiveness and safety**	**Very expensive and time consuming**
Best design to draw conclusions on **causality** (clear sequence of events)	Often **limited follow-up**
Randomisation is a **powerful tool to control for confounding** (known + unknown factors), minimise selection bias	**Inefficient** for rare events or diseases with delayed outcomes
Blinding minimizes bias	**Ethical constraints**: not always ethical or feasible to randomise
Can test **multiple hypotheses** (e.g. factorial design)	**Complex design and analysis** if cluster randomised trial
Can assess incidence of disease and **multiple outcomes**	**Generalisability**: those enrolled in trials may not be representative of the target population

ACTIVITY!

- Go to www.menti.com and enter the code 2908 5998
  - Or follow the direct link in the chat https://www.menti.com/4tu8ehn9o4

- Answer the multiple choice questions on the screen

QUIZ – Q1

A randomised controlled trial (RCT) could be used to answer which of the following research questions?

A. Does smoking increase the risk of liver cancer in adults living with HIV?

B. Is rotavirus vaccination safe and effective in children living with HIV?

C. Does HIV infection increase the risk of having a small for gestational age baby?

QUIZ – Q2

Which is the main reason for blinding in an RCT?

A. To reduce confounding

B. To increase the power of the RCT

C. To protect against information bias

QUIZ – Q3

An RCT is being conducted to determine whether promotion of hand washing in primary schools reduces risk of gastrointestinal infections in school children. Schools are randomised to receive promotional materials. What sort of trial is this?

A. Factorial
B. Cluster
C. Parallel

OBSERVATIONAL STUDIES

Experimental v observational

Experimental (Clinical Trials)

- Studies which evaluate a new treatment or intervention and compare outcomes in treated and untreated, or conventionally treated, group

Observational

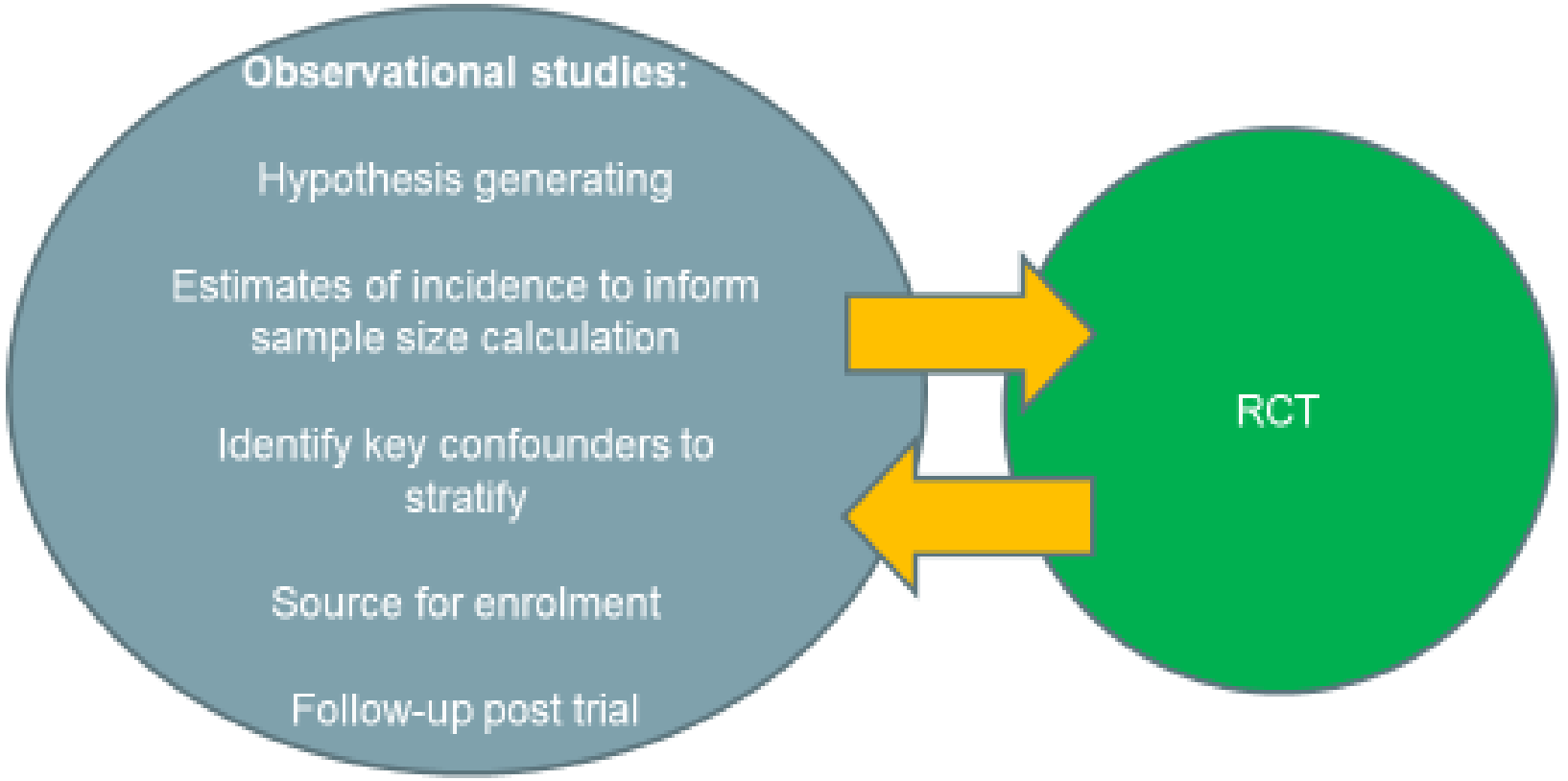
- Studies which involve careful recording of exposures, treatments and outcomes as they occur normally or routinely, with no study-specific intervention or treatment

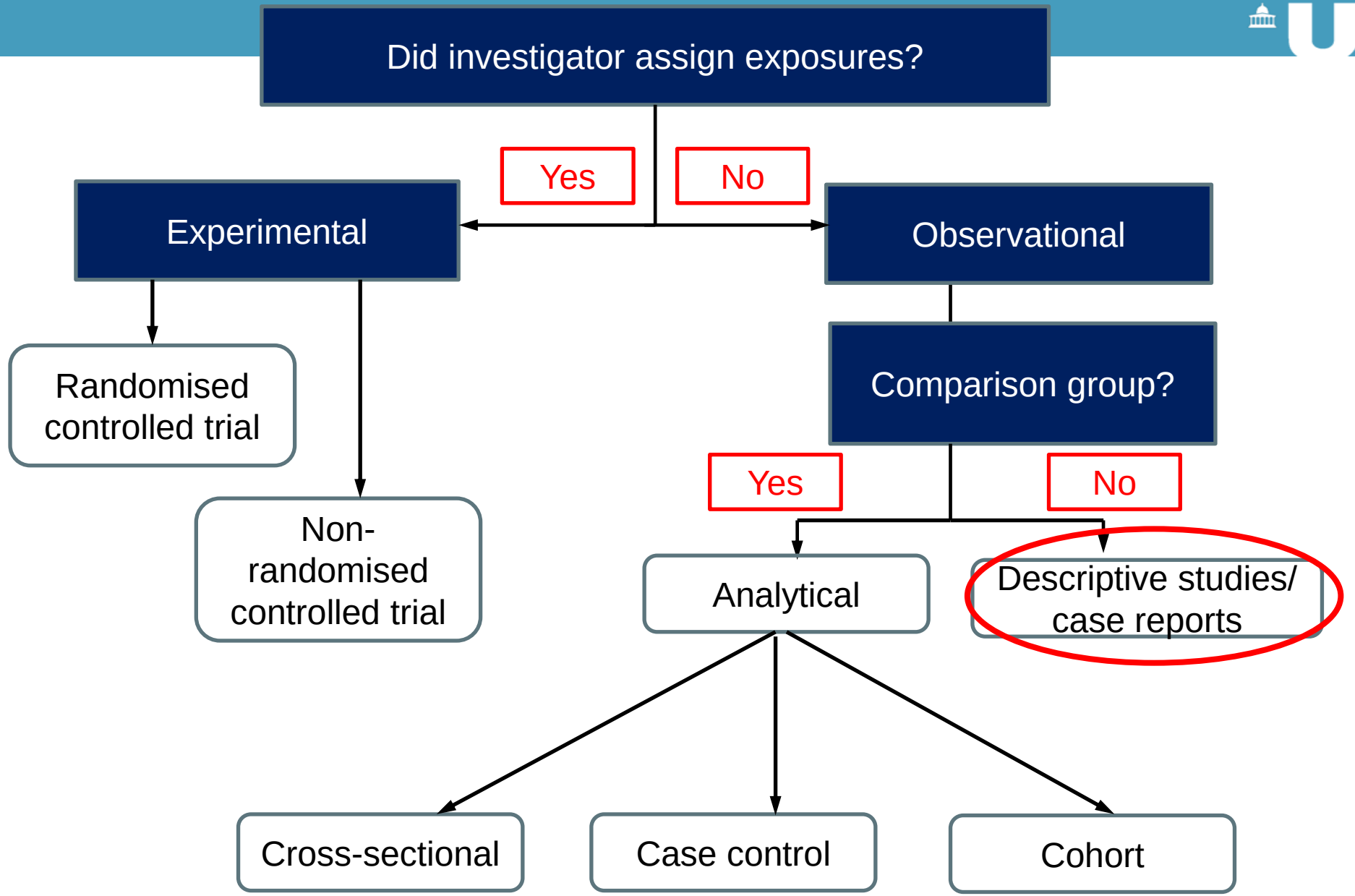
Why not do an RCT?

- Impossible / unethical to randomise
  - Does smoking cause dementia?
  - Does diabetes increase risk of tuberculosis?
- Insufficient evidence to justify a trial
- May need a very large sample size, e.g. for rare outcomes, which is not practical/feasible to achieve
- Do not provide answers how effective the intervention in routine settings
- Usually take long time to complete

Choosing the appropriate design …

- Observational studies and RCT can compliment each other:



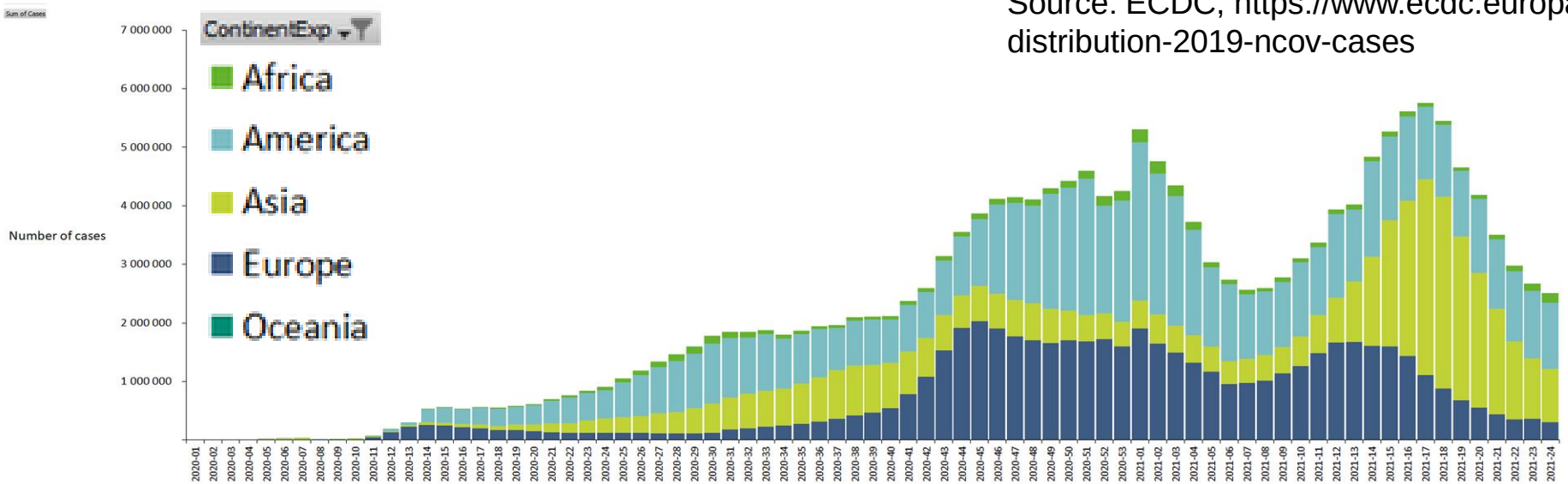


Adapted from Schulz and Grimes, The Lancet Handbook of Essential Concepts in Clinical Research

Descriptive studies

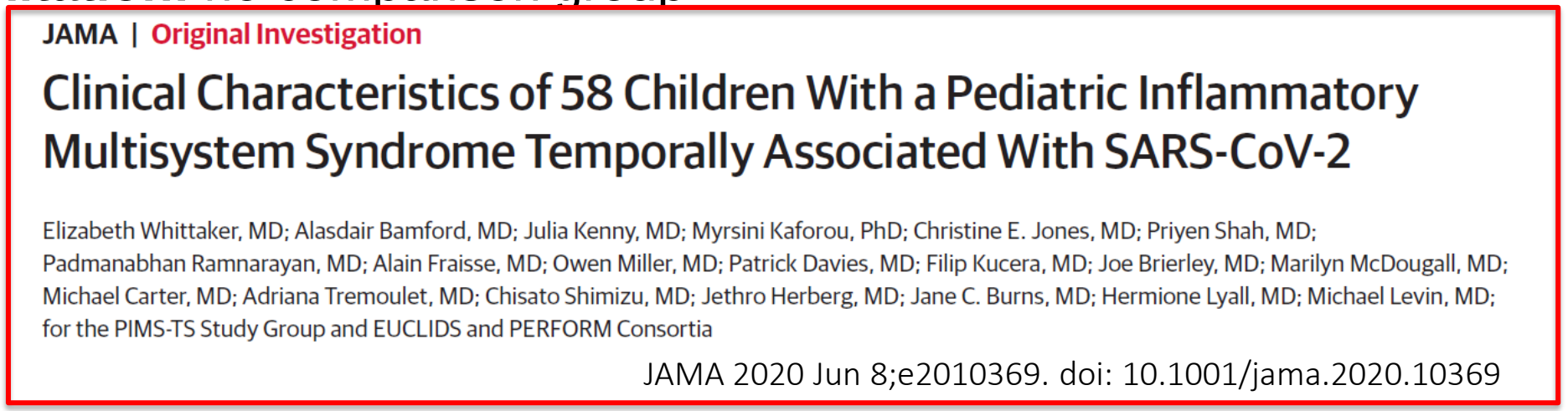
- Describe the frequency of a disease in a population
  - Trends over time, by population group and geographical regions
- Limited quantitative assessment of risk factors
- Data sources may be:
  - Routine statistics e.g. hospital admissions, causes of death
  - Surveys, special disease registries

Number of reported COVID-19 cases by region
Source: ECDC, https://www.ecdc.europa.eu/en/geographical-distribution-2019-ncov-cases



Case reports and case series

- **Case reports**
  - Detailed descriptions of one or a few cases
  - Unusual disease, complication, or unusual outcome
- **Case series:** collection of patients with common characteristics
  - Critical for new emerging diseases
- **Key limitation:** no comparison group

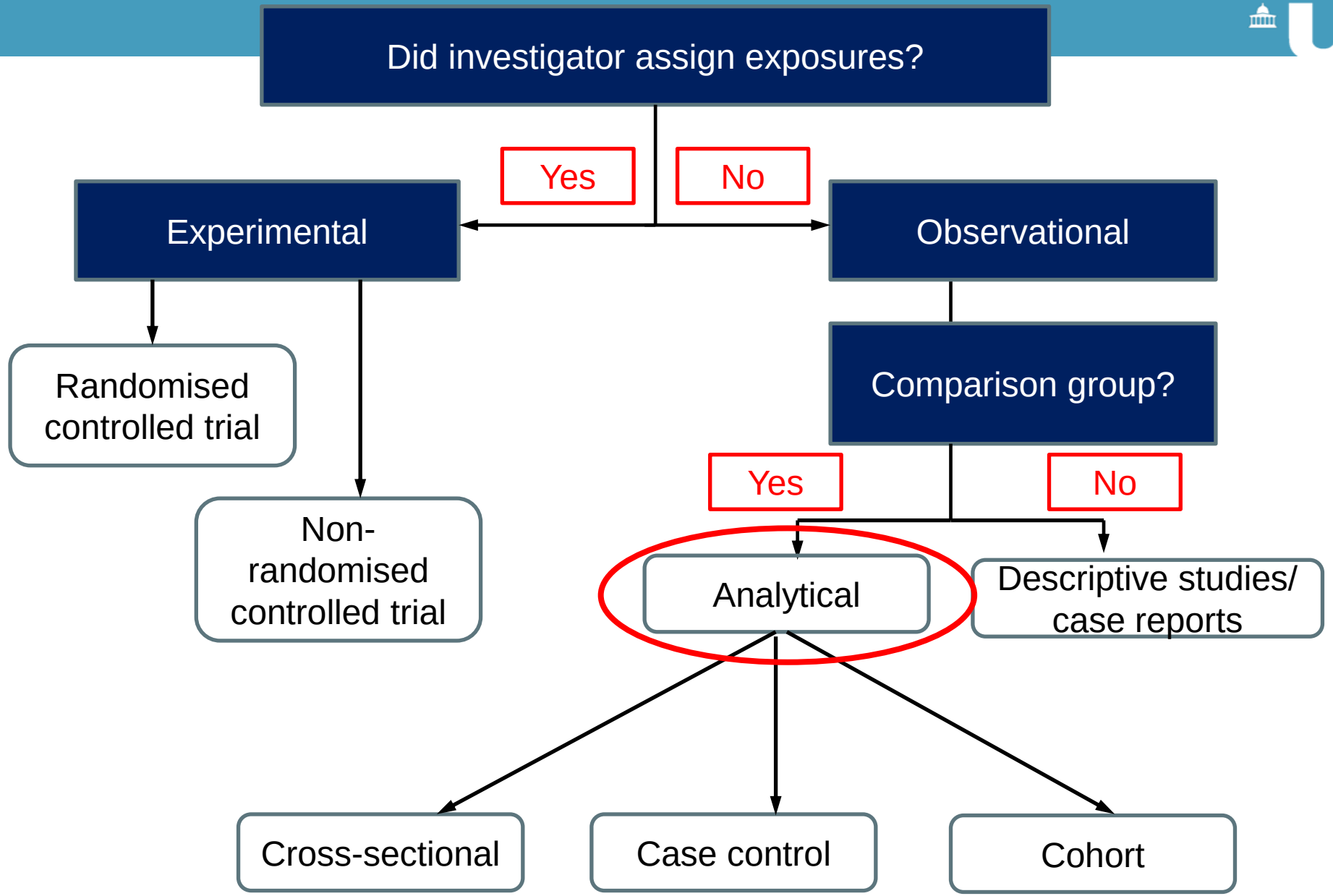


JAMA | Original Investigation

Clinical Characteristics of 58 Children With a Pediatric Inflammatory Multisystem Syndrome Temporally Associated With SARS-CoV-2

Elizabeth Whittaker, MD; Alasdair Bamford, MD; Julia Kenny, MD; Myrsini Kaforou, PhD; Christine E. Jones, MD; Priyen Shah, MD; Padmanabhan Ramnarayan, MD; Alain Fraisse, MD; Owen Miller, MD; Patrick Davies, MD; Filip Kucera, MD; Joe Brierley, MD; Marilyn McDougall, MD; Michael Carter, MD; Adriana Tremoulet, MD; Chisato Shimizu, MD; Jethro Herberg, MD; Jane C. Burns, MD; Hermione Lyall, MD; Michael Levin, MD; for the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia

JAMA 2020 Jun 8;e2010369. doi: 10.1001/jama.2020.10369



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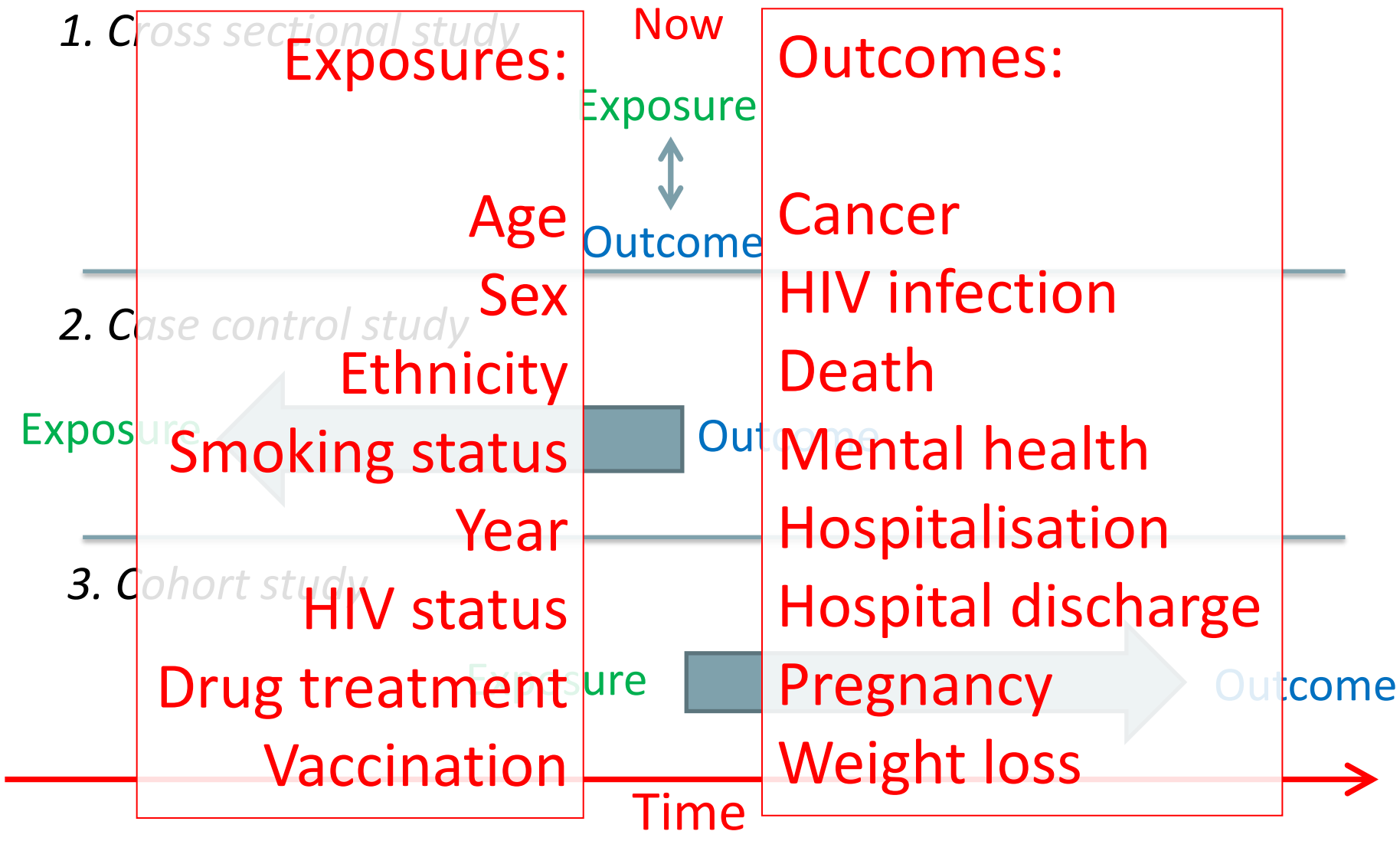

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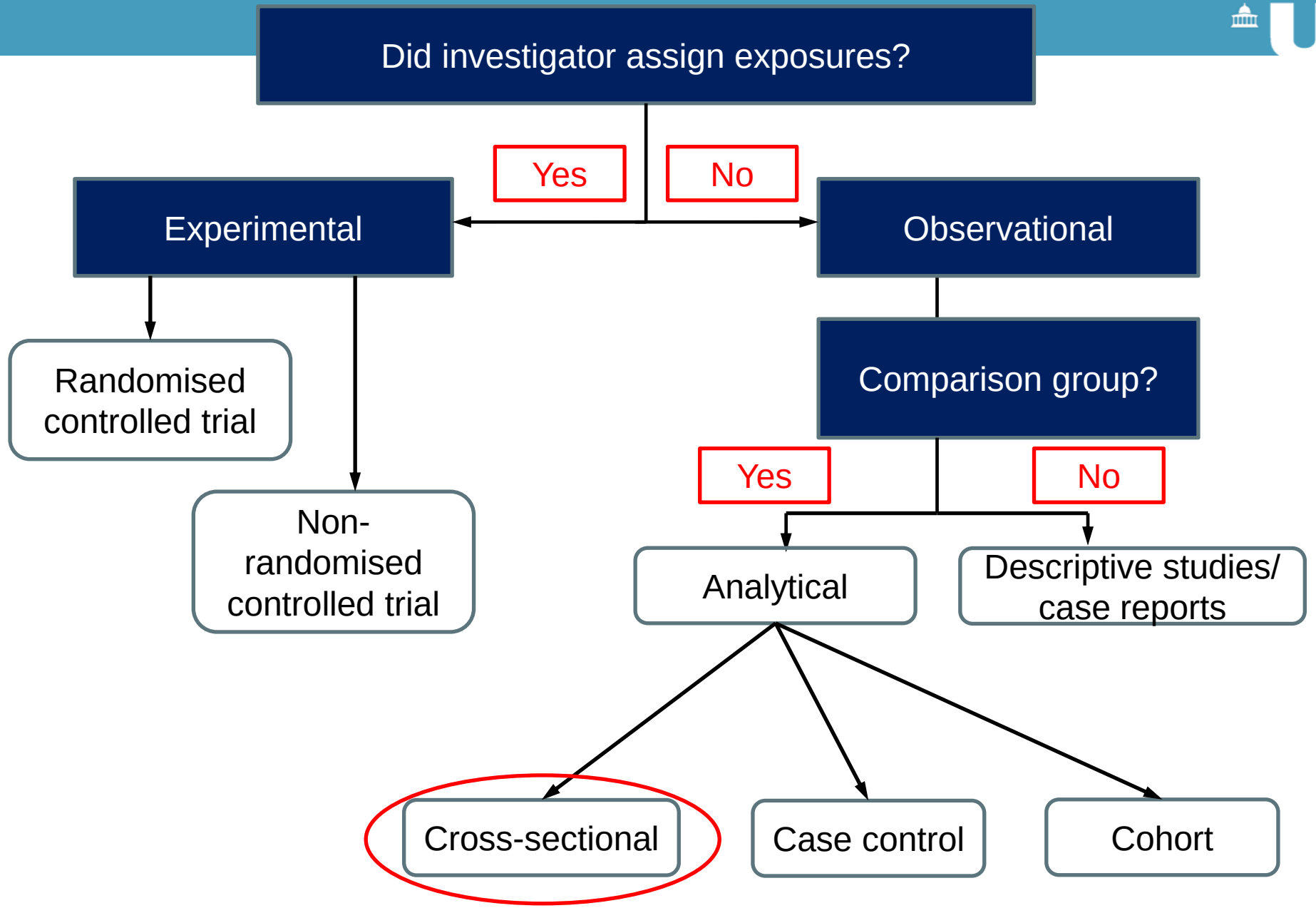
CROSS-SECTIONAL STUDIES



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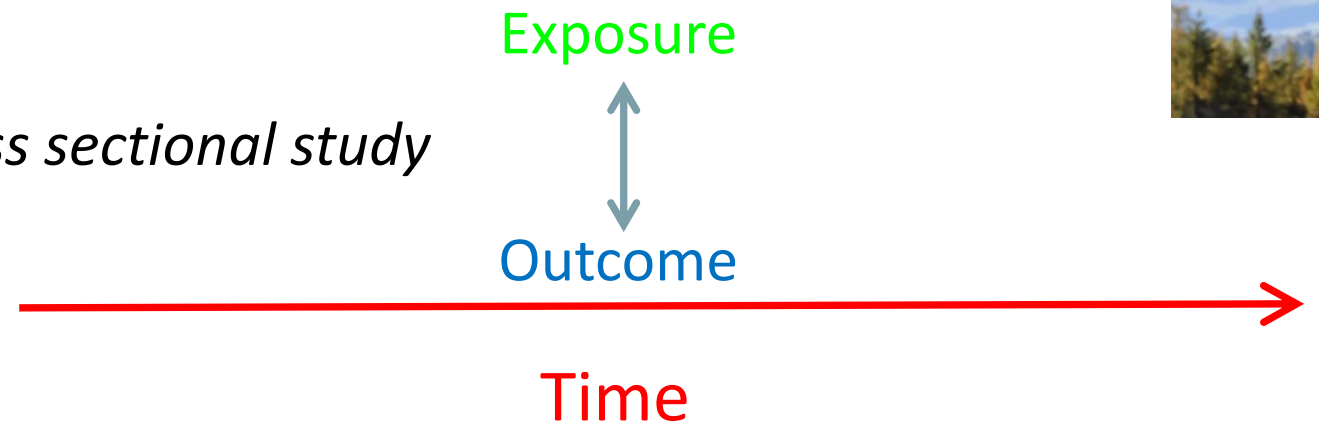
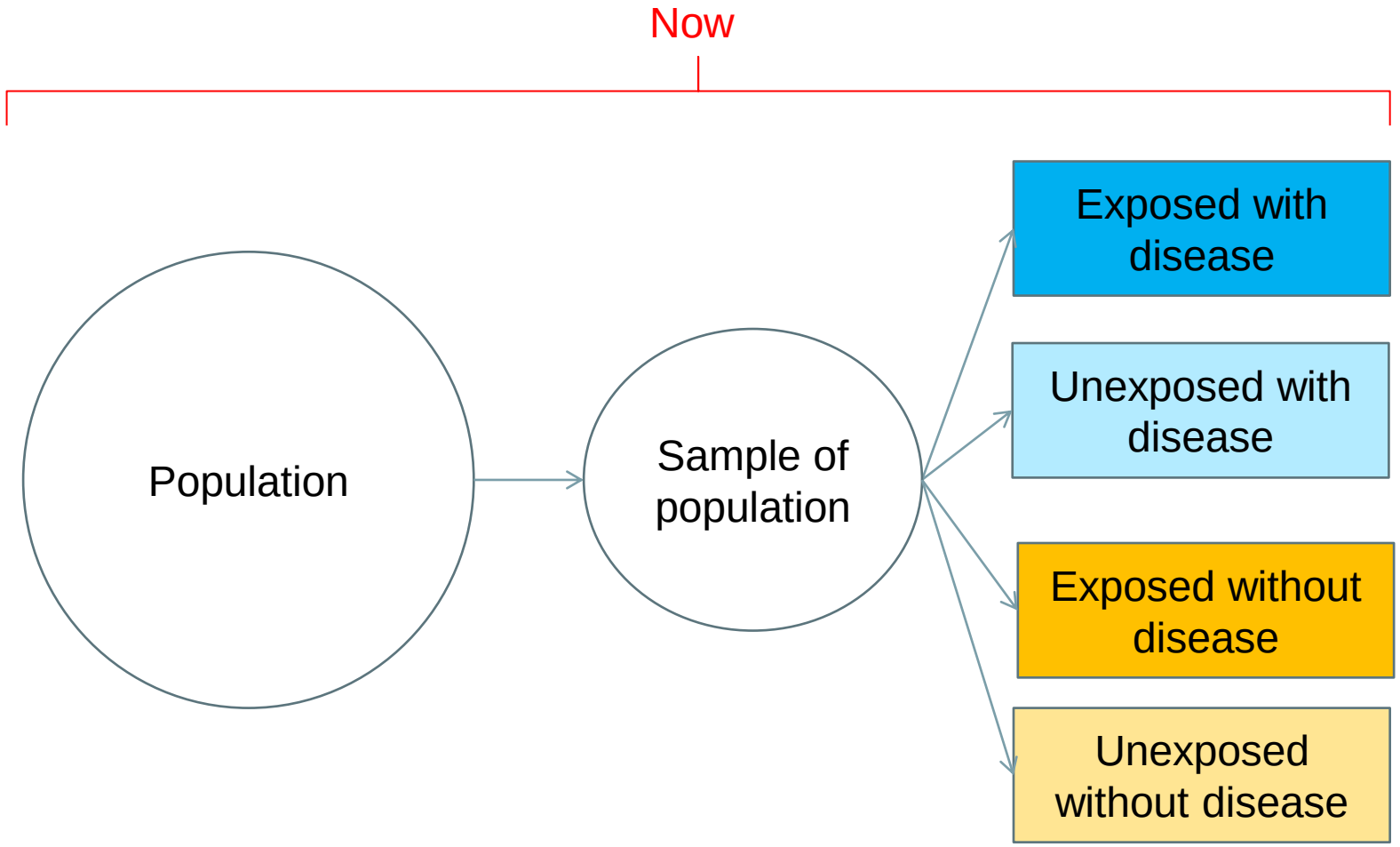
Cross-sectional studies



- Observe presence or absence of exposures AND outcomes at the same time point
- Advantages: cheap, quick, useful for estimating prevalence
- Limitation: does exposure precede outcome? (Could it have caused the outcome?)

Cross sectional studies



Cross sectional study examples

JIAS JOURNAL OF THE INTERNATIONAL AIDS SOCIETY Open Access

Research Article | Open Access

Multisystem impairment in South African adolescents with Perinatally acquired HIV on antiretroviral therapy (ART)

Lisa J Frigati, Karryn Brown, Sana Mahtab, Leah Githinji, Diane Gray, Liesl Zühlke, Peter Nourse
... See all authors

First published: 23 August 2019 | https://doi.org/10.1002/jia2.25386 | Citations: 1

- Prevalence of multi-system impairment in adolescents with perinatal HIV
- Prevalence of liver disease in adults living with HIV

icle

Prevalence, Predictors, and Severity of Lean Nonalcoholic Fatty Liver Disease in Patients Living With Human Immunodeficiency Virus

Adriana Cervo, Jovana Milic, Giovanni Mazzola, Filippo Schepis, Salvatore Petta ...

Clinical Infectious Diseases, ciaa430, https://doi.org/10.1093/cid/ciaa430

Published: 13 April 2020

.... We conducted a retrospective, **cross-sectional** study from the liver disease in **HIV** (LIVEHIV), Modena **HIV** Metabolic Clinic (MHMC),

Example: exercise and cardiovascular disease (CVD)

- A cross-sectional study might find that people with cardiovascular disease do less exercise than people without (on average)

Example: exercise and cardiovascular disease (CVD)

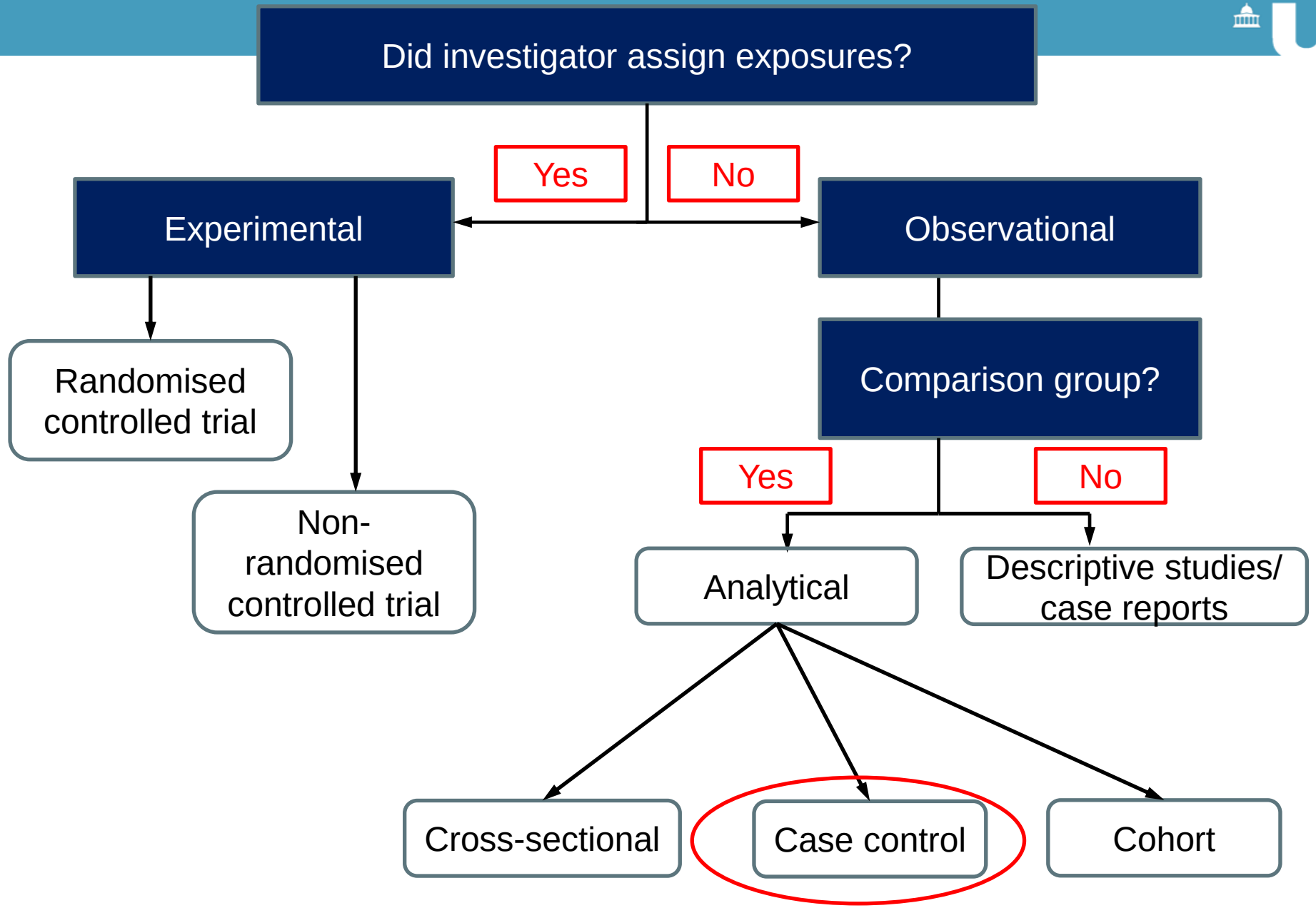
- A cross-sectional study might find that people with cardiovascular disease do less exercise than people without (on average)

  → Lack of exercise leads to CVD?

  Or CVD makes exercise difficult?

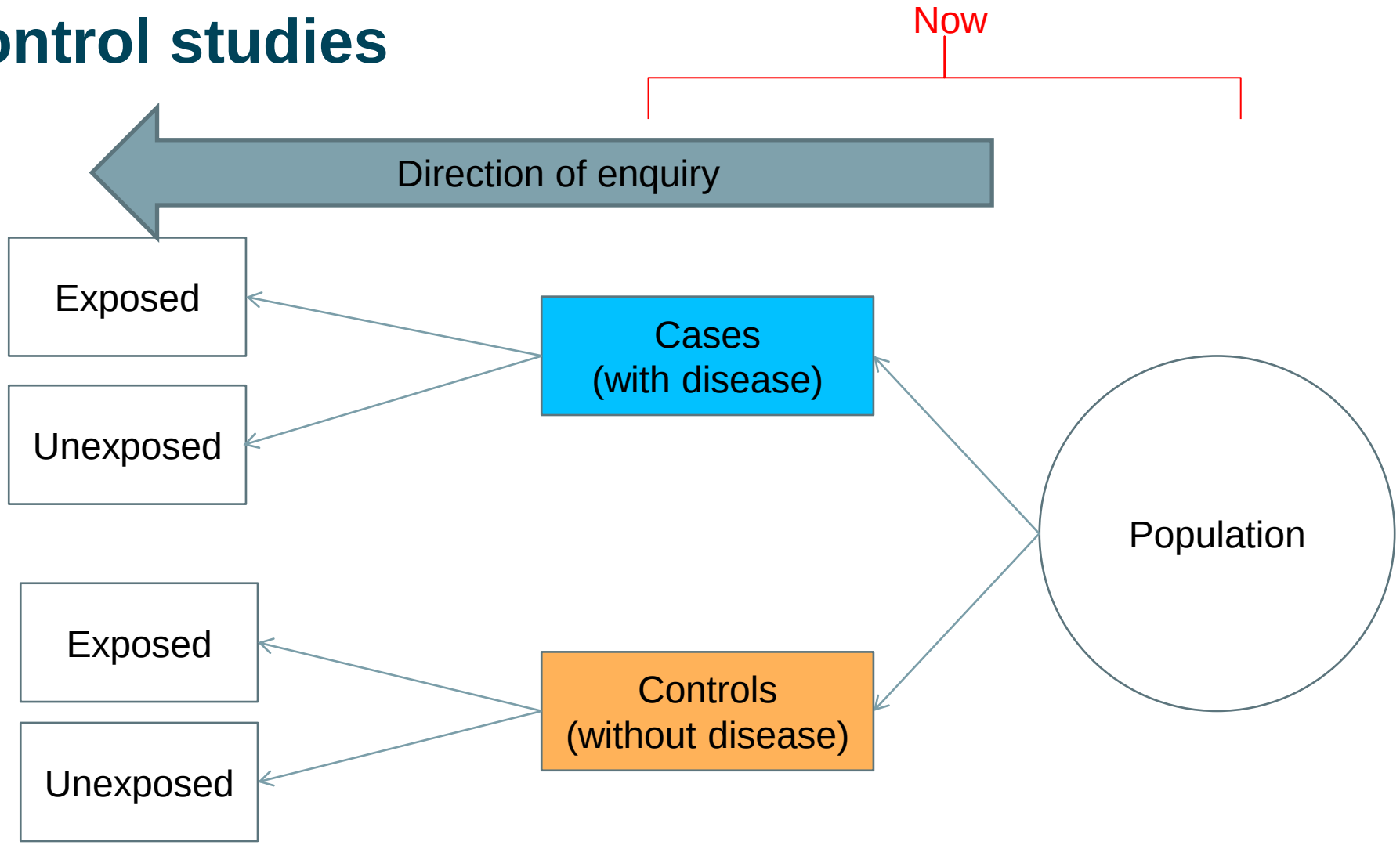
Strengths	Weaknesses
Quick and cheap to conduct	Cannot assess **incidence**
Useful for **providing evidence** for planning future studies/trials	Inefficient for studying **rare exposures and outcomes**
Useful for **estimating prevalence**	Difficult to determine **sequence of events**
Can **explore associations** between multiple exposures and outcomes	

CASE CONTROL STUDIES

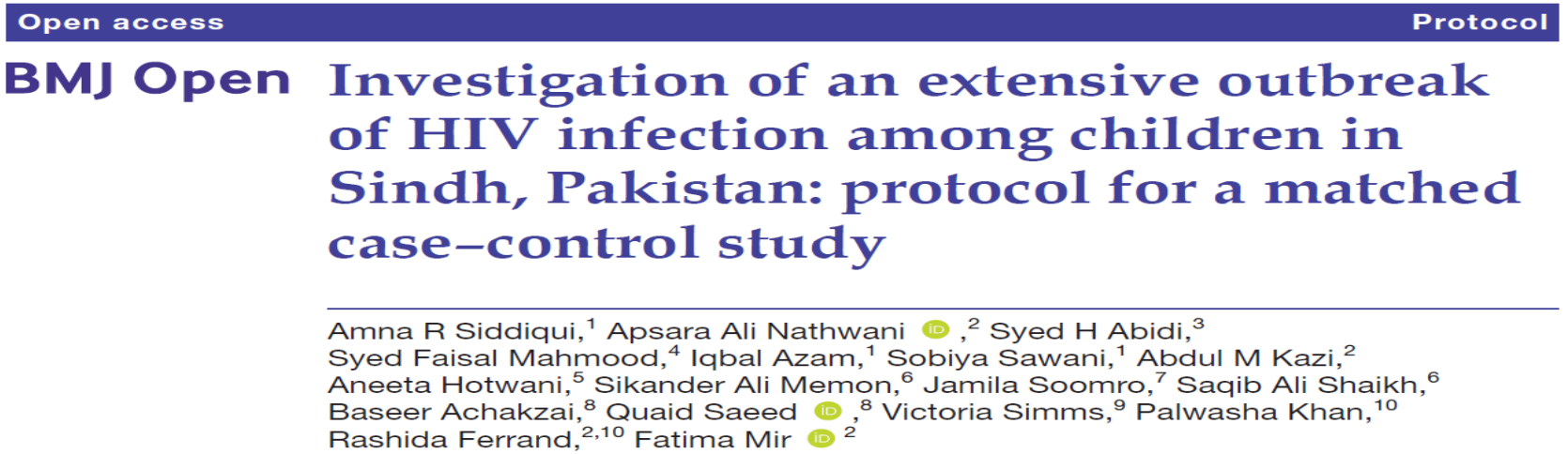


Adapted from Schulz and Grimes, The Lancet Handbook of Essential Concepts in Clinical Research

Case-control studies



Case-control example



Open access Protocol

BMJ Open

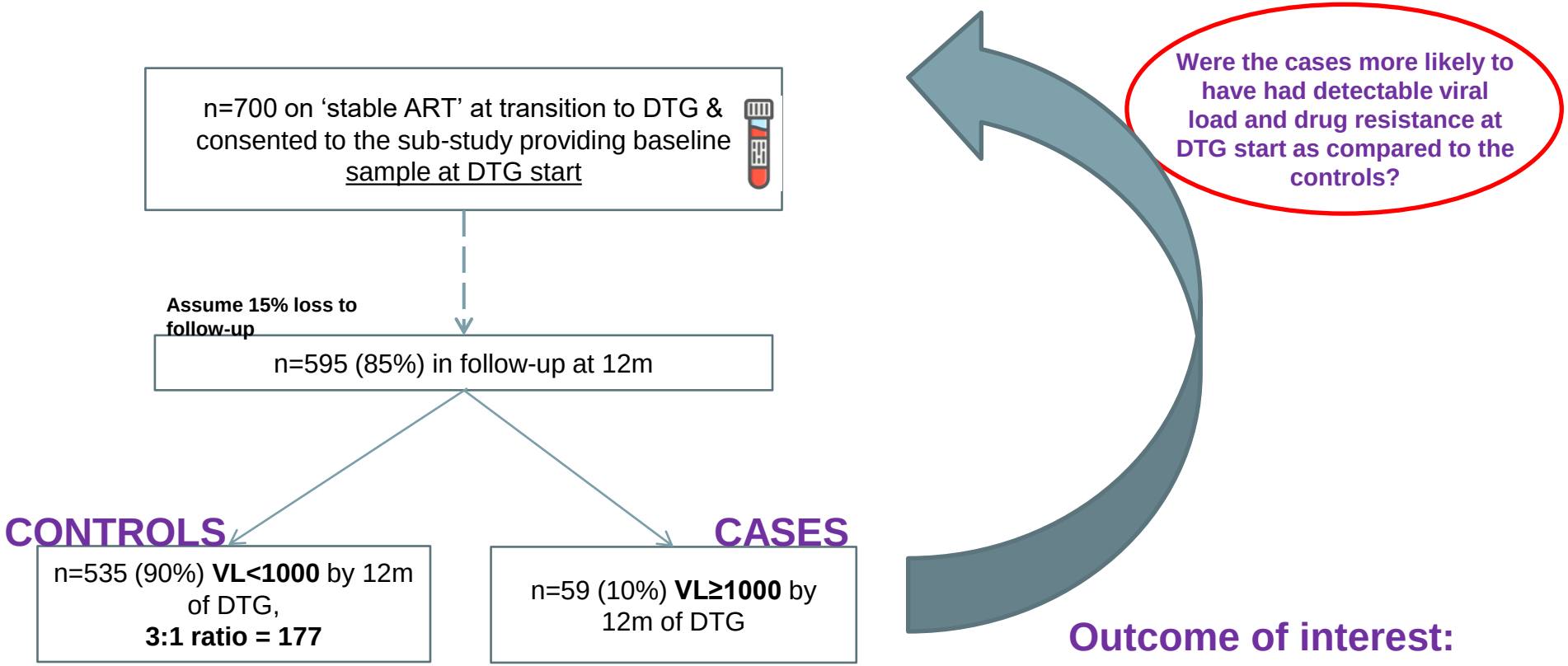
Investigation of an extensive outbreak of HIV infection among children in Sindh, Pakistan: protocol for a matched case–control study

Amna R Siddiqui,[1] Apsara Ali Nathwani ,[2] Syed H Abidi,[3] Syed Faisal Mahmood,[4] Iqbal Azam,[1] Sobiya Sawani,[1] Abdul M Kazi,[2] Aneeta Hotwani,[5] Sikander Ali Memon,[6] Jamila Soomro,[7] Saqib Ali Shaikh,[6] Baseer Achakzai,[8] Quaid Saeed ,[8] Victoria Simms,[9] Palwasha Khan,[10] Rashida Ferrand,[2,10] Fatima Mir [2]

BMJ Open. 2020 Mar 25;10(3):e036723. doi: 10.1136/bmjopen-2019-036723

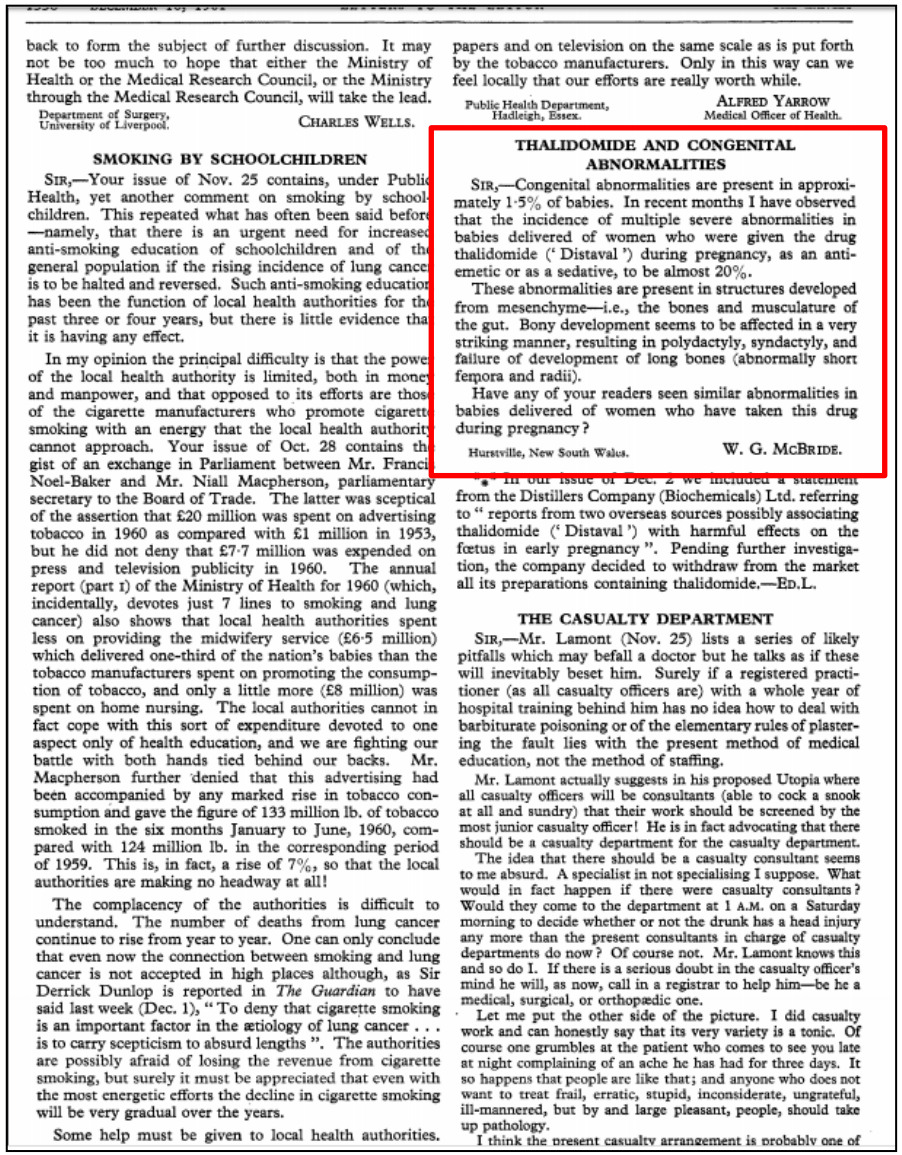
- ***Cases***: children with HIV
- ***Controls***: children without HIV, matched for age, sex and neighbourhood
- Risk factors for HIV to be assessed: use of healthcare services, injections, surgery, blood transfusions

UP-ART case-control study



Case control studies - Thalidomide

- “Wonder drug" for insomnia, colds, headaches
- Licensed in 1957/58
- Effective over the counter anti-sickness agent, used by pregnant women for morning sickness
- Case reports of links to congenital anomalies



back to form the subject of further discussion. It may not be too much to hope that either the Ministry of Health or the Medical Research Council, or the Ministry through the Medical Research Council, will take the lead.

Department of Surgery, University of Liverpool. CHARLES WELLS.

SMOKING BY SCHOOLCHILDREN

SIR,—Your issue of Nov. 25 contains, under Public Health, yet another comment on smoking by school-children. This repeated what has often been said before—namely, that there is an urgent need for increased anti-smoking education of schoolchildren and of the general population if the rising incidence of lung cancer is to be halted and reversed. Such anti-smoking education has been the function of local health authorities for the past three or four years, but there is little evidence that it is having any effect.

In my opinion the principal difficulty is that the power of the local health authority is limited, both in money and manpower, and that opposed to its efforts are those of the cigarette manufacturers who promote cigarette smoking with an energy that the local health authority cannot approach. Your issue of Oct. 28 contains the gist of an exchange in Parliament between Mr. Francis Noel-Baker and Mr. Niall Macpherson, parliamentary secretary to the Board of Trade. The latter was sceptical of the assertion that £20 million was spent on advertising tobacco in 1960 as compared with £1 million in 1953, but he did not deny that £7·7 million was expended on press and television publicity in 1960. The annual report (part 1) of the Ministry of Health for 1960 (which, incidentally, devotes just 7 lines to smoking and lung cancer) also shows that local health authorities spent less on providing the midwifery service (£6·5 million) which delivered one-third of the nation's babies than the tobacco manufacturers spent on promoting the consumption of tobacco, and only a little more (£8 million) was spent on home nursing. The local authorities cannot in fact cope with this sort of expenditure devoted to one aspect only of health education, and we are fighting our battle with both hands tied behind our backs. Mr. Macpherson further denied that this advertising had been accompanied by any marked rise in tobacco consumption and gave the figure of 133 million lb. of tobacco smoked in the six months January to June, 1960, compared with 124 million lb. in the corresponding period of 1959. This is, in fact, a rise of 7%, so that the local authorities are making no headway at all!

The complacency of the authorities is difficult to understand. The number of deaths from lung cancer continue to rise from year to year. One can only conclude that even now the connection between smoking and lung cancer is not accepted in high places although, as Sir Derrick Dunlop is reported in *The Guardian* to have said last week (Dec. 1), "To deny that cigarette smoking is an important factor in the ætiology of lung cancer . . . is to carry scepticism to absurd lengths". The authorities are possibly afraid of losing the revenue from cigarette smoking, but surely it must be appreciated that even with the most energetic efforts the decline in cigarette smoking will be very gradual over the years.

Some help must be given to local health authorities.

papers and on television on the same scale as is put forth by the tobacco manufacturers. Only in this way can we feel locally that our efforts are really worth while.

Public Health Department, Hadleigh, Essex. ALFRED YARROW Medical Officer of Health.

THALIDOMIDE AND CONGENITAL ABNORMALITIES

SIR,—Congenital abnormalities are present in approximately 1·5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

These abnormalities are present in structures developed from mesenchyme—i.e., the bones and musculature of the gut. Bony development seems to be affected in a very striking manner, resulting in polydactyly, syndactyly, and failure of development of long bones (abnormally short femora and radii).

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

Hurstville, New South Wales. W. G. MCBRIDE.

*** In our issue of Dec. 2 we included a statement from the Distillers Company (Biochemicals) Ltd. referring to "reports from two overseas sources possibly associating thalidomide ('Distaval') with harmful effects on the fœtus in early pregnancy". Pending further investigation, the company decided to withdraw from the market all its preparations containing thalidomide.—ED.L.

THE CASUALTY DEPARTMENT

SIR,—Mr. Lamont (Nov. 25) lists a series of likely pitfalls which may befall a doctor but he talks as if these will inevitably beset him. Surely if a registered practitioner (as all casualty officers are) with a whole year of hospital training behind him has no idea how to deal with barbiturate poisoning or of the elementary rules of plastering the fault lies with the present method of medical education, not the method of staffing.

Mr. Lamont actually suggests in his proposed Utopia where all casualty officers will be consultants (able to cock a snook at all and sundry) that their work should be screened by the most junior casualty officer! He is in fact advocating that there should be a casualty department for the casualty department.

The idea that there should be a casualty consultant seems to me absurd. A specialist in not specialising I suppose. What would in fact happen if there were casualty consultants? Would they come to the department at 1 A.M. on a Saturday morning to decide whether or not the drunk has a head injury any more than the present consultants in charge of casualty departments do now? Of course not. Mr. Lamont knows this and so do I. If there is a serious doubt in the casualty officer's mind he will, as now, call in a registrar to help him—be he a medical, surgical, or orthopædic one.

Let me put the other side of the picture. I did casualty work and can honestly say that its very variety is a tonic. Of course one grumbles at the patient who comes to see you late at night complaining of an ache he has had for three days. It so happens that people are like that; and anyone who does not want to treat frail, erratic, stupid, inconsiderate, ungrateful, ill-mannered, but by and large pleasant, people, should take up pathology.

I think the present casualty arrangement is probably one of

Thalidomide and congenital abnormalities

Sir, Congenital abnormalities are present in approximately 1.5% of babies. In recent months I have observed that the incidence of multiple severe abnormalities in babies delivered of women who were given the drug thalidomide ('Distaval') during pregnancy, as an anti-emetic or as a sedative, to be almost 20%.

[…]

Have any of your readers seen similar abnormalities in babies delivered of women who have taken this drug during pregnancy?

McBride WG. Thalidomide and congenital abnormalities. *Lancet* 1961; 278: 1358

Thalidomide Case-control study

41 mums used thalidomide

5 didn't use thalidomide

Cases

46 children with limb malformations

0 mums used thalidomide

300 didn't use thalidomide

Controls

300 children without malformations

	Limb malformations	No limb malformations
Thalidomide	41	0
No Thalidomide	5	300

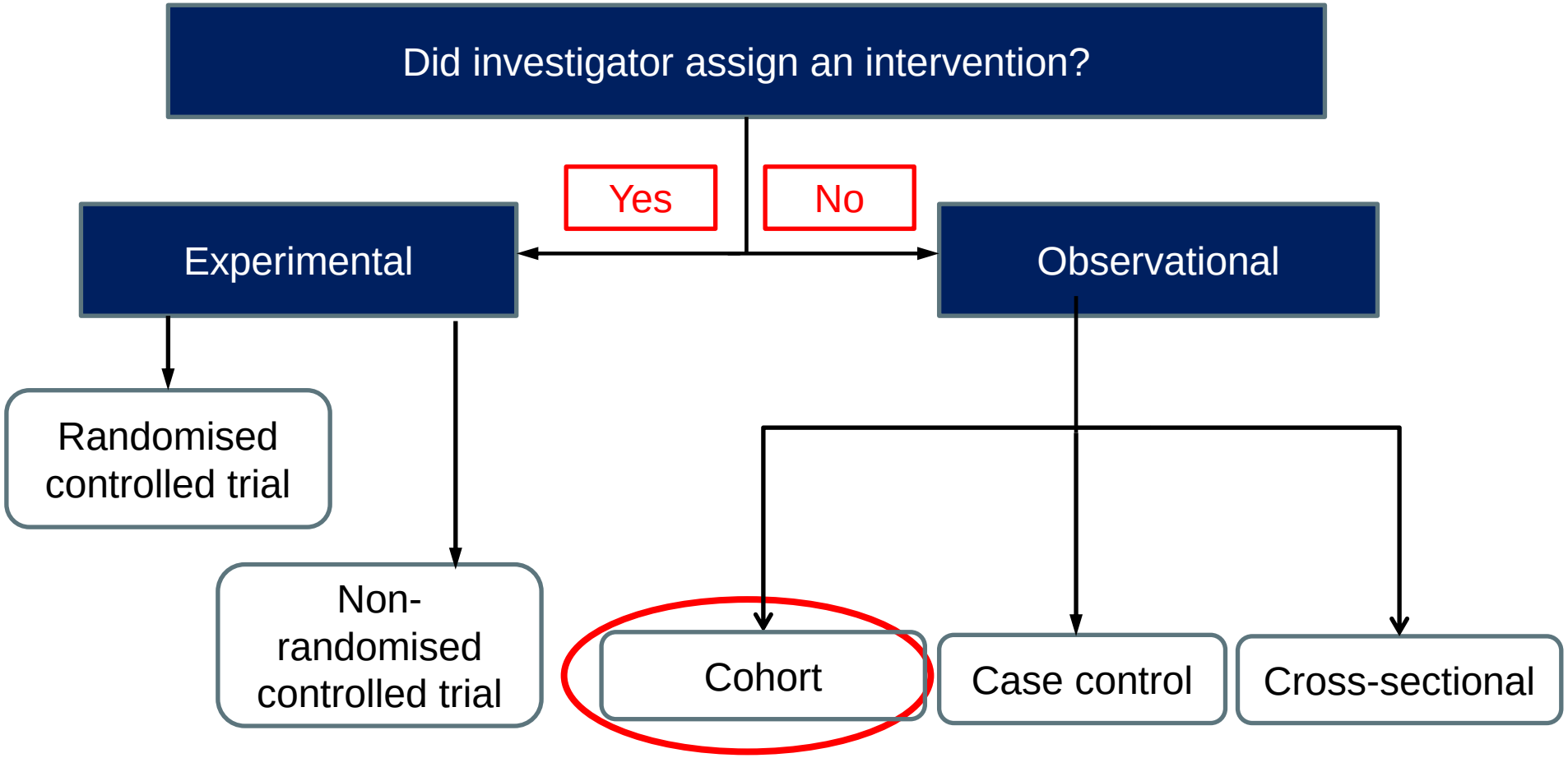
Mellin GW, Katzenstein M. N Engl J Med 1962; 267: 1238-44.

Case-control study

- Select a ‘case’ group of people who have the outcome of interest and a ‘control’ (or comparison) group without the outcome
  - Compare the proportions with the exposure of interest in each group
  - Establish whether exposure to any past factor has occurred more or less frequently in cases than controls
- Can study conditions with a long latency period, e.g. tobacco smoking and lung cancer
  - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2038856/pdf/brmedj03566-0003.pdf

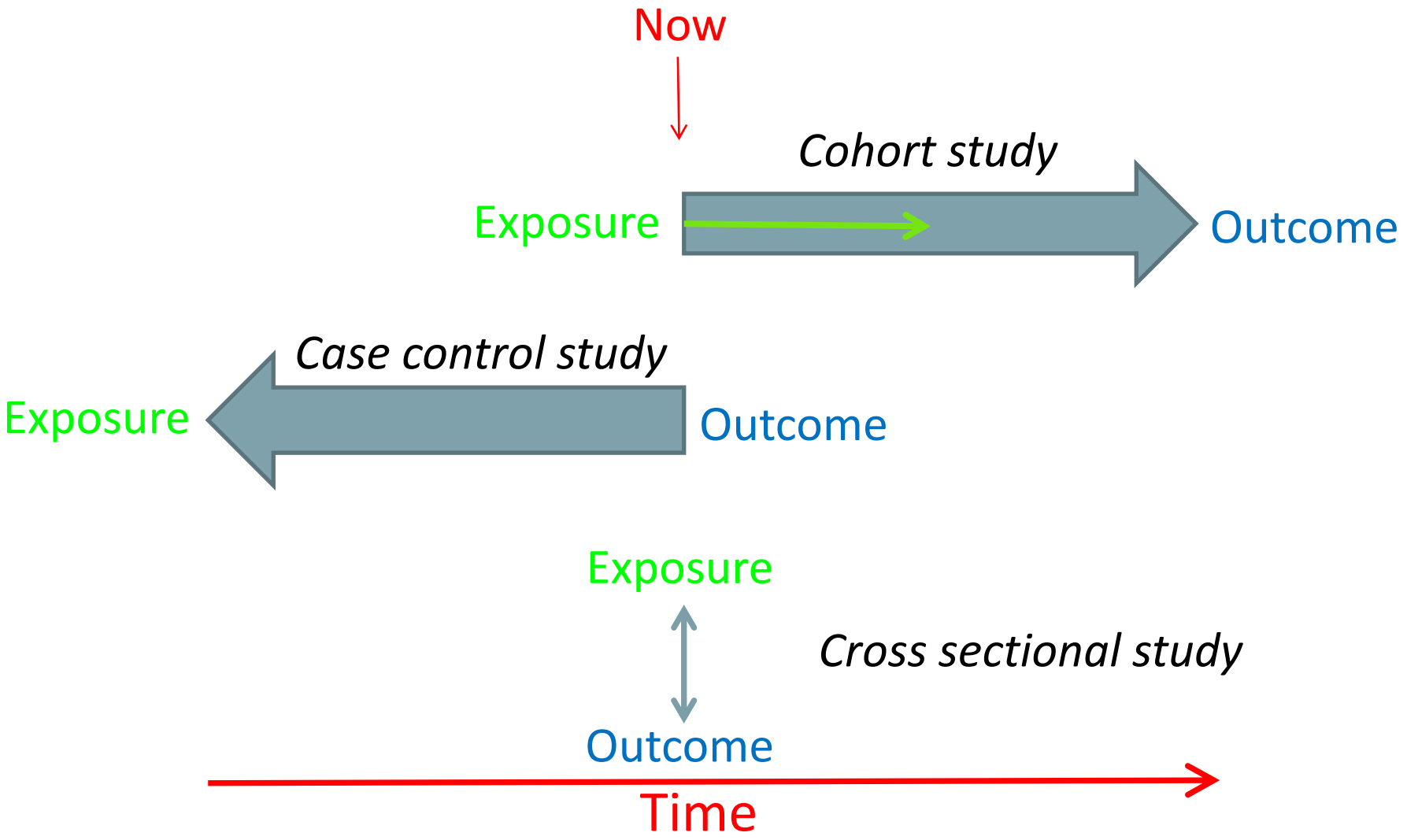
Strengths	Weaknesses
Quicker and cheaper than cohort studies	Cannot usually be used to assess **incidence**
Useful for **rare outcomes**	Inefficient for studying **rare exposures**
Useful for evaluation of **diseases with a long latent period**	Difficult to determine **sequence of events**
Can **explore associations** between multiple exposures and a single outcome	**Selection and recall** bias

COHORT STUDIES



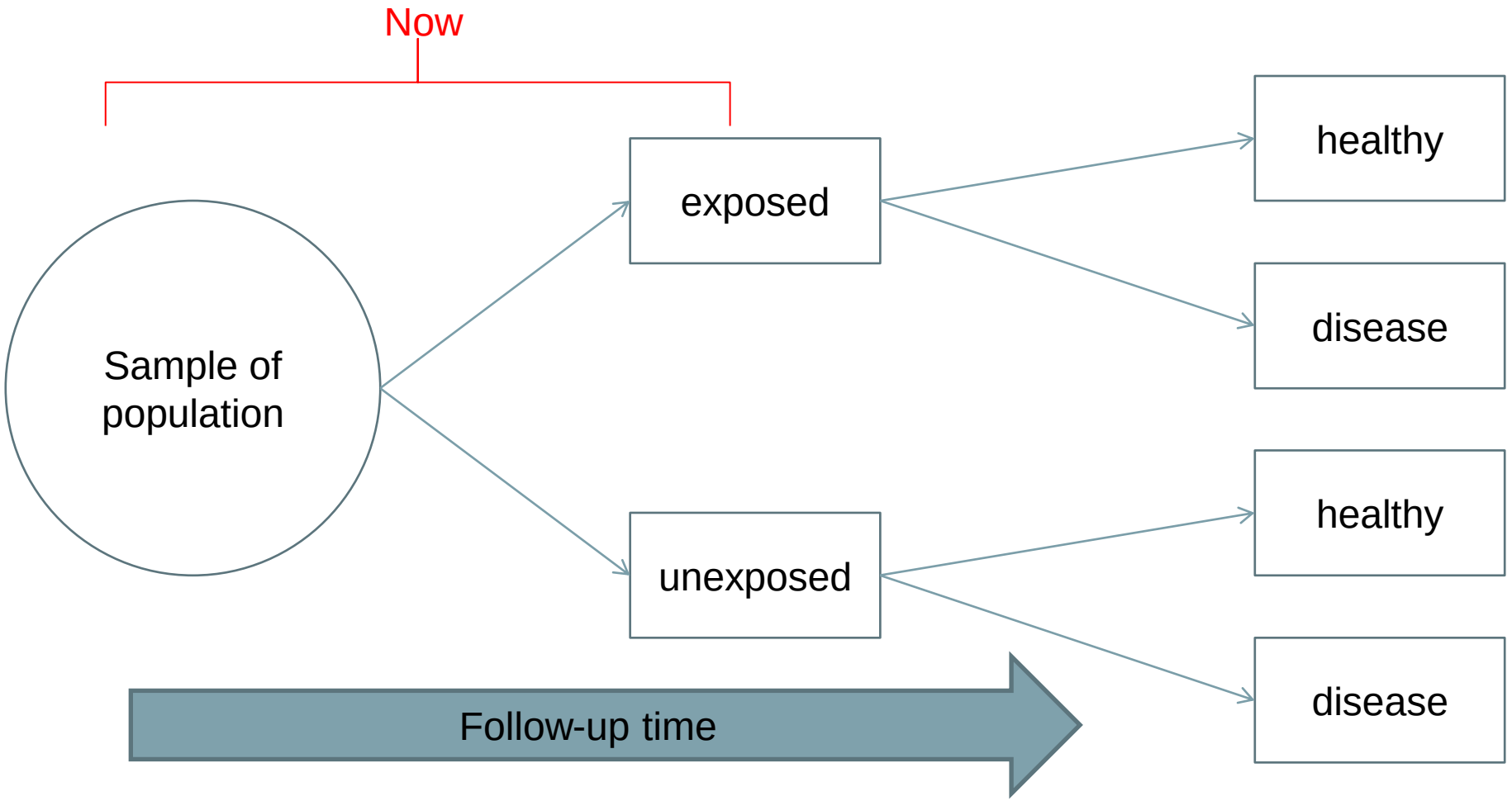
Adapted from Schulz and Grimes, The Lancet Handbook of Essential Concepts in Clinical Research

Time/ exposures & outcomes



Adapted from Schulz and Grimes, The Lancet Handbook of Essential Concepts in Clinical Research

Cohort study: Take a sample of a population and see what happens to them…



Cohort studies

- Observe a group sharing a characteristic (cohort)
- There may be two groups – “exposed” and “unexposed”
- Follow cohort longitudinally
- Determine who experiences the outcome
  - Lung cancer, death; cognitive function, HIV-related morbidity
  - Incidence rates
- Looks forward (prospective) from exposure to outcome
  - Stronger causal inferences than cross-sectional designs (Bradford Hill and causality)

Examples of cohort studies

- **Uganda Birth Cohort Study (UBC)**– longitudinal prospective cohort study of pregnant women and their newborns (https://clinicaltrials.gov/ct2/show/NCT04233944)

- **European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC)**- multi-country cohort collaboration conducting epidemiological research on pregnant women and children living with HIV, and children exposed to HIV in utero https://www.ctu.mrc.ac.uk/studies/all-studies/e/eppicc/

- **PIAMA Birth cohort-** Dutch longitudinal prospective cohort study of pregnant women and their newborns (https://piama.iras.uu.nl/)

Uganda Birth Cohort Study (UBC)

- Enrolled >3000 women and infant pairs from 2014 to 2016
- Recruited participants in 8 subcounties in northern and south-western Uganda
- Mother–infant pairs prospectively followed from pregnancy, until infants reached 12 months of age
- Nutritional Outcomes
  - Stunting
  - Wasting
  - Anemia

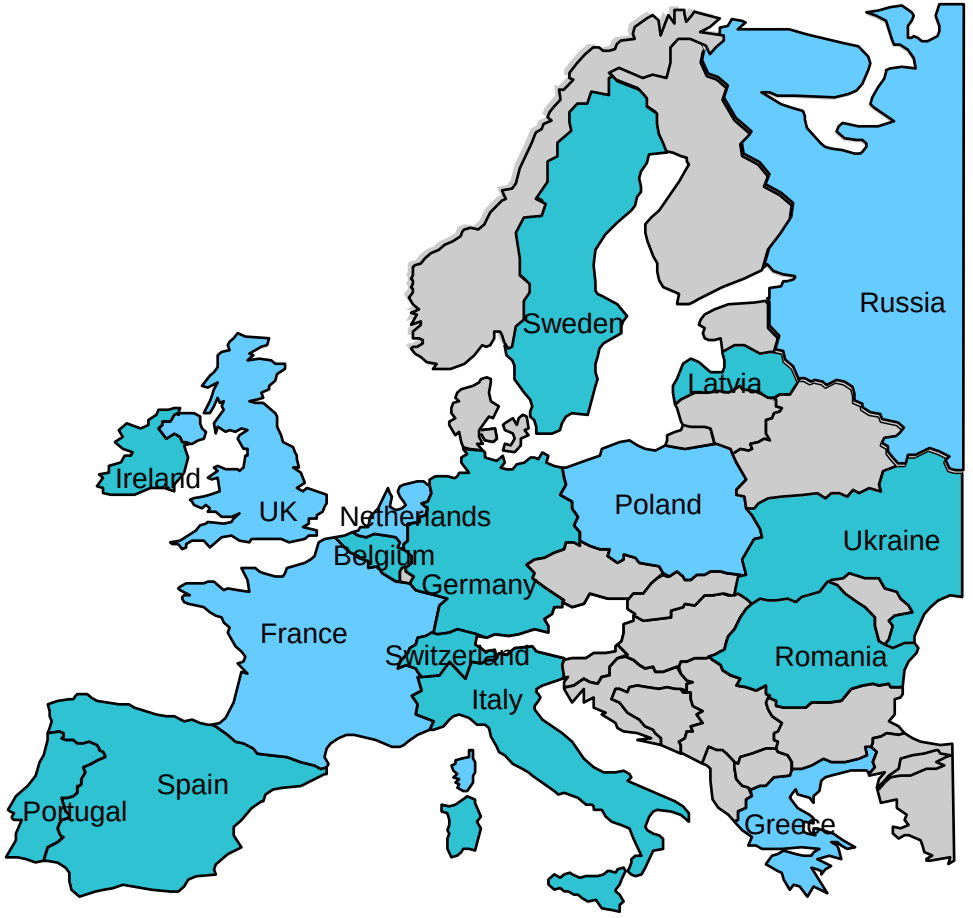
Example: UBC

TABLE 2 Cox proportional hazards models for incidence of underweight for children aged 3–12 months by prenatal DDS in the Uganda birth cohort, 2014–2016

	Maternal diet diversity score (DDS)				
	Q1 (0–2)	Q2 (3)	Q3 (4)	Q4 (5–9)	*p* for trend
Underweight[a]					
n/N	66/720	61/1128	50/842	34/589	
Univariate HR (95% CI)					
HR (95% CI)	1	0.63 (0.56, 0.70)***	0.64 (0.57, 0.73)***	0.65 (0.56, 0.74)***	<0.001***
Multivariable model HR (95% CI)[b]					
HR (95% CI)	1	0.65 (0.57, 0.72)***	0.67 (0.59, 0.75)***	0.70 (0.62, 0.80)***	<0.001***
Multivariable model controlling for birthweight[c]					
HR (95% CI)	1	0.66 (0.59, 0.74)***	0.67 (0.60, 0.76)***	0.70 (0.61, 0.80)***	<0.001***

Example: EPPICC

2016 data merger: 17 cohorts from 15 countries



Example: EPPICC

Exposure

Various exposures investigated e.g.

- Age, country of birth, exposure to HIV treatments e.g. DTG, LPV/r, TAF.

Outcomes

- Followed up to investigate various outcomes, e.g.
  - Anthropometric growth
  - Clinical progress (Viral load, CD4)
  - Drug safety
  - Malignancies

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America | hivma hiv medicine association | OXFORD

Time to Switch to Second-line Ant Children With HIV in Europe and

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group i

Background. Global data on durability of first-line antiretroviral thera virus (HIV) are limited. We assessed time to switch to second-line therapy ir

HIV Medicine published by John Wiley & Sons Ltd on behalf of British HIV Association

DOI: 10.1111/hiv.12745
HIV Medicine (2019), 20, 456–472

ORIGINAL RESEARCH

CD4 recovery following antiretroviral treatment interruptions in children and adolescents with HIV infection in Europe and Thailand

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) Study Group in EuroCoord*

PLOS | MEDICINE

RESEARCH ARTICLE

Long-term trends in mortality and AIDS-defining events after combination ART initiation among children and adolescents

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group in EuroCoord¶, Ali Judd¹*, Elizabeth Chappell¹, Anna Turkova¹, Sophie Le Coeur²,³,

Height and timing of growth ... young people living with vertical ... Europe and Thailand

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) study group*

Example: PIAMA Birth Cohort

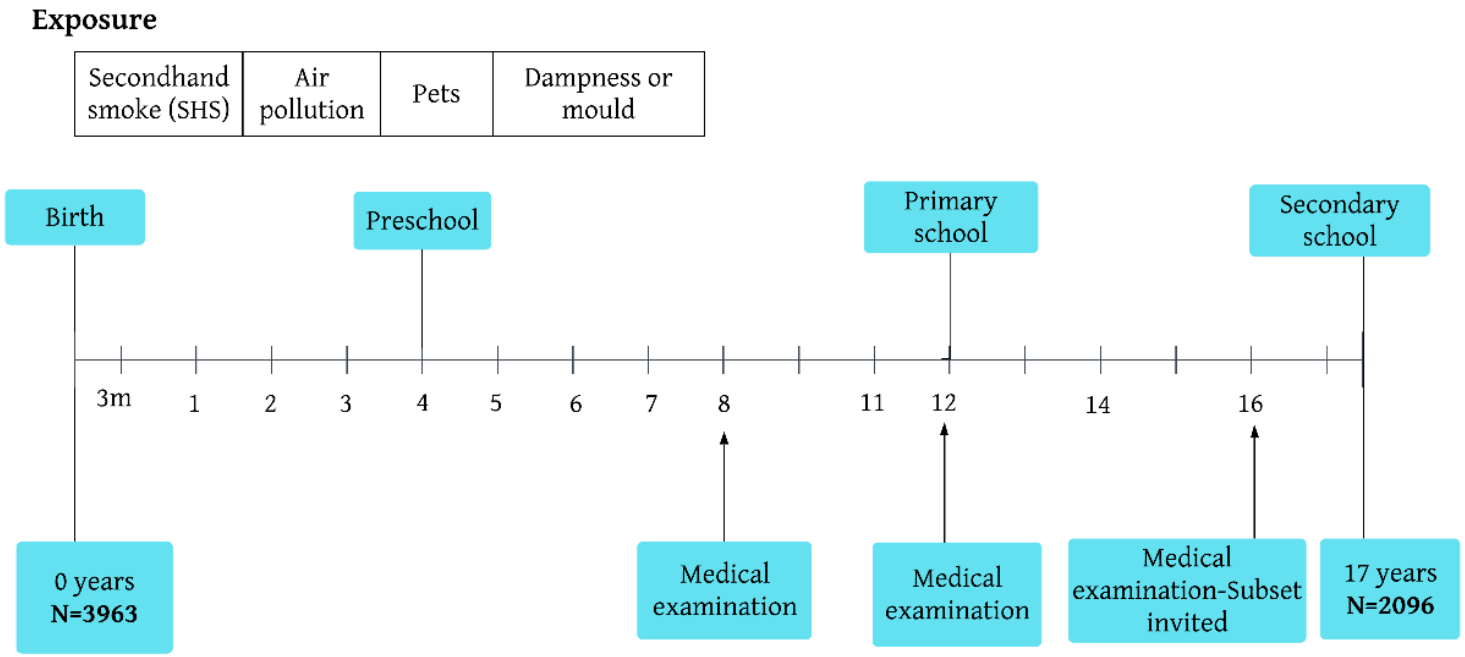
- *Dutch Population-based birth cohort*– Enrolled pregnant mothers and followed them and their new-borns until 17 years of age
- **Exposure** (at birth/in utero)

  -Air pollution

  -Second-hand smoke… etc.
- **Outcomes**

  -Respiratory outcomes e.g. asthma, lung function in childhood and adolescence

Example: PIAMA BIRTH COHORT



Outcomes

Asthma	Lung function	Sensitization

Example: PIAMA BIRTH COHORT

Table 4. Additionally adjusted associations of preschool time window average air pollution exposure with lung function growth from age 8 to 16 (N=871)[α]

	Increment	Difference in FEV_1 % (95% CI)	Difference in FVC % (95% CI)
NO_2	7.8 μg/m³	-0.31 (-0.47 to -0.14)	0.01 (-0.14 to 0.16)
$PM_{2.5}$ absorbance	0.3 10^{-5}/m	-0.33 (-0.51 to -0.16)	0.05 (-0.11 to 0.22)
$PM_{2.5}$	1.2 μg/m³	-0.26 (-0.49 to -0.03)	0.24 (0.03 to 0.45)
PM_{10}	0.9 μg/m³	-0.20 (-0.33 to -0.08)	-0.02 (-0.13 to 0.09)
PM_{coarse}	0.5 μg/m³	-0.17 (-0.28 to -0.06)	-0.01 (-0.11 to 0.09)

Retrospective cohort studies

- Investigator looks back in time at archived data/registries/ electronic medical records to examine whether the risk of outcome was different between exposed and non-exposed patients.
- Participants selected based on current exposure status and outcome data, which was measured in the past

- Differ from case control studies in that they compare the risk of outcome to some already known exposure factors

Example– retrospective cohort study

BMJ Open

Retrospective cohort study of admission timing and mortality following COVID-19 infection in England

Ahmed Alaa,[1] Zhaozhi Qian,[2] Jem Rashbass,[3] Jonathan Benger ,[3] Mihaela van der Schaar[2]

- 14 150 COVID-19 patients admitted between March and May 2020 in England
- Linked to electronic medical records to establish relationship between timing of hospital admission and other known factors
- Healthcare workers and individuals from a black or ethnic minority background were at greater risk of later admission

Prospective versus retrospective cohorts

- **Prospective**: exposure might have already occurred, but not the outcome of interest
- **Retrospective:** both the exposure and disease have already occurred
- May be a **combination** of both!

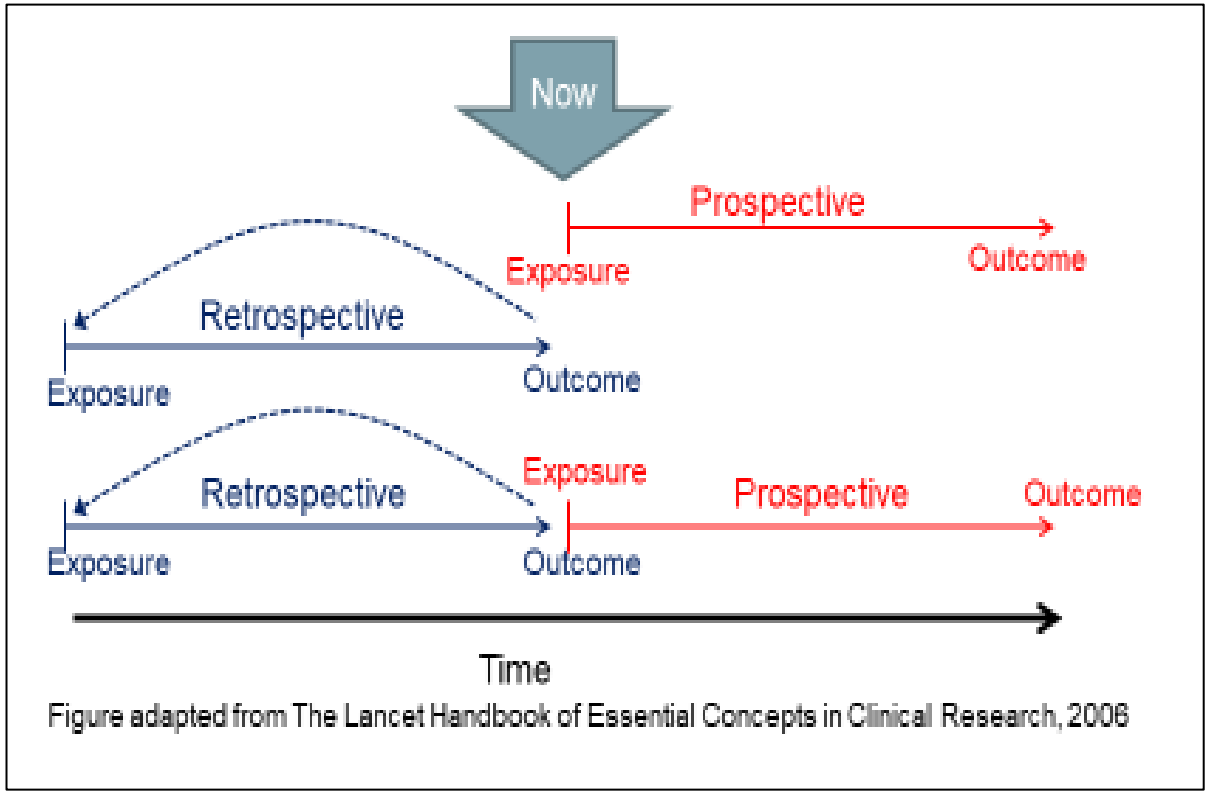


Figure adapted from The Lancet Handbook of Essential Concepts in Clinical Research, 2006

Strengths	Weaknesses
Assessing outcomes of rare exposures	Assessing rare outcomes
Can explore multiple research questions, multiple outcomes and multiple exposures	Very time consuming and expensive
Temporal sequence of events	Retrospective relies on adequate records
Can assess prevalence, incidence, associated factors	May not capture important confounding factors
Can explore outcomes in standard of care settings	Validity of results may be questioned if high losses to follow up

ACTIVITY!

- Go to www.menti.com and enter the code 2908 5998
  - Or follow the direct link in the chat https://www.menti.com/4tu8ehn9o4

- Answer the multiple choice questions on the screen

QUIZ – Q4

Which of these could not be efficiently assessed in a cohort study?

A. The relationship between a very rare disease and an exposure of interest, for which the disease develops several decades after exposure

B. The effects of multiple exposures on a single disease

C. The effect of a single exposure on multiple, relatively common, diseases

QUIZ – Q5

You would like to do a case-control study to see whether a high-fat diet is associated with stomach cancer. Which of the following would you do?

A. Identify people with stomach cancer and people without stomach cancer, ask them about their diet history
B. Identify people with high-fat and low-fat diets and follow them up over time to see who develops stomach cancer
C. Assess the fat intake of a group of people with stomach cancer

QUIZ – Q6

Which study design is usually considered the gold standard for assessing whether an intervention influences an outcome?

A. Case-control study

B. Cohort study

C. Randomised controlled trial

QUIZ – Q7

Adolescents with HIV are recruited and followed up once every 5 years for 20 years, to assess the impact of life-long HIV and long-term antiretroviral therapy (ART). What type of study is this?

A. Prospective cohort study

B. Cross sectional study

C. Retrospective cohort study

D. Case control study

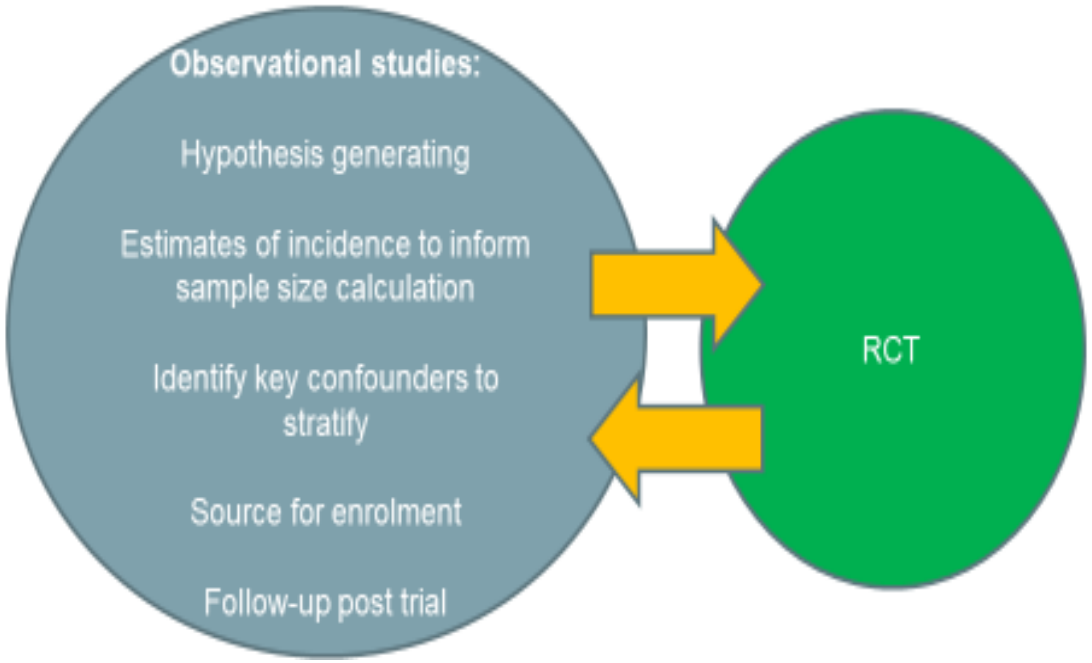
CHOOSING A STUDY DESIGN

Choosing a study design

- Urgency of question (rapid design needed?)
- Disease (outcome) frequency
  - Common or rare
- Natural history
  - Chronic, acute, fatal, long latency, symptomatic
- Risk factors (exposures)
  - Single or many, known or suspected, measurable

Choosing the appropriate design …

- Observational studies and RCT can compliment each other:



PLOS ONE

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and t
resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of peop
in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal effica
trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to recei
two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μ
per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RN
vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 fu
length spike protein. The primary end points were efficacy of the vaccine again
laboratory-confirmed Covid-19 and safety.

RESULTS

A total of 43,548 participants underwent randomization, of whom 43,448 receiv
injections: 21,720 with BNT162b2 and 21,728 with placebo. There were 8 cases
Covid-19 with onset at least 7 days after the second dose among participants a
signed to receive BNT162b2 and 162 cases among those assigned to placeb
BNT162b2 was 95% effective in preventing Covid-19 (95% credible interval, 90.3
97.6). Similar vaccine efficacy (generally 90 to 100%) was observed across subgrou
defined by age, sex, race, ethnicity, baseline body-mass index, and the presence
coexisting conditions. Among 10 cases of severe Covid-19 with onset after the first

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-020-18926-3 OPEN

Check for updates

A population-based cohort study of socio-demographic risk factors for COVID-19

Articles

Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data

Eric J Haas, Frederick J Angulo, John M McLaughlin, Emilia Anis, Shepherd R Singer, Farid Khan, Nati Brooks, Meir Smaja, Gabriel Mircus, Kaijie Pan, Jo Southern, David L Swerdlow, Luis Jodar, Yeheskel Levy, Sharon Alroy-Preis

Summary

Background Following the emergency use authorisation of the Pfizer–BioNTech mRNA COVID-19 vaccine BNT162b2 (international non-proprietary name tozinameran) in Israel, the Ministry of Health (MoH) launched a campaign to immunise the 6·5 million residents of Israel aged 16 years and older. We estimated the real-world effectiveness of two doses of BNT162b2 against a range of SARS-CoV-2 outcomes and to evaluate the nationwide public-health impact following the widespread introduction of the vaccine.

Methods We used national surveillance data from the first 4 months of the nationwide vaccination campaign to ascertain incident cases of laboratory-confirmed SARS-CoV-2 infections and outcomes, as well as vaccine uptake in

Lancet 2021; 397: 1819–29
Published Online
May 5, 2021
https://doi.org/10.1016/S0140-6736(21)00947-8

See Comment page 1783

Public Health Services, Israel Ministry of Health, Jerusalem Israel (E J Haas MD, E Anis MD,

Notes

ANY QUESTIONS?