What is an RCT, and why is it considered a gold standard design

Cape Town 2013

RCTs in Mental Health – AFFIRM short course

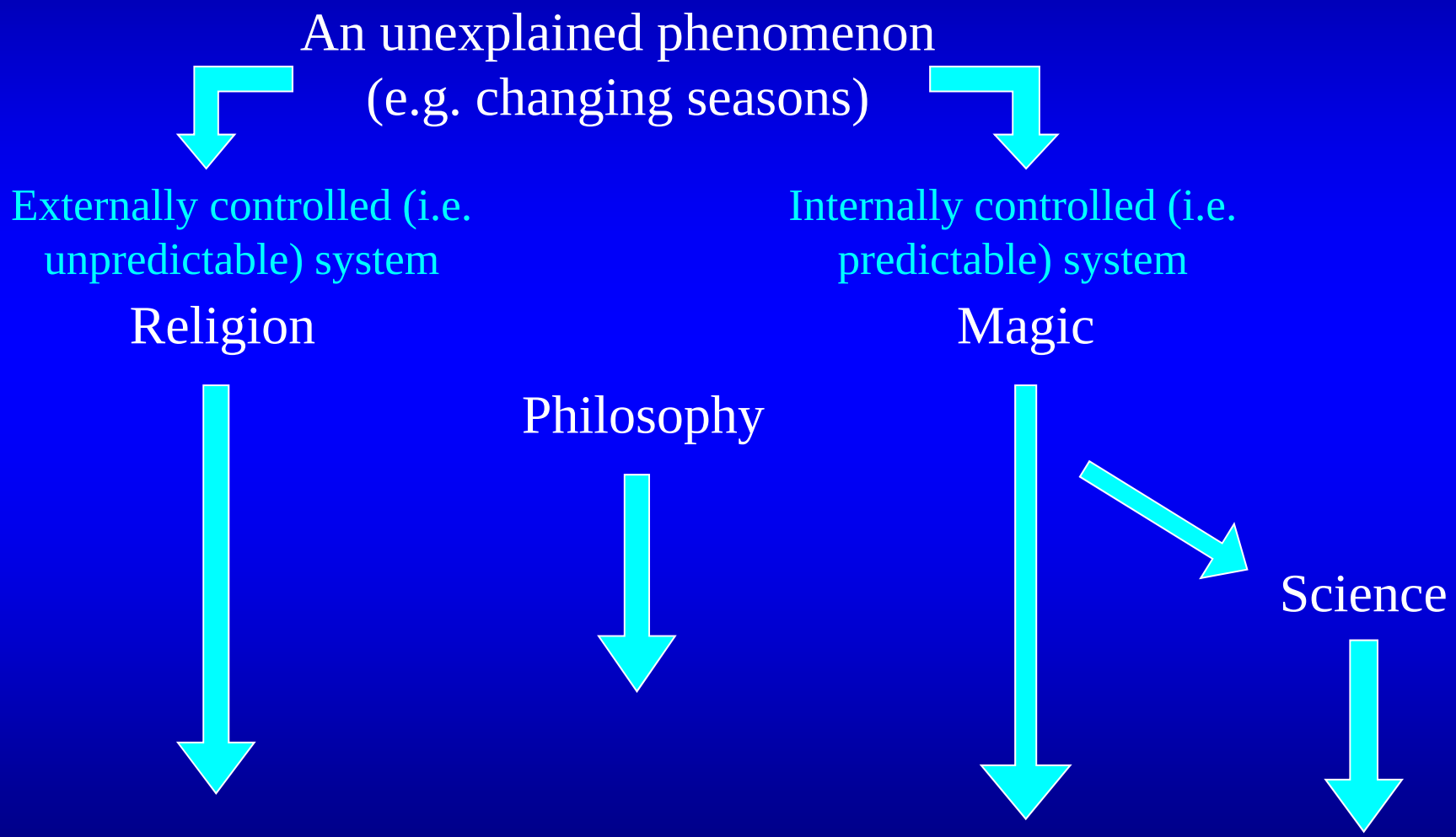
Prof Martin Prince –

KCL Centre for Global Mental Health

Agenda

- Concepts of cause and effect
- Philosophy of scientific inference
  - Inductivism
  - Refutationism
- Advantages of hypothesis-driven research
- The RCT in context with other study designs
- The RCT and causality
  - Inherent strengths
  - Residual limitations

Causation theory – origins



Causation – inductivist theory

- How do we infer cause and effect?
- Bacon (1620): Make generalizations from observations
  - e.g. flick of light switch -> light
  - e.g. Jenner - milkmaids don't get smallpox, hence cowpox confers immunity against smallpox
- But…
- …however many times one event follows another, one cannot infer a cause and effect relationship
  - causality cannot be directly observed
  - Does the sun rise because the rooster crows?

Causation – refutationist theory

- Hume et al (philosophy), Popper et al (modern science)
  - Scientific hypotheses can never be proven
  - Only found to be consistent with observation
  - However, one observation that is inconsistent with a hypothesis allows it to be refuted
    - e.g. remove the rooster and the sun still rises
    - e.g. The hypothesis ‘Water always boils at 100C’ is consistent with multiple observations at ground level, but can be rejected after once boiling water at altitude

A consensus for modern science?

Inductivism for hypothesis generation
Refutationism for hypothesis testing

‘rapidly advancing fields are propelled by scientists who are busy constructing and testing competing hypotheses; other fields are sick in comparison, because they have forgotten the need for alternative hypotheses and disproof’

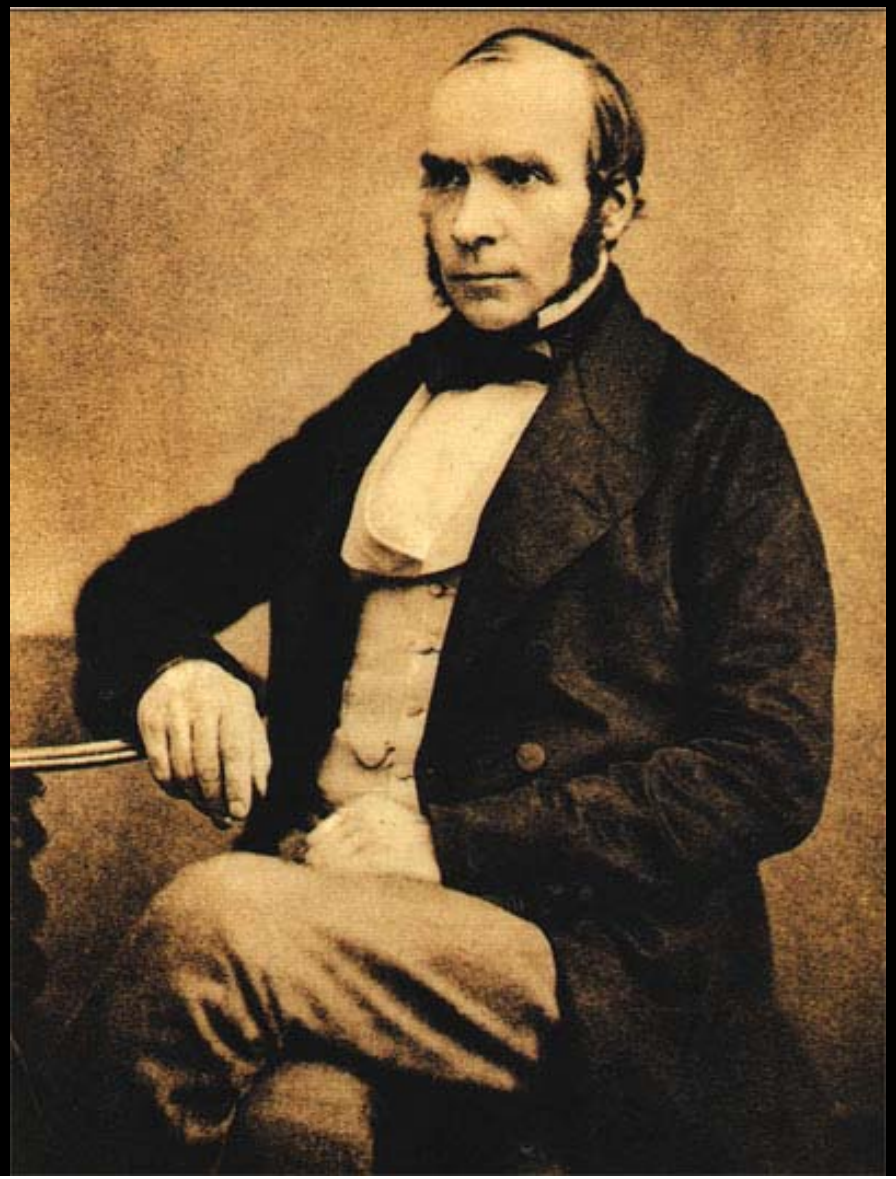
Platt, 1964

The hypothesis

- Characteristics
  - *a priori* (rather than *post hoc*)
  - Clearly stated
  - Testable and refutable
  - Not a research question or objective
  - Leading to a sample size calculation, and an appropriate design and analysis

- Advantages
  - Greater credence given to validity of findings
  - Less risk of type I error (‘false positive’ results)
  - Ease of replication

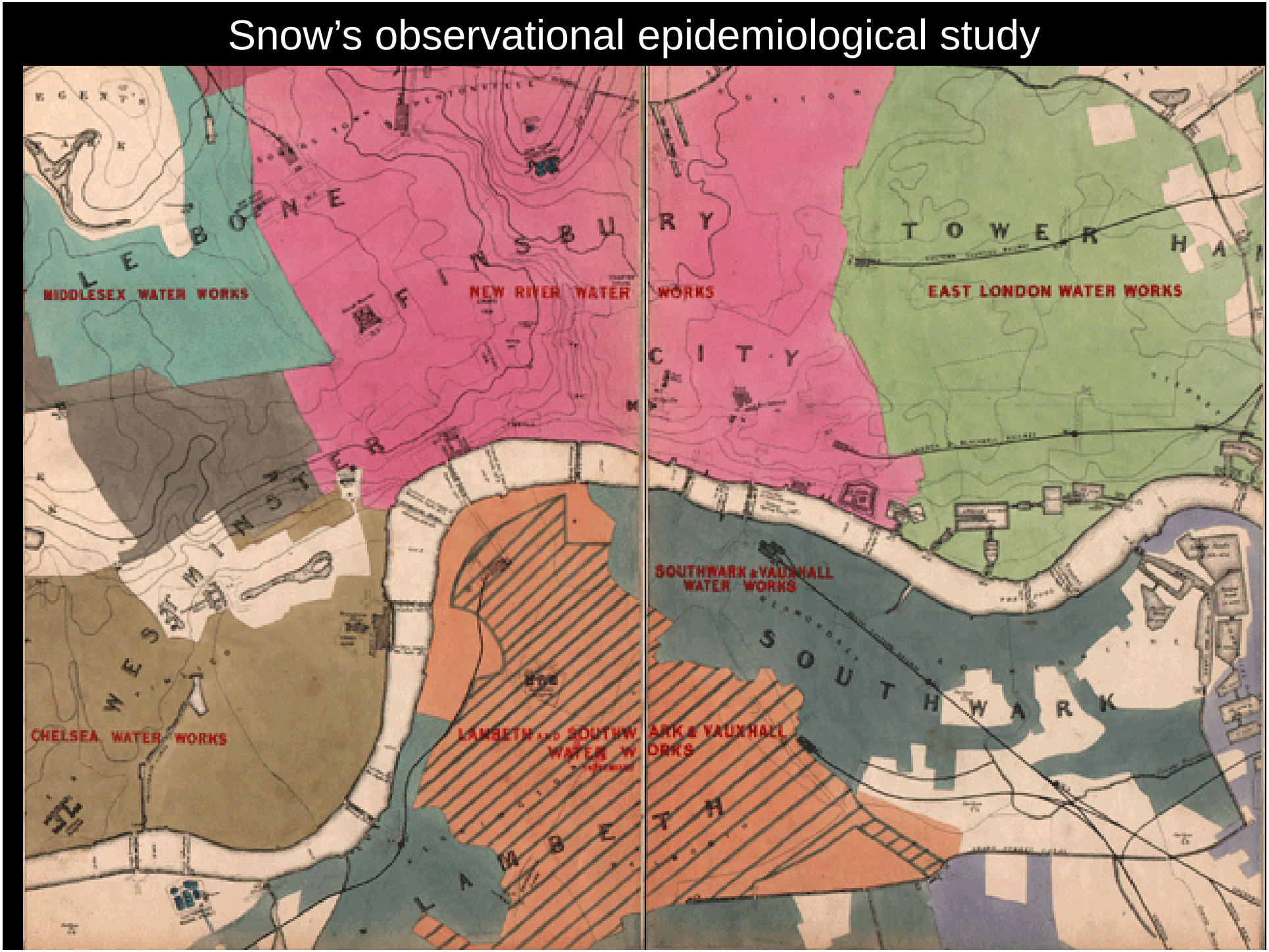
John Snow, 1813-1858



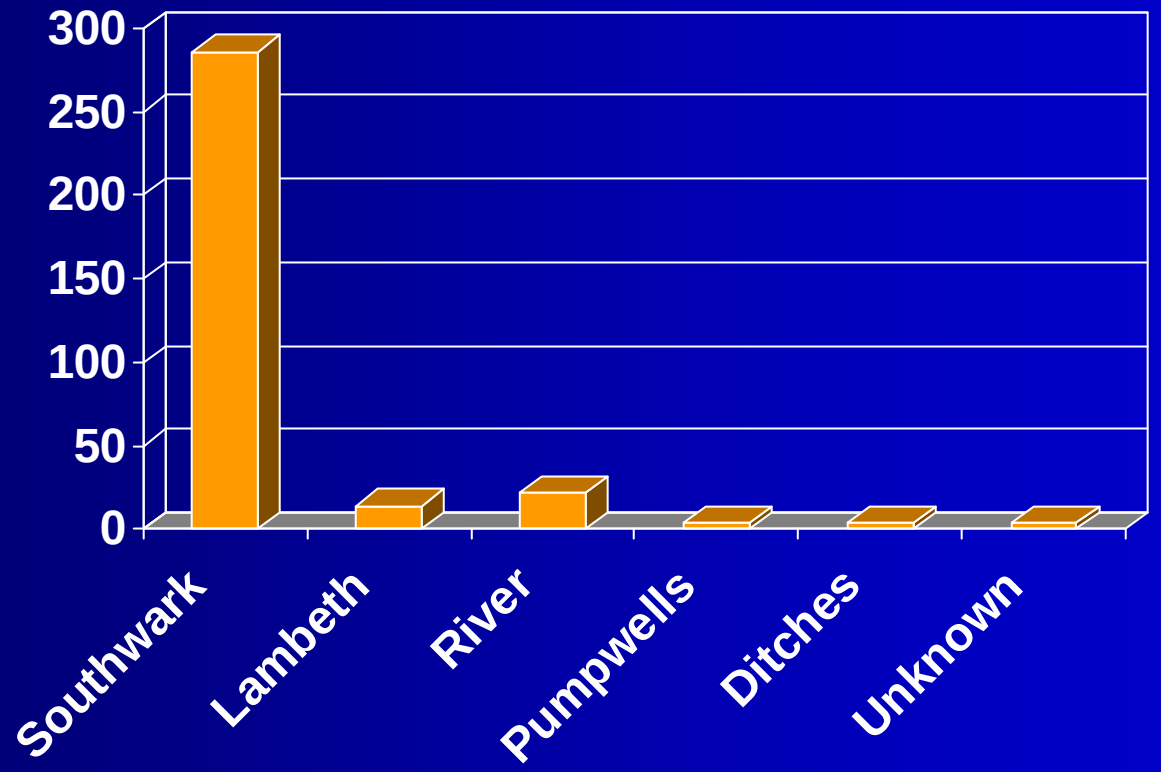
LONDON 1854

- John Snow ‘on the mode of communication of cholera’ 1855
- Cholera epidemics were feared, last 1832
- Prevailing theory – miasma (bad air)
- Snow’s observations -> hypothesis – water-borne contagion

Snow's observational epidemiological study



DISTRIBUTION OF DEATHS: BY WATER COMPANY



DISTRIBUTION OF DEATHS: RATES BY AREA SUPPLIED

Area supplied by	*Population 1851 census*	*Deaths by cholera*	*Deaths rate per 100,000*	Relative Risk
Southwark & Vauxhall	167,654	844	503	5.4
Lambeth	19,133	18	94	1.0
Both companies	300,113	652	217	2.3

DISTRIBUTION OF DEATHS: RATES BY HOUSE SUPPLIER

Source of water	*Total number of houses*	*Deaths by cholera*	*Deaths per 10,000 homes*	Relative Risk
Southwark & Vauxhall	40,046	1263	315	8.5
Lambeth	26,107	98	37	1.0
Rest of London	256,423	1422	59	1.6

The Soho Epidemic 1854

‘the chain of causation….’

Broad Street Pump

What are the functions of research?

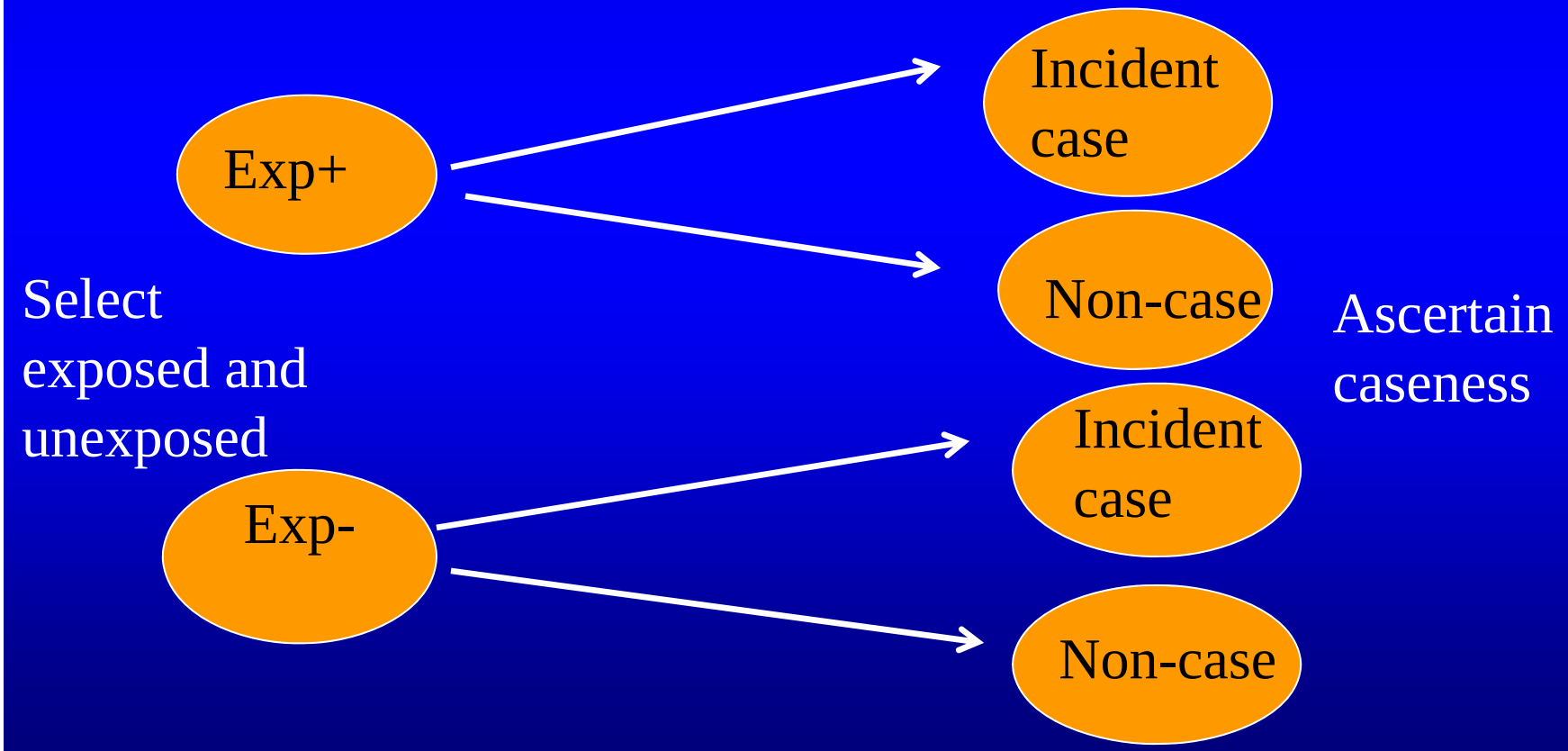
- Describe
- Explain
- Evaluate

Where do randomised controlled trials fit in?

- Descriptive epidemiology (DESCRIBE)
  - Case series
  - Cross-sectional surveys
- Analytical epidemiology (EXPLAIN)
  - Case-control studies
  - Cohort studies
- Evaluative studies (EVALUATE)
  - Quasi-experimental studies
  - Randomised controlled trials

An analytical (observational) study design

- Cohort studies



Cohort Study

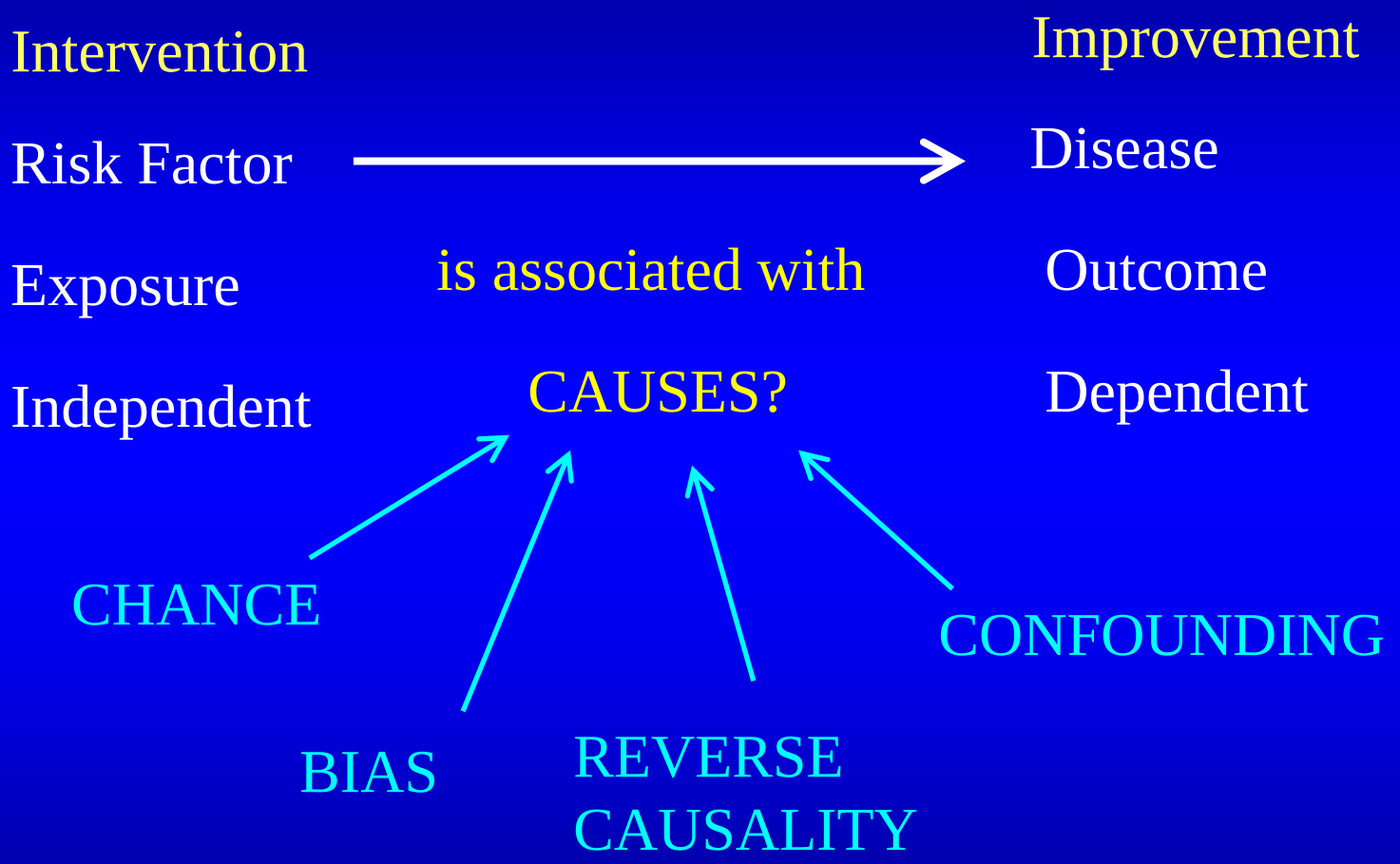
Schizophrenia and city life

	Incidence rate	RR (crude)	RR (adj*)
Rural	31.2	1 (ref)	1 (ref)
Small towns	39.8	1.3 (0.9-1.8)	1.3 (0.9-1.7)
Large towns	43.2	1.4 (0.9-2.1)	1.4 (0.9-2.1)
Urban	51.4	1.7 (1.2-2.3)	1.6 (1.1-2.2)

* for parental divorce, family hx and SES

Swedish conscripts study - Lewis et al. Lancet (1992)

Causation


Intervention
Risk Factor
Exposure
Independent
is associated with
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Improvement
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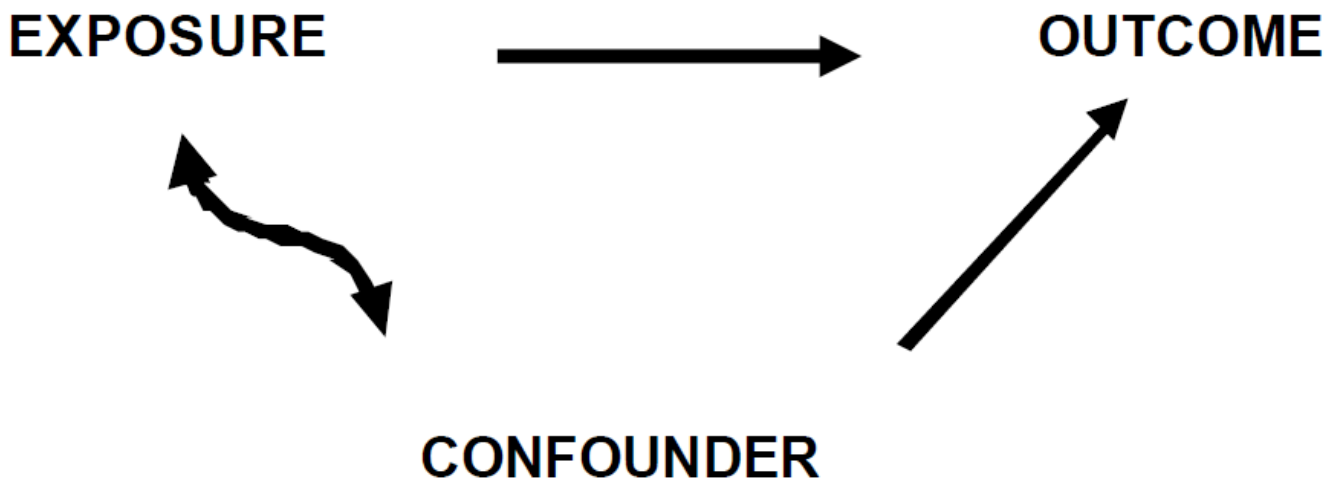
CHANCE
BIAS
REVERSE CAUSALITY
CONFOUNDING

Confounding



- The confounder must be associated with the exposure
- The confounder must be **independently** associated with the outcome

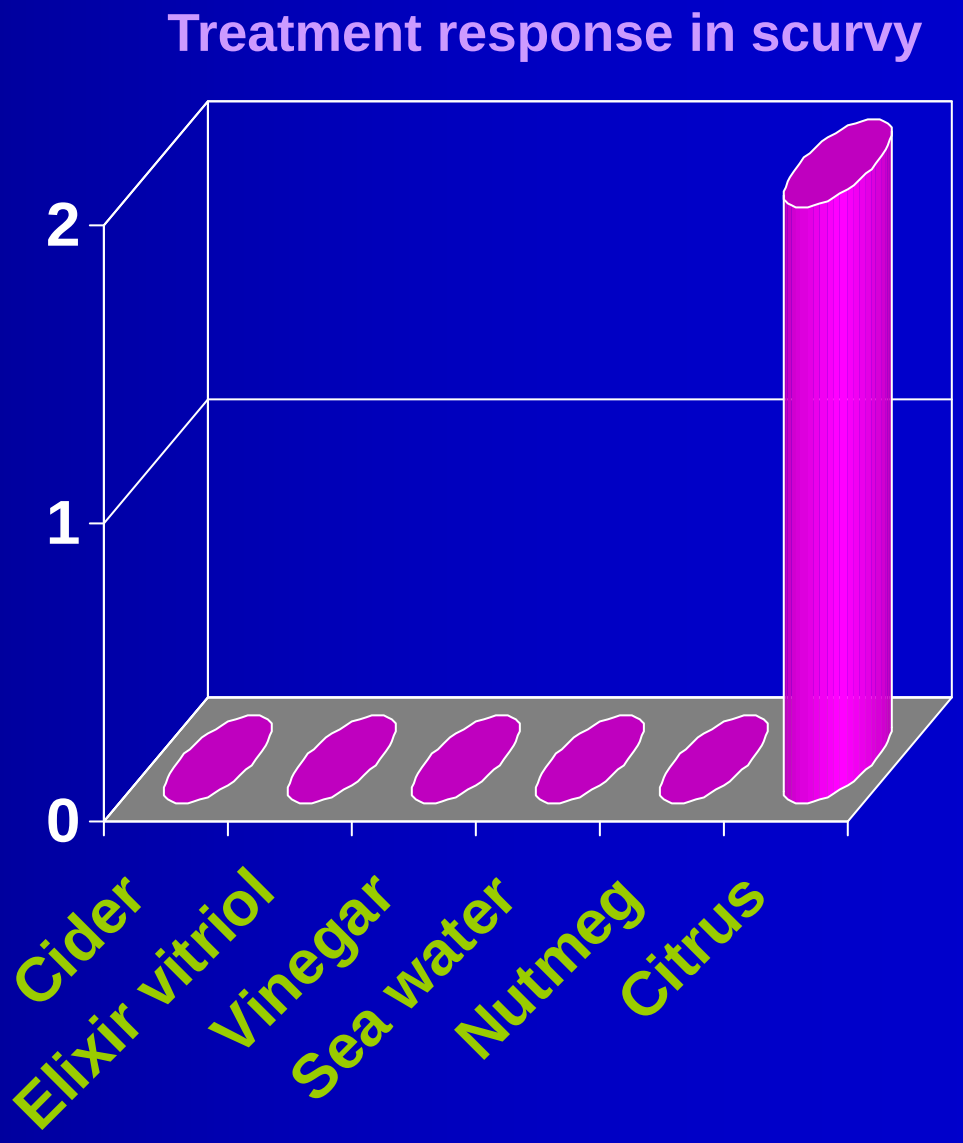
What is an RCT?

- “The most scientifically rigorous method of hypothesis testing available in epidemiology” (Last, 1995)

- Experiment
- Random allocation to ‘study’ and ‘control’ groups to receive a new procedure/treatment
- Outcome in the two groups compared

An early clinical trial

- James Lind 1747 ship's doctor on HMS Salisbury
- 12 patients with scurvy 'as similar as possible'
- 6 intervention groups of 2 sailors



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TREATISE

OF THE

SCURVY.

IN THREE PARTS.

CONTAINING

An inquiry into the Nature, Cauſes, and Cure, of that Diſeaſe.

Together with

A Critical and Chronological View of what has been publiſhed on the ſubject.

By *JAMES LIND*, M. D.

Fellow of the Royal College of Phyſicians in *Edinburgh*.

EDINBURGH:

Printed by SANDS, MURRAY, and COCHRAN.

For A. KINCAID & A. DONALDSON.

MDCCLIII.

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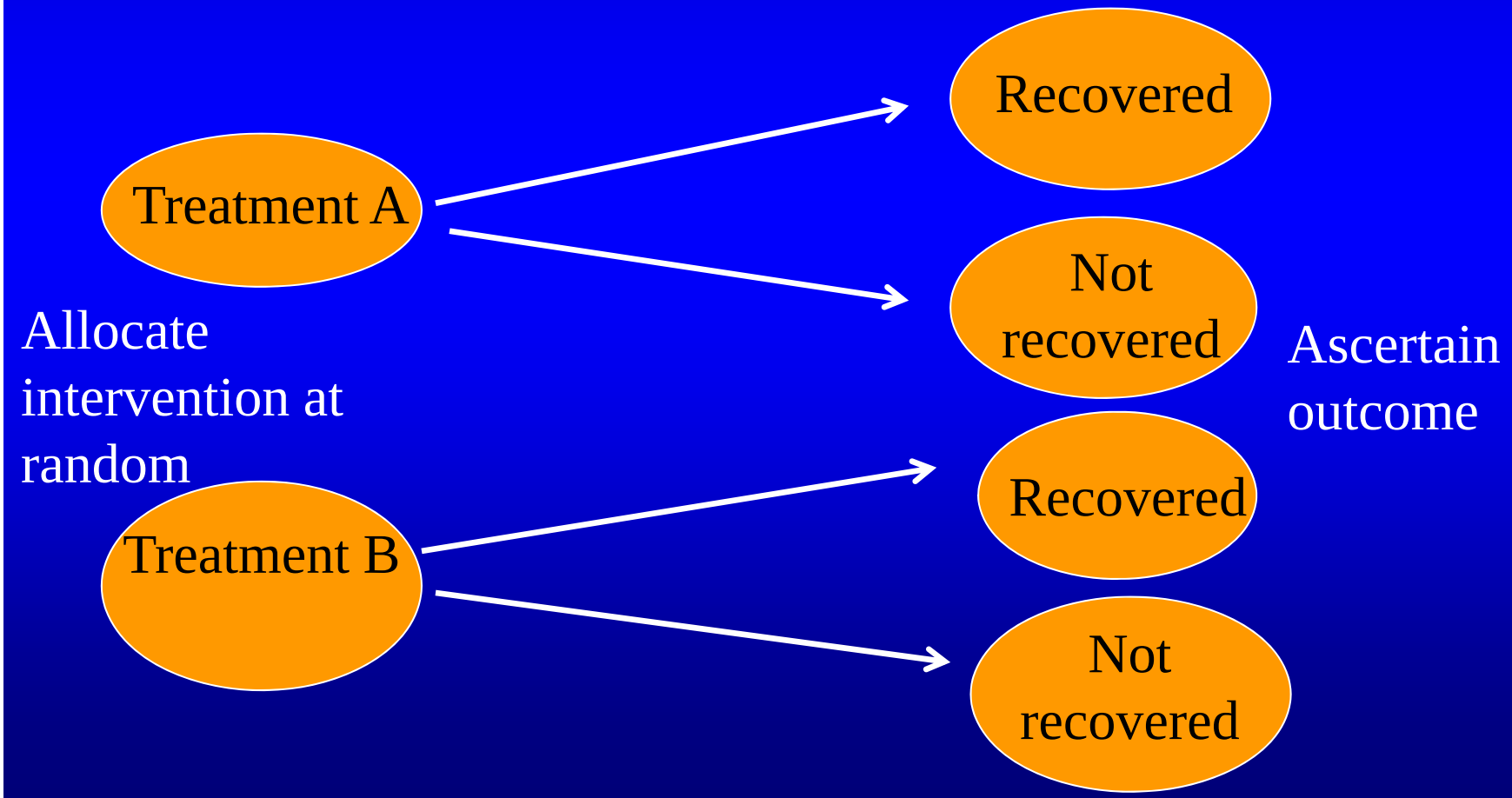
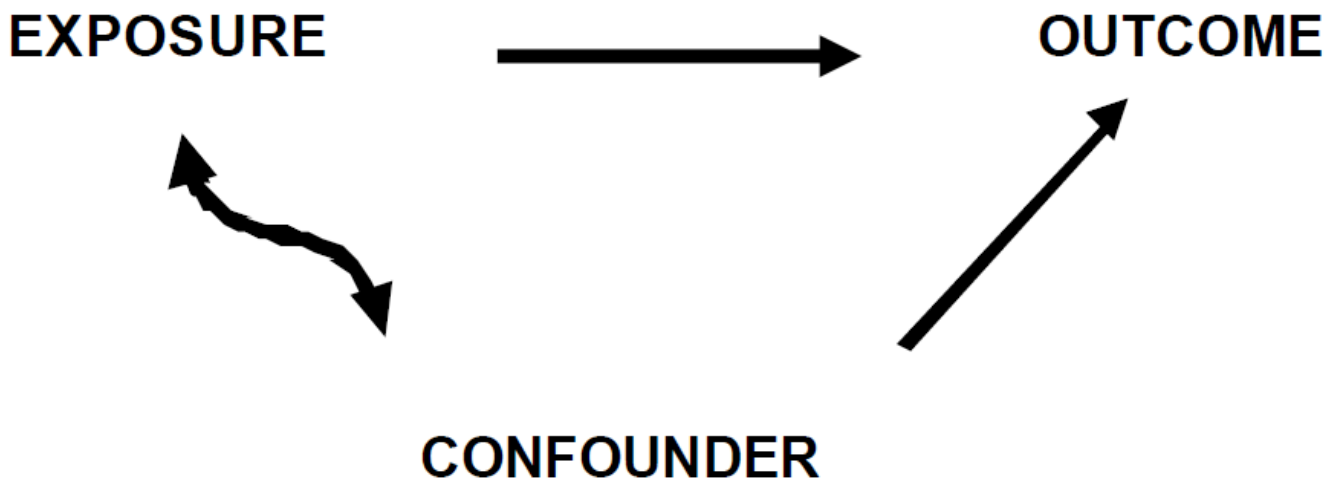
REGISTERED AS A NEWSPAPER

Experimental designs

- Randomised controlled trials



Confounding



- The confounder must be associated with the exposure
- For an RCT the exposure is the RANDOMISED allocation
- The confounder must be **independently** associated with the outcome

Benefits of randomisation

- Should ensure that the two groups to be compared are as like as possible, excepting the allocated interventions
- This includes ALL factors that could influence outcome
  - anticipated confounders e.g. duration of untreated psychosis
  - unanticipated confounders, which may not even be known or measurable e.g. genes influencing treatment response

Benefits of randomisation

- ‘Perfect’ control for confounding
- All things being equal, differences in outcome should be attributable to the intervention, and the intervention alone

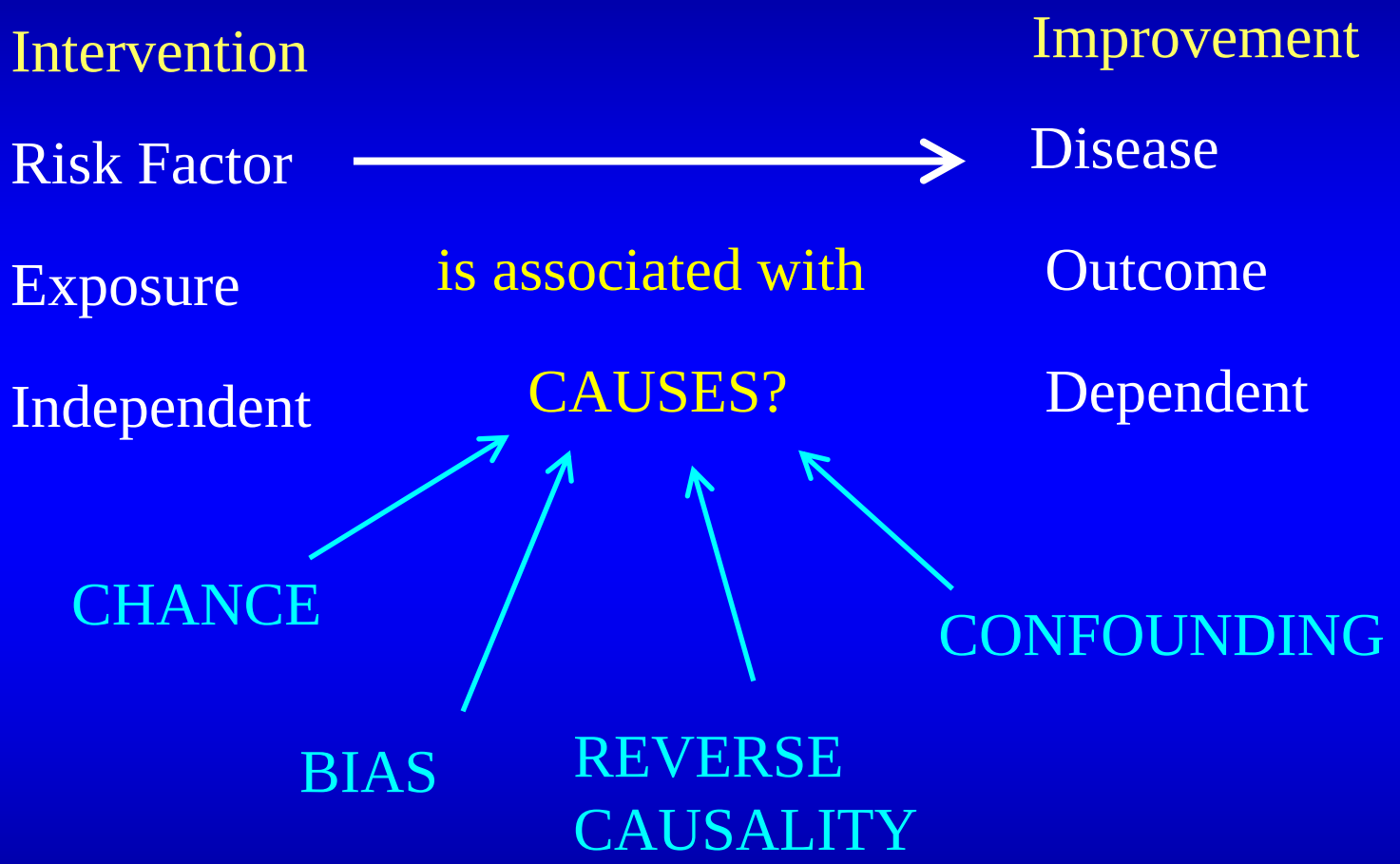
Pitfalls of randomisation

- Randomisation may not be implemented properly, leading to non-random allocation
- Randomisation may be implemented properly, but group differences may occur – through chance
  - No point in statistical testing, since we know that the difference has occurred through chance (sampling error)
  - Larger differences more likely to occur with smaller trials

Precautions

- Truly random allocation
  - method of assignment and concealment of allocation is important
  - process needs to be entirely removed from recruiting researchers
  - remove possibility of knowing or unknowing manipulation of recruitment
- Anticipate important confounders
  - Measure and control for them in the analysis
  - Use randomisation technique e.g ‘stratified permuted block’ to minimise group differences

Causation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CONFOUNDING

Chance

- There is a finite chance (p) of making a ‘Type 1 error’ (rejecting the null hypothesis, when there really is no benefit associated with the intervention)
- This arises from random sampling error – a difference in the sample, but not in the base population
- Larger trials increase precision and power to detect a treatment effect of given size. Failing to identify a clinically significant treatment effect = ‘Type II error’

Chance (sampling error) and precision

- If we repeated the same trial of the same intervention on the same base population, we would not expect the same result (why?)
- 95% confidence intervals give range of possible true effect sizes, given what has been observed
- e.g. three trials of the same intervention
  - +0.26 (+0.01 to +0.51), p=0.05, n=200
  - +0.40 (-0.10 to +0.90), p=0.59, n=40
  - +0.40 (+0.35 to +0.45), p<0.001, n=2,500

Bias

- Information bias
  - Recall bias (patient)
  - Observer bias (clinician/ RA)
- Loss to follow-up
  - e.g. if those who had a bad outcome are selectively more likely not have that outcome recorded in the intervention than in the control condition

Addressing Bias

- Information bias
  - Mask (blind) to hypothesis
  - Mask to intervention allocation
  - Assess effectiveness of masking to allocation
- Loss to follow-up
  - Maximise follow-up – seek to get outcome data, even if participants drop out of trial (intention to treat analysis)
  - Impute missing data
  - Sensitivity analyses under range of assumptions, including maximum bias

Intervention Fidelity

- The gap between ‘theory’ and ‘practice’
- Dane & Schneider (1998) identify 5 aspects:
  - Adherence – program components are delivered as prescribed;
  - Exposure – amount of program content received by participants;
  - Quality of the delivery – versus a theory-based ideal in terms of processes and content;
  - Participant responsiveness – engagement of the participants; and
  - Program differentiation – features of the intervention are distinguishable from other programs (including the control condition)

Use ‘theory of change’ to plan assessment of fidelity

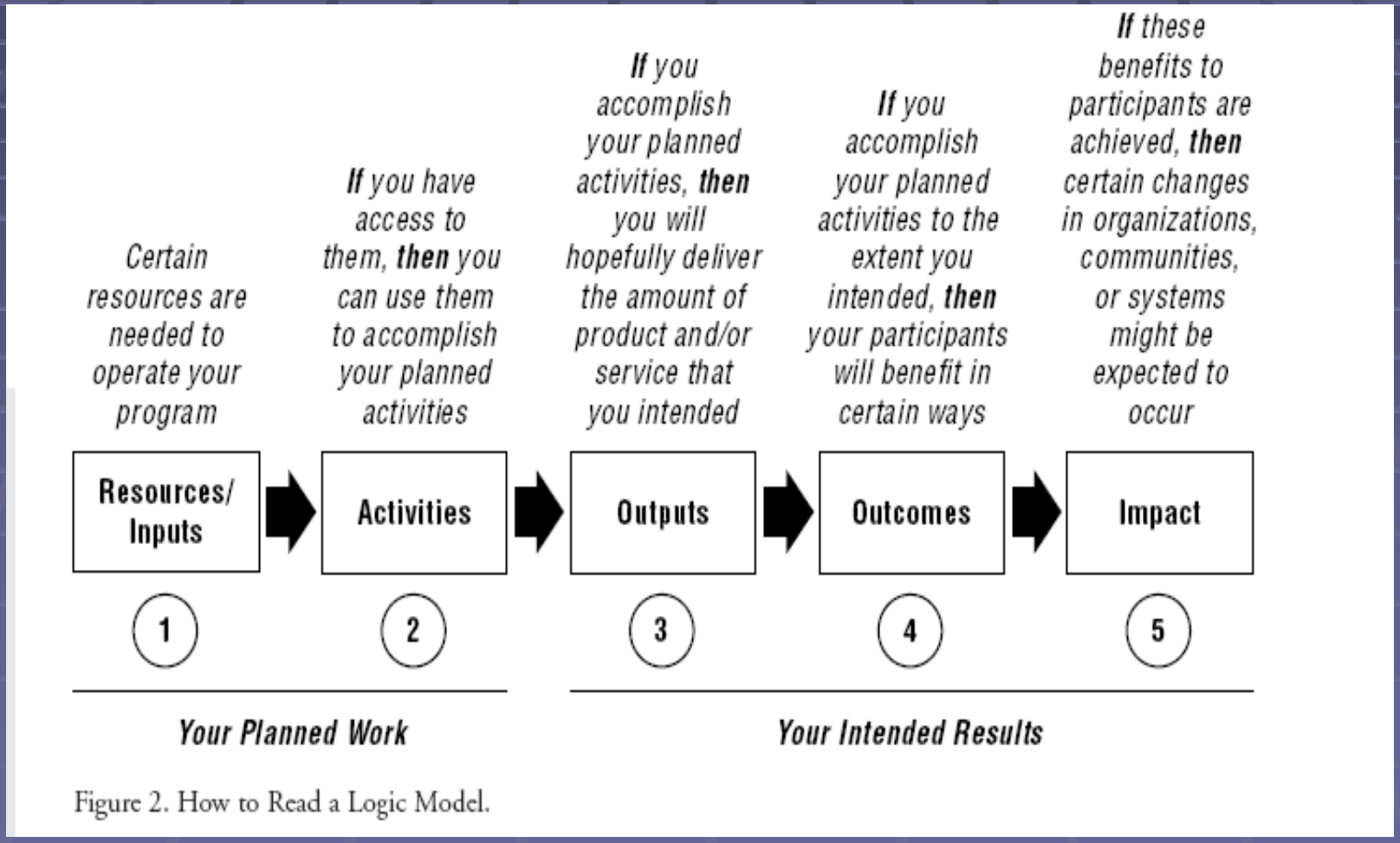

Figure 2. How to Read a Logic Model.

From: W.T. Kellogg Foundation, 2004

Effectiveness and efficacy

- **EFFICACY** - The extent to which a specific intervention…produces a beneficial result under ideal conditions

- **EFFECTIVENESS** - The extent to which a specific intervention…when deployed in the field, in routine circumstances, does what it is intended to do in a specific population

Efficacy vs effectiveness trials

- Efficacy trials
  - designed to maximise effect size
  - multiple exclusions
  - tightly controlled implementation (fidelity)
  - allow trial to be as small as possible
  - most likely to have a positive outcome (‘proof of concept’)
  - distance from effectiveness varies with disorder and intervention
  - ‘proof of concept’
  - high internal validity
  - limited generalisability?

Consensus - theory

- A single study is not enough to support or refute a hypothesis
- Scientific knowledge is advanced gradually through the accumulation of research…
- …leading to a gradually accepted ‘verdict’ of causality
- limits of generalisability

Consensus - mechanics

- Research synthesis
- Meta-analysis
- Evidence-based medicine

- NB heterogeneity/ outliers?

Broad Street Pump