ARISTOTLE UNIVERSITY OF THESSALONIKI

FACULTY OF HEALTH SCIENCES - SCHOOL OF MEDICINE

MSc Health Statistics and Data Analytics

Observational Studies

Stergios Polyzos
Assistant Professor
First Laboratory of Pharmacology
School of Medicine, AUTh

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MSc Health Statistics & Data Analytics

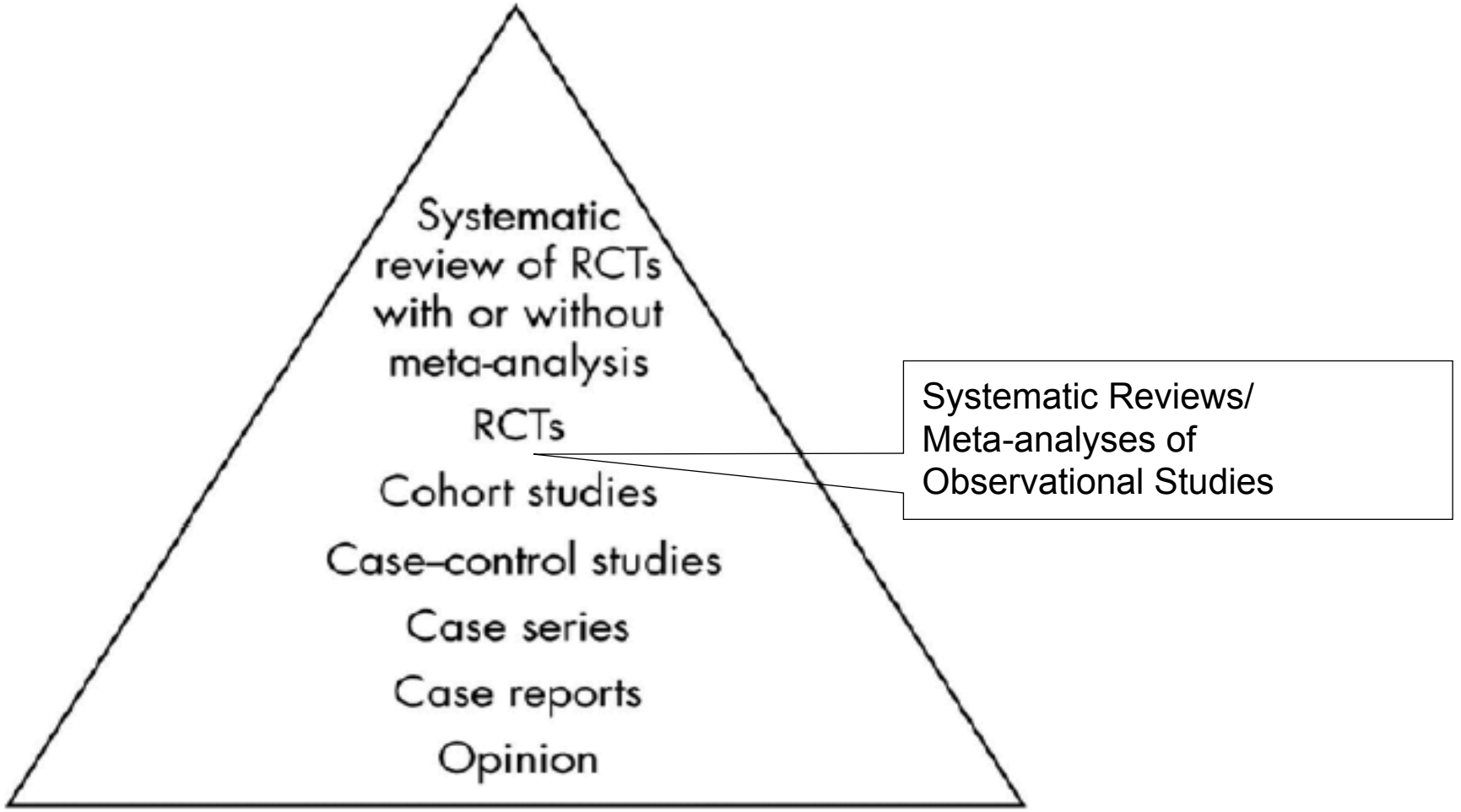
Are you going to observe or experiment?

- **Observational**
  - Identify participants
  - Observe and record characteristics
  - Look for associations

- **Experimental**
  - Identify participants
  - Intervene
  - Evaluate effects of intervention

Groves T. BMJ Group

Hierarchy of research evidence



Kisely S et al. Australas Psychiatry 2015

Searching for the best information

Type of Question	Ideal Type of Study
Therapy	RCT
Prevention	RCT > Cohort Study > Case Control
Diagnosis	Prospective, blind controlled trial comparison to gold standard
Prognosis	Cohort Study > Case Control > Case Series/Case Report
Etiology/Harm	RCT > Cohort Study > Case Control
Cost analysis	economic analysis

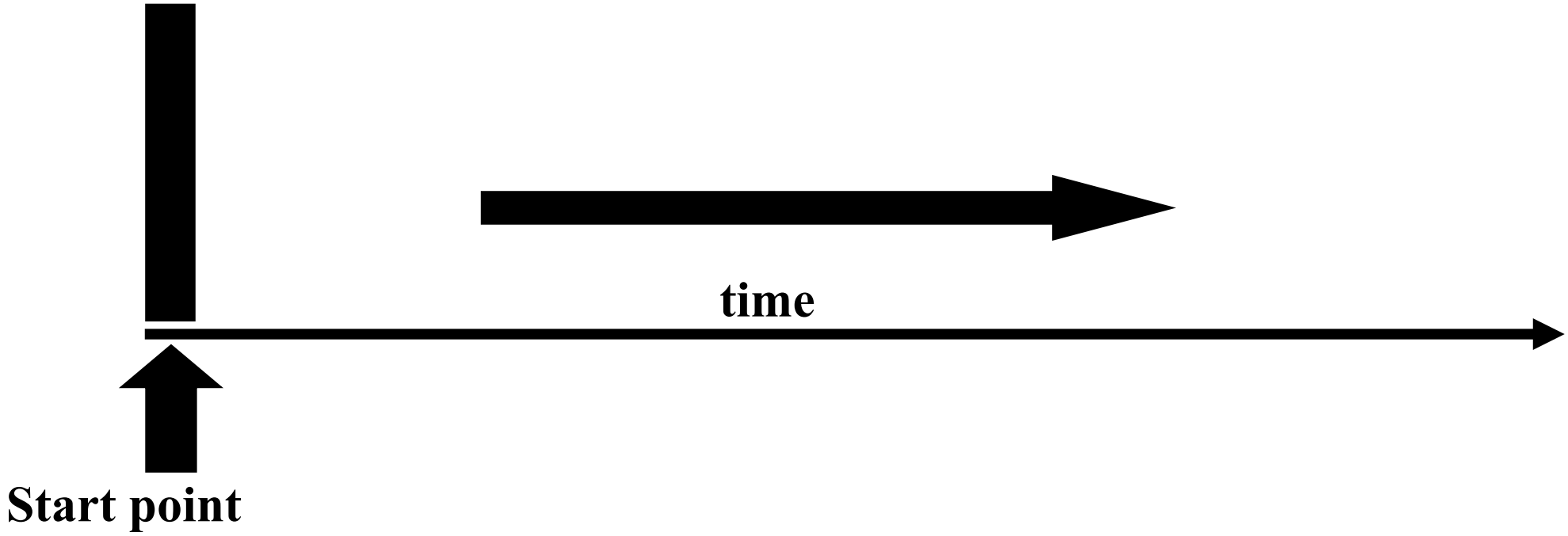
Note: Meta-analyses and systematic reviews, when available, often provide the best answers to clinical questions.

Quality of life: RCT

www.dartmouth.edu

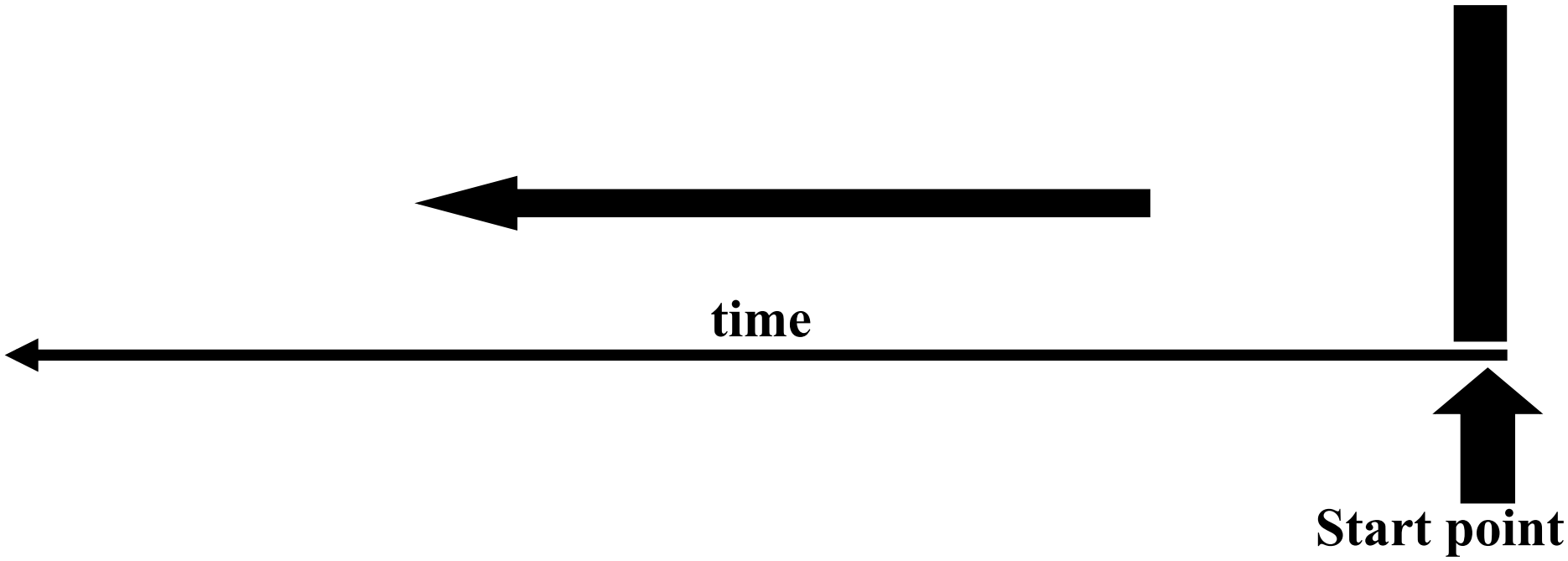
Prospective study

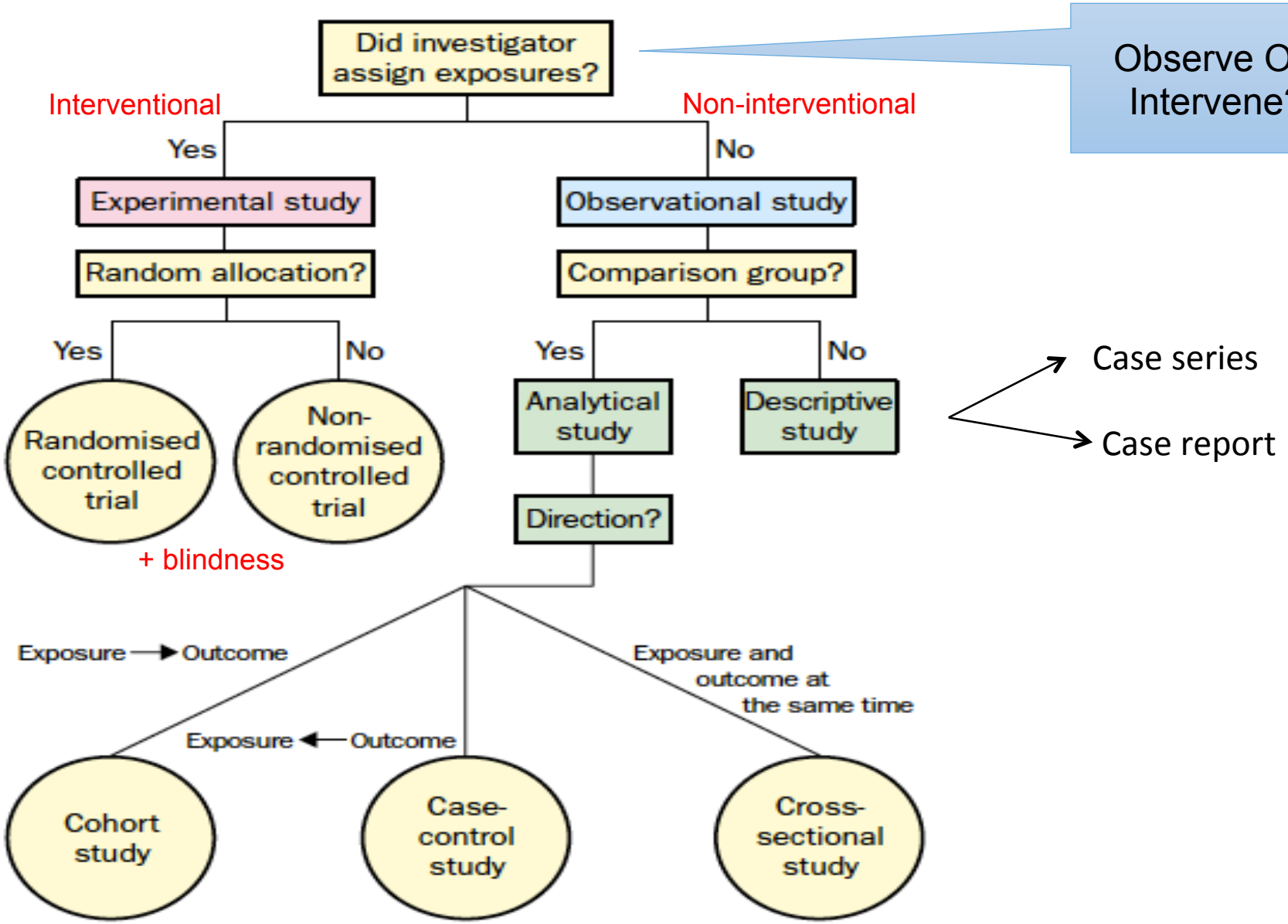
Looks forward, examines future events, follows a cohort, condition, concern or disease into the future



Retrospective Study

Looks back, looks back in time to study events that have already occurred





Grimes DA. Lancet 2002 (adapted)

Descriptive studies

Case Reports

- Detailed presentation of a single case

- Generally reports a new or unique finding
  - Previously undescribed disease
  - Novel or unexpected link between diseases
  - Novel or unexpected therapeutic effect
  - Novel or unexpected adverse events

Case Series

- Experience of a group of patients with a similar diagnosis
- Cases may be identified from a single or multiple sources
- Generally report on new/unique condition, i.e. a novel or an off-label treatment
- Feasible design for rare disorders

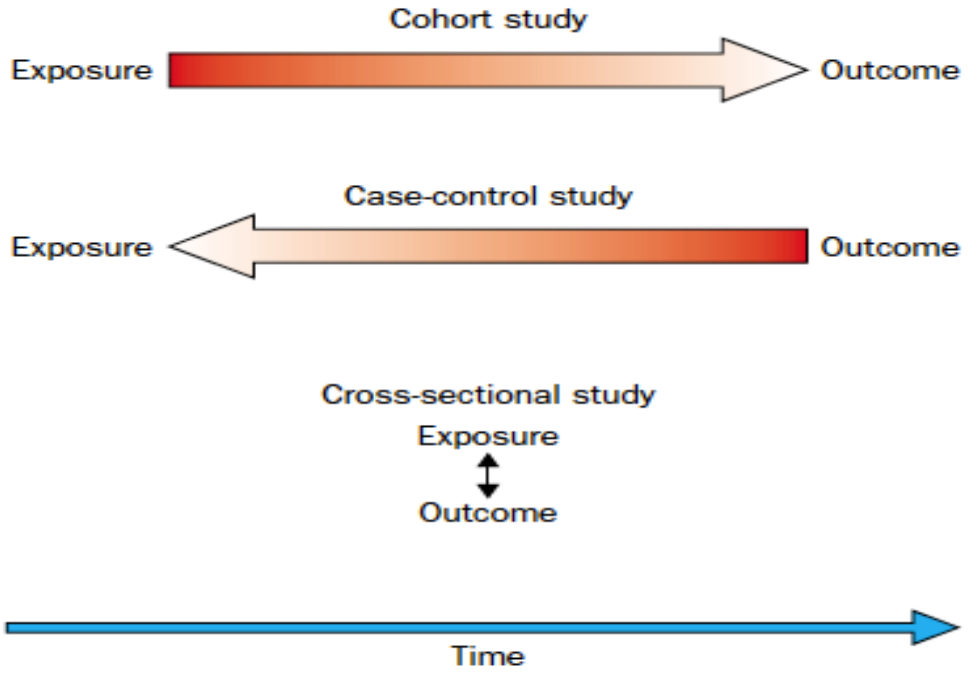
Case Series

- **Advantages**
  - Informative for rare diseases with few established risk factors
  - Characterizes averages for disorder
  - Useful for hypothesis generation

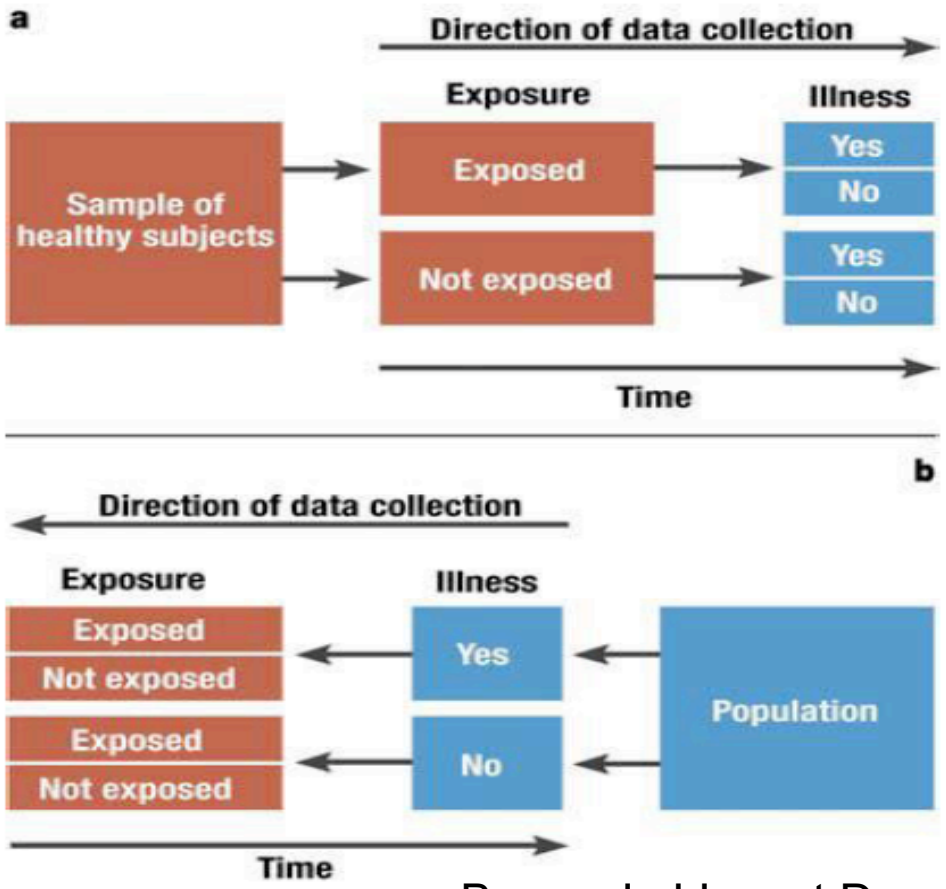
- **Disadvantages**
  - Cannot study cause and effect associations
  - Cannot assess disease frequency

Analytical studies

Temporal direction of analytical studies



Grimes DA, Lancet 2002



Besen J. J Invest Dermatol 2014

Cohort study

Suitable for studying effects of risk factors on an outcome

Estimates Relative Risk (RR)

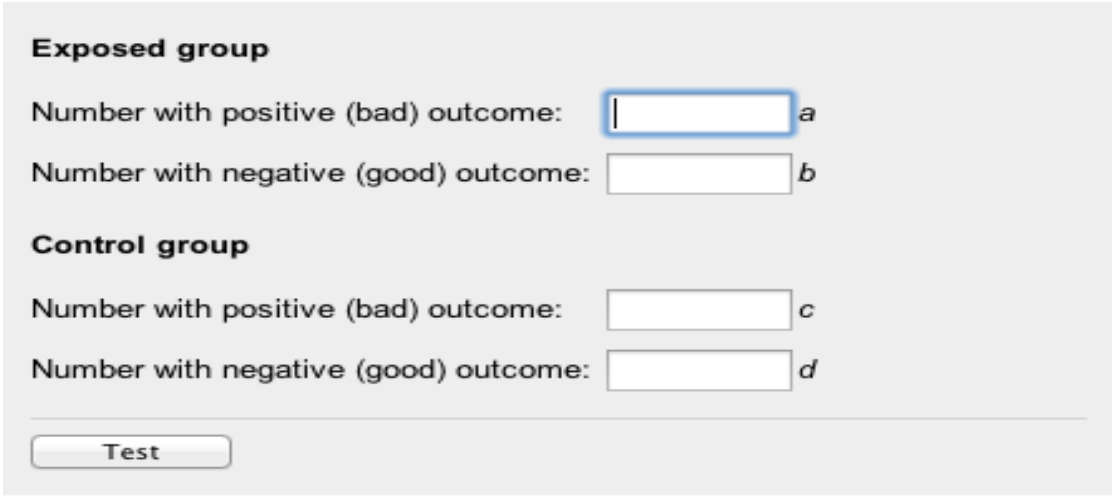
$$RR = \frac{a/(a+b)}{c/(c+d)}$$

Advantages

- Indicate timing and directionality of events
- Participants can be matched
- Ethically safe

Disadvantages

- Cost and time
- Cannot show causality
- Confounders
- For rare disease, large sample sizes or long follow-up necessary



www.medcalc.org

Case-control study

Suitable for studying rare diseases

Estimates odds ratio (OR)

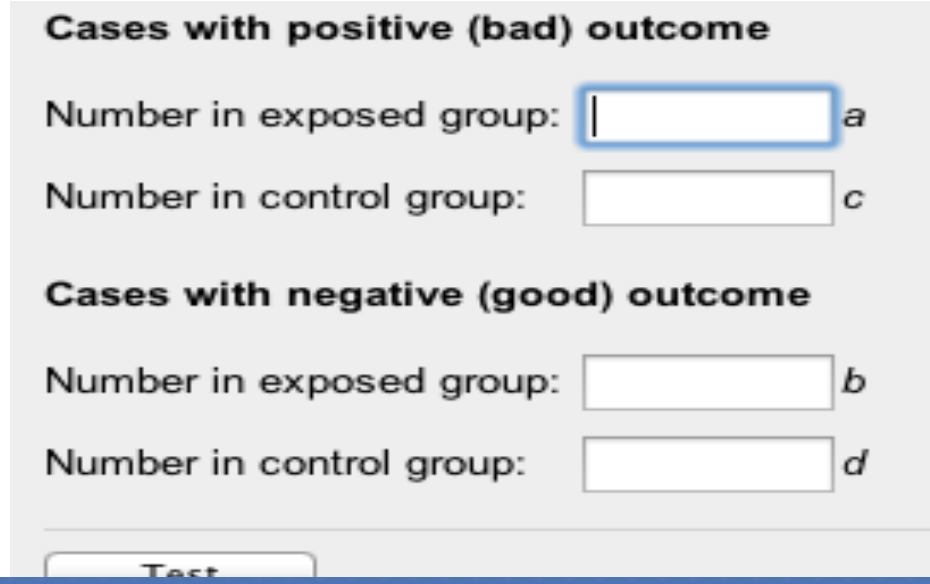
Advantages

- Quicker and less expensive than cohort study
- Ideal for rare disorders or those with long lag between exposure and outcome
- No need for follow-up
- Ethically safe

Disadvantages

- Cannot show causality
- Bias: recall, selection
- Confounders

$$OR = \frac{a/b}{c/d} = \frac{a \times d}{b \times c}$$



www.medcalc.org

Cross sectional study

Both exposure and outcome measured at the same time

Quantifies prevalence, risk or diagnostic test accuracy

Advantages

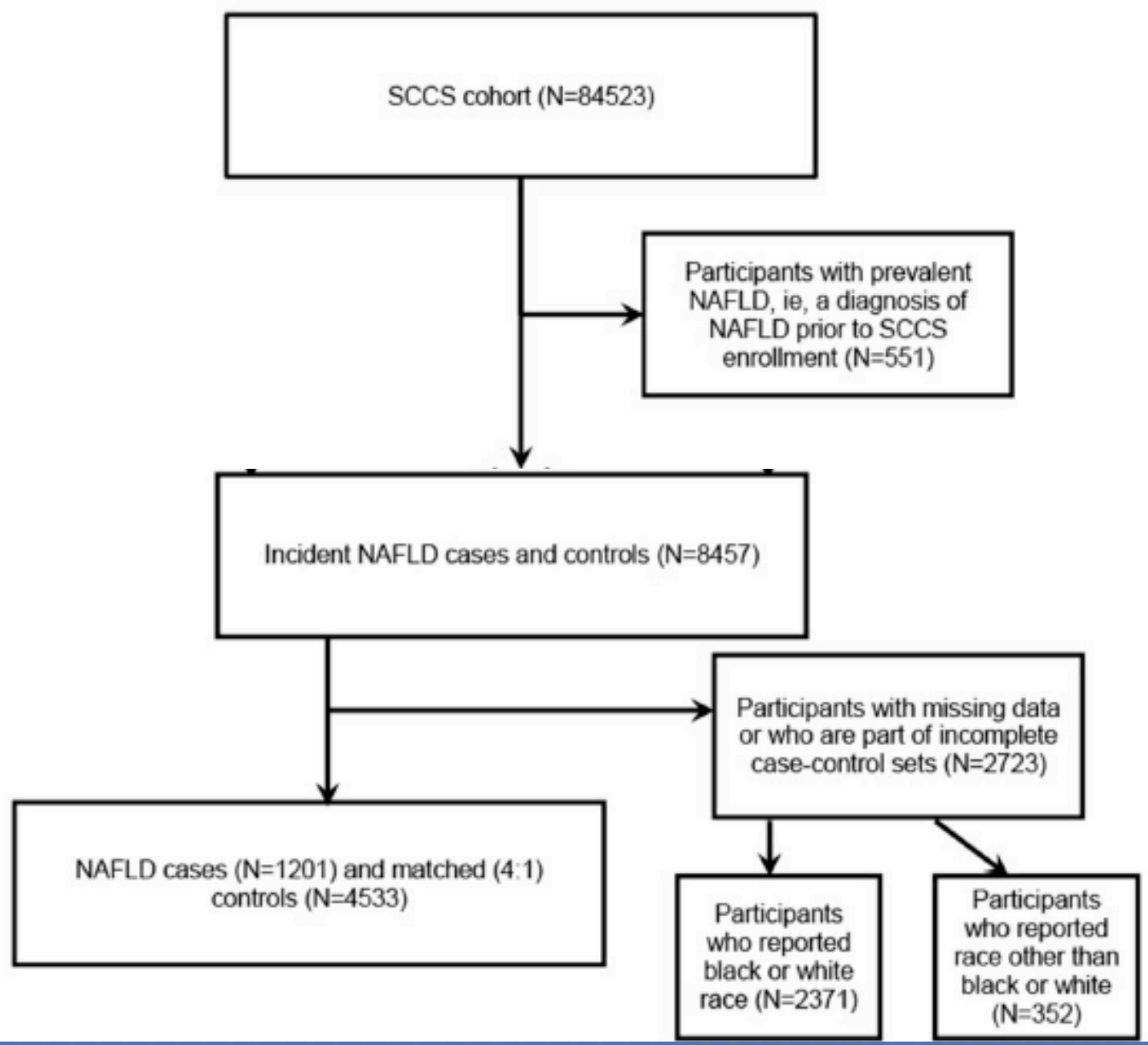
- Ideal for preliminary research
- Cheap and simple
- Ethically safe

Disadvantages

- Establishes association, not causality
- Bias: recall, selection
- Confounders

Nested case-control

- Hybrid design
  A case-control study is nested in a cohort study



Sarkar S et al. Front Nutr 2020

Summary of advantages and disadvantages of different study designs

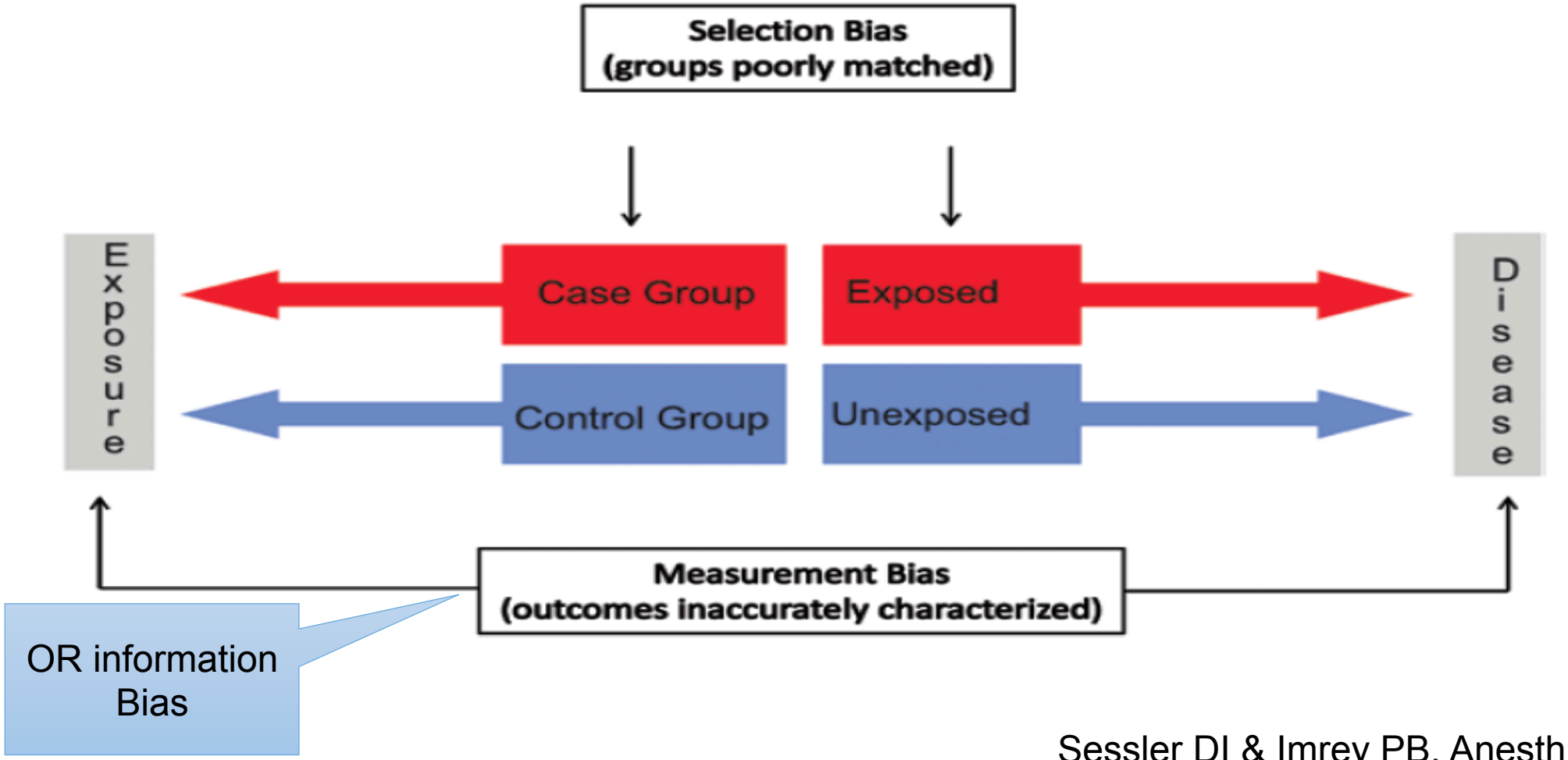
Table 1. Comparing study designs in clinical research

Study design	Description	Advantages	Disadvantages
RCT	Interventional Subjects randomized to treatment or control	Gold standard for evaluating therapy effects Can determine causality Minimizes bias/confounding	Cost and time Potential for low generalizability
Cohort	Observational Subjects followed over time for disease development	Can help identify risk factors of disease More generalizable than RCT	Cost and time Difficult to show causality Potential for bias/confounding
Case–control	Observational Disease cases retrospectively compared with controls for exposure status	Fewer cost and time concerns Ideal for rare diseases No patient follow-up needed	Difficult to show causality Potential for bias/confounding
Cross-sectional	Observational Assess prevalence of disease and exposure status at one time point	Fewer cost and time concerns Evaluates associations between exposure and disease	Cannot determine causality Potential for bias/confounding
Case report/case series	Observational Describes a rare finding in a patient or group of patients	Rapidly bring attention to new findings Preliminary research	Definitive conclusions cannot be made Potential for bias/confounding

RCT, randomized controlled trial.

Besen J. J Invest Dermatol 2014

Selection and measurement bias



Sessler DI & Imrey PB. Anesth Analg 2015

Confounding

- Example: Comparison of fracture rates between two groups without considering age and/or sex.

- Observational studies more prone
  - Main ways of management
    - Matching
    - Adjustment

- RCTs less prone
  - Inclusion & exclusion criteria
  - Placebo, randomization, blinding
  - Drug washout

Panel 1: **What to look for in observational studies**

Is selection bias present?
In a cohort study, are participants in the exposed and unexposed groups similar in all important respects except for the exposure?

In a case-control study, are cases and controls similar in all important respects except for the disease in question?

Is information bias present?
In a cohort study, is information about outcome obtained in the same way for those exposed and unexposed?

In a case-control study, is information about exposure gathered in the same way for cases and controls?

Is confounding present?
Could the results be accounted for by the presence of a factor—eg, age, smoking, sexual behaviour, diet—associated with both the exposure and the outcome but not directly involved in the causal pathway?

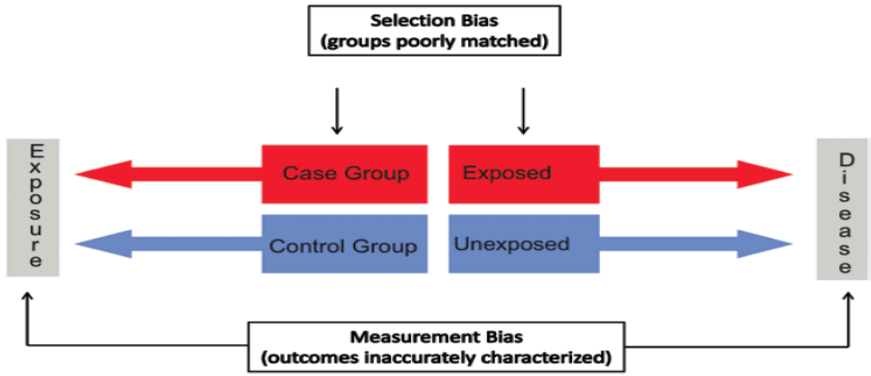
If the results cannot be explained by these three biases, could they be the result of chance?
What are the relative risk or odds ratio and 95% CI?[11,12]

Is the difference statistically significant, and, if not, did the study have adequate power to find a clinically important difference?[13,14]

If the results still cannot be explained away, then (and only then) might the findings be real and worthy of note.

How was the recruitment performed?

Recall bias: more important in case-control & cross-sectional



Sessler DI & Imrey PB, Anesth Analg 2015

Grimes DA. Lancet 2002

Analysis

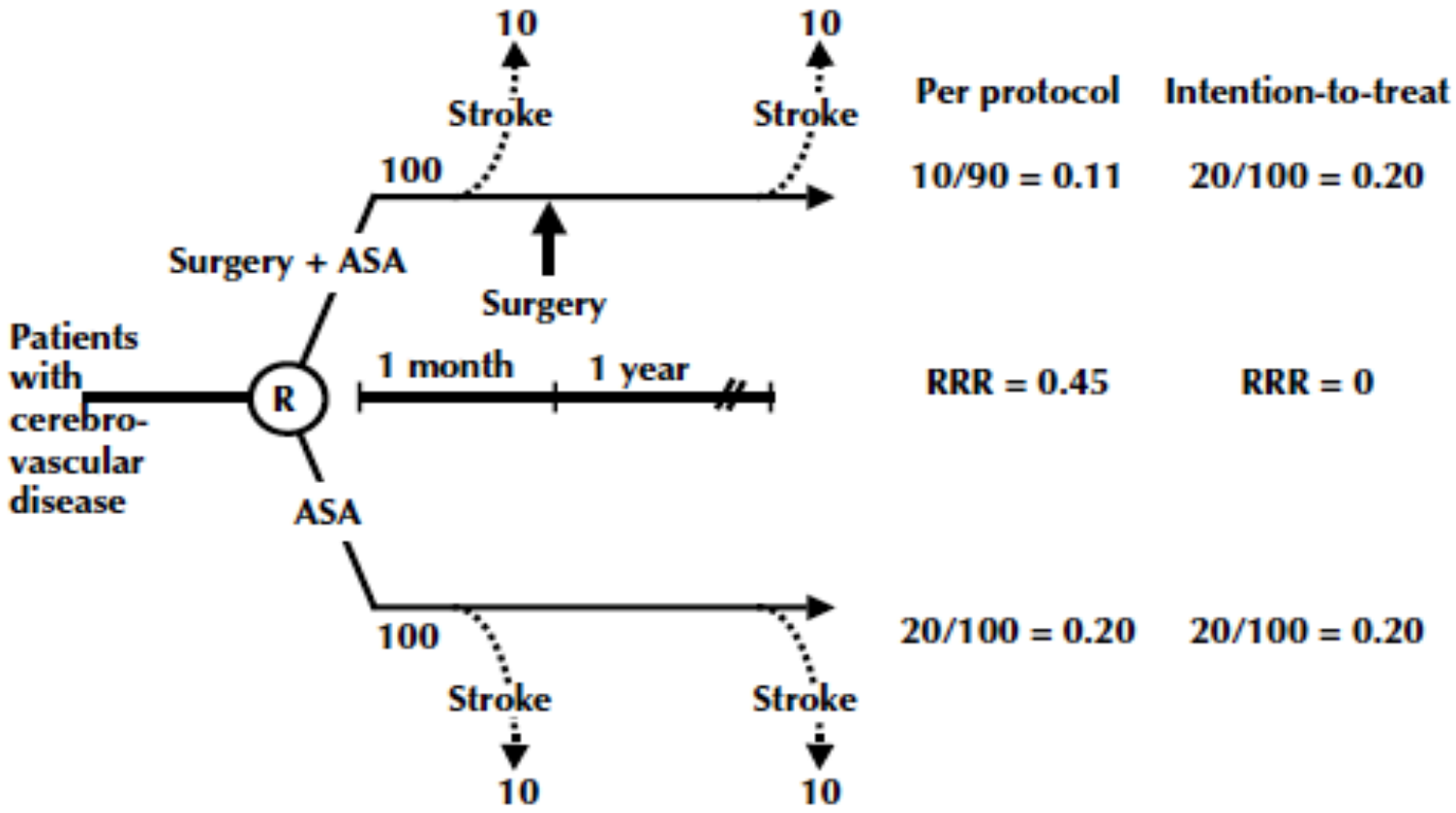
Intention-to-treat

- Analysis includes all the participants, even if some of them were dropped out before the completion of the study
- Minimization of bias and more conservative in evaluation of the results

Per protocol (on treatment)

- Analysis includes only the participants who completed the study
- More prone to bias
  - The most compliant participants and those who did not experience an adverse effect are more likely to complete the study

Intention-to-treat vs. per-protocol analysis



Montori VM & Guyatt GH. CMAJ 200

Lost of follow-up

- Bias
  - E.g., those who experience an adverse effect are more likely to be lost to follow-up
- Ideally, lost of follow-up is similar between compared groups
- Decreases the power of study
  - It should be pre-considered at *a priori* power calculation
- Acceptable rate <20% (conventionally)
- Common bias at the extensions of studies

Reporting statement

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journal homepage: www.journal-surgery.net

Guideline

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for reporting observational studies☆

Erik von Elm [g,*], Douglas G. Altman [b], Matthias Egger [a,c], Stuart J. Pocock [d], Peter C. Gøtzsche [e], Jan P. Vandenbroucke [f], for the STROBE Initiative

[a] Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland
[b] Centre for Statistics in Medicine, Oxford, United Kingdom
[c] Centre for Infectious Diseases Epidemiology and Research (CIDER), University of Cape Town, South Africa
[d] London School of Hygiene and Tropical Medicine, University of London, London, United Kingdom
[e] Nordic Cochrane Centre, Copenhagen, Denmark
[f] Department of Clinical Epidemiology, Leiden University Hospital, Leiden, The Netherlands
[g] Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, IUMSP – Institut universitaire de médecine sociale et préventive, Lausanne, Switzerland

Table 1
The STROBE Statement—checklist of items that should be addressed in reports of observational studies.

	Item number	Recommendation
Title and Abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants (b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case

There are three principal means of acquiring knowledge: observation, reflection and experimentation:

Observation collects facts

Reflection combines them

Experimentation verifies the result of that combination.

Denis Diderot (1713-1784)