Understanding the basics of research study design

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Clinical research versus basic (laboratory) research
ability to control experimental conditions

Low value versus high value
case report → RCT

Low quality versus high quality
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Clinical Study Types

Experimental Studies

Observational Studies

Quasi-experimental Studies
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Observational Studies

General Principles
- formulating a question
- directionality
- timing

Classifications/types

Strengths and weaknesses
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Formulating a question

- Common to all clinical research
- Clear delineation of the question will clarify the next steps, and type of research
- Must understand the problem
- Know where current knowledge ends and “ignorance begins”
- An iterative process during development
- Plausible/feasible

“It is not the answer that enlightens, but the question”
Ionescu
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Knowledge base for question

- Epidemiology of the content area
- Biological basis of process
- Internal validity of study design/variables
- External validity of answers
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Framing the question (one method)

P patient or population
I intervention (exposure)
C comparison group
O outcome
T time

Not all parts relevant to all study designs
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Things to consider

Outcome
   True versus surrogate (death v ICD discharge)
Exposure, predictor and descriptor variables of interest
Method of measurement of variables
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Choice of study impacted by

- purpose of the study
- resources
- population available
- time
- frequency of outcome
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Directionality

how we view (examine) the relationship between the exposure and the outcome

in general, we assume that the outcome of interest follows some sort of exposure or intervention

this exposure can be a “natural” event or experiment
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Forward Directionality

E → O

exposure + +
outcome - -
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Backward directionality

E  O
exposure  outcome
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No Directionality

Exposure and outcome identified at the same time
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Timing

When does the outcome occur in relation to the study?

- Prospective
- Retrospective

Mixed – data collected prospectively, question posed retrospectively
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Bias

“any systematic error in the design, conduct, or analysis of a study that results in a mistaken estimate of an exposure’s effect on the risk of disease”

Schlesselman

Selection Bias (eg, non-responders)

Information Bias (eg recall)

“Result of an error in the design or conduct of a study”

Gordis
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Observational Studies

**Descriptive**
- Case reports
- Case series
- Cross-sectional
- Ecological

**Analytical**
- Case-control
- Cohort
- Cross-sectional
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Cross-sectional Studies

• Exposure and outcomes measured at same time
• Information obtained once
• Snapshot at a particular time
• Mostly descriptive (prevalence studies)
• Occasionally analytic

association between exposure/outcome
threats to validity (exposure variables must be stable)
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Example of a cross-sectional study:

Symptomatic heart failure is the most important clinical correlate of impaired quality of life, anxiety, and depression in implantable cardioverter-defibrillator patients: a single-centre, cross-sectional study in 610 patients

Johansen et al, Europace (2008) 10, 545-551

Exposure = ICD; Outcome = measures of QoL, anxiety
All who wished to (or could) participate
Cross-sectional studies

**Advantages**
- quick/cheap
- prevalence estimates
- several factors/outcomes
- hypothesis generating
- initiate a cohort study

**Disadvantages**
- association E/O
- not temporal sequence
- biases
  - sampling
  - survivor
  - length-biased samples
- not feasible for rare conditions
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Cohort Studies

• a cohort (group/sample) of individuals are studied and then followed until the development of an outcome

• initially free of disease (outcome)
• classified according to exposure
• followed over time

• Do the exposed and unexposed differ in the development of the outcome of interest?
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Cohort Studies

• Forward directionality
• Prospective
• Retrospective
  ▪ often relying on previously collected data to ascertain exposure
  ▪ quicker and cheaper
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Example of a cohort study

“Oral erythromycin and the risk of sudden death from cardiac causes”


Cohort = Tennessee Medicaid patients
Exposure = erythromycin
Modifiers = cyto P3A inhibitors
Outcome = sudden death
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Cohort Study

Advantages
• temporal sequence established
• causality
• unbiased exposure assessment
• multiple outcomes/diseases
• rare exposures recruited
• establishes incidence of disease
• less incorrect information

Disadvantages
• expensive
• time consuming
• loss of relevance
• follow up loss (bias)
• information quality may change (bias)
• exposed may be followed more closely
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Case-control studies

• subjects selected based on disease/outcome status
• cases have disease/outcome, controls do not
• cases and controls then compared with respect to exposure

• Backwards directionality and retrospective

• methodological challenges
  • selection of cases/controls
  • information bias
  • matching
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Example of a case-control study:

“Sudden cardiac arrest associated with early repolarization”

Haissaguerre et al; NEJM (2008); 358;19:2016-23

Case Outcome = resuscitated SCD
Controls = no RSCD
Matching = age, sex, race, physical activity level
Exposure = presence of early repolarization
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Case-control studies

**Advantages**
- Inexpensive and quick
- Rare or uncommon conditions
- Diseases with long latencies
- Multiple exposures
- Smaller sample size

**Disadvantages**
- One outcome
- Temporal sequence not established
- Cannot estimate risk
- Prone to biases
  - Selection
  - Misclassification
  - Survivor
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Summary

• Brief overview of basic study designs used in Observational Studies
• The development of the question, followed by an assessment of resources, time, available population, rarity of disease or exposure will often indicate the best study design, for the circumstances
• Maximal efforts required to understand potential sources of bias for a given design so they can be minimized
• Associations between exposures and outcomes can be made, however causality can only be inferred some of the time (cohort study).
• Fancy statistical analysis cannot really overcome design or data flaws that occur in many uncontrolled, nonrandomized, observational studies.

Next step – Randomized Controlled Trials