Introduction to Research Methods

Session 1: Basis Study Design

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Overview:

- Evidence-based medicine
- Why is trial design important?
- Observational designs
  - fundamental features
  - common design mistakes
- Experimental designs
  - fundamental features
  - common design mistakes
- Levels of evidence

Evidence-based Medicine:

- Is there an association between exposure and outcome?
- Does the exposure cause the outcome?
- Evidence-based medicine gathers the best available information to weigh up this causality
- Isaacs & Fitzgerald. Seven alternatives to evidence-based medicine *BMJ* 1999; 319:1618

Evidence-based Medicine:

Research question
- the reason that a study is undertaken
- when answered, will allow the researcher to apply newly found knowledge

Research hypothesis
- a bold statement of what we think the answer will be
- a statement of the relationship between two variables
- the study is to weigh the evidence for the hypothesis

Select a design to answer the research question
- e.g. radiation of the foetus
Evidence-based Medicine:

Observational Study designs
• the challenge is to find a naturally occurring ‘experiment’
• compare two or more groups to evaluate the hypothesis

Experimental Study designs
• active expose the study subjects to a variable of interest
  i.e. the ‘intervention’
• measure the effects of this manipulation
  i.e. the ‘outcomes’

Observational designs:
1. Ecological (group-based) studies
• based on data collected at the level of the whole population
• does not require data about the exposures or outcomes of individuals
• appropriate design for examining health effects of environmental exposures

Observational designs:
1. Ecological Study example:

<table>
<thead>
<tr>
<th>Country</th>
<th>Incidence of bowel cancer (kg meat/person/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UK</td>
<td>X</td>
</tr>
<tr>
<td>Australia</td>
<td>X</td>
</tr>
<tr>
<td>Spain</td>
<td>X</td>
</tr>
<tr>
<td>Sweden</td>
<td>X</td>
</tr>
<tr>
<td>Mexico</td>
<td>X</td>
</tr>
<tr>
<td>Japan</td>
<td>X</td>
</tr>
</tbody>
</table>

Observational designs:
2. Cross-Sectional study
• the present association between two variables is examined
  i.e. exposure and outcomes
  e.g. smoking marijuana and depression
• data on exposure and outcome is collected at one point in time
• no information on sequence of events, just a ‘snapshot’
• data collected from populations databases or surveys etc
• the main outcome measure is prevalence
• Beware ‘causation trap’ – Diets and Dying
2. Examples of Cross-Sectional studies:

Descriptive cross-sectional studies
e.g. prevalence of cervical cancer in Australian women

Analytical cross-sectional studies
Investigate the association between a possible risk factor for the outcome (e.g. a specific disease) and the outcome itself.
e.g. the characteristics of individuals (age, sexual practice, socioeconomic status) and the presence or absence of cervical cancer

3. Case-Control Studies

• find ‘cases’ who have the disease e.g. lung cancer
• find ‘controls’ (matched) who do not
• compare the previous exposures to risk factors
• estimate the Odds Ratio (OR) of disease occurring in those exposed
e.g. heavy smokers are at 10-fold higher risk of lung cancer than non-smokers

3. Case-Control Studies example
• relationship between the use of thalidomide and the development of limb defects in new-born babies.

41 mothers had received thalidomide

46 cases of mothers with infants having limb defects

1 mother had received thalidomide

300 controls with normal infants

Time moving forward

Advantages:
• quick and cheap
• range of possible risk factors
• good for rare diseases

Disadvantages:
• selection bias
• measurement bias
• problem sorting out sequence of events
4. Cohort Studies - prospective

- opposite of the Case-Control study
- begin with a cohort of individuals, without disease, that contains:
  - individuals who have been exposed to the risk factor of interest
  - individuals who have not been exposed
- follow the cohort prospectively, often for years, to assess the development (incidence) of disease
- compare the risk of developing disease between the two groups
  - Relative Risk (RR)

Advantages:
- Exposure is measured before disease onset (unbiased)
- Rare exposures can be examined by appropriate cohort selection
- Multiple outcomes (diseases) can be studied for one exposure
- Incidence of disease can be measured (calculate RR)

Disadvantages:
- Time consuming and expensive
- Changes over time in exposure status and in diagnostic criteria
- Classifying an individual as diseased may be influenced by exposure
- Losses to follow-up may introduce serious bias

Observational designs:

4. Cohort Studies – prospective example

Is there a relationship between cholesterol level (TC) and risk of cardiac disease?

Compare the incidence of cardiac disease

Low TC level

Large cohort of men

Moderate TC level

High TC level

Observational designs:

4. Cohort Studies - retrospective

- begin with a cohort in the past
- past levels of exposure (to the risk) must be known
- follow the cohort from the past forward to the present and into the future
- measure the amount of disease that occurs
- compare disease risk with past levels of exposure
- exposure assessment must rely on past records
- less certainty about the temporal relationship between exposure and disease
  - Did exposure precede the disease by enough time for it to actually be able to cause the disease?
4. Cohort Studies – retrospective example

- a Hepatitis B vaccine trial started in 1978
- heterosexual and homosexual men took part
- the serum samples were stored
- HIV tests developed in 1984
- samples tested for HIV antibodies
- essential information on the prevalence, incidence and natural history of HIV infection
- The samples represented a gold mine!
- Measles vaccination!

5. Pre/Post-event study designs

- Some ‘event’ happens to a population
- Compare the population characteristics pre- and post-event
- Information on the effect of the event

* e.g. mental/physical health of Christchurch earthquake survivors
  * Depression
  * Suicide
  * Myocardial infarction
6. Case series

- simply lists of individuals with exposures and outcomes of interest
- limited level of evidence
  - accuracy of level of exposure doubtful
  - no comparison group
  - descriptive only

E.g.
- Calls to VPIC following chemical exposures to the eye
- Patients with side effects following ingestion of a ‘mushroom’

Observational designs:

- Bias
- Confounding
- Sampling
- Response rate
- Sample size
- Loss to follow up

Data collection:

- Retrospective designs
  - Data not collected for the research purpose
    - incomplete
    - inaccurate
  - Selection bias
  - Many variables unknown

- Prospective designs
  - Specifically designed data collection documents
  - All variables collected & verified in real time

Experimental designs:

- The researcher is no longer an observer but an experimenter!
- An intervention is introduced and its effect evaluated:
  - medication
  - device or procedure
  - preventive strategy
  - diagnostic strategy

- Before clinical trials there was no suitable strategy available to resolve conflicting claims
- Many useless or harmful treatments were adopted
  - Benjamin Rush
1. Parallel Group trials
   - Randomised, controlled, clinical trial
   - Prospective investigations
   - Compare two or more groups
     - one exposed to the intervention (experimental group)
     - one not exposed (control group)
   - The exposed and unexposed groups must be similar
     - equal distribution of confounding variables e.g. age, gender
     - randomisation
     - stratification
   - Gold standard method to evaluate the value of medical practices

2. Pre/Post-intervention trials
   - Deliberate introduction of an intervention into practice
   - Data collected pre- and post-intervention
   - Data from both periods compared
   - Patients not randomised
   - Pre- and post- groups may not have the same characteristics
   - Other factors may have occurred that ‘confound’ the data
   - Useful but not a high level of evidence

1. Parallel Group trial example
   - acutely agitated patients
   - midazolam
   - midazolam + droperidol
   - midazolam + olanzapine
   - efficacy & safety

2. Pre/Post-intervention trials - examples
   - Ambulance Victoria management of SVT
     - verapamil traditionally used but has problems
     - adenosine, a newer drug, is safer
     - intervention: the change from verapamil to adenosine
     - outcomes: reversion success, incidence of side effects
   - Patient satisfaction in the ED
     - intervention: ‘patient liaison nurse’
     - outcome: patient satisfaction
     - confounders: different patients, other changes in the ED
3. Two-period Crossover trial

- Compares two treatments
- All patients exposed to both treatments
- Patients randomly allocated to two groups
- One group receives treatment A, later ‘crosses over’ to B
- Other group receives treatment B, later ‘crosses over’ to A
- Both treatments are studied in the same patient

- Applicable for conditions which return to an initial state while treatment is withdrawn e.g. hypertension
- Treatment effect can be identified using a much smaller number of subjects than an RCT

4. Cluster Trial designs

- Individual patients not randomised
- Clusters of patients randomised e.g. hospitals

- Useful when patients cannot be randomised
- Confounders may not be equally distributed

3. Two-period Crossover trial example

The effect of drugs while scuba diving

<table>
<thead>
<tr>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>pseudoephedrine</td>
<td>pseudoephedrine</td>
</tr>
<tr>
<td>dimenhydrinate</td>
<td>dimenhydrinate</td>
</tr>
</tbody>
</table>

Effects:
- reaction
- accuracy
- memory

4. Cluster Trial design example

- TARGET Pain Study
- ‘clinical tool’ introduced to improve pain management
- 10 EDs randomised to:
  - usual care (n=5)
  - use of the clinical tool (n=5)
- Measurement of patient satisfaction
  - baseline
  - 3 months after usual care or clinical tool use
  - 3 months after the usual care group ‘crosses over’ to the clinical tool
5. Factorial Trials

- allows the simultaneous evaluation of two (or more) treatments
- used for large trial to maximise return

Randomisation
- aspirin
- placebo

Betacarotene - group A
- placebo - group B
- betacarotene - group C
- placebo - group D

‘Intention to Treat’ Analysis

- If a patient is enrolled, they need to be included in the data analysis
- Relates to effectiveness not just efficacy
- Avoids serious bias

Example:
- One group randomised to Drug A
  - good efficacy but 50% of patients had side effects and dropped out
- One group randomised to Drug B
  - good efficacy but no side effects and no one dropped out
- Data analysed for those remaining: 100% of first group had a good result
- Data analysed for all patients: only 50% of first group had a good result

Randomisation
- a process by which patients are allocated to one of two or more treatment groups, purely by chance.
- aims to distribute confounding variables equally
e.g. age, gender, s-e class, co-morbidities
- overwhelming advantage: prevents any manipulation by the investigators in the creation of the treatment groups
- the results cannot be foreshadowed on account of any pattern of patient characteristics
- computer programs, random number tables

Blinding
- The most effective method of eliminating systematic error
- Increases accuracy of endpoint measurement
- Single blind trials: patients are unaware of their treatment
- Double blind trials: neither the patients nor the investigators know

Single dummy design:
- patients receive 1 medication that is either active or placebo

Double dummy design:
- patients receive 2 medications, either active or placebo

Triple dummy design:
- patients receive 3 medications, either active or placebo
Unbiased Assessment

- Research questions answered by measuring *response variables* (endpoints)
- Some are ‘hard outcomes’ e.g. mortality, incidence of a disease
  - Minimal bias in measurement
- Some are ‘soft outcomes’ e.g. satisfaction, level of pain
  - Susceptible to bias in measurement
- Assessment minimised by:
  - Blinding techniques
  - Use of hard endpoints, where possible
  - Calibration/standardisation of machines
  - Use of validated tools e.g. questionnaires, scales

Experimental designs:

- *Bias*
- *Confounding*
- *Sampling*
- *Response rate*
- *Sample size*
- *Loss to follow up*

Levels of Evidence:

**Level I**
- A systematic review of all relevant randomised controlled trials

**Level II**
- At least one properly designed randomised controlled trial

**Level III-1**
- Well-designed pseudo-randomised controlled trials

**Level III-2**
- Cohort and case-control studies

**Level III-3**
- Comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group

**Level IV**
- Case series, pre/post-test

Old RCTs

We have actually been doing RCTs for centuries:

“Let us take out of the hospitals, out of the corps or from elsewhere, 200 or 500 poor people that have fevers, pleurisy etc”

“Let us divide them into halves, let us caste lots, that one half of them shall fall to my share and the other to yours”

“We shall see how many funerals both of us shall have”

“Let the reward of the wager be 300 florins deposited on both sides”

Holland 1662