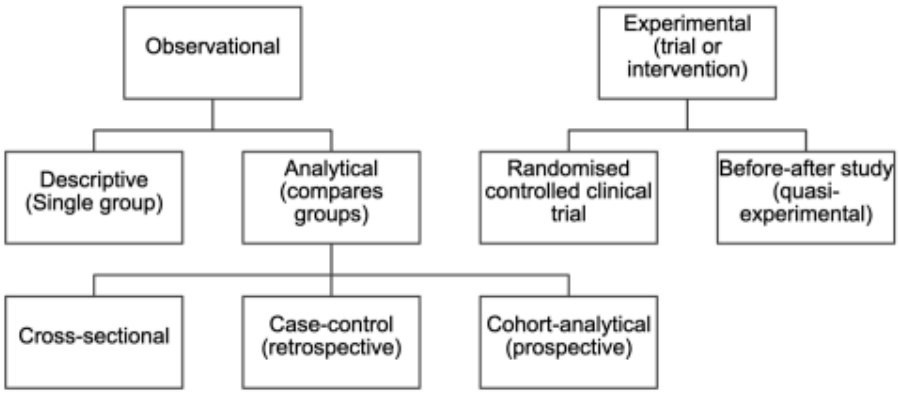
Week 2 Lectures	
Introduction to Research Ethics	

Introduction to research ethics	• To do research on animals and humans, the research must be approved by the University Research Ethics Office.
	• To get grants, it is frequently necessary to have had research ethics training.
	• To publish trials, they may need to be registered (e,g with NHMRC) and there must be evidence of ethics review.
	• To understand research ethics is an important skill needed to become a researcher.
	• History of human research
	  ○ 19–20th century: Pasteur (1822-1895) is known for finding the first rabies vaccine; some died of rabies and smallpox; consent was not questioned.
	  ○ Smallpox is the only human disease that has been globally eradicated through vaccines. It is also responsible for the first known vaccine, created by the English physician Edward Jenner in 1796.
	  ■ After observing that milkmaids who caught cowpox (a milder disease) seemed to gain immunity to smallpox, Jenner inoculated an eight-year-old boy using a milkmaid's cowpox lesion.
	  ■ He then exposed the boy to smallpox, and when the boy did not develop any symptoms of the deadly disease, Jenner realised he had developed a way to prevent it.
	  ○ This led further questions to be raised:
	  ■ Hansen (Norway; 1841-1912) discovered Mycobacterium leprae as the causative agent of leprosy, defying the hereditary affliction theory of disease.
	  • Hansen had attempted to inject at least one female patient with leprosy without consent and although no damage was caused, that case ended up in court and Hansen lost his post at the hospital.
	  • This initiated self-imposed self-testing.
	  ○ Before WWII, in Germany, there was growing concern in the early 1900s.
	  ○ In the US, there was more push than concern.
	  ■ Yellow fever in the army; soldiers were given 100 gold coins to sleep in mosquito infested tents; 100 more coins if they got the fever.
	  ○ Research on humans became worse during and post-WWII.
	  ■ Atrocities were not limited to German concentration camps.
	  ■ Many medications, chemicals and poisons were tested on trapped prisoners who died in hundreds.
	  • E.g Nuremberg trials; Nuremberg Code of Ethics 1946
	  ○ Japanese in China (1935–1945)
	  ■ Unit 731 – set up 132 covert experimentation camps undertaking biological and chemical warfare research and development of human lives; lethal human experimentation.
	  ■ 250000-500000 people died in sheer terror and agony.
	  ■ Around 1985, this all came to light, but no one was trialled when prisoners were taken to the USA in exchange for data.
	  ○ 1946 Nuremberg Code – 10 requirements for ethical research
	  ■ Voluntary consent
	  ■ Experiment will yield fruitful results
	  ■ Previous research justifies its conduct
	  ■ No unnecessary physical or mental suffering
	  ■ No reason to expect death
	  ■ Risk never exceeds humanitarian importance
	  ■ Prior arrangements to protect subjects
	  ■ Conducted only by scientifically qualified persons
	  ■ Subject can withdraw at any time
	  ■ Researcher can terminate study if too high risk

    - 1964 Declaration of Helsinki
        - Adopted by the World Medical Association
        - 18 basic principles for all research
            - Well-being of subject takes precedence over science and society
            - Duty of physician to protect life
            - Subject must be volunteers and informed participants
            - Assessing risks and benefits and giving greater weight to lessen the risks
- Main principles of human and animal research ethics
    - Research has merit and is beneficial
    - Researchers have integrity
    - Benefits and burdens of research participation are justly shared
    - Risks to participants are minimised and justified by potential benefits
    - Human participants are respected as people; consent
    - That animals are not placed under excess suffering (need to justify)
- The emergence of bioethics
    - Autonomy – respect for the individual
    - Justice – fair dealings with all persons and species
    - Beneficence – to do good
    - Non-maleficence – to do no harm
- Post WWII research – what else could go wrong?
    - IP (intellectual property) – who owns it?
    - Collaborative research – domestic and international
    - Authorship dispute – sponsors, research teams
    - Conflicts of interest – identifying and disclosing
    - Peer review – implicit and explicit bias
    - Plagiarism – academic honesty, data intervention
    - Data management – privacy, security
- In Australia, the National Statement on Ethical Conduct in Human Research consists of several guidelines made in accordance with the National Health and Medical Research Council Act 1992.
    - The National Statement is subject to rolling review.
    - Purpose – to promote ethically sound research; requires that participants are accorded the respect and protection that is due to them and involves fostering research that is of benefit to the community.
    - Sections – (1) values and principles of ethical conduct, (2) themes in research ethics: risk and consent, (3) ethical considerations specific to research methods or fields, (4) ethical considerations specific to participants, (5) processes of research governance and ethical review
    - Limitations
        - Australian law governs research through statutes, common law and contracts.
        - Advice about compliance with legal obligations is not in the scope of the National Statement.
        - Some Commonwealth legislation specific to research is identified.
        - Responsibilities in the statement are intended to be consistent with international human rights instruments Australia has ratified.
        - Responsibility of institutions and researchers to be aware of relevant legal obligations.
    - (1) Values and principles of ethical conduct
        - Four values are used to shape relationships between researchers and participants – research merit and integrity, justice, beneficence, respect for human beings
        - These apply to all types of human research and are used to organise the substantive content of the NS.
- Processes involved in human and animal research ethics
    - Research proposals are reviewed and approved by the human or animal research ethics committee.

Classification of quantitative study designs



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- Research question
  - Background questions – how does it work, what is the best method for measuring, etc
  - Foreground questions – therapy, harm, prognosis
- Formulating research questions
  - PICO – population, intervention, comparison, outcome
  - PECO – population, exposure, comparison, outcome
  - Time may be considered
- Study designs
  - Randomised control trials
    - Target population → selection criteria → random allocation
      - Intervention group → exposed to intervention → follow-up → outcomes
      - Control group → not exposed to intervention → follow-up → outcomes
    - Randomisation – study subjects are randomly allocated the intervention or control
    - Equal probability of intervention and control; controls in place for systematic and unsystematic bias
    - Advantages – controls for unknown biases, rigorous evaluations of a single variable in a precisely defined population, prospective design, evaluates a pre-defined hypothesis
    - Disadvantages – limited applicability, limited generalisability, lack of presentation of population groups in trial, expensive and time consuming, sometimes unethical
    - Sources of bias – selection of study population, randomisation, deviation from intervention, missing outcome data, measurement, selective reporting
    - Potential interventions – cross over between intervention and control groups; group/cluster randomisation
  - Quasi-experimental design
    - No randomisation (e.g natural experiment)
  - Cohort study
    - Two or more groups with differences in exposure (agent or presence of prognostic factor)
    - Followed up
    - Numbers in each group with outcome (e.g particular disease)
    - Usually measured over a number of years
    - Similar to RCT without randomisation; determination of exposure of interest results from preference and circumstance.
    - Advantages – establishes a sequence of events, reduces bias in measuring predictor variables (recall or measurement bias), reduces survivor bias (includes undiagnosed, misdiagnosed or dead), can study multiple outcomes over time, measures incidence and relative risk

Week 5 Lectures	
Critical Appraisals	

Introduction	• A systematic review aims to identify, appraise and synthesise all the empirical evidence that meets pre-specified eligibility criteria to answer a specific research question using explicit, systematic methods that are selected with a view aimed at minimising bias, to produce more reliable findings to inform decision making.
	• Assessing the risk of bias is a key step involved in systematic reviews.
	• Systematic reviews depend on the validity of the included studies.
	  ○ Biased studies = misleading reviews
	• Bias involves the characteristics that can introduce systematic errors in the magnitude or direction or results.
	• Bias is not the same as:
	  ○ Impression – random error due to sampling variation; reflected in the confidence interval
	  ○ Quality – bias can occur in well-conducted studies; not all methodological flaws introduce bias.
	  ○ Reporting – good methods may have been used but not well reported.
	• Sources of bias
	  ○ Selection bias – systematic difference in baseline characteristics between two groups (e.g participants with different age characteristics or health status)
	  ○ Performance bias – systematic difference in treatment (aside from intervention) of two groups (e.g participants who are aware they are not receiving the intervention may seek other treatments)
	  ○ Attrition bias – systematic difference in loss to follow up (or study withdrawal) between the two groups (e.g participants may be lost due to adverse treatment effects that must be accounted for)
	  ○ Detection bias – systematic difference in how outcomes are determined between two groups (e.g if the researcher is aware of which group is the treatment, the outcome may be assessed with bias)
	  ○ Reporting bias – systematic difference in between reported and unreported findings (e.g selective reporting bias when only reporting positive results)
	  ○ Funding bias – systematic difference in the direction of results or effect sizes (e.g industry sponsored studies report more favourable results on the study sponsor's product under evaluation).
	• Cochrane risk of bias tool – RoB 1.0
	• Cochrane risk of bias assessment
	  ○ Involved 7 evidence-based domains
	  ○ Review author's judgement – low risk of bias, high risk of bias, unclear
	  ○ Support for judgement
	  ○ Evidence/quotes from the paper or other sources
	  ○ Review author's explanation

Cochrane Rob 2.0 tool	• Importance of critically appraising research – systematic assessment of strength of evidence and risk of bias
	  ○ Assessment criteria is linked to factors known to affect outcome.
	• Three steps in critical appraisal
	  1. Gather information on what was done – study reports, published protocols, registry entries
	  2. Make judgements based on specific criteria – low risk, some concerns or high risk of bias
	  3. Incorporate into analysis and interpretation – plan in advance how this will be done; helps to explain what is found
	• Cochrane RCT risk of bias tool
	  ○ Selection bias – randomisation process
	  ○ Performance and detection bias – deviations from intended interventions
	  ○ Attrition bias – missing outcome data