Research in Medicine (W1)

Key principles of evidence-based medicine (L1.1)

Scenario: Mark's Dilemma

- Mark, aged 60 has had some arthritis in his knee for a couple of years. He has heard about glucosamine on the TV, from friends and neighbours, and he has seen it advertised at the local chemist. There seems to be lots of brands available and some of them combine glucosamine with something called chondroitin. He wonders whether he should try it. He does a quick Google search but there are over 6 million hits and he is not sure which website to believe
- So he decides to ask you… should Mark take glucosamine for his arthritis in the knees?

Where do we obtain medical advice from?

- A friend's testimonial
- An expert opinion or a case report
- A scientist's data
- A traditional approach
- The media report
- Large study with a large generalisable population is **best evidence**
  - "We all got better compared to the control group"

What is evidence-based medicine (EBM)?

- "The conscientious, explicit, judicious and reasonable use of modern, best evidence in making decisions about the care of individual patients"
- **EBM integrates**:
  - Clinical experience
  - Patient values and preferences
  - Best available research information

Questions you need evidence to answer

- How could this treatment **help me**? Has it been studied in people like me?
- Is it likely that this drug will harm me? Am I more likely to get **side effects** than other people? (For example, older people sometimes have more side effects.)
- How **strong** is the evidence that this **treatment works**? Are the results of the research published in a medical journal? Is just one person telling their story on television?
- What are the **alternatives** to the treatment being offered?
- What are the **costs** of the treatment

Evidence based practise… why?

- Make use of effective treatments and rule out treatments that do harm
- Example: Dr Spock's 'Handbook' on Baby and Childcare
- Not example accurate: "Babies should be put to sleep on their fronts"
- Evidence by the 1970s that this advise was BAD
- Evidence not implemented until the late 1980s
- Estimated 50,000 unnecessary deaths

5A's of Evidence based practise

- **Ask**: Ask an answerable question
- **Access**: Locate the best evidence
- **Appraise**: Critically appraise the literature
- **Apply**: Apply to the patient
- **Assess**: Reflect on the process/evaluate

Step 1 - Ask

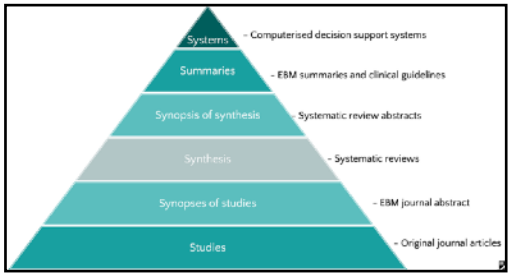
- Formulating an answerable question
  - **P** — patient/participants/participation
  - **I** — Intervention/exposure
  - **C** — Comparison/control
  - **O** — Outcome(s)
- Note: comparator could also be another active treatment

PICO Example
- P: Overweight men
- I: Meal replacement
- C: Usual eating
- O: Weight loss
- PICO question: In **overweight men** is use of the **meal replacement product**, the man shake, as **compared to usual diet**, **effective for weight loss**?

"Beating Autism: How I Saved My Son"
- Cover of US magazine in 2008
- Jenny McCarthy publicly blames the MMR vaccine for her son's autism
- She claims to have cured this via diet with a dairy-free and wheat-free diet

Using PICO
- P: children
- I: MMR
- C: No vaccination
- O: Autism
- In children does vaccination with the MMR vaccine, compared to not vaccinating, increase the risk of autism?

Using PICO
- P: Autistic children
- I: Dairy and wheat-free diet
- C: Standard diet (or no comparison)
- O: quality of life
- Does providing autistic children with a dairy and wheat-free diet, compared to a standard diet, increase quality of life



Where is the best evidence?
- Systems: Computerised decision support systems
- Summaries: EBM summaries and clinical guidelines
- Synopsis of synthesis: Systematic review abstracts
- Synthesis: systematic reviews
- Synopses of studies: EBM journal abstract
- Studies: Original journal articles

Role and steps within a systematic review (L1.2)

Why systematic reviews?
- Efficient way to access the body of research
  - Reduce time required for searching
  - Critical **appraisal**
  - **Interpretation** of results
  - Identify **gaps** in the literature/future research
- Reliable basis for decision making
  - Health care
  - Policy
  - Future research

Types of systematic reviews
- Intervention
- Diagnostic test accuracy (DTA)
- Prognostic
- Methodological
- Qualitative
- In BMS3052: Your review is a review of an intervention

Steps of a systematic review
1. Define the question/clear objective (PICO)
2. Plan eligibility criteria (RCT, co-morbidities)

3. Plan methods
4. ~~Publish protocol~~
5. Search for studies
6. Apply eligibility criteria
7. Collect data
8. Assess studies for risk of bias
9. Analyse and present results
10. Interpret results and draw conclusions
11. ~~Improve and update review~~

Systematic review vs Narrative review:

Variable	Systematic Review	Literature Review or Narrative Review
Research question	Focussed on a single question	May be focussed and may describe an overview of topic
Protocol	Peer reviewed	No protocol is included
Background	Provides a summary of the available literature on the topic	
Objectives	Clear objectives specified	Objectives may or may not be indentified
Inclusion & exclusion criteria	Criteria stated at the outset	Criteria not specified
Search strategy	Comprehensive, documented and reproducible	Not described
Process for selecting articles	Clearly described and documented	Not described
Process for evaluating articles	Comprehensive and systematic evaluation using set criteria Assessing the risk of bias	Evaluation may or may not be included
Results and data synthesis	Clear summarise the describe outcomes and quality of evidence	Summaries based on selected studies where the quality is unclear and may potentially influence the authors.
Discussion	A detailed discussion of results by experts using the results obtained.	

Your task
- In teams of 5/6 you will research and write a systematic review
- This is an authentic assessment
  - SRs are a common pre-requisite for research funding
  - They are part of the pathway to get research into practise
- SRs are a specific research method
  - This is actually a complete piece of research you are undertaking
- We will guide you through the steps in tutorials

Role of research methods in population health (L1.3)

Variability is the law of life
- Diseases are complicated and difficult
- No two individuals are the same
- No two individuals will react or behave the same way

Controversies in research
- Controversies in medical research often have impact on daily life and stem from variable reporting
- e.g. autism and vaccines

Controversy amongst researchers: Statin Wars
- To take a statin or not to take statins?
- That is the question
- What is the impact on patient
- TheBMJ (side effects) vs The Lancet (benefits)

A clinical trial of statin therapy for reducing events in the elderly (STAREE)
- The STAREE study will examine whether treatment with statin (atorvastatin 40mg) compared with placebo will prolong overall survival or disability free survival amongst healthy elderly people (≥70 years)

Challenges in Biomedical Research (L2.1)

Overview of the challenges for Biomedical Research
- Government
  - Legislation and guidelines
  - Funding
- Slow pace from bench to bedside
- Escalating costs
- Funding bad science
- Publishing negative data
- Strategic plan

Health and Medical Research
- Health and medical research has made a significant contribution in the last century to improved health outcomes around the world
- Increasing life expectancy

- Australia has world leading expertise in health and medical research, and Australian governments, companies and individuals make significant investments in health and medical research

The value of Biomedical Research
- **Improving health**
  - Biomedical Research in Australia has improved treatment and prevention of several cancers, infectious diseases and heart failure
- Training the **next generation** of scientists
  - Research grants provide opportunities for graduate and post-doctoral students to gain hands-on laboratory experience
- Increasing **knowledge**
  - Eight Australian biomedical researchers have been awarded a Nobel Prize in Physiology/ Medicine
- Strengthening the **economy**
  - Basic research supports the growth of a healthy and robust economy from creating new industries to improving quality of life
  - for every $1 spent on research, $2.17 was generated in additional economic/health benefits
- Developing **new technologies, products, and industries**

Attitudes of Australians to health and medical research
- Majority of people believe in government funding of biomedical research
- Biomedical research can lead to reduction in health costs

Australian Health and Medical Research Funding
- ~7.9 billion dollars is spent on health and medical research (H&MR) in Australia each year
- 4% of all spending on health is spent on H&MR (total health expenditure in 2018-2019 was $196 billion)
- More than half of all Australian H&MR is undertaken in the higher education sector
- H&MR accounts for one third of all R&D expenditure in higher education institutions
- 19% of all H&MR expenditure is in the private sector (mostly on pharmaceutical R&D)

Escalating costs
- The ageing of Australia's population, chronic diseases, consumer expectations and new health technologies are factors in the growing expense of health and hospital services

Challenges in Biomedical Research (L2.2)

Why does it take so long from bench to bedside?
- Long process

1. Discovery
   - Idea and basic research
2. Development
   - Clinical trials (Phase I, II, III)
   - 8+ years
   - Dozens of millions of dollars
3. Delivery

- Regulatory approval
- Patient care

Animal and/or laboratory studies
- Does the therapy work in:
  - Different models of the disease?
  - With co-morbidities?
  - Of either sex?
  - With different medications

Phase I
- Is the therapy safe? (LADME)
  - Different doses
  - Different time

    - Different administration
- 15-30 patients

Phase II
- Is the therapy effective (pharmacodynamics)
- <100 patients

Phase III
- Is the new therapy better than what is currently available?
- 100s to 1000s of patients

Australia innovation delivers a life-changing return on investment
- Australia funds more than 700 clinical trials and invests more than $1 billion annually in research and development
- Of the 795 medicines approved for use in Australia over the last 10 years, 224 were a breakthrough using a newly discovered molecule
- These 224 breakthroughs:
    - Were on average of 15 years in the making - requiring testing of 10,000 new molecules
    - Were a $1.4 billion investment in research and development
    - Have changed the way 52 diseases are treated

Improving bench to bedside
- Remove red tape and improve processes
- Open **interactions among researchers**, and more **effective relations among companies**, government, foundations, and universities
- Increase resources
- Have researchers/clinicians working in parallel
- Less focus on mechanisms

Dubious and/or conflicting biomedical value
- Inappropriate commercial exploitation
    - Vitamins and nutritional supplements
    - Funding i.e. tobacco or alcohol industry
- Conflicting findings
    - Reproducibility

Reproducibility (funding bad science)
- Growing concern about the inability to replicate key scientific findings
    - 90% of some 1,576 researchers surveyed now believe there is a reproducibility crisis in science

How/why does this occur?
- False positive data
    - Low statistical data
    - Poor experimental design
- Trimming and cooking the data
    - Failing to report all the data
- Publish or perish
    - Impact publications
    - Number of publications
- Decreased funding

Translation - from animal models to humans
- Disparate (different) animal species and strains, with a variety of metabolic pathways and drug metabolites, leading to variation in efficacy and toxicity
- Different models for inducing illness or injury, with varying similarity to the human condition
- Variations in drug dosing schedules and regimens of uncertain relevance to the human condition
- Small experimental groups with inadequate statistical power; simple statistical analyses

- Nuances in laboratory technique that may influence results, for example, methods for blinding investigators, being neither recognised nor reported
- Selection of outcome measures, which being surrogates or precursors of disease, are of uncertain relevance to the human clinical condition

Publishing negative data
- Since researchers are engaged in competition for positions and funding, many are choosing not to publish their non-significant findings that have:
  - Less scientific interest
  - Fewer citations
  - Can generally only be published in lesser impact journals
- The amount of non-significant data reported is progressively declining
- Negative findings are a valuable component of the scientific literature because
  - They force us to critically evaluate and validate our current thinking, and fundamentally move us towards unabridged science

10 strategic imperatives
- Research Australia has created 10 strategic imperatives to strengthen health and medical research

1. A healthy and empowered community
2. Encourage giving
3. Research active health services deliver higher quality care
4. Developing implementation science - turning evidence into action
5. Collaborating for success
6. World class research needs world class researchers
7. Funding research
8. Encourage commercial investment in R&D
9. A strategic national approach
10. Reduce red tape

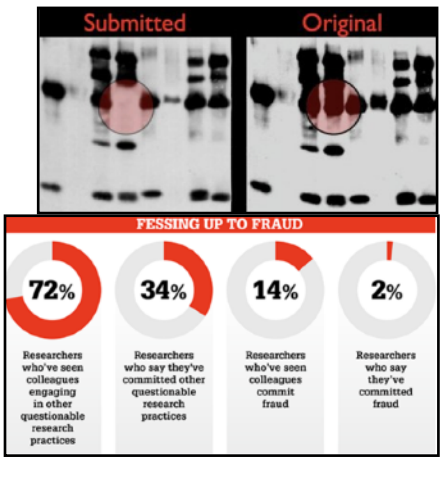
10 strategic imperatives
- It is thought that these 10 Strategic Imperatives will enable us to make better use of the resources to:
  - Contribute to human knowledge and understanding
  - Meet the challenges of an ageing population and using chronic disease
  - Contribute to an efficient and effective health system
  - Boost wellbeing and productivity
  - Create new jobs and prosperity

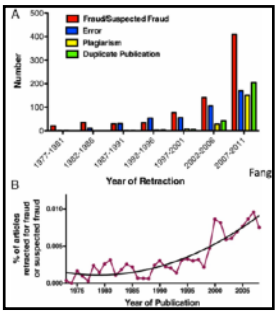
Ethics of Biomedical Research (L3.1)

Definition: Ethics
- Ethics (noun): moral principles that govern a person's behaviour or the conducting of an activity

Research Integrity
- In 2007 the National Health and Medical Research Council, the Australian Research Council and Universities Australia released the Australian Code for the Responsible Conduct of Research.
- The purpose of ***the Code*** is to guide both institutions and researchers by describing what is considered to be the underpinning values of "**good research practice**" and provide institutions with a framework to resolve allegations of research misconduct

Research Integrity
- Plagiarism
- Falsifying/fabricating data
- Duplicating results
- Inappropriate finance management (need to manage funding appropriately)
- Concealing conflicts of interest
- Stealing other peoples research





Increase in publications retractions
- Increasing
- Hard to get funding
- Increased compromised peer reviews

Animal and Stem Cell Ethics (L3.2)

Public opinion about using animals for Biomedical Research
- Overtime, public support is decreasing

Overview of Animal Ethics at Monash
- At Monash there are School or Faculty Animal Ethics Committees (AECs)
- The AECs are the legal committees in Victoria and must **approve each application** to use animals in research and teaching, before the project may commence
- Monash adheres to the Victorian Prevention of Cruelty to Animals Act and Regulations 1986 (the law), and the NHMRC Australian Code for the Care and Use of Animals for Scientific Purposes (8th edition, 2013)

Overview of Animal Ethics at Monash
- By law, and in accord with Code, AECs must have at least one member from each of the following categories:
  - A veterinarian (Category A)
  - An animal researcher (Category B)
  - A welfare member (Category C, ”a person with demonstrable commitment to, and established experience, in furthering the welfare of animals”)
  - An independent lay person (Category D, "an independent person who does not currently and has not previously conducted scientific or teaching activities using animals”)
- Each AEC also has the Animal Facility Manager or an animal technician as a member and the Animal Ethics Officer or Animal Welfare Officer in attendance. The C and D members are not employed by the institution

Justification and Use of Animals
- The three R’s
  - **Reduction**: any strategy that will result in fewer animals being used in research
  - **Refinement**: modification of experimental procedures to minimise pain
  - **Replacement**: methods which avoid or replace the use of animals in research

Animal Ethics Committee
- Committees must consider and evaluate requests to use animals for research or teaching activities on the basis of applicants' responses to a comprehensive set of questions including
  - The justification for the research
  - Its likely impact on the animals
  - Procedures for preventing or alleviating pain and distress
- Experiments are tightly regulated (this includes strict documentation being kept)
- Vets often inspect animals, especially when there is a problem (i.e. sick animals)

Proportion of Animals Used for Studies of Diseases
- Specific to animals diseases (9.19%)
- Human cardiovascular diseases (7.88%)
- Human nervous and mental disorders (20.2%)
- Human cancer (excluding evaluations of carcino hazards) (16.76%)
- Other human diseases (45.97%)

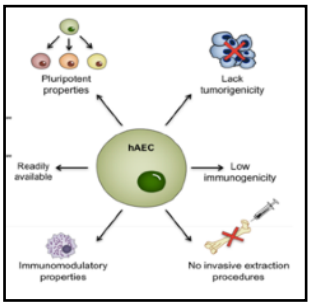
Should we use non human primates for research?
- 2016: Yes (27.27%) No (11.82%) Depends (60.91%)
- 2022: Yes (22.94%) No (5.63%) Depends (70.56%)

Non-human primate research
- Polio vaccine
- Insulin for diabetes

- Coronary bypass surgery
- Hip replacements
- Kidney dialysis and transplants • Organ transplants
- Organ rejection medications
- Medications for
- bipolar disorder
- depression
- Blood transfusions
- Chemotherapy
- Hepatitis B vaccine
- HIV/AIDS medications
- Child lung transplants for cystic fibrosis • Anthrax
- Parkinson's disease treatments
- Prostrate cancer treatments

<u>2014/15 Ebola Outbreak</u>
- Since the 2014 outbreak:
  - >28,000 infected
  - >11,000 deaths

<u>Using Stem cells for Biomedical Research - Is it ethical?</u>
- In Australia, a researcher must obtain a licence from the NHMRC Licensing Committee to use excess human IVF embryos for research, including the derivation of new embryonic stem cell lines
- The two polar views within the community can be summed up by the following statements:
  - Some people regard research on human embryos created by any means, and at any age, as unethical, believing that **human life begins when a human egg gains the ability to form an embryo**
  - Conversely, there are others with the strongly held view that **embryonic stem cells hold the promise of sufficient benefit to human health** to justify the use of human embryos for research purposes
- All research that uses human tissues of any kind must be conducted under the highest ethical standards. This includes:
  - Embryonic stem cells
  - Adult stem cells
  - Induced pluripotent stem cells
- While some forms of stem cells are more widely accepted by the community, they all use donated human tissue and should be subject to the highest level of scrutiny



<u>Amnion Epithelial Cells (hAEC) - adult stem cell</u>
- Pluripotent properties
- Lack tumourigenicity
- Low immunogenicity
- No invasive extraction procedures
- Immunomodulatory properties
- Readily available

Cardiovascular Disease, Stroke and Pulm. Hypertension (W2)

Cardiovascular Disease Prevention (L1.1)

World Heart Vision 2030:

1. Paving the way for cardiovascular health equity
2. Leveraging innovation and technologies for cardiovascular health
3. Fostering timely implantation of knowledge
4. Placing cardiovascular health at the heart of health and climate policies

Cardiovascular Disease (CVD) Health Equity

- Global disparities
- CVD deaths are expected to increase by 4% in high income countries (HICs) between 2020 and 2030 (and by 19% until 2050), but by 44% in low-income countries (LICs) (and by 190% until 2050)
- Healthcare spending distributed unevenly – Africa accounts for 1% of spending but 18% of the total global population
- Approximately ½ worlds population unable to access essential medicines – out of pocket spending 2 x proportionally higher (41 vs 21%) in LICs

CVD Health Equity

- Not a disease of the rich - those with lower SES are more likely to be exposed to risk factors.
- Also, once affected becomes a vicious cycle
- Awareness and literacy
- Access to care
- Minority groups
- Starts before birth
- Research populations

Timely implantation of knowledge

- “I want to talk to you about one of the biggest myths in medicine, and that is the idea that all we need are more medical breakthroughs and then all of our problems will be solved.” - Quyen Nguyen
- Knowledge translation describes the process of transferring evidence from research into clinical practise or policy to ultimately improve patient outcomes
- If it doesn’t occur there are evidence-practise gaps

Barriers to implementation

- What is ‘normal’ (changing norms?) - difference in anatomy and physiology
- Utility of clinical guidelines
- Workforce availability
- Fragmentation
- Policy

Hypertension

- Easy to diagnose, easy to treat, and easy to control
- Worldwide, less than one in two people with hypertension know they have hypertension
- Even less are treated
- Control rates are only about 20%
- This is similar for cholesterol and statin prescription

Detecting heart failure

- Use of AI in cardiac care
- Software analyses patients breathlessness and severity of heart disease
- Via weekly one minute phone call
- Easier and cheaper home monitoring

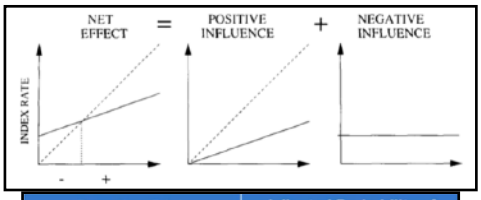
Health and climate

- “The future of health must be built on health systems that are resilient to the impacts of epidemics, pandemics and other emergencies, but also to the impacts of climate change, including extreme weather events and the increasing burden of various diseases related to air pollution and our warming planet” - Dr Tedros Adhanom Ghebeyesus

StaREE Trial (L1.2)

There is usually a long delay before rewards appear

- Prevention in ageing population:
  - Preventive interventions for asymptomatic conditions in older adults may have immediate risks and delayed benefits
  - Increased age, comorbidities and functional limitations are strong risk factors for complications and side effects of interventions, further increasing the chances that prevention would harm rather than help
  - If an older adult's life expectancy is substantially shorter than the time to benefit for a preventive intervention, introducing that intervention may expose them to the immediate risks of the intervention with little likelihood of them surviving long enough to benefit



Net treatment effects

- Net effect = positive influence + negative influence
- Time to benefit and time to harm

Baseline Risk in individuals 66-74 yr	Adjusted Probability of Statin Prescription
Low	37.7%
Intermediate	26.7%
High	23.4%

Cardiovascular Treatment-Risk paradox

- Misconceptions re benefit-harm trade-offs
- Misjudgement re capacity for adherence
- Inattentiveness in setting of multiple diseases

Effects of Statins in Elderly (primary prevention)

- **Pravastatin (40mg)** in the ALLHAT-LLT trial (followed 2,867 people 65 years or older for 6 years) did **not significantly reduce CHD events** (RRR 20%, NS) or **mortality** (increase 15 %, NS).
- **Rosuvastatin (20mg)** in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (followed 5695 people 70 years or older for 2 years) did **significantly reduce MACE** (RRR 39%, p=0.004) but **not mortality** (RRR 20%, NS).
- **Rosuvastatin (10mg)** in the Heart Outcomes Prevention Evaluation (HOPE 3) trial (followed 3086 people 70 years or older for 5 years) did **not significantly reduce MACE** (RRR 17%, NS) or **mortality** (RRR 9%, NS).

Guidelines for older adults

- 2013 ACC-AHA Cholesterol Guidelines, JACC Vol. 63, No. 25, 2014
- No recommendation for statin treatment for primary prevention if >75 years

Uncertain statin benefits in the elderly

- High absolute risk
- Epidemiological studies suggest relationship between TC and CVD is less clear
- Trials have not included sufficient older adults (>70 and >75 yr)
- Trials not consistent and no mortality benefit
- Trials have not included multi-dimensional geriatric assessments
- Underutilisation of statins in the elderly for usual indications

AMI and Heatwaves (L1.3)

Heatwaves

- Ambient heat - whole body heating
- Thermoregulation vs cardiac work
- Dehydration overlay
  - **Decrease** central **blood volume** and **decrease arterial pressure**
  - **Increase red blood cell** count, blood **viscosity**, **neutrophils** and **platelet** counts -> **thrombosis**
  - Increased concentration of blood products -> **increased clotting**
- Additional factors: air pollution, stress, impeded access to healthcare
- Increase in heart attacks on hot days (heatwaves)