THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

MACH Melbourne Academic Centre for Health

Kicking off your research: how to craft a well-defined research question

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- You are welcome to leave your video on or off as you prefer.
- If you have any questions, please feel free to enter them in the chat box. We will review them throughout the presentation.
- Note that this presentation will be recorded. The recording will be available here: **https://machaustralia.org/**

MISCH Hub

- **M**ethods and **I**mplementation **S**upport for **C**linical and **H**ealth research Hub

- Our aim is to provide support to researchers and affiliated researchers of the University of Melbourne in health research.

- We provide support on core research methods of Biostatistics and Clinical Epidemiology, Health Economics, Clinical Trials, Implementation Effectiveness and Co-Design and Health Informatics (REDCap).

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Kicking off your research: where to begin?

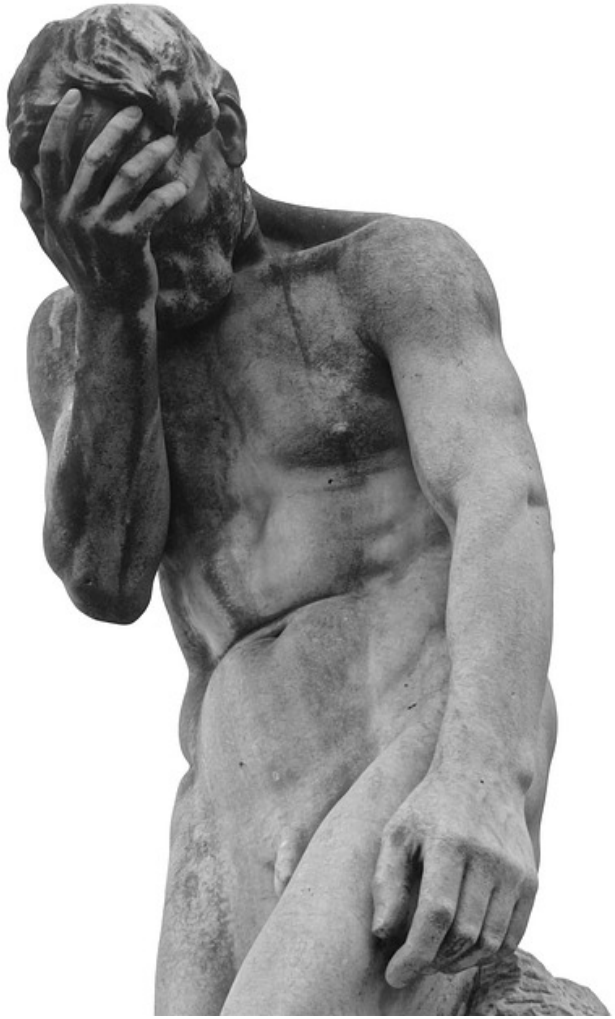
- You have been reading the research literature to try and identify gaps in knowledge
- You find a gap and start developing an exciting research idea
- You want to collect data* to assess the effect of an intervention (or exposure) on a health or behaviour outcome

* or use existing data

Statistics: the science of disappointment?

- We statisticians can often find clients or collaborators become bemused or disappointed when they come to meet with us

- Often this is because they come to us too late in the research process for us to be of greatest use

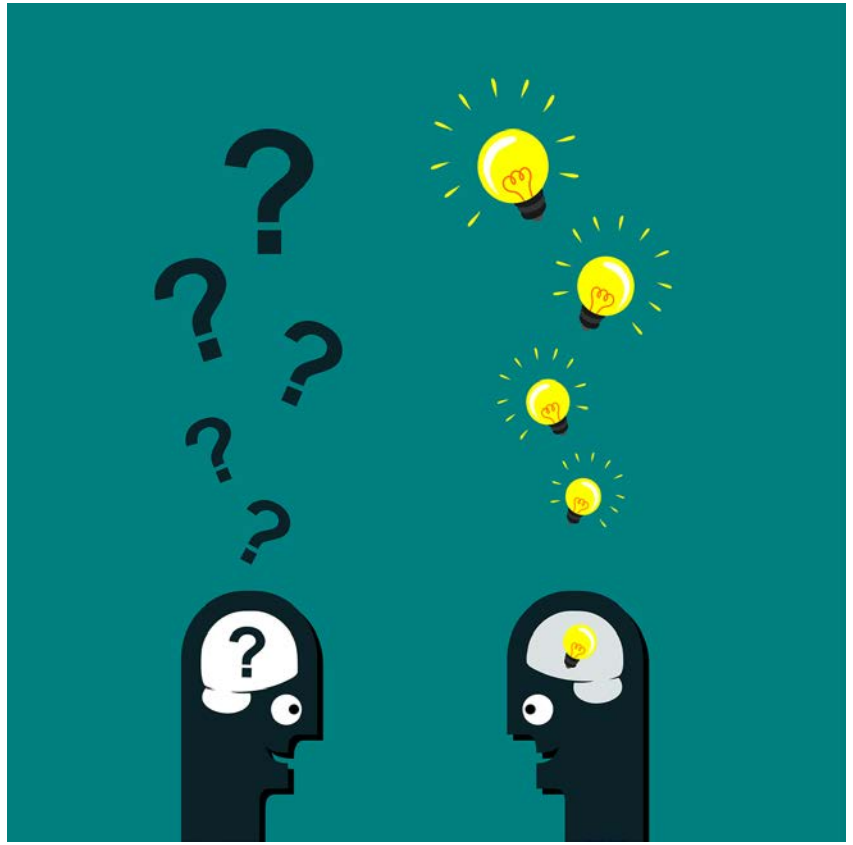


Why statistical thinking is key

- Statistics (and statisticians) are important for the **design**, **conduct**, **analysis** and **interpretation** of study findings.

- Statisticians supporting studies check that the **research plan flows** clearly from the research question and hypotheses to the study design to the methods.

- Refining the research question is critical to ensuring your design is appropriate.



PICOTs

- Consider **PICOTs** to help frame your **research question**
- This helps identify important statistical information to include in your protocol or study plan

Population	Who should be in the study?
Intervention	Intervention/Exposure
Comparator	Control
Outcome	What is the outcome of interest?
Time	Over what time period?
(**s**tudy design)	Study design features (e.g. parallel-group)

Population/Participants (PICOTs)

- It is important to clearly state **who** will be taking part in the study.
- Are the **participants appropriate** to answer the research question? For example, adults aged 65 years and over will be recruited as the health condition is common in this age group.
- How will participants be **selected** or **recruited**? For example, a random sample from the population or all patients presenting to a particular hospital ward during a pre-defined period of time.
- What are the **inclusion/exclusion** criteria?

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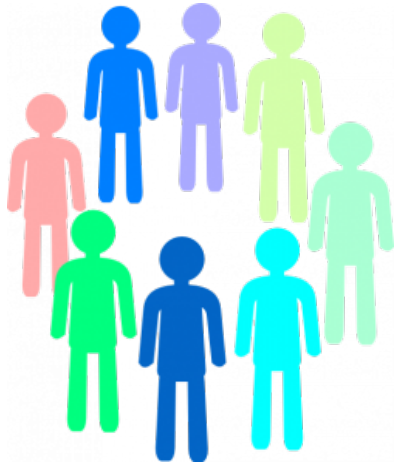
Population/Participants (PICOTs)



- Thinking about the **number of participants** is critical when thinking about your population for your research study
- **Sample size calculations** are key and are typically looked for in ethics submissions and grant applications for research studies
- Many studies are too small meaning estimates are imprecise and it is not possible to detect important public health or clinical associations
- Underpowered research is unethical
- Studies with insufficient sample size are a waste of limited research resources

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/describ.htm#intro

Quiz: Population/Participants

- A researcher comes to you with the following research question:

"In children with acute otitis media, is cefuroxime effective in reducing the duration of symptoms compared to amoxicillin?"

QUESTION: What is the population of interest?

A. Children

B. Children with acute otitis media

C. Children with acute otitis media receiving cefuroxime

Aslam (2010) Formulating a researchable question: A critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS 31(1): 47-50.

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Quiz: Population/Participants

- A researcher comes to you with the following research question:

"What is the effect of dexamethasone on organ failure in COVID-19 patients?"

QUESTION: What is the population of interest?

A. Patients

B. Patients with COVID-19

C. Patients with COVID-19 and organ failure

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Population/Participants (PICOTs)

- While a **sample size calculation** should be provided to justify that sufficient numbers will be available, it is important to consider whether these numbers can be recruited.

- Think about how many patients or subjects you will **invite** to participate and how many you **expect** to take part.

- The **sample size** is the number who **agree to participate**, not the number invited.

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Sample size calculations – what NOT to do

"A previous study in this area recruited 150 subjects and found significant results (p=0.014), and therefore a similar sample size should be sufficient here."

- This does **NOT** mean the prior study was sufficiently powered!
- This could be a chance finding.
- Sample size calculations must be calculated for your specific study and the effect you wish to detect.

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/size.htm

Sample size calculations – what NOT to do

- This is something statisticians commonly hear when working with researchers.
- It is important to make a concerted effort to find prior relevant published information.
- Alternatively, a small study could be conducted to obtain the required information.
- General sample sizes can still be undertaken if some information (e.g., standard deviation of the outcome) is not available.

"Sample sizes are not provided because there is no information on which to base them."

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/size.htm

Sample size calculations – what NOT to do

"The throughput of the clinic is around 50 patients a year, of whom 10% may refuse to take part in the study. Therefore over the 2 years of the study, the sample size will be 90 patients."

- This is valuable information to include in your grant and helps highlight the **feasibility** of the study being undertaken.
- It does **NOT** mean your study will be **powered**. Underpowered studies are a waste of resources and are unlikely to get funded.
- A sample size calculation is required to determine the power to detect differences of interest.
- If the sample size is too small, you may want to extend the study length or collaborate with other centres.

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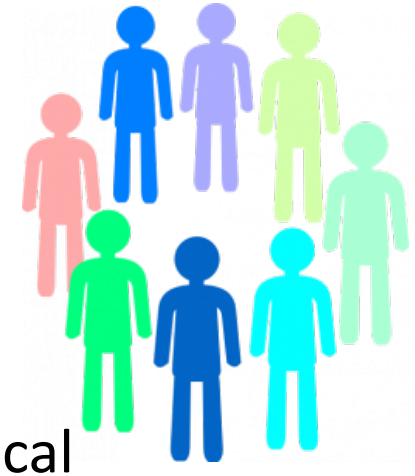
Population/Participants (PICOTs)



- If designing a prevalence study to estimate the **prevalence** of a particular disease, condition or characteristic in a population, it is critical to highlight how you will ensure the sample will be **representative** of the population of interest.

- Poor **response rate** could bias the study so highlight how the study will be conducted to ensure a good response rate.

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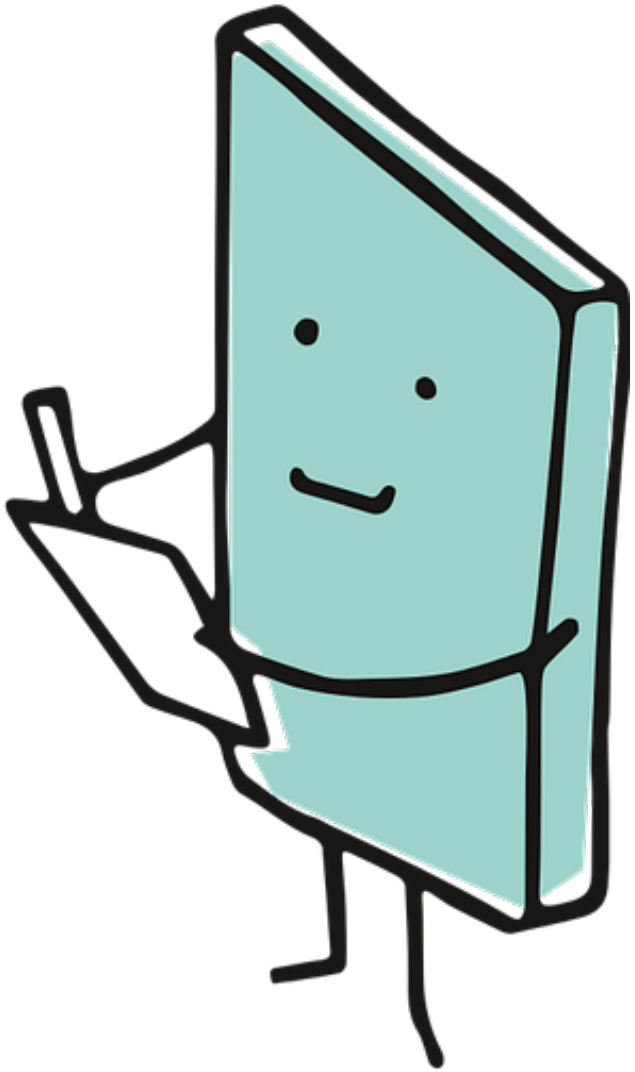
The data (PICOTs)

- Study quality can depend on how data are collected.
- It is important to think carefully about how this information will be obtained and clearly specify this in your study plan.
- How will your data be **measured** (e.g., questionnaire, blood test)?
- If a questionnaire is used, how will it be administered (e.g., postal or interviewer administered)?



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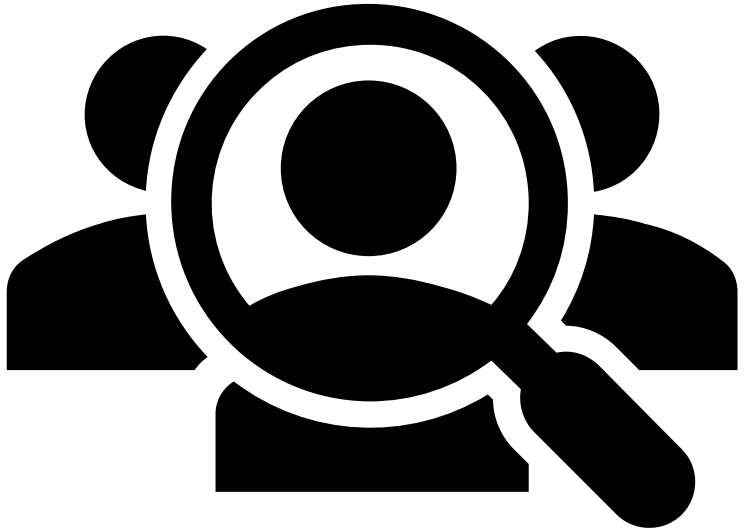
The data (PICOTs)

- What data are you collecting and why?
- What is your **intervention** or **exposure**?
- What is your **comparator** (if appropriate)?
- What is your **outcome** variable?
- Are there other important variables (e.g., strata, confounders)?



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Outcome and exposure variables

- **Outcomes** (or dependent variables) are the variables we want to know more about
- **Exposures** (or independent variables) are the variables we think might explain the variation in the outcomes (e.g., treatment group in a randomised controlled trial)
- Statistics quantifies the association between outcomes and exposures

The data (PICOTs): trials

- It is common to propose only one key outcome for a trial, although some may have another key outcome of interest.
- This outcome is known as the **primary outcome** or **primary endpoint**.
- The sample size calculation should be conducted for the **primary outcome** (or outcomes if more than one primary is specified).
- The statistical analysis section in your study plan should make it clear how the primary outcome will be analysed.

The data (PICOTs): observational studies

- Some observational studies only have a single outcome of interest (e.g., depression, time to death, birthweight)
- However, you may have **multiple outcomes** of interest in an observational study, particularly if an exploratory study.
- It is important to think about how (and why) all of the outcomes will be measured (used) and defined
- Beware that conducting multiple tests on the same data set leads to a higher chance of **Type I error**.

Type I error: False Positives

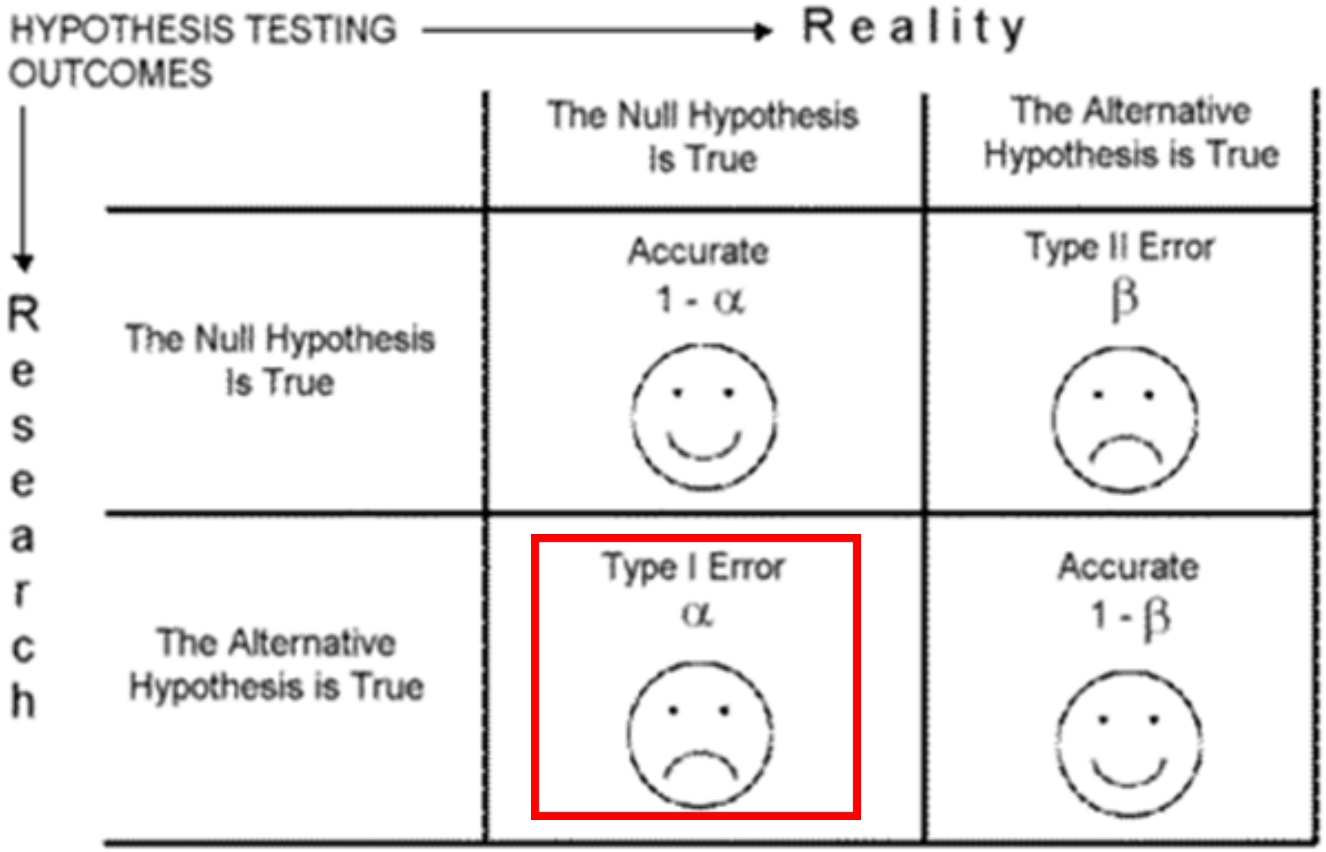

Image source: https://allpsych.com/stats/unit4/26-2/

Quiz: Outcomes

- A researcher comes to you with the following research question:

"In children with acute otitis media, is cefuroxime effective in reducing the duration of symptoms compared to amoxicillin?"

QUESTION: What is the outcome in this study?

A. Acute otitis media

B. Acute otitis media symptoms

C. Duration of acute otitis media symptoms

Aslam (2010) Formulating a researchable question: A critical step for facilitating good clinical research. Indian J Sex Transm Dis AIDS 31(1): 47-50.

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Quiz: Outcomes

- A researcher comes to you with the following research question:

"What is the effect of dexamethasone on organ failure in COVID-19 patients?"

QUESTION: What is the outcome in this study?

A. Organ failure

B. COVID-19

C. Dexamethasone

Quiz: Outcomes

- A researcher comes to you with the following research question:

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QUESTION: What is the outcome in this study?

A. Organ failure

B. COVID-19

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The data (PICOTs): trials

- The type of treatment may have implications for the trial design so it is important to be clear about this (e.g., blinding may not be possible depending on treatment type).

- To determine the effect of a new treatment, it is necessary to compare a group of participants on the new treatment with a group of participants who do not receive the new treatment (the **control** or **comparator**).

- The control group should be comparable to the treated group in all respects (i.e., in the **same place**, at the **same time**, **same distribution of disease severity and prognosis**, and receiving the **same care apart from the treatment** of interest).

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/trials.htm

The data (PICOTs): trials

- There usually is a clear idea of what the new intervention or treatment will be when designing a study.
- However, choosing the **control** or **comparator** group can be challenging.
- If no current treatment is available to compare to the new treatment then the control group will be untreated (a placebo could be used to maintain blindness).
- If there is an existing treatment, you may decide to test the new treatment in addition to an existing treatment while the control group receive only the existing treatment (with a suitable placebo in addition where appropriate).

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/trials.htm

The data (PICOTs): observational studies

- Rather than an *intervention*, we typically think of **exposure(s)** in observational studies.

- Exposure variables can take different forms.

- For example, in an observational study of smoking and lung cancer, smoking could be **binary** (e.g., smoker or non-smoker), **categorical** (e.g., smoker, ex-smoker, non-smoker) or **continuous** (e.g., cigarettes smoked per day).

- It is important to be clear on the form your exposure(s) will take. This is important for your sample size calculation and can have an impact on your statistical analysis.

St George's University of London 'Statistics Guide for Research Grant Applications' https://www-users.york.ac.uk/~mb55/guide/trials.htm

Quiz: Intervention/Exposure (I)

- A researcher comes to you with the following research question:

"In children with acute otitis media, is cefuroxime effective in reducing the duration of symptoms compared to amoxicillin?"

QUESTION: What is the intervention or exposure in this study?

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B. Amoxicillin

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A. COVID-19

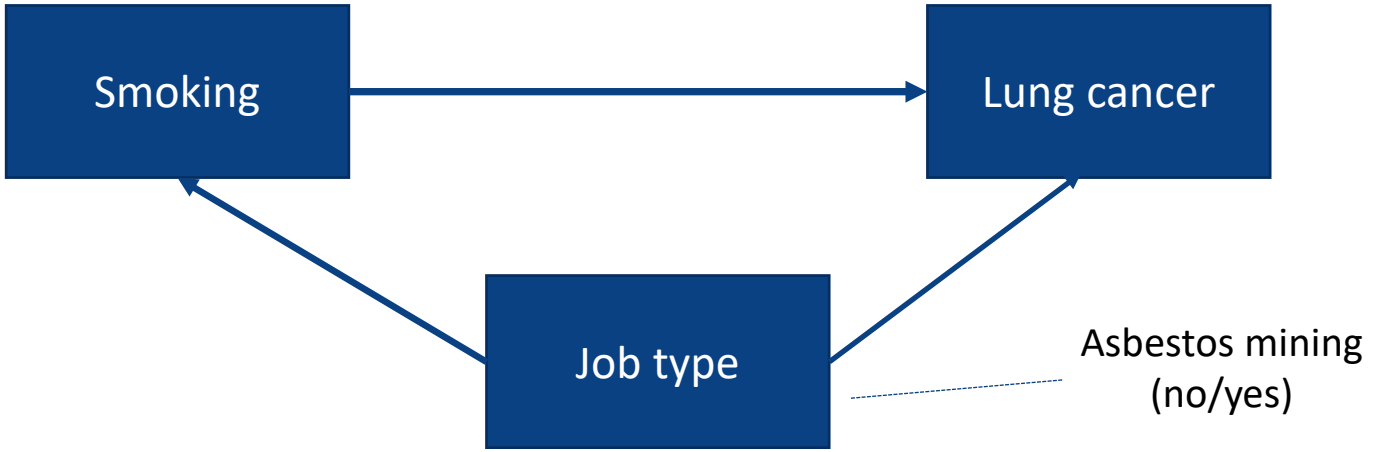
B. Dexamethasone

C. Organ failure

The data (PICOTs): observational studies

- In addition to the outcome and exposure, it can be important to consider **confounders** in observational studies.

- A confounder is an alternative explanation for an observed association between an exposure and outcome. Confounders are undesirable as they obscure the 'real' effect of an exposure.



- Asbestos mining is a known risk factor for lung cancer
- Smoking is a risk factor for lung cancer
- Miners tend to smoke more cigarettes due to job stress

Rothman (2008) Modern Epidemiology (3rd Edition) Lippincott Williams & Wilkins; Skelly (2012) Evid Based Spine Care J 3(1): 9-12

The data (PICOTs): observational studies

- When planning an observational study it is important to think about potential confounders.
- What confounders could influence the exposure and outcome relationship?
- If you have multiple possible exposures and multiple possible outcomes, confounders can differ dependent on the relationship under study.
- How will confounders be measured and how and when will this information will be collected?
- How will the statistical analysis take into account these potential confounders?

The data (PICOTs)

- What is the **data type** (e.g., continuous, ordinal, categorical)?
- This should be specified for both the **outcome** and the **exposure** (where appropriate)
- This information is critical to inform both the **sample size calculation** and how the **statistical analysis** should be conducted.

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Time (PICOTs)

- When will you be collecting the data?
- Most randomised controlled trials and cohort studies are prospective so participants will be followed over time.
- Considering the length of follow-up of participants is critical when thinking about the feasibility and cost of undertaking your study.
- Need to clearly specify **how many** measurements will be taken over the course of the study and how often measurements will be taken.
- What is the **primary time-point** of interest?

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Time (PICOTs)

	Baseline	Day 1 of every 3 week treatment cycle	Every 9 weeks on treatment	At 18 weeks or on stopping chemotherapy	Follow-up visits at 6 and 12 weeks post treatment, then at least every 12 weeks
History and examination	x	x		x	x
Weight	x	x		x	x
Vital signs	x			x	x
Haematology	x	x		x	x
Biochemistry	x	x		x	x
Urinary pregnancy test	x				
Tumour response	x		x	x	X (and every 12 weeks until progression)
Blood samples for predictive markers[§]	x		x (week 9 only)		
Concomitant medication	x	x		x	x
Administer chemotherapy		x			
QOL questionnaire	x		x	x	X (12 weeks only)
Adverse event monitoring		x		x	x

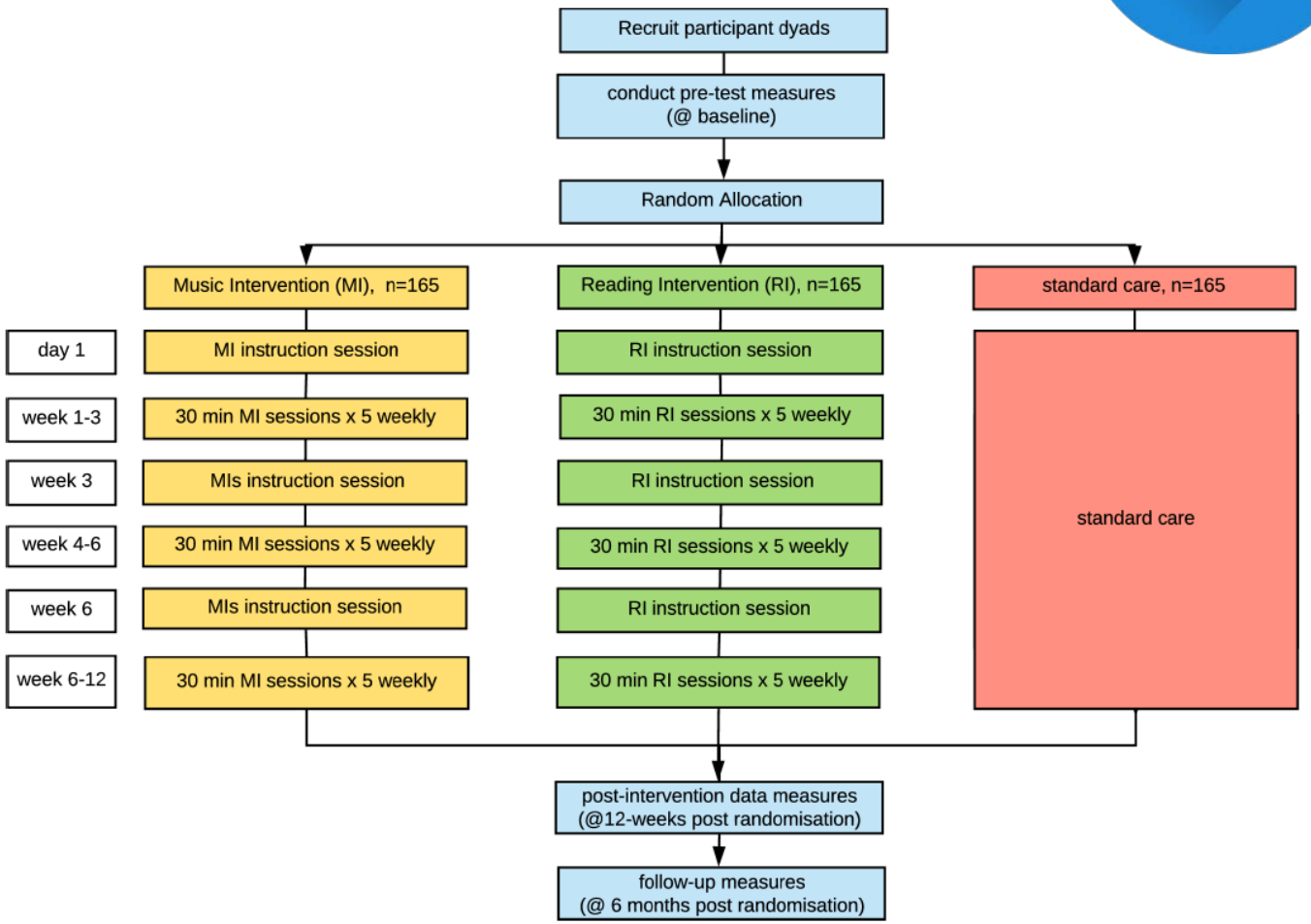
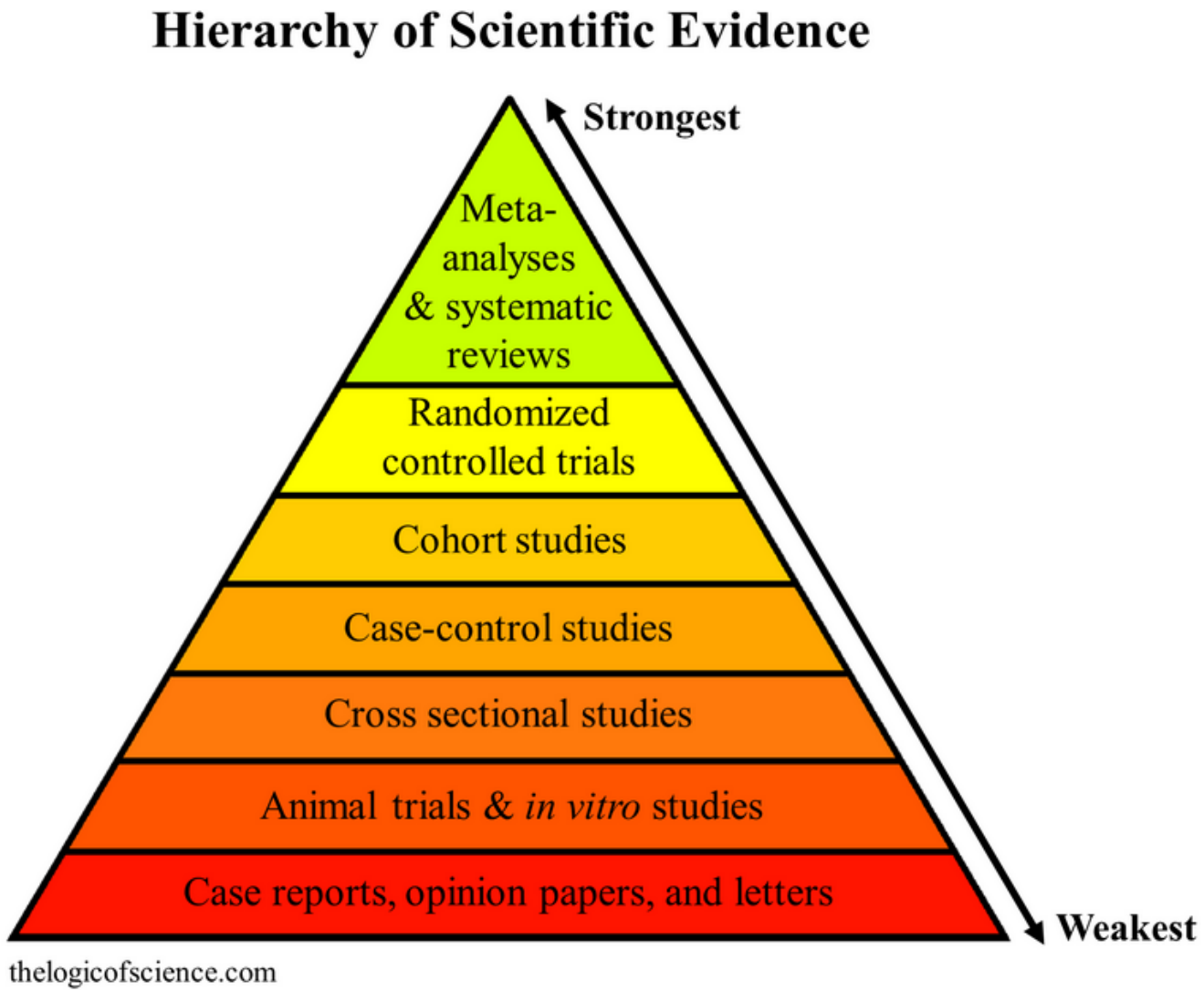


Figure 2 HOMESIDE illustration of study design.

Table: MISCH Statistical Analysis Plan template, copied from https://www.cuh.nhs.uk/document-library/cctu-standard-operating-procedures-sops. Figure: Baker (2019) BMJ Open 9: e031332

Study design: hierarchy of scientific evidence



Study design (PICOTs)

- The **study design** is not officially part of the PICO (or PICOT) framework but it is critical to consider the appropriate design to answer your research question.

- For example, if you want to determine if a new drug is effective in lowering cholesterol you should consider undertaking a randomised controlled trial.

- Alternatively, if you want to know what factors are linked to increased risk of breast cancer, you should consider an observational study.

Pilot and exploratory studies (PICOTs)

- While funding may be sought for pilot or exploratory studies, it is important to be clear on what these studies are seeking to determine and why a fully powered study cannot be conducted at this stage.
- A pilot study is a small study designed to gather information prior to a larger study.
- A well-designed pilot study should improve the quality of the final study.
- Importantly, a pilot study is **NOT** a study which is too small to provide an answer to the research question.

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Pilot and exploratory studies (PICOTs)

- Exploratory studies may be necessary when research ideas are at a preliminary stage.
- For example, a full scale study could require many different hospitals but preliminary data is required from a single hospital before other hospitals will be willing to participate.
- Alternatively, there may be insufficient information to design a definitive study if no one has considered the research question at all.
- A smaller study can be conducted to explore the research question.

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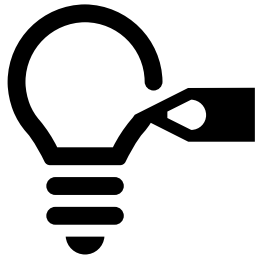
Study design (PICOTs)



- It is essential to consider the methods proposed to tackle the research question in sufficient detail to ensure the study is feasible.

- If submitting your research proposal for ethical review or to seek grant funding, you must show that the question under investigation is important but that it is also **methodologically sound** and **feasible**.

- The topics to consider depend on the nature of the study.

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Study design (PICOTs)

- There are many elements to consider when thinking about the study design.
- If a randomised controlled trial will be used, will the study be **blinded**?
- Blinding refers to the **concealment of treatment allocation** for one or more individuals in a clinical research study.
- The best strategy to minimise bias in trials is to blind as many people as possible (e.g., participants, clinicians, data collectors, outcome assessors, data analysts).

Karanicolas (2010) Blinding: Who, what, when, why, how? Can J Surg 53(5): 345-358.

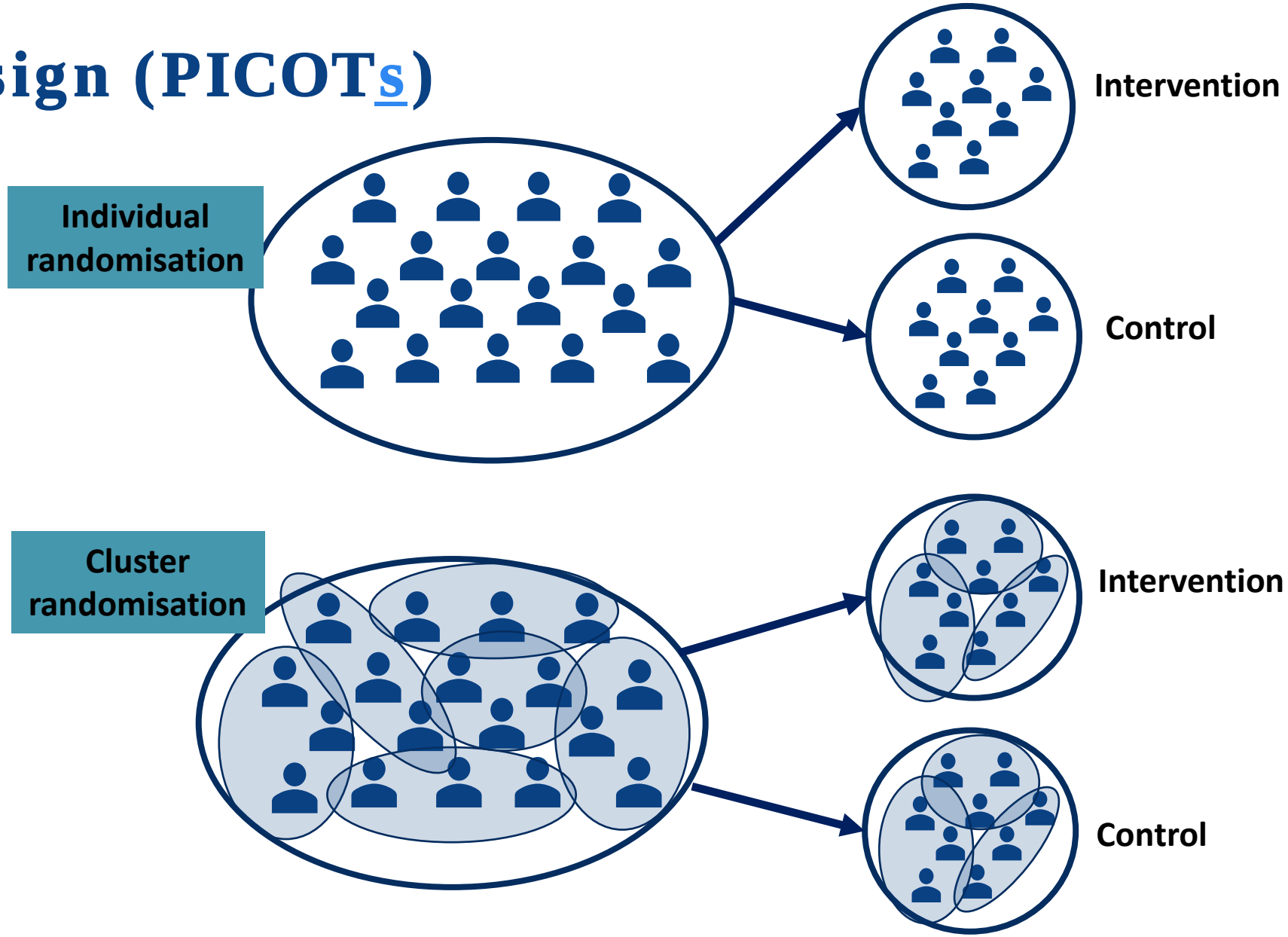
Study design (PICOTs)

- Although blinding reduces bias in estimating the treatment effect but it may not be possible to have a **double blinded** study.
- In a double blinded study, both participants and assessors are blinded.
- However, participant blinding would not be possible if comparing a new surgical intervention to an existing non-invasive treatment, for example.

Study design (PICOTs)

- Can the treatment be allocated at an **individual** or a **cluster** level?

- For example, a trial designed to improve the physical activity of children using active lessons would allocate treatment at a class or school level rather than an individual level.



Ensure sufficient time for statistics!

- It is important to think about the statistics as early as possible in the planning stage.
- Statisticians can assist with framing the research question(s) and identifying the best design.
- This can take time!

Finally…

- This seminar gives a taste of important considerations when starting off in health research.
- If you want to learn more, you may find the research methods training courses at the Murdoch Children's Research Institute useful.
- The cycle of three courses begins with ***Designing Your Research Study*** which will run online across two half days **1st – 2nd March 2022**. This course for new or aspiring researchers goes into further details about refining research questions, research design and drafting an analysis plan, among other things.
- Interested? You can find out more and register here: **https://www.mcri.edu.au/research/facilities-resources-and-training/cebu-short-courses-and-training/quantitative-research-0**

THE UNIVERSITY OF MELBOURNE

Faculty of Medicine, Dentistry and Health Sciences

MACH Melbourne Academic Centre for Health

Thank you

- Recording:- https://machaustralia.org/
- MISCH Newsletter:- https://clinicalresearch.mdhs.unimelb.edu.au/collaborate/contact-us/misch-newsletter-sign-up
- Website:- https://clinicalresearch.mdhs.unimelb.edu.au/
- Email:- misch-info@unimelb.edu.au