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How to design a good research study: a guide for medical students

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Good research does not happen by chance. It requires detailed planning to ensure that it is worthwhile and contributes to the sciencific literature. Good research design depends on utilising the optimal methodology and study type for the research question. This article will clarify the steps that need to be undertaken to ensure one's research is of good quality and high impact. A good understanding of the terms used in this article will equip you well for theacademic foundation programme interview process.

This article will include:

- Description of different study types and their various advantages and disadvantages
- Explanation of the concept of levels of evidence in research
- Advice on how choose a suitable research question and outcome measures
- Clarification of the differences between internal and external validity
- An introduction to fundamental research concepts such as power and bias

What different types of research study are there?

There are various forms of research study. A *primary* research study is one that generates new data about a specific research question. A *secondary* research study is one carried out using existing data from previous research studies. The main types are summarised below with a brief description and an example.

Primary studies

1. **Randomised controlled trial (RCT):** A study in which participants are randomly allocated into different treatment groups that receive different interventions. Classically one group receives a new intervention (which is being evaluated) and the other group receives either the current gold standard or a "placebo". The participants are controlled in that they are made as similar as possible in terms of important clinical details. A defined outcome measure over a set period of time is used to compare the effect of the different interventions.

Example: Obermair, Andreas, et al. "Improved surgical safety after laparoscopic compared to open surgery for apparent early stage endometrial cancer: results from a randomised controlled trial." *European Journal of Cancer* 48.8 (2012): 1147-1153.

Advantages	Disadvantages
• Rigorous evaluation of a single variable in a specifically defined group of patients • Minimal bias due to comparing 2 identical groups	• Expensive • Time consuming

Fact: The first ever RCT was carried out by James Lind in 1747 [1]. Lind selected 12 men from the ship HMS Salisbury, all suffering from scurvy, and divided them into two groups, one on the basic diet and one receiving citrus fruits in addition to the basic diet. Those fed citrus fruits (rich in vitamin C) experienced a remarkable recovery and famously he discovered the cure for scurvy.

2. **Cohort study:** A study in which two groups are followed over a set period of time, with each being exposed to different variables. A defined outcome measure is used to compare the effect of the different exposures.

Example: Hubert, Helen B., et al. "Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study." *Circulation* 67.5 (1983): 968-977.

Advantages	Disadvantages
• When investigating rare exposures • Prospective and therefore is not subjected to recall bias *(see Types of Bias section)*	• Requires large patient populations • Difficult to prove causation • Time consuming and expensive

3. **Case control study:** A study where participants with different clinical outcomes are analysed retrospectively to see what previous exposures are different between the groups. Any difference in exposure is presumed to have led to the change in clinical outcome i.e. causality is assumed.

Example: Yusuf, Salim, et al. "Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study." *The Lancet* 364.9438 (2004): 937-952.

Advantages	Disadvantages
• Quick and cheap • When investigating rare conditions	• Recall Bias • Difficult to prove causation

4. **Case series and case reports:** A case report is a description of a single case that reveals a novel finding that will contribute to the current literature. A case series is when numerous cases are used.

Example: Saw, Jacqueline, et al. "Spontaneous Coronary Artery Dissection in Patients With Fibromuscular Dysplasia A Case Series." *Circulation: Cardiovascular Interventions* 5.1 (2012): 134-137.

Advantages	Disadvantages
• Quick and cheap • Can identify new clinical issues and may lead to development of hypotheses	• Subject to bias • Depend on the availability and accuracy of data records

Secondary studies

An advantage of secondary research is that it can be done relatively quickly as there is no need to generate new data through experimentation [2]. Additionally, previous studies are now easily accessible and large amounts of data can be used to provide statistically reliable results. Nevertheless disadvantages include the fact that the data might not be up-to-date and previous research might not have covered the same research question as you. There are two main types of secondary research study:

i. **Literature review:** A body of text that aims to review the critical points of current knowledge in the scientific literature related to a particular topic. This is often undertaken prior to commencing a research project to best evaluate current understanding and to identify any unsolved questions in the field.

Example: Chevalier, Z., P. Kennedy, and O. Sherlock. "Spinal cord injury, coping and psychological adjustment: a literature review." *Spinal cord* 47.11 (2009): 778-782.

ii. **Systematic review:** an extensive summary of the literature relevant to a defined research question. The literature is taken from a particular point in time and a specific set of inclusion and exclusion criteria are defined. The results of various different studies are compared and an answer to the research question evaluated.

Example: Palacio, Santiago, et al. "Effect of Addition of Clopidogrel to Aspirin on Mortality Systematic Review of Randomized Trials." *Stroke* 43.8 (2012): 2157-2162.

iii. **Meta-analysis:** Statistical method of combining the results of several studies that address a set of related research hypotheses. It is the statistical element that characterizes this type of study, epitomised by a *forest plot* diagram that shows how the main findings in the seminal studies compare.

Example: Parikh, Manish, et al. "Surgical strategies that may decrease leak after laparoscopic sleeve gastrectomy: a systematic review and meta-analysis of 9991 cases." *Annals of Surgery* 257.2 (2013): 231-237.

What is the Evidence-Based Pyramid?

In the academic field it is common wisdom that not all scientific studies are equal in terms of the impact of their results. For instance, a systematic review of randomised controlled trials carries more weight that a sole case series. This represents the notion of a hierarchy of evidence and the *evidence-based pyramid.*

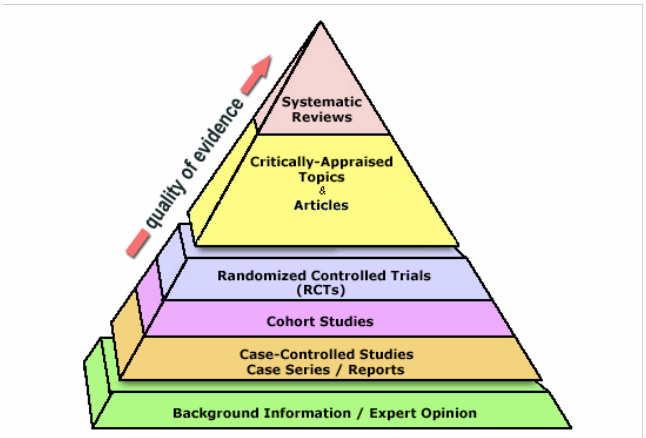

Figure 1. The evidence-based pyramid

The higher up the pyramid a study type is, the better quality of evidence it is thought to offer. Therefore a study type at the top is described as having a higher level of evidence than study types near the bottom. Nevertheless, all studies have their place in the literature though and help guide the next research in the field. For instance, a case report can spark an idea for a cohort study, which in turn might justify a RCT that might possible feature later in a systematic review.

Deciding the research question and outcome measure

In the early stages of designing a study one must identify what the research question is i.e. what question you plan to answer through conducting the research. For research to be worthwhile, the research question must add to the literature in some way. This can happen in different ways, such as by adding new knowledge to the literature or by disputing current theories in the literature. The best way to identify a worthwhile research question is to undertake a literature research to identify "gaps" in the literature and therefore determine ways in which one's research will enhance the scientific community of the research topic. *Confirmatory* research aims to prove or disprove a hypothesis in the literature whereas *exploratory* research aims to generate new hypotheses. Thus exploratory research collects data that in turn leads to new hypotheses whereas in confirmatory research a current hypothesis is evaluated and either accepted or rejected [3].

Another crucial factor to decide when undertaking research is the variable that will be measured and used as the output of your research - this is referred to as an outcome measure. Research can be broadly divided into:

i. *Qualitative* studies: research not using numerical data but providing non-numerical output e.g. surveys

ii. *Quantitative* studies: research that generates new numerical data. Generally quantitative studies are preferred as they allow direct comparisons in results between different studies.

The primary outcome measure of a study focuses on the most important question being asked by the research, typically whether the new intervention leads to less disease-related death than the current gold standard. Secondary outcome measures are also often used and their purpose is to address any other relevant questions related to the intervention, such as was there a reduction in disease measures other than death.

Ideally the outcome measure of a research study will be clinically relevant. For example, a study that uses a reduction in the level of an enzyme with an unproven function to justifying the use of one intervention over another provides results of uncertain clinical significance. Indeed the study demonstrates a reduction of the enzyme but the clinical implications of this are not known and therefore the value of the study is limited. Such an outcome measure is referred to as a *surrogate* endpoints, which are defined as " physiological or biochemical markers that can be relatively quickly and easily measured, and that are taken as being predictive of important clinical outcomes" [4]. It is preferable to use clinically significant outcome measures such as mortality rate as the effect of the intervention is investigated in terms that have obvious clinical implications.

Also, the outcome measure largely determines what statistical analysis should be performed. Generally authors should state what their outcome measure is and what statistical analysis will be used. When critically appraising a study, if a different statistical analysis is used to the one outlined in the methods section then the credibility of the results is called in to question. This can indicate that the authors are trying to "manufacture" a finding and consequently any deviation from the methods section must be justified.

What is Internal Validity?

Internal validity refers to the ability of the study to ensure the results it yields are not due to bias or confounding. It is a desirable property as it indicates the extent to which a causal relationship can be assumed from the intervention and the outcome.

Types of Bias

Bias refers to a systematic deviation from the true value [5]. There are numerous types of bias that can affect research, which are outlined in the table below:

Type	Description
Selection bias	Results from differences are present between the groups in terms of baseline characteristics
Recall bias	Results from the fact that a patient is more likely to recall an exposure if it has a harmful effect. This is pertinent in case control studies.
Publishing bias	Results from the fact that studies that show a positive findings are more likely to get published and disseminated in the literature
Analysis bias	This refers to a situation when On Treatment (OT) analysis is used instead of Intention To Treat (ITT) analysis [6]. OT analysis analyses patients by what group they actually end up in at the end of a study. ITT analysis considers participants by what group they were in initially despite of whether they changed group or dropped out of the study. Potential bias is avoided with ITT because of the fact participants who change groups might be systematically different from those who complete the study e.g. might have refractory disease or unacceptable side effects
Treatment bias	Results from the fact that in a research study patients are often treated differently to how they are in actual clinical practice. For instance, the more frequent check-ups and clinical monitoring that occur in research might lead to better outcomes than in clinical practice.

Confounding

A confounding factor is something that is related to both the dependent variable and the independent variable [7]. In order for the confounder not to influence the results, the confounder must be controlled between the two research arms. This is achieved through inclusion criteria in RCTS and cohort studies and matching in case controls. Failing to control confounding factors can lead to misinterpretation of the findings and incorrect conclusions. For instance, a study might show that people who carry gas lighters are more likely to develop lung cancer. However, this does not mean that it is the gas lighter leading to lung cancer. Rather, as is well documented, it is the act of smoking (the confounder in this case) that is responsible for the association.

What is External Validity?

External validity refers to the extent to which a study's findings can be generalised to other patient populations in actual clinical practice [8]. For strong external validity to be present the characteristics of the study population must be similar to the actual population. Indeed if the study population reflects the majority of general population then the results of the study can be thought to apply to larger general practice within the community. However, if the study population differs in certain ways, such as age or

degree of comorbidities, then applying teh resukts to the larger general population is unjustified - indeed such a study would have poor external validity. The aim of translational research is to impact on clinical practice and in order to do this it must demonstrate strong external validity, meaning that it the study reflects the true state of affairs outside of the research setting.

Other considerations when designing a research study

a) Financies and time scale

Research should ideally take place for the smallest amount of time required to observe a difference in the outcomes between different groups. It is undesirable and unethical to have research that does not last long enough for a treatment effect to be observed. On the other hand, it is unethical to have research studies lasting unnecessarily long and depriving one group of patients of a superior intervention. This is why some trials end early if a clear difference in efficacy can be seen between interventions.

b) Pilot studies

A pilot study is a relatively small scale preliminary study conducted prior to a full-scale research project [9]. There are various reasons why pilot studies are carried out with common reasons including:

- to provide proof of concept and to evaluate time and cost
- to test the feasibility of the methodology
- to ascertaining tolerability of the patients to the intervention and to evaluate adverse events

c) Statistical power

A power calculation is used to determine the amount of participants required in a study to have a certain likelihood of getting a defined statistically significant result of clinical significance [10]. Often it is calculated following analysis of the results of a pilot study. Power calculations help design research that is likely to show a difference if indeed a difference between interventions does exist. Indeed such analyses prevent unnecessarily large patient groups being entered to studies when smaller groups would suffice.

d) Ethical Approval

Unethical research is a thing of the past. The Declaration of Helsinki and the Nuremberg code mean that modern day research has a strong ethical code with the upmost respect of human participants. Permission from a research ethics committee is required before commencing a research study using humans participants to ensure the rights and well-being of human participants is not compromised. Additionally, the actual researchers themselves need to have taken the Good Clinical Practice (GCP) course to be allowed to participate in research using humans.

In summary:

- Good quality research relies on a meticulous and careful design process
- Different study types exist, each with their own advantages and disadvantages and *level of evidence*
- Determining the optimal methodology requires an understanding of outcome measures and the threats to internal validity (bias and confounding) and external validity

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10. Lieber, R. L. (1990). Statistical significance and statistical power in hypothesis testing. *Journal of Orthopaedic Research*, *8*(2), 304-309.

Figure 1: Available at: http://www3.mdanderson.org/library/evidence-based/pyramid.html. Last accessed (19/09/13)

Suggested external resources:

- Trisha Greenhalgh. *How to Read a Paper: The Basics of Evidence-Based Medicine (4th Edition)*. Wiley-Blackwell, 2010.