

Module 3 – Study Designs I



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Overview

Introduction

There are many different ways to conduct research. Most research questions could be answered with several different study designs. However, each design has advantages and disadvantages. Your choice ultimately becomes a trade off between good science and feasibility. It is possible to classify these different approaches into classes of design. While there are different names for the designs depending on which text you read, there are three basic premises:

- How the control group (if any) is formed
- Whether or not the investigators have control over the allocation of subjects
- Whether the data will be collected prospectively or retrieved from the past.

This module will show you how to answer questions which are exploratory or hypothesis testing using three common study designs: randomized clinical trial, cohort study and case control study. Descriptive studies, whether qualitative or quantitative, will be covered in module 4.

Objectives

To understand the different architectures of study design and to decide which is the most appropriate for each type of question. At the end of module 3, you will be able to:

- Recognise the differences between the study designs, cohort, case-control and randomized clinical trial.
- Identify potential biases (systematic errors) inherent in each design
- Understand the effect of different biases on the outcome and interpretation of the study
- Decide which design is the most efficient and feasible for your question(s)

Key Concepts

- Cohort Study
- Case control study
- Randomised clinical trial
- Potential biases for each design
- Feasibility – size of study, availability, time and cost
- Flow charting software

Activities

- With your question in hand look at the three designs to see which (if any) would answer your question.
- Assess the strengths and weakness of each design
- Assess and write down potential biases
- Assess the feasibility of the study design you have chosen
- Assess the sample size and the availability of subjects
- Assess the potential cost and time taken to conduct the study

Quick Links

- Hulley SB, Cummings SR. “Designing Clinical Research: An epidemiological approach
- Centre for Health Evidence: “Users’ Guides to Evidence Based Practice” www.cche.net/usersguides/main.asp
- Guide to Research Designs: <http://library.downstate.edu/ebm/2toc.htm>
- Flow-charting Software: <http://www.inspiration.com/freetrial/index.cfm>
- CASP Statements: http://www.phru.nhs.uk/casp/critical_appraisal_tools.htm
- CONSORT Statement: <http://www.consort-statement.org/Downloads/download.htm>

Highlighted Tools

- Flow-charting Software: Inspiration™
- CASP Statements
- CONSORT Statement

Module 3: Study Designs I

Background

There are many different ways to conduct research and most questions could be answered with several different designs. However, each design has advantages and disadvantages, and the choice ultimately becomes a trade off between good science and feasibility. It is possible to classify these different approaches into classes of design. While there are different names for the designs depending on which text you read, there are three basic premises:

- How the control group (if any) is formed
- Whether or not the investigators have control over the allocation of subjects
- Whether the data will be collected prospectively or retrieved from the past.

This module will concentrate on the three most common classes of design for answering questions which are exploratory or hypothesis testing. Descriptive studies, whether qualitative or quantitative, will be covered in module 4.

Using this method of classification will allow you to look at your questions with a fresh eye and decide which design looks to be the most promising. Some designs will allow you to conduct the research relatively quickly and at low cost but will come with disadvantages, namely the quality of the data may be suspect, and the interpretation of the study may be dicey. However, these designs are useful where the treatment effect is likely to be much bigger than the potential error. Other designs, such as prospective cohort studies or randomized clinical trials are much more difficult and costly to conduct but the results are less prone to bias and are more believable. After all, you are trying to find out what works and doesn't work so that you can feel more capable looking after patients.

Strategy for module

Interactive Session: Sections 3.3 to 3.7 cover the steps in the process of looking at your question (which may still be in the embryo stage), choosing what you hope is the best design and then deciding again whether it will be feasible within the time and cost restraints that you face. This is also a good time to explore the potential biases of your study, to see if you can try to minimize the

effect they will have on the outcome and assess how good your answer is likely to be – i.e. can you convince your peers that you are correct.

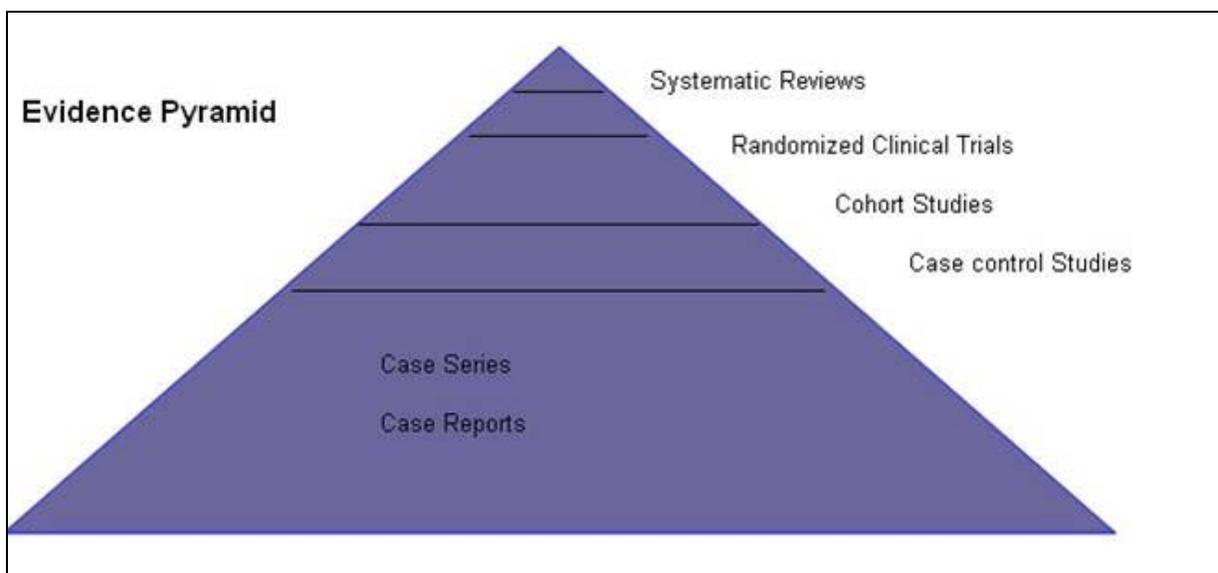
If you are a resident or a fellow there is little point in aiming to conduct a multicentre clinical trial that will take four years to complete. You would only be a small part of the process and an infinitesimal part of the paper writing. If you are more senior and aim to stay in Vancouver for ever, then you can contemplate such a luxury! If, after this exercise, you realize that your question is not viable, it is time to go back to the drawing board and not try to force the question through a process that will not be successful. If you have more than one question on paper from module 1, then repeat the exercise with each and decide which of your questions is the one that you wish to pursue.

If you have the questions from your own practice, then use the practice as the source of subjects and data for your questions.

Interactive Session: Choosing the best design for exploratory or hypothesis testing studies

Remember, in the first module, we talked about the types of research and suggested that exploratory research is used to look for the “how” and “why” and “who”. Hypothesis testing studies are “explanation” studies.

The evidence pyramid shows designs from the strongest to the weakest (top to bottom) and the frequencies of such studies (width).



As you can see, the studies with strong evidence are in short supply!!

Apart from the systematic reviews which are a synthesis of existing studies, the three main designs are Cohort Studies; Case Control Studies and Randomised Clinical Trials. Each of these designs has a control group and demonstrated strengths and weaknesses, potential biases and feasibility issues. Each design will be summarized here with examples from Belltown. If you are looking for more detail on any design go to the links or to the recommended readings.

Cohort studies

EXAMPLE: In Belltown, concern has been expressed that workers in one of the sections of the smelter just outside of town have been exposed to toxic chemicals which could lead to liver damage at a later time. Norm is concerned since he spent some time in that section of the smelter and he is happy that someone is going to look into the problem. To study whether this is true or not, the workers in that section of the smelter are undergoing yearly liver enzyme tests and will be followed for fifteen years. To check whether the rate of liver damage is greater than would be expected, the study is also following a group of workers who are not in that section of the smelter. The outcome is abnormal liver function.

OBJECTIVE: To assess whether workers exposed to toxic chemicals at the Smelter are more likely to develop liver damage than those who are not exposed to the chemicals. The design of the study is summarized by the 2 x 2 table.

The study is PROSPECTIVE, meaning that the workers have not shown any signs of liver damage at the start of the study and they will be followed to check for first signs of damage.

		OUTCOME	
		Liver Damage	No Liver Damage
EXPOSURE	Toxic Chemicals	24	368
	No Toxic Chemicals	13	672

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Direction of sampling: prior to appearance of outcome

One of the most obvious biases that might affect the outcome is that those who work in the toxic chemical section are likely to be different from those who are in the control group in many ways. They may be more healthy, but may smoke and drink more alcohol because of the stress of working in a difficult environment. The work may be more physically demanding and hence the workers may be younger on average. The **strengths** of the cohort study are that the data are collected prospectively, so that many of the potential confounders (factors that affect the outcome independent of the exposure) such as smoking, age, other health problems etc. can be collected as the study progresses. The data can be checked and any questionable information clarified. Ethically, it is very acceptable since the workers are not being asked to do anything different from their normal occupation and no one is being coerced into being in the exposed or control group.

The **weaknesses** are that the study will be costly and take many years to find an answer (the number of years depends on the latency between biological onset and diagnosis). The size of the study will be large if the outcome has a low incidence. Worse still, there is frequent drop out as workers leave the plant, the town, or the province, and these missing data make the results difficult to interpret.

Check your question to decide if it fits this type of design

Case control studies

EXAMPLE: In Belltown, concern has been expressed that workers at the smelter just outside of town are showing signs of liver damage at a higher rate than might be expected. This is worrying Norm since he has spent time in the section of the plant that has now been declared to contain toxic chemicals and he is happy that someone is going to study whether the exposure to the chemicals in this section could be contributing to the liver damage. To study whether this is true or not, all of the workers at the plant who have had a diagnosis of liver damage are identified. To find out whether exposure to chemicals could be the culprit, a matched group of workers without a diagnosis of liver damage is chosen to form the control group. Matching is done on attributes that might affect the outcome independent of the exposure (known as **confounders**). In this example confounders might include length of employment at the smelter, age, gender, and physical demands of the job. To check whether the exposure to toxic chemicals is likely to be implicated in the liver damage, a history of exposure is obtained from cases and from controls. The word “history” indicates that the study is going to be retrospective – the outcome is known and the exposure is determined. This is the opposite of the cohort study.

OBJECTIVE: To assess whether liver damage is more likely to have developed in workers exposed to toxic chemicals at the smelter than in those not exposed. The design of the study is summarized by the 2 x 2 table.

The study is RETROPROSPECTIVE, meaning that the workers have already developed the liver damage at the start of the study and the exposure will be measured going back in time.

		OUTCOME	
		Liver Damage	No Liver Damage
EXPOSURE	Toxic Chemicals	24	368
	No Toxic Chemicals	13	672

<-----

Direction of sampling

The **strengths** of a case control design are that the cases are already defined for you and all you have to do is to choose an appropriate control group. Since the endpoint has been reached, the study is going to be of short duration and hence much cheaper than a cohort study. There are no ethical problems since the outcome has already happened and no intervention is taking place. This type of design is very useful (and frequently the only one possible) when the incidence of the outcome is rare as in some cancers and exotic diseases such as E. Bola and now SARS.

The **weaknesses** of a case control study lie in the difficulties of choosing a good and appropriate control group. While you can match on a few of the obvious confounders, it is not possible to match on all the known confounders and impossible to take care of the confounders you don't know about. It is rarely easy to extract information from either participants or records. Obtaining information about exposure to the chemicals is usually difficult and relies on good record keeping (an oxymoron if ever there was one). There are also many queries about the quality of the data and very few answers. Finally, the size of the study will be limited by the number of cases. Even adding two or more control subjects per case will not compensate for the fact that the number of cases is low.

Check your question to decide if it fits this type of design

Randomized controlled trials

EXAMPLE: On one of the shifts in emergency in the hospital in Belltown, Effie has been brought into the ER with asthma by a distraught parent. You would normally give Effie prednisone but wonder if you are doing the best for the child (since prednisone has side effects) and wonder if you could use a non-steroidal drug instead. You know that a new drug “Asthmasafe” has just been released by Novadrug and you think that this might be better than prednisone, shortening the time in the ER and reducing the number of children who would require to be admitted to hospital. However, you worry about whether this new drug might induce more exacerbations resulting in an increased number of visits to the ER.

OBJECTIVE: To assess the effectiveness of the “Asthmasafe” in shortening the time a child spends in ER, reducing the number of admissions and to assess the safety of “Asthmasafe” as measured by number of exacerbations and return visits to the ER. While it would be possible to use a cohort study to test this new drug, the fact that the clinician or the parent could choose whether to give the child Asthmasafe or prednisone leads to many potential sources of bias which would lead to the requirement for a larger study. The most efficient design for this (these) questions is a randomized clinical trial where the act of randomization takes the choice of the treatment out of the hands of the clinician or parent and results in a balance between the experimental group and the standard treatment group both in the confounders that you know and the **confounders** you don't know. The design of the study is summarized by the 2 x 2 table. It is similar to the Cohort study but now adds the randomization component

The study is PROSPECTIVE, meaning that the children will be entered into the study at the time that they are first admitted to the ER and before any treatment has been given. Following the treatment with either Asthmasafe or prednisone, the children will be followed until they leave the ER or been admitted to hospital for the first part of the study and then followed for some time after to check on the safety of the intervention.

		OUTCOME	
		Admission	No Admission
EXPOSURE (Random)	(→) Asthmasafe	24	368
	(→) Prednisone	13	672

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Direction of sampling

The main **strength** of a randomized clinical trial is that the allocation to receive either the intervention under study or the standard (or placebo) treatment is unbiased i.e. the clinician cannot introduce bias by deciding which patient gets which treatment based on their clinical impressions. Also, the act of randomization allocates equally to each arm the confounders that you know and the confounders you don't know so that the comparison is balanced and you don't have to worry about keeping track of the extraneous details. As with the cohort study, information can be collected as the study progresses; the quality of the data checked and extra information obtained if required. Ultimately, the clinical trial provides the least biased estimate of the effect of each intervention and is the most efficient in terms of sample size (since you don't need to account for the differences in structure of the groups).

The **weaknesses** of a randomized clinical trial are that the design raises ethical concerns in some clinicians' minds. If a clinician truly believes that he knows the best treatment (whether or not he is correct) then he should not be part of the trial. However, trials are usually undertaken when there is no universal agreement or when the answer is unknown, as in this case. All new drugs (and devices) must undergo rigorous testing which in practice means being tested in a clinical trial. One of the weaknesses (or downsides) of a clinical trial is that rigour in data gathering requires extra care in collecting the data and hence usually extra staff over and above the clinical staff, This becomes costly and RCTs can be very expensive to run.

Check your question to decide if it fits this type of design

Now look at the research questions you have written so far to see if you can identify what type each one falls under. This will make life easier for you in the following modules. If none of these fit, move on to the next module

Assessing potential biases

The goal of any research is to find an answer that you can trust. In other words, the answer is reliable and valid. Well, all research gives you results you can believe, doesn't it? "NO" is the long answer. There are many biases that could alter the results so that although the results look great on the surface, the conduct of the research has introduced so many systematic errors (biases) that the study is flawed and the answers cannot be reproduced. At each stage in the process of developing a research protocol, it is worth while taking a long hard look to decide where potential biases might arise and what you can do to minimize their effect. In each of the above designs, there are opportunities for bias. For a **cohort study**, remember that it may take a long time to reach the outcome. Think through all possible scenarios and decide what can happen to your study sample as you wait for the outcome to happen. In the smelter problem workers (in either the exposed or not exposed group) could:

- leave the company and move to Sudbury
- shift occupation within the company so that they have changed exposure
- die from some other cause such as a road accident
- become administrators or managers
- win the lottery
- become health aficionados and start going to the gym and eating well
- start smoking
- take early retirement

For a **case-control study**, your cases already have the outcome so where are the biases? The biases in retrospective studies are numerous. For the smelter problem, they include:

- The choice of control group could be faulty (you could end up over or under matching)
- The data from the record is usually incomplete and often of doubtful quality
- Recall data from individuals is suspect, more so if the recall is more than a week or two. (In this example, it could be several years)
- Exposure data is difficult to quantitate
- Other life events will be haphazardly reported

- *Affected individuals may exaggerate their history of exposure*

For a **randomized clinical trial**, although biases are minimized by the randomization process, they are not totally absent (despite what some texts tell you). The choice of population to sample becomes critical and many of the biases for the other two studies may also occur. For the asthma trial, only mild patients may be included which alters the interpretation of the result.

- Patients could die (asthma was a symptom of more serious problems)
- Patients are not available for follow-up
- Patients could not take tolerate the Asthmasafe

** Write down your thoughts about biases as they occur to you*

How you deal with each potential bias impacts on the quality of your results. *It is worth developing solutions before you go further.*

Assessing feasibility – sample size

Now that you have a question and you have decided on a design, the next stage is to estimate what size of study you are contemplating. At this stage, many a research project fades so it is worth checking out the size of study before you spend a great deal of time and effort on the manoeuvres and measurements. Details for doing quick and dirty calculations yourself appear in module 8. If you have more than one question in your research plan, it is worth seeking help. Remember that all sample size calculations are estimates, not exact, and are based on some previous ideas. If you don't have these baseline data, then you have choices. Use information from your literature reviews, check existing records (that may require some chart review) or develop a simple pilot study to provide you with the data.

** Is the sample size you calculate a reasonable number? If not, what could you do to make it reasonable?*

Assessing feasibility – availability of subjects

For some reason, unknown to researchers, as soon as you decide to study a problem and spend a lot of time preparing a protocol, the problem disappears and you can't find the subjects when you are looking for them. If you find that you need 300 exposed workers in the cohort study and actually

there are only 120 who work in the section with the chemical exposure, there is going to be a problem with the interpretation of the results. For the case control design, the number of cases may be only a handful, which limits the research interpretation. In clinical trials, there is an additional hazard. There may be a sufficient number of patients, but each subject has to give informed consent and only half of the potential pool agrees to enter the study. Time to rethink!

** Will you be able to amass the appropriate sample size in a reasonable time frame?*

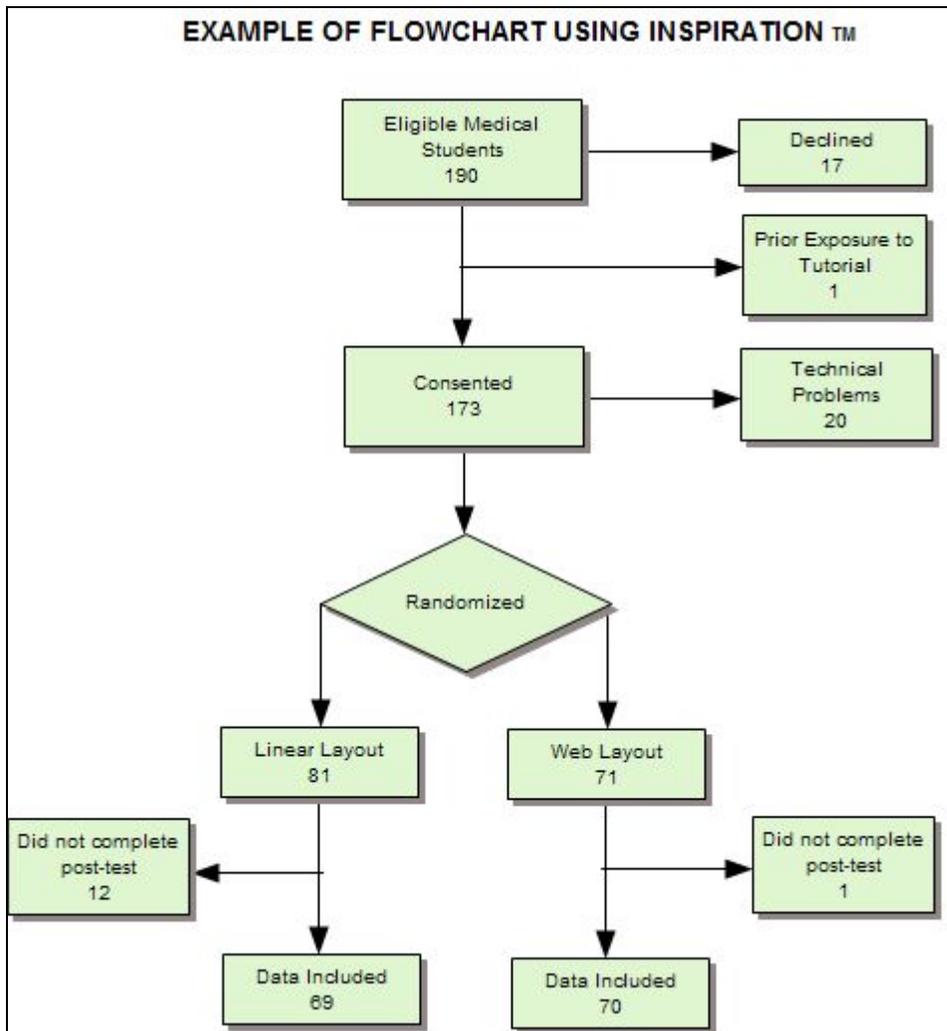
Assessing feasibility – timing and costs

Once you have answers to the sample size and subject availability, you now have the information you need to calculate how long the study will take. Now you have to guess (only a ball park guess) how much money you will need to be able to conduct the study. Details on how to do a complete budget are in the grant writing module. At this stage once again you need to decide whether it is worth going further.

Flow charting software

The intricacies of your study design may be easier to communicate using flowcharting software than with text. While Microsoft Word and PowerPoint have rudimentary graphics capabilities you are well advised to become familiar, early in your career, with a simple dedicated flow-charting software package. We recommend “Inspiration” not least because it was first developed for Elementary School Students and so is affordable and simple to use!

You can get a free trial at: <http://www.inspiration.com/freetrial/index.cfm> An example of an Inspiration flow chart describing a Randomized Controlled Trial is available here.



Checklists

There are wonderful checklists available to you to make certain you haven't missed anything, no matter which study design. Here are three popular resources:

- Centre for Evidence-Based Medicine
(<http://www.cebm.utoronto.ca/teach/materials/caworksheets.htm>)
- CONSORT Statement for RCT's
(<http://www.consort-statement.org/Downloads/download.htm>)

Summarize your progress

At this point write up the next part of your protocol – the Methods section! You can write up a summary of the design, potential biases and feasibility. If you are writing a **Letter of Intent (LOI)** to a funding agency, you are close to having all the information you would need to complete it. Include a flowchart of what will happen to the participants in your study.

Readings

- Hulley: Chapters 8 and 10
- Users' Guide to the Medical Literature JAMA series
- Cohort and Case control studies and RCTs :
- Cohort: http://www.phru.nhs.uk/Doc_Links/cohort%2012%20questions.pdf
- Case Control: http://www.phru.nhs.uk/Doc_Links/Case%20Control%2011%20Questions.pdf
- RCT: http://www.phru.nhs.uk/Doc_Links/rct%20appraisal%20tool.pdf
- Internal and External Validity:
- [http://www.une.edu.au/WebStat/unit_materials/c2_research_design/validity_internal_exte
rnal.htm](http://www.une.edu.au/WebStat/unit_materials/c2_research_design/validity_internal_external.htm)