Conducting research in HPB – LEARNING THE BASICS
By Dr Chik Ian (Hospital Canselor Tuanku Muhriz, UKM)

Albert Einstein once said, “If we knew what it was, we were doing, it would not be called research, would it?”. Research is the backbone for growth in any sector and helps to solidify any practice with proper evidence. The start of any good research, is a good question requiring an answer or solution, hence leading to the appropriate type of study.
While there is a level of evidence to show a strength of a study, each study has it advantages and disadvantages.

So, the big question is, which study should one do? Especially if one is just starting off. The first is to understand the purpose of each study (i.e., looking for a cause, looking at effect, looking at risk factors etc.) and its pros and cons. With a little basic understanding, one can decide on asking an important question, whether for everyday practice or for basic understanding of a disease or drug.

There are observational studies versus experimental studies. Observational studies do not change the course of a disease, but rather an examination of a process or disease pattern. Experimental studies, however, usually involves intervention into a patient’s disease. All types of studies are then graded by the level of evidence, giving one a rough idea of how good the evidence is provided by a study. Below are the types of studies, in accordance to the level of evidence provided.

Level of Evidence	Type of Study
1a	Systematic review of (homogeneous) randomized controlled trials
1b	Individual randomized controlled trials (with narrow confidence intervals)
2a	Systematic review of (homogeneous) cohort studies of "exposed" and "unexposed" subjects
2b	Individual cohort study / low-quality randomized control studies
3a	Systematic review of (homogeneous) case-control studies
3b	Individual case-control studies
4	Case series, low-quality cohort or case-control studies
5	Expert opinions based on non-systematic reviews of results or mechanistic studies

Figure 1: Level of evidence according to type of study[1]

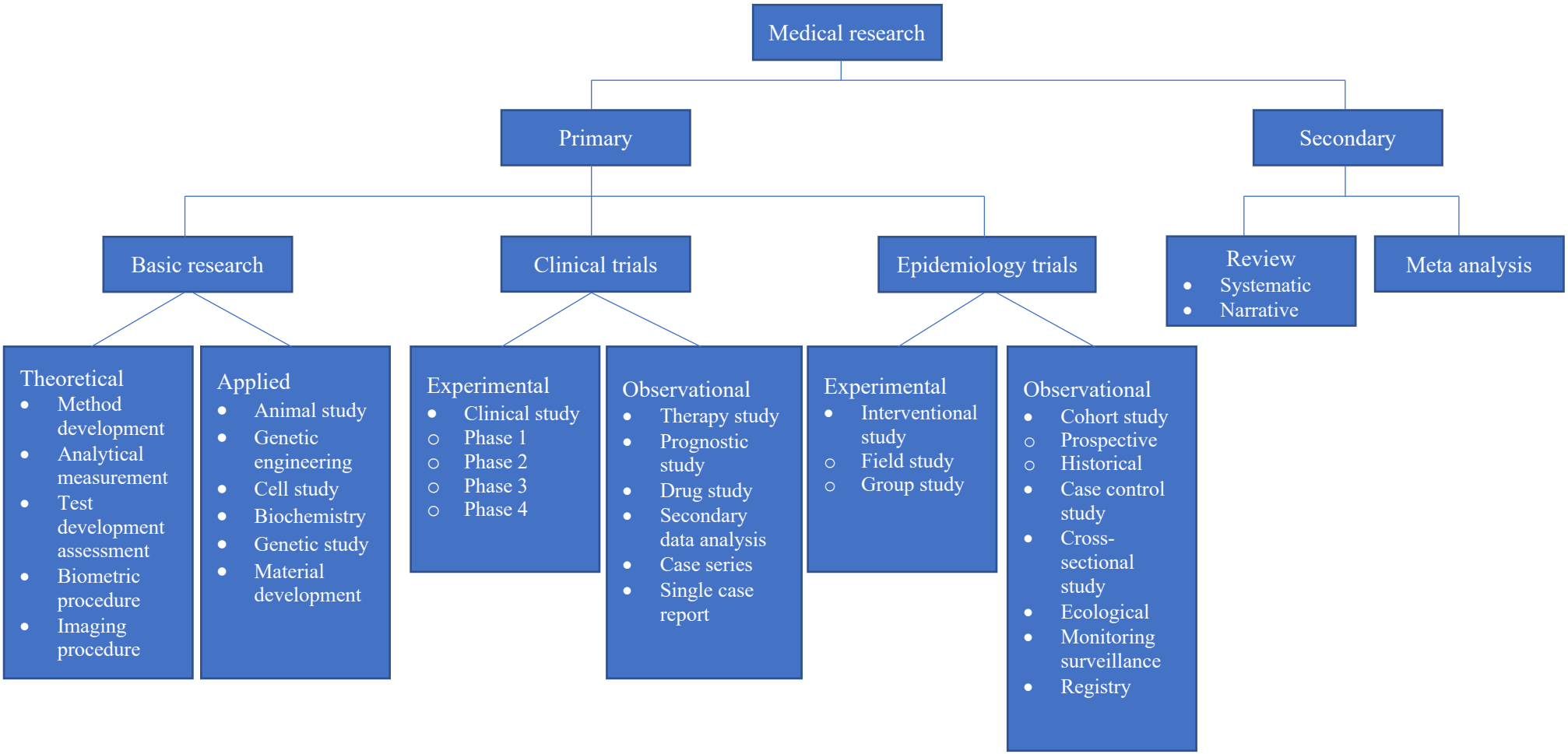

Figure 2: Types of medical research[2]

While it's good to aim for level 1 evidence, a lower level evidence type of study is important as well. In certain diseases where it is uncommon, a case report or series may be important to outline any kind of relating literature on possible management. We further elaborate the different types of studies usually performed.

OBSERVATIONAL STUDIES:

Case control study[3,4]

A case-control study will be looking retrospectively into possible exposures that lead to a disease. This may be important for early intervention or early detection/diagnosis of disease.

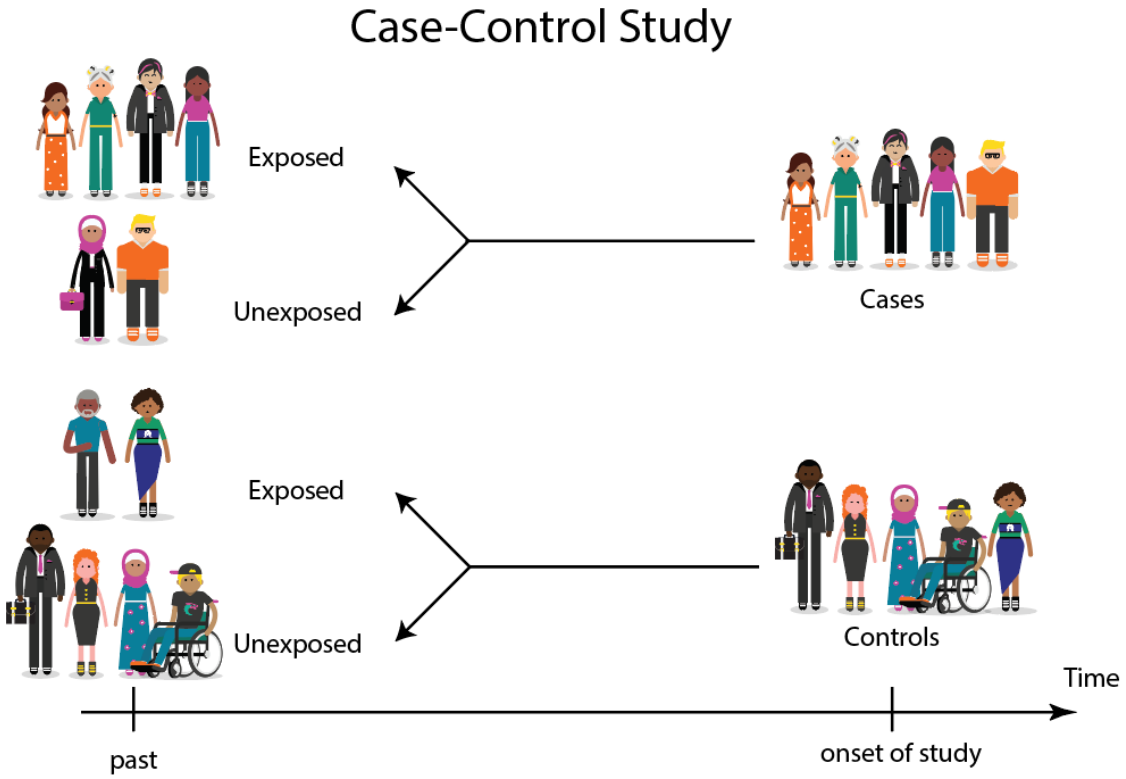

Figure 3: Case control study[5]

Pros

1. When the disease or outcome being studied is rare.
2. When the disease or outcome has a long induction and latent period (i.e., a long time between exposure and the eventual causal manifestation of disease).
3. When exposure data is difficult or expensive to obtain.
4. When the study population is dynamic.
5. Case-control studies are useful to study the association of risk factors and outcomes in outbreak investigations.
6. useful to study multiple exposures in the same outcome
7. relatively faster and cheaper to conduct (1)

Limitations:
1. Cannot look at rare exposures
2. cannot estimate incidence or prevalence
3. looks at single outcome
4. may not have accurate time between exposure and outcome
5. may have recall and/or selection bias

Cohort study[6,7]

A cohort study can be retrospective or prospective, and it looks at exposures leading to a outcome. It is prospective when the disease or outcome has not yet occurred and is retrospective when it has.

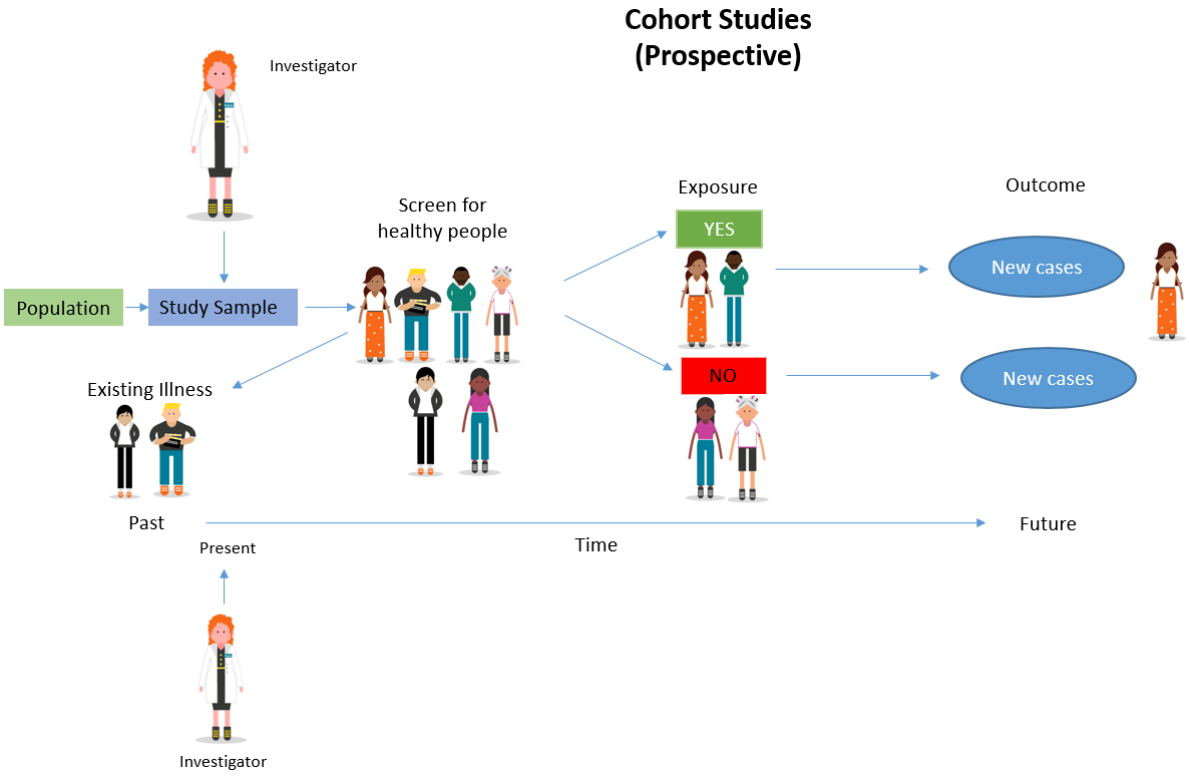

Figure 4: Prospective case cohort[5]

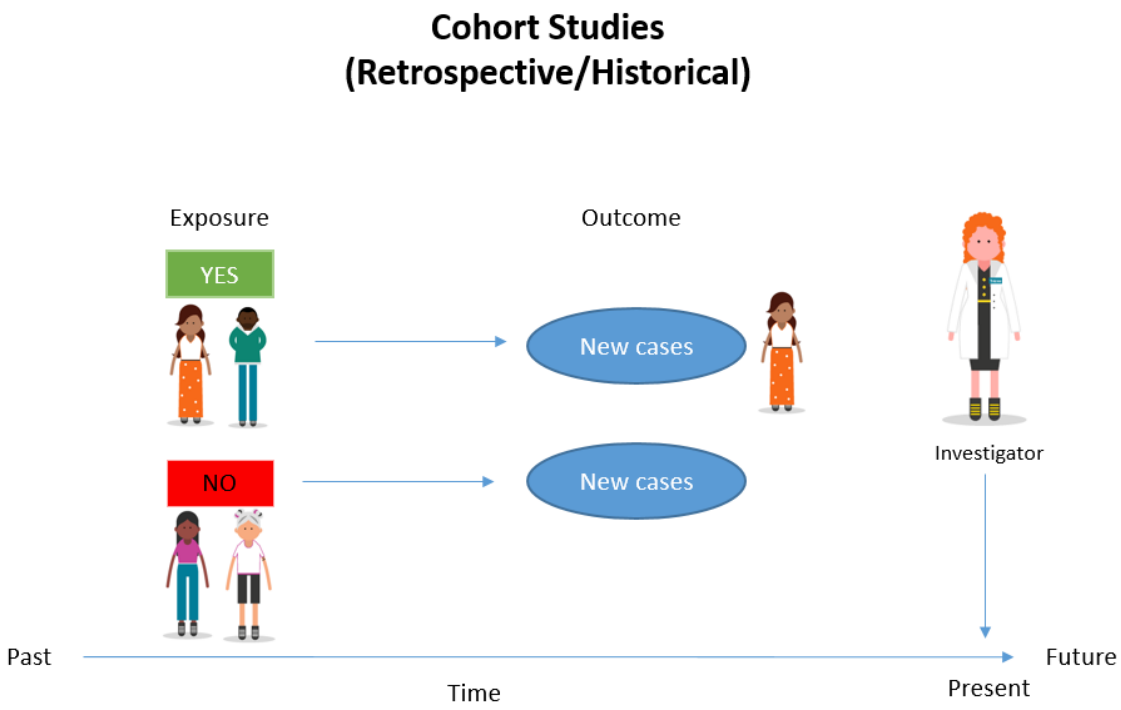

Figure 5: Retrospective case cohort[5]

Pros:

1. able to measure and control better the outcome, predictor, and confounding variables, hence can look at multiple outcomes
2. allows study of rare exposures
3. has correlation with time, as exposures may be multiple over time
4. prospective cohort – more accurate collection of data due to control of data, and can measure multiple more variables, as pre planned to collect data
5. retrospective cohort – easier data to collect, inexpensive, easy to get large data set
6. can measure incidence
7. may be able to infer causality

Limitations

1. prospective cohort – may be long follow up required, expensive
2. retrospective cohort – may have inconsistent data, less control, information and recall bias
3. susceptible to loss of follow up
4. many confounding variables
5. may not be most efficient for study of rare outcomes

Cross sectional study[8]

Another type of observational study, but only studies its outcomes and exposures at that given time. This is usually to look at prevalence of outcome and exposure. The odds ratio can also be calculated from this study.

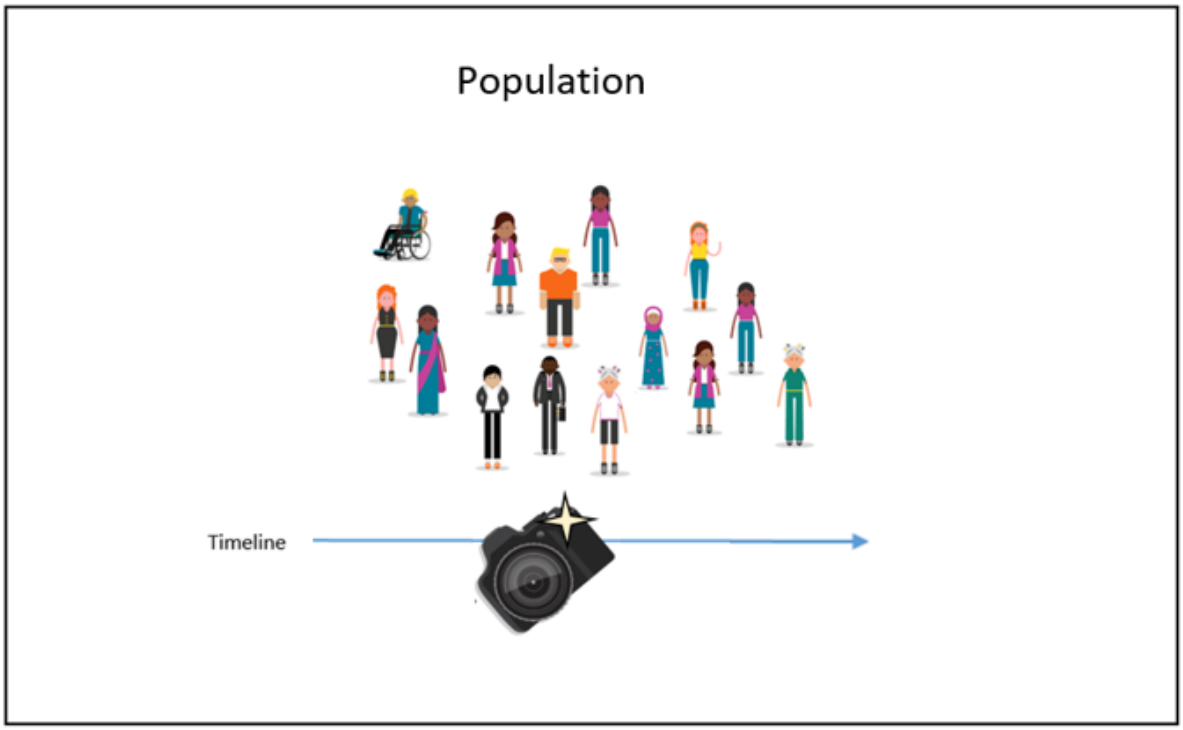

Figure 6: Cross sectional study[5]

Pros:

1. Can be done relatively fast and inexpensive.
2. Used as a baseline before deciding to progress to cohort study.
3. Can be used for public health planning, monitoring and evaluation.

Limitations

1. Unable to derive casual relationships, as there is no progression of time.
2. Certain biases applicable as there unable to look at change in exposure, but only exposure at point in question.
3. May not be able to look at trend of disease, as again, limited to one point in time.

Experimental Studies[9]

As the name suggest, this type of study involves an experimentation and often involves intervention. It is also known as a clinical trial, as usually it involves a new drug or technique not previously used for a certain indication. These studies usually involves two groups, with comparison of new drug versus no treatment (placebo) or standard treatment. Commonly, many drug companies will talk about a new drug with its phase of trials (I-IV)
Briefly, the trial phases are shown below:

Phase I : done after animal studies. These are done to test safety of drug, and to study pharmacokinetics and pharmacodynamics of drug.
Phase II: looks at efficacy of drug at various doses, and some safety profile.
Phase III: usually RCT. To evaluate effectiveness of the drug
Phase IV: post marketing survey and to look at side effects in the general population.

These studies are usually randomized to reduce confounding factors that will affect the result of the study. If possible, they are blinded, whether single, double or beyond. Single blinded studies are where the assessor or patient is oblivious to the treatment, whereas in double, both are unaware. In one arm, the new treatment is used, while in the second arm, it may be placebo or the current treatment. These studies usually test if a treatment is better, at par with current treatment or not any worse than current treatment. As these studies actually involve patient care, there must be strict ethics and protocol for the study.

Systemic review and meta-analysis[10]

The highest level of evidence comes from a systemic review and meta-analysis. These two vary slightly in terms of data calculation, but essentially is a culmination of many types of previous studies investigating a similar issue. Based on certain criteria, these studies are gathered and then combed through to ensure the reduction of bias of a narrative review. The summation of all the studies then leads to a conclusion whether a treatment is possibly helpful or not. The studies included can vary from RCT to case control studies.

In a systemic review, there isn't much analysis of data, while in meta-analysis, extensive and complex statistical methods are required. Forest plots and publication bias are common things reported in a meta-analysis.

SUMMARY

With all the information in mind, one can now look for a study best suited to a research question that needs to be solved. A simple search or literature review via search engines such as PubMed, Scopus, Web of Science or Google scholar would give one an idea whether this question has been previously answered. Do not despair if the research question has been answered as oftentimes there are differences in protocol or methodology in each research conducted. Understanding previous studies are equally important to help improve or reduce biases should a study be needed.

A good grasp of statistics is key to understanding the data put forth by other papers, but also important to analyse own data. There must be some basic understanding of statistics for this, and more advanced level if one wants to analyse more difficult data. Enlisting the help of a statistician on your team for this will be helpful, if one's grasp on statistics is not quite advanced.

Finally, networking is also key, as carrying out a research is mostly a team effort and helps in certain efforts, especially when a sample size is not adequate in one's practice. However, different centres may sometimes affect outcomes due to different population type, or even different management/treatment styles in each centre. This may need to be taken into account when planning a multi-centre study.

While this paper does not discuss extensively on how to perform research per se, the summary of each type of research is described. Hopefully, this can encourage one's aspiration and interest to conduct a research. I would suggest, that one could start with an easier study protocol with zero or small budget, and that is retrospective. With that, I bid you good luck on this adventure of research!

References:
1. Website: https://www.cebm.ox.ac.uk/resources/levels-of-evidence/oxford-centre-for-evidence-based-medicine-levels-of-evidence-march-2009
2. Kapoor MC. Types of studies and research design. Indian J Anaesth. 2016;60(9):626-630. doi:10.4103/0019-5049.190616
3. Website: https://sphweb.bumc.bu.edu/otlt/mph-modules/ep/ep713_case-control/EP713_Case-Control4.html
4. Setia, Maninder Singh. "Methodology Series Module 2: Case-control Studies." Indian journal of dermatology vol. 61,2 (2016): 146-51. doi:10.4103/0019-5154.177773
5. Website: https://deakin.libguides.com/quantitative-study-designs
6. Xiaofeng Wang, Michael W. Kattan. Cohort Studies Design, Analysis, and Reporting. Supplement: An Overview Of Study Design And Statistical Considerations| Volume 158, Issue 1, Supplement , S72-S78, July 01, 2020
7. Setia MS. Methodology Series Module 1: Cohort Studies. Indian J Dermatol. 2016;61(1):21-25. doi:10.4103/0019-5154.174011
8. Setia MS. Methodology Series Module 3: Cross-sectional Studies. Indian J Dermatol. 2016;61(3):261-264. doi:10.4103/0019-5154.182410
9. Setia MS. Methodology Series Module 4: Clinical Trials. Indian J Dermatol. 2016;61(4):393-402. doi:10.4103/0019-5154.185702
10. Setia MS. Methodology Series Module 6: Systematic Reviews and Meta-analysis. Indian J Dermatol. 2016;61(6):602-607. doi:10.4103/0019-5154.193663