

Understanding Clinical Study Design

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You have defined a clinical question, searched the medical literature and have found articles you might use to answer your question. Now you will need to begin to sift through the articles in order to judge the evidence. The first step should be to read the Methods section of each article in order to determine the type of study design. This can be the first way to assess an article to determine if it offers the best evidence to answer your clinical question.

Appraising an article includes understanding its methodology, assessing its validity, and determining how closely it applies to your individual patient. This part of the series will focus on various clinical research study designs, including the randomized controlled trial, cohort study, case-control study, case report and cross-sectional study. Table 1 is a quick reference and summarizes the information presented here.

RANDOMIZED CONTROLLED TRIAL

This study design is best suited to determine cause and effect, especially in regard to clinical questions of treatment, prevention or harm. If you are lucky enough to have found a randomized controlled trial (RCT), the evidence will likely be strong. Some important characteristics of a RCT include that it is longitudinal and therefore studies patients over time.

A RCT is always prospective rather than retrospective. When a RCT is conducted, a group of subjects is recruited, then randomly assigned to either a treatment group or a control group. While an intervention is imposed on the treatment group, the control group should be treated in exactly the same manner in all respects, except the intervention. After a period of time, the treatment and control groups are compared for outcomes. Although a RCT often gives the best type of evidence, it can be difficult to find, because this type of study can be expensive and can take years to complete.

At any stage in the process of a study such as a RCT, unintended factors may favor one result in preference to another. This is considered bias. To avoid bias in a RCT, patients are assigned to study groups in a "double-blinded" manner, such that the investigators and the subjects know nothing about who is in the treatment group. If the study is "single-blinded," only the patients are unaware of treatment and investigators may treat patients differently depending on whether or not they are receiving the intervention in question.

COHORT STUDY

If you are unable to find a RCT to answer a clinical question of treatment, prevention or harm, the next best study design is a cohort study. When asking a question about prognosis or risk factors, the cohort study actually provides the best evidence. A cohort study is longitudinal and prospective, similar to a RCT, although in a cohort study, subjects are disease-free at the onset of the study. Any of the individuals in the study could develop the outcome of interest and are grouped according to possible risk factors, for example, smokers vs. non-smokers or high cholesterol vs. normal cholesterol. Subjects are then observed for development of disease, and it is possible to relate outcomes to initial risk factors. The most well known examples of cohort studies are the Nurses Health Study and the Framingham Heart Study.

It may be difficult to find a cohort study to answer a clinical question, since these costly studies often follow large numbers of subjects over a long period of time in order to see diseases develop and draw conclusions. Since subjects are not randomized, one of the weaknesses of a cohort study is that you may not be able to account for some of the differences between groups resulting in unintended bias. In addition, cohort studies may limit their subjects to a reliable population that may be easier to follow, such as relatively compliant nurses or physicians. Findings in these studies may have

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Table 1: Summary of study designs

Study Design	Description	Best Answers Questions About:
Randomized controlled trial	A group of subjects are either treated or observed depending on a random assignment. Outcomes are measured prospectively	Treatment Prevention Harm
Cohort	A group of subjects are observed over time for development or progression of disease	Prognosis Risk factors
Case-control	Retrospective comparison of patients with and without disease	Risk factors
Case Report Case Series	Report on details of a patient or group of patients	Previously unknown or rare findings
Cross-sectional	Measurement at one point in time: a survey	Prevalence in a population

limited generalizability, depending on factors such as race and socioeconomic status of the study population compared to your patient population.

CASE-CONTROL STUDY

When asking a clinical question about risk factors, a case-control study may also provide evidence, although usually less strong. In a case-control study, a group of patients with a disease of interest is compared to a group of patients without the disease with respect to previous exposures or risk factors. The defining factor of this study is that it is retrospective, unlike the studies already described. This is less compelling evidence, since retrospective analyses may have more potential for bias. One type of bias is "recall bias," where patients with or without a disease may remember an exposure differently. A good case control study will try to anticipate potential sources of bias and adjust for them in the statistical analyses.

CASE REPORT AND CASE SERIES

When searching the literature, there are times when the only evidence to answer your question comes from a case report or case series. These are detailed descriptions of a patient or series of patients. Because by definition there is no comparison or control group, these studies, although a rich source of hypotheses, are inadequate to provide an explanation or determine a cause and effect relationship.

CROSS-SECTIONAL STUDY

One last type of study design is the cross-sectional study. Usually found as a survey or poll, this type of study measures a variable at one point in time in a

sample from the population of interest. It is the best way to measure the prevalence of a disease or behavior, such as how many medical students are depressed or how many women use hormone replacement therapy. Because a cross-sectional study is not longitudinal, it is not the appropriate study to determine prognosis or causation.

EXAMPLE

To illustrate how understanding study design can be important, we offer the following example. Your hospital has prepared a guideline for the treatment of community-acquired pneumonia under pressure from the local managed care organization. The guideline calls for immediate treatment with cefuroxime plus azithromycin after appropriate cultures are obtained, among other measures. Physicians were educated and encouraged, but not required to use the guideline. Ever skeptical, the internal medicine physicians decide to test the guideline. Simultaneously, the hospital QA committee decides to do the same.

The internists reviewed charts retrospectively for six months. A group of 30 patients treated according to the guideline protocol was identified. Another group of 30 patients was identified who had been treated with "real world" decision making of the attending physician, rather than by protocol of the guideline. These groups were matched for age, sex, smoking and other obvious clinical variables. Clinical outcomes were compared and duration of hospital stay was calculated. The two groups had similar outcomes but the guideline group had 1.3 fewer days in the hospital.

The QA Committee randomly assigned patients with pneumonia to usual care or guideline care at

the time of admission. The admitting physicians were advised to follow the assigned strategy and compliance was excellent. Two groups of around 30 patients were assembled and analysis revealed that the groups were similar with respect to age, sex and other major clinical variables. At discharge, all charts were reviewed by a person "blinded" to the protocol being used. The guideline group stayed in the hospital 1.8 days longer, although the clinical outcomes were the same as in the internists' study. Which results would you trust the most? The choice of antibiotics for pneumonia is a question of treatment, so the best type of study design to answer this clinical question is a randomized controlled trial (RCT). The internists' study is a case control type and is retrospective since the patient sample was selected after the treatment was given. The sample of patients for the QA Committee's study was assembled at the time of diagnosis and treatment was assigned randomly, therefore it was a randomized controlled trial. The reviewer and the patient were blinded to the assignment, adding credence to the results. Because the QA Committee's study was the best possible evidence to answer a question of treatment, its results should be considered more seriously.

In summary, the design of a study has great impact on the trustworthiness of its results. In finding and appraising evidence, one can gain great insight by understanding different types of study design and recognizing the strengths and limitations of each.

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