

NIKKEN RESEARCH INSTITUTE



WHITE PAPER

UNDERSTANDING CLINICAL STUDIES

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1. Introduction

A clinical study, also referred to variously as a clinical trial or research study, is the means that science uses to evaluate a hypothesis (a belief or theory based on observed evidence). For example, if a new drug is discovered, or the efficacy of an existing one is in question, a clinical trial is the test that researchers apply to see if it “works.”

Here is a sample of how a clinical study is used. If it were supposed that aspirin can cure a headache, the scientific community would not accept this as fact simply because people who have taken aspirin have reported relief from headaches. There may have been other factors unrelated to the administration of aspirin that were actually the reason for their pain relief.

Therefore, to test the hypothesis — to see if aspirin does what it is reported to do — researchers will enlist two or more groups of people to serve as test subjects. Ideally, these groups will be selected using parameters to allow for or cancel out any individual variations between subjects. When the testing begins, half of these people will be given aspirin and the other half what is known as a placebo — a pill that may look like aspirin but has no active ingredient. This is also called the sham or control. At the conclusion of the study, if significantly more subjects in the aspirin-receiving group report relief from headache pain than those in the placebo or control group, the researchers may conclude that aspirin indeed does relieve headaches.

Clinical studies are based upon what is called the scientific method. Typically, science is thought of as defining truth. However, this is not the case. Instead, science uses this process of experimentation to answer questions. The scientific method involves several key steps.

2. Observation

The first step takes place when an observation is made regarding some event or characteristic occurring in the known universe. In turn, the observation may lead to a question. In one example, radiologists noticed that patients with hip implants reported a lessening of the pain associated with the implant after an MRI (magnetic resonance imaging) scan. The clinicians then thought about the possible implications of those reports and wondered if the magnetic energy from the MRI could be the cause of this pain relief.

3. Hypothesis

In attempting to answer the question, a scientist will create a hypothesis, which may not actually be more than an educated guess, regarding the possible answer to the question. In the case of the hip replacement patients, many possible causes for the pain reduction existed, but the researchers chose the one they believed was the most likely.

4. Experimentation

None of the steps in the scientific method is more crucial than experimentation. In order to prove or disprove a hypothesis, a researcher will design an experiment to test it. When devising the experiment, in this case a clinical study to determine why the patients experienced less hip pain after MRI, care and understanding were required to control (cancel out or neutralize) all other known factors that might influence the results.

The scientific method is not a recipe for making original discoveries or inventions. It does not prescribe the pathway that must be followed to attain success. Instead, the goal is to determine whether or not a hypothesis is true to some degree.

Moreover, the nucleus of the scientific method is the confrontation of an idea with the data that result from examining it, applied objectively. In this sense there are no good or bad ideas. Even an off-the-wall hypothesis can be considered and tested this way — and sometimes the results surprise everyone, including in many cases the researchers.

Throughout history, the scientific method has upset countless instances of what is called conventional wisdom. For example, it seems intuitive and obvious that when dropped from a height, a very heavy object should fall to the ground more quickly

than a lightweight one. At one time every sensible person “knew” this. Then Galileo conducted his famous experiments in physics, and proved what he had already hypothesized — that the force of gravity acts equally on every object, regardless of its mass. A dropped sphere weighing 100 pounds and a similar sphere weighing only one ounce fall at the same speed and reach the ground at the same time. This astounded many people when the demonstration was performed in the 1600s but it accords perfectly with the laws of the universe as we presently understand them.

Within the discipline of medicine, interest in the validation of individual experience developed in several ways. The scientific method attempts to minimize the influence of the scientist’s bias (his belief or notion of how matters are) on the outcome of the experiment. When testing a hypothesis, the investigator must be open to the possibility that the idea is incorrect. It is important that his views do not affect the results or the interpretation of them.

5. Clinical research

Clinical investigations are an important part of the medical research process. Using clinical trials, scientific discoveries can lead to better ways of preventing, detecting and treating diseases and medical conditions. Clinical studies are vital in finding out which treatments work, which do not, and why. In addition to testing a new product or treatment, these studies often contribute new knowledge about diseases and medical circumstances.

Each clinical trial rigorously follows a protocol. This is a written and detailed plan that explains the need for the study, what the study will do, and how it will be conducted. The different types of clinical trials include treatment, quality of life, prevention, early detection, and diagnostic.

Regardless of the type of trial being conducted, their protocols all contain the same basic elements.

6. Controlled and uncontrolled studies

Uncontrolled studies — where there is no control or placebo group — have limited value. Often only they serve as indicators of the validity of the hypothesis. An open-trial study affords some information regarding the efficacy of the approach under question, but is most often used strictly to establish its safety. Well-controlled studies are essential to obtaining definitive data regarding effectiveness of the treatment or drug being investigated.

Controlled studies all involve the use of a placebo or sham. Each is designed to resemble the actual experimental drug or treatment as closely as possible. An example of a placebo is a pill containing sugar or starch instead of the pharmaceutical compound being studied. By giving one group of participants a placebo and the other group the active treatment, the researchers can compare how the two groups respond and thereby get a truer picture of the real effects.

For example, in a study involving the effectiveness of static magnets, the sham would have the same outward appearance as the active magnets, but would not be magnetized. When a treatment is to be compared to a sham, the procedures that the patients follow should be the same for each group, and differ only in whether they received the magnetized or unmagnetized versions of the same object.

7. Blinding

As already stated, one of the key factors in conducting a meaningful clinical study is the elimination or minimization of bias. Conducting a sham- or placebo-controlled study has little value if the participants are aware of which group they are in. A patient who knows he has been given the sugar pill or the unmagnetized disc will be likely to report that his treatment had no effect. Similarly, if a study participant knows that he has been placed in the group receiving the item being tested, he is more inclined to believe that he has experienced a positive result.

In order to eliminate this type of bias, a technique known as blinding is used. As the name implies, a blind test ensures that the patient is unaware of whether he is receiving the treatment being evaluated.

The patient is not the only participant in the study who can inject bias into the results. The clinician interacting with the study participant can also commit this error. If a nurse, doctor or study administrator personally has no confidence in the treatment

being investigated, he or she may influence the patient's reported results. The converse is also true; a study administrator who strongly believes in the treatment and knows which group has been assigned the active ingredient, may lead the study subject to interpret the results more favorably. Sometimes this is intentional, and in other instances it may be accidental.

For this reason, the most reliable form of clinical testing is a double-blind study; that is, during testing neither the subjects nor the test administrators know which is the active group and which is the control.

8. Randomization

Before the study takes place, candidates are carefully screened in order to ensure they meet both the inclusion and exclusion criteria. Both criteria describe parameters of the study population.

One trial may be looking for adult males in the age range of 45 to 50. Females and those younger than 45 or older than 50 years of age will be excluded. The reason for this is so that the results will be an apples-to-apples comparison. When the study groups are composed of subjects who are as alike as possible, this helps to eliminate other factors that could influence the results.

In other, wider-ranging clinical trials, a much broader cross-section of the population may be recruited, so that the study helps to assess the efficacy of the treatment in individuals of every type.

For those meeting the selection criteria, some may appear more likely than others to benefit from the experimental treatment. This also could skew the study results. Consequently, a computer-driven procedure is used to randomly assign those qualifying for enrollment to the active or sham groups.

9. Multi-center trials

Bias contributed by the staff, instruments, technical ability or even the environment of an institution involved in the study can be minimized or negated by using a multi-center approach. Distributing the project between several different clinical settings can help to correct for this bias and deliver a more objective result.

10. Conclusion

Randomized, double-blind, sham-controlled, multi-center trials are the mainstay of clinical studies intended to demonstrate the safety and efficacy of a medical approach.