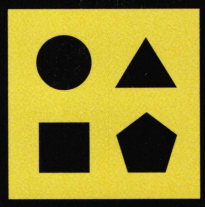
THE ESSENTIAL ELEMENTS (AND HISTORY) OF CLINICAL TRIALS



By Nancy Sokoler Steiner

● THE COMPARATIVE GROUP

What's the Difference

To reach a conclusion about the effectiveness of a new treatment or technique, scientists must be able to compare it to the current method.

An early example of this can be seen in the Bible, when **Daniel** convinces **King Nebuchadnezzar's** aide to let him and his group have 10 days to eat legumes and water instead of the usual diet of meat and wine. After the elapsed time, "their countenances appeared fairer and fatter in flesh than all the children which did eat the portion of the king's meat." Because they could demonstrate that they were as healthy as (or, in this case, healthier than) the people who ate the standard fare, Daniel and his group were allowed to eat their preferred foods.

In **1747**, Scottish naval surgeon **James Lind** conducted one of the first known trials using a control group. Lind tried adding a different food to the diets of each of six pairs of sailors with scurvy. Those eating oranges and lemons recovered.

"Their cases were as similar as I could have them," Lind wrote. He understood that groups must be alike to minimize the risk for a characteristic of one of the groups to account for any differences in results.

▲ RANDOMIZATION

The Luck of the Draw

To assure that groups will be similar and treatments assigned impartially, scientists use randomization. Study participants are assigned to either the control group or experimental group randomly.

Sir Ronald Fisher developed and applied the idea of randomization when looking at plant genetics in the early **1900s**. He was instrumental in developing many statistical methods that are still used today. In **1931**, **James Burns Amberson** used the concept of randomization in his study of a treatment for pulmonary tuberculosis. He described dividing patients into two comparable groups: "Then by a flip of the coin, one group became identified as Group I, the other as Group II.... The patients weren't aware of any distinctions in the treatment."

Another early randomized, controlled trial was conducted by researchers in London, who in **1948** tested the effectiveness of streptomycin in treating tuberculosis. Because the drug was in short supply, physicians used a control group that did not receive the drug. The physicians were prevented from knowing or influencing whether the patients were assigned to the experimental or control groups.

Throughout history, humans have sought to increase their knowledge about themselves and the world around them. The development of clinical trials is a product of this quest.

"Clinical trials are the best way we have to conduct fair comparisons," says Steven Piantadosi, MD, PhD, director of the Samuel Oschin Comprehensive Cancer Institute and Professor of Medicine. "They are the best means we have to draw reliable conclusions without corrupting the scientific process with human errors."

True clinical trials have existed only since the mid 20th century, although some of the elements they incorporate can be seen from early times. Dr. Piantadosi has identified several key concepts that distinguish clinical trials from other types of scientific inquiry.

As for the future, Dr. Piantadosi expects that the need for clinical trials will continue to rise. "We've learned that cancers we once thought of as homogeneous are not—they are several different diseases, with differences in the genetics or characteristics of the tumor, for example. That means we need more testing of therapies and combinations of therapies," says Dr. Piantadosi.

He adds that clinical trials are vital to solving medical issues beyond cancer, such as how to respond to unanticipated events like new diseases, resurgence of old diseases, and pandemics.

Finding the resources for future trials may remain a challenge. However, the trials themselves represent the most thorough, reliable, and ethical way scientists have to achieve true advances in medicine.

ETHICS

Do The Right Thing

Today, regulations are in place to assure that participants are not harmed in the course of clinical trials, and that trials are conducted in an ethical manner.

The **Nuremberg Code** was adopted after the world learned that the Nazis had conducted experiments on human beings. It articulated 10 concepts essential to ethical experimentation, including voluntary consent and the right of participants to leave a trial at any time. In **1973**, a national commission was formed to create ethical guidelines for medical research. Its recommendations, called the **Belmont Report**, listed three fundamental ethical principles for using any human subjects in an experiment: respect for participants, obligation to minimize harm and maximize benefits, and fair distribution of the benefits of research. These principles are the basis for the federal government's human-subject protection regulations.

Dr. Piantadosi notes an ethical dilemma in performing clinical trials: By definition, one group will receive a different treatment than the other. However, investigators do not know which treatment is superior—that is the very reason for the trial. Because of this, Dr. Piantadosi believes there is an ethical imperative to learn from trials as quickly and efficiently as possible to ensure the best available treatment for all.

RULES AND REGULATIONS

The Drug Development Paradigm

The federal government's regulations for drug safety and development have helped shape clinical trials and promoted their widespread use. The **1938 Food, Drug, and Cosmetic Act** (now the Food and Drug Administration, or FDA) required that new drugs be proven safe before they could be marketed. It came on the heels of an incident involving a drug given to children for streptococcal infections. The drug was produced using antifreeze as a solvent, and 107 children died as a result of ingesting it.

The **1962 Kefauver-Harris** amendment was added in part as a response to the crisis with thalidomide, a drug that caused birth defects. The amendment required that the FDA be given proof of effectiveness and safety of a drug before it could be marketed. It also mandated that advertisements include all benefits and risks, and that any adverse effects be reported to the FDA.