3000 Years of Medical Research

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Introduction

While clinical research as a profession is a relatively new concept, the field itself has been evolving since biblical times. Current training and education programs for clinical research professionals include a review of important historical events and documents which are still relevant today, but a more in-depth historical look can complement an individual's core competencies by providing additional insight and perspective.

The Cornerstones and Precursors of Modern Research

Standard training for clinical research professionals includes familiarity with landmark historical documents including the Nuremburg Code (1947), Declaration of Helsinki (first adopted in 1964), and Ethical Principles and Guidelines for the Protection of Human Subjects of Research (better known as the Belmont Report) (1978). Each of these documents was based on certain events which demanded humanitarian action; the Nuremburg Code was developed in response to unethical medical practices by the Nazi party during World War II, the Declaration of Helsinki expanded upon the Nuremburg Code's points to issue a formal code of medical ethics, and the Belmont Report was written at least partially in response to the Tuskegee Syphilis Study.

Another important, but perhaps lesser known, historical document is Henry K. Beecher's "Ethics and Clinical Research" article published in the New England Journal of Medicine in 1966. In his paper, Beecher brought to light the issue of participant exploitation in America. One of the examples in Beecher's paper was a study in which mentally-delayed children were injected with hepatitis to study the period of infectivity. Beecher concluded his paper by highlighting two critical ethical components of research; 1) informed consent, and 2) the "more reliable safeguard provided by the presence of an intelligent, informed, conscientious, compassionate, responsible investigator.. Beecher's comment that research publications must include a statement of ethics and his suggestion that data obtained unethically should not be published was ultimately adopted by the International Committee of Medical Journal Editors (also known as the Vancouver Group).

The documents described above, together with numerous domestic and international regulations and guidance documents, constitute the foundation of modern clinical research.

The Inception and Modernization of Clinical Research

Now let's take a look at some older examples of clinical research before it was known as such, starting with what is arguably the earliest documented study, and how it helped shape research conducted today. The examples described herein highlight the advancement of the field and include such concepts as control groups, placebos, randomization, and subject compensation.

Scholars generally agree that the oldest recorded clinical trial can be found in the Bible's book of Daniel. Around 600 BC, King Nebuchadnezzar II mandated that a group of children consume only meat and wine for three years, as the king believed the prescribed diet would confer the greatest health benefits. Daniel and three other boys objected to the king's diet, and it was agreed that this group of boys would eat only vegetables and water for ten days. After ten days, the king's impression was that vegetarian group appeared healthier and fitter than the meat-eating group. As a result of the experiment, the king switched all

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of the children to a vegetarian diet. After King Nebuchadnezzar's experiment, many centuries passed without significant advances in the field of research.

In 1537, a French barber-surgeon named Ambroise Paré was particularly interested in mitigating surgical pain and made an accidental discovery when treating battlefield wounds. When Paré ran out of the boiling oil solution which was standardly used to treat open wounds at that time, he made a mixture of egg yolks, rose oil, and turpentine, and applied it to the fresh wounds of multiple soldiers. The next morning, he was surprised to observe that the soldiers who were treated with the new mixture were faring significantly better than the soldiers who were treated with the boiling oil solution. From that point forward, Paré's philosophy was to treat patients only via means which he had personally observed to be beneficial. Although his approach was unique at the time, his writings would influence the practice of medicine for centuries to come.

The act of paying someone to participate in a medical research experiment was first documented in 1667 by the prolific diarist, Samuel Pepys. The historical event is in stark contrast to how subject compensation is managed today. In his diary, Pepys described the musings of his contemporaries; that perhaps if a lamb's blood were to be transfused into a dog, the dog may transform into a sheep, and if blood were exchanged between two people who were unhappily married, their differences would thereby be reconciled (presumably by becoming more similar to each other). To explore the effects of blood transfusion, a "poor and debauched" man was paid a relatively small sum to have sheep blood let into his body. The man was reported to have survived the experiment with no ill effects, though Pepys did not record specifics of the procedure itself.

Many clinical research professionals are already aware of Dr. James Lind's 1747 investigation on potential treatments for sailors afflicted with scurvy. In Dr. Lind's study, twelve sick sailors were divided into six pairs and were assigned different treatments including 1) a daily quart of cider, 2) 25 drops of an elixir of vitriol (sulfuric acid), 3) a daily cup of seawater, 4) a spicy paste of horseradish, mustard and garlic plus barley water, 5) six daily spoonfuls of vinegar, and 6) two oranges and one lemon daily. By the end of six days, one of the citrus-group sailors was fully cured and the other was well enough to care for those who were still sick. The study results were first published in 1753, but neither Dr. Lind nor the medical community at large was convinced that citrus fruit alone could cure scurvy. In 1794, ongoing Naval experience with citrus consumption eventually led to a daily ration of lemon juice on a 23-week voyage with no serious outbreak of scurvy. One year later, the Admiralty accepted a recommendation that lemon juice be issued routinely for the prevention of scurvy.

The field of clinical research as we know it today began to take shape at a much faster rate starting in the 1800's. The concept of a placebo was introduced in the early part of the century and was first included in a clinical trial by U.S. physician Austin Flint in 1863. Dr. Flint gave thirteen patients suffering from rheumatism an herbal extract which served as a placebo rather than the drug that was typically prescribed at the time. This study gave rise to what is now termed the "placebo effect."

Randomization was introduced in 1923 but was not implemented until 1946 by the Medical Research Council (MRC) of the UK. The MRC

Streptomycin in Tuberculosis Trials Committee was able to ethically conduct a randomized trial on tuberculosis (TB) patients due to the shortage of streptomycin at the time. In the trial, subjects were randomized using numbered envelopes to either 1) bed-rest plus streptomycin or 2) bed-rest alone. The results of the trial demonstrated that streptomycin was indeed beneficial for treating TB; however, they also showed that Mycobacterium tuberculosis could develop resistance to streptomycin. The trial was exceptionally well-designed and the randomization model used in the study was quickly adopted by the growing research community.

Full Circle: Current Clinical Trials Rooted in Ancient Medicine

Now that we've explored examples of early documented research, let's go back even further to a time when medical experimentation efforts were perhaps more rudimentary than those described in the previous section and focused primarily on natural remedies. Interestingly, many of these natural remedies are being revisited today and research is being conducted to explore their potential biological and/or chemical platforms.

The ancient medical system Ayurveda originated in India over 3,000 years ago and was first mentioned in the Vedic text, Rig Veda. Ayurvedic medicine is a holistic approach which includes the use of herbal compounds, minerals, and metal substances. While today's standard research practice is to randomize large groups of study subjects to pre-defined treatments, Ayurveda is more of an individualized approach, taking into consideration things such as universal connectedness, the body's constitution, and life forces. Therefore, the traditional "research" aspect of Ayurveda can be viewed as many separate experiments at the n=1 subject level.

These single-subject experiments have provided valuable medical insight over time by serving as miniature observational trials. Some modern researchers with a particular interest in Ayurveda have designed research trials to study Ayurvedic treatments using current research techniques including large sample sizes and randomization. In May 2017, a search of the database ClinicalTrials.gov using the search terms 'Ayurveda' and 'Ayurvedic' produced a combined result of 45 studies. A relatively recent publication on curcumin (the active ingredient in turmeric) describes the potential use of this herbal remedy for treatment of a variety of conditions including multiple myeloma, pancreatic cancer, colon cancer, psoriasis, and Alzheimer's disease (Hatcher et al, 2008).

Traditional Chinese Medicine (TCM) is another example of ancient medicine and is estimated to have an approximately 2,500 year history. Like Ayurveda, TCM is a holistic treatment approach and includes the use of herbal therapy. However, TCM employs a number of other techniques such as acupuncture, Tai chi, and cupping which distinguish it from Ayurveda.

According to the University of Minnesota's Center for Spirituality and Healing, TCM has undergone some of the most rigorous testing and research of all the treatment options offered by complementary and alternative therapies. In May 2017, a search of the database ClinicalTrials.gov using the search term 'Traditional Chinese Medicine' produced a result of 785 studies. A recent meta-analysis compared TCM + Western medicine to Western medicine alone for the treatment of irritable bowel syndrome (IBS). The results showed that

the TCM + Western medicine groups experienced a significant improvement in symptoms compared to the Western medicine only groups (Li et al, 2015). Another recent TCM-related publication showed that the addition of Speranskia tuberculate essential oil to paeoniflorin (PF) for treatment of rheumatoid arthritis greatly increases drug absorption in mice knee joints (Zhang et al, 2017).

Honey is an ancient natural remedy which spans many cultures and geographies. As far back as 8,000 years ago, the use of honey was documented in Stone Age paintings. It was used medicinally by ancient Egyptians, Assyrians, Greeks, and Romans, and is also a component of Ayurveda. Historically, honey has been used for a wide variety of ailments including gastrointestinal, cardiovascular, dermatological, and hepatic problems. Today, a specific type of honey, Manuka honey, is of particular interest in the wound care field. Manuka honey is produced by bees which pollinate Manuka bushes in New Zealand, and differs from other types of honey in that its antibacterial property is due to methylgloxal rather than hydrogen peroxide. This special property makes Manuka honey a better choice for combatting biofilms. A search of the ClinicalTrials.gov database in May 2017 using the search term 'Manuka honey' produced a result of 12 studies, and a search using the term 'honey' produced a result of 100 studies. A recent study sought to explore the efficacy of a natural anti-bacterial agent in light of increasing resistance of various bacteria to conventional antibiotics. The study showed that the addition of Manuka honey to two specific antibiotics (colistin and tobramycin) created a synergistic effect and significantly enhanced the drugs' ability to destroy Pseudomonas aeruginosa and Burkholderia cepacia bacterial strains. The authors concluded that the addition of Manuka honey to a treatment regimen for chronic respiratory infections may be beneficial for cystic fibrosis patients (Jenkins et al, 2015).

Summary

The field of clinical research has been evolving for thousands of years, and it continues to evolve today. As researchers, we live in an exciting time with a vast pool of knowledge and experience at our fingertips thanks to the efforts of curious and enterprising individuals who came before us.

For assistance with identifying and fully utilizing all of the regulatory and clinical research-related tools available today, contact Samantha Thrun at mailto:sthrun@rcri-inc.com or 952-224-2260 to be put in touch with an RCRI expert.

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