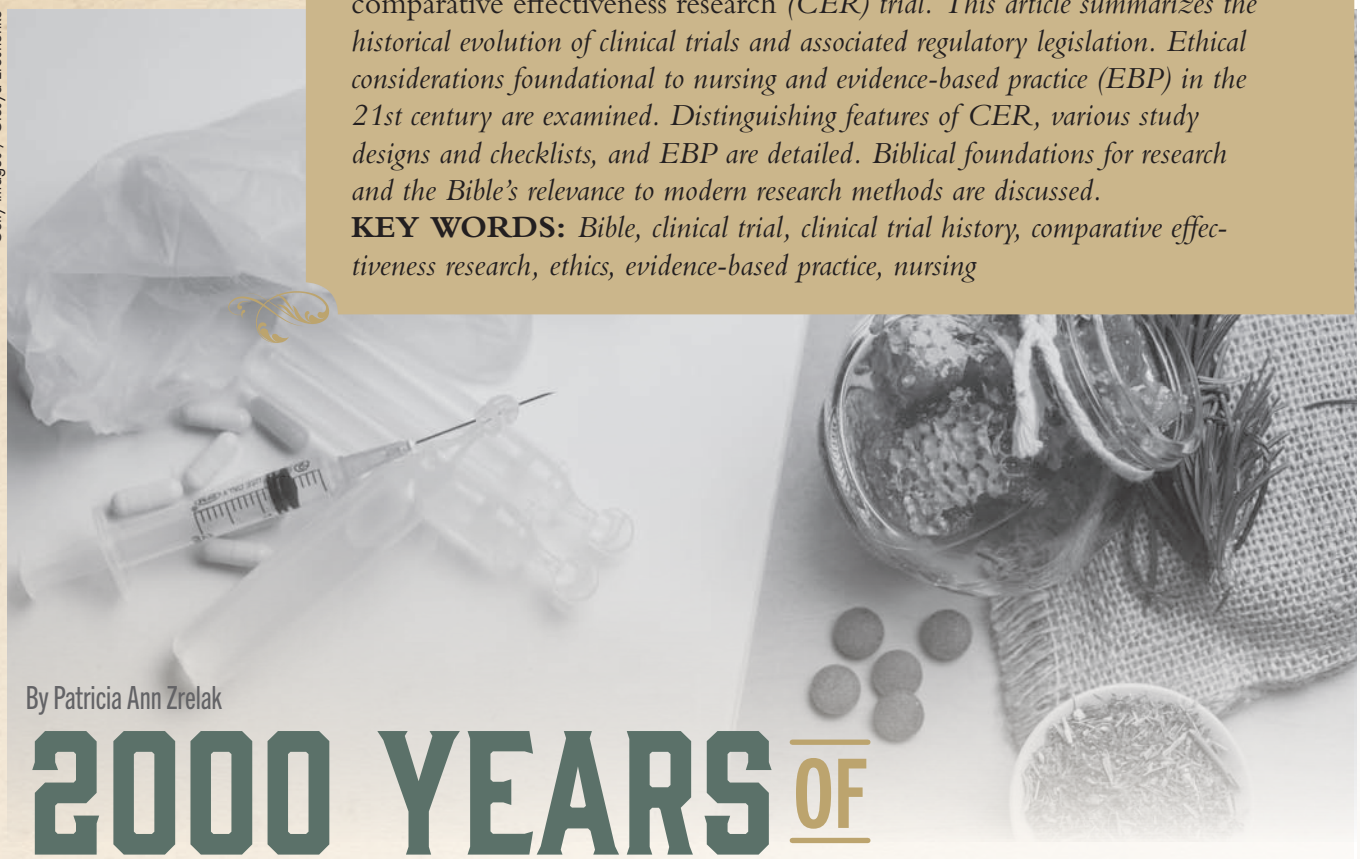
HISTORICAL SPOTLIGHT

ABSTRACT: *Although the first documented clinical trial as described in the biblical book of Daniel dates to 606 BC, the prophet Daniel's nutrition study is contemporary in both approach and topic and could be considered the first* comparative effectiveness research *(CER) trial. This article summarizes the historical evolution of clinical trials and associated regulatory legislation. Ethical considerations foundational to nursing and evidence-based practice (EBP) in the 21st century are examined. Distinguishing features of CER, various study designs and checklists, and EBP are detailed. Biblical foundations for research and the Bible's relevance to modern research methods are discussed.*
KEY WORDS: *Bible, clinical trial, clinical trial history, comparative effectiveness research, ethics, evidence-based practice, nursing*



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By Patricia Ann Zrelak

2000 YEARS OF CLINICAL TRIALS: THE EVOLUTION OF EVIDENCE-BASED PRACTICE

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The author declares no conflict of interest.
Accepted by peer review 3/11/2022.

DOI:10.1097/CNJ.0000000000001047

SDC **Supplemental digital content** is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of the article at journalofchristiannursing.com.

Although clinical trials first became popular in the mid-20th century (Redmond & Colton, 2001), the earliest known well-documented clinical trial dates to 606 BC, as recorded in the biblical book of Daniel. Daniel was ahead of his time! Today, the clinical trial is the backbone of *evidence-based practice* (EBP), the idea of basing healthcare practices on the best evidence available along with clinical expertise and patient preference (Sackett et al., 1996). This article relays the historical evolution of clinical trials, associated regulatory legislation, and ethical considerations important in EBP for nurses practicing in the 21st century, emphasizing the biblical foundations and relevance of newer clinical research methods, such as *comparative effectiveness research* (CER).

THE ABCs OF CLINICAL TRIALS

As detailed in Redmond and Colton (2001), clinical trials in their simplest form involve the application of at least one experimental variable (also known as

an intervention) under the control of the experimenter or researcher. The research team applies the intervention to an individual or group. The observation of the treatment effect (also known as the endpoint or clinical outcome) is then measured and compared to either the baseline measurement or—as further detailed below—to a comparator outcome in a comparison group. Consequences are defined before the start of the trial and are infinite in type. The most common outcomes are death, occurrence or recurrence of a morbid condition, or other types of measure indicative of a clinical change, such as a change in weight, blood pressure, serum cholesterol, or mental state.

In a controlled trial, the researcher measures the effect of the treatment against a comparison or comparator (Redmond & Colton, 2001). When the treatment assignment is randomized, the trial is known as a randomized clinical trial (RCT). Essential to the conduct of the clinical trial, researchers must administer the comparison type treatment, if present, over the same time interval and under similar conditions. Often the comparison is "usual care." When usual care is the standard of care based on a high level of evidence, it is unethical for researchers and providers to withhold standard care, regardless of trial status. The exception to this rule is limited to situations where the experimental treatment has sufficient evidence to demonstrate *equipoise*, known as similar clinical efficacy (Redmond & Colton, 2001).

Sometimes a placebo is used, especially when the intervention is a medication. A placebo provides a form of treatment blinding or masking. Blinding and masking, along with randomization, are essential to prevent the introduction of measurement or selection bias (Redmond & Colton, 2001). If the participant is blinded (which is very important), the study is single blinded. The clinicians, especially those involved in ascertaining the outcome variable, also should be blinded to treatment allocation (a double-blinded study). Additionally, the statistician should be blinded. For most studies, it is best when the patient/participant, treating provider, the person assessing the response, and data handlers are all blinded (complete blinding; Redmond & Colton, 2001). Randomized and blinded clinical trials, in general, are designed to maximize internal study validity.

THE FIRST KNOWN CLINICAL TRIAL

One of the earliest clinical trials documented in the literature is the nutritional study in Daniel 1:1-17 (Bhatt, 2010; Ederer, 2005). Daniel was an Israelite from Judah who had been taken captive to Babylon, one of the "young men without any physical defect, handsome, showing aptitude for every kind of learning, well informed, quick to understand" (Daniel 1:4, NIV). Leading up to this trial, King Nebuchadnezzar of Babylon had ordered Daniel and three fellow Hebrew captives (Hananiah, Mishael, and Azariah), along with princes and "the King's seed" (v. 3, KJV), to eat the provision of his meat and wine each day for 3 years so that they might "stand before the King" (v. 5, KJV; be in peak condition). Not wanting to defile himself (by eating food not allowed for Jews), Daniel asked his guard if he and his companions could eat "pulse" (v. 12, KJV), a type of legume, and water instead of the king's prescribed diet. Though the guard was skeptical and scared about the king's response, the guard granted the four Jews a 10-day trial. At the end of the trial, Daniel and his three companions had countenances (faces), as hypothesized, that appeared fairer and fatter in the flesh than all the children who ate the king's meat and wine. God also blessed them with the patient-centered outcome of knowledge and skill in all learning and wisdom.

We have returned to basic research principles outlined in the Bible.

This is the first known example of an unblinded and non-RCT with a comparison group (Bhatt, 2010). See Figure 1 for an outlined hypothesized research question using the PICOT typology. In addition to being the first documented experimental trial, this trial targets new thoughts on clinical trial design, as well as addresses two contemporary dietary topics: (1) benefits of a plant-based diet versus a diet that includes meat, and (2) the potential health benefits versus harm of ingesting wine.

EVOLUTION OF CLINICAL TRIALS AND ETHICAL CONSIDERATIONS

After the Daniel trial, it was not until 1537 that a subsequent clinical trial was made known. To treat gunshot wounds after running out of boiling oil, Ambroise Paré, a French surgeon, tried an alternative treatment: an ointment made of egg yolks, oil of roses, and turpentine (Bhatt, 2010). Paré discovered that soldiers treated with the boiling oil developed fevers and had swelling and pain around their wounds. On the contrary, those treated with the new concoction experienced little pain, slept through the night, and their injuries were neither swollen nor inflamed. Based on these results, Paré vowed to never again burn the wounds of gunshot victims (Packard, 1921/2019).

A famous trial was conducted by the physician James Lind in 1747, targeting treatment for scurvy (Bhatt, 2010; Redmond & Colton, 2001). Although historians can trace the disease to 1550 BC, when scurvy was effectively treated with onions and vegetables, tales from pirates and British sailors in the 1700s made scurvy infamous (Maxfield & Crane, 2022). Lind treated six groups of two people per group for 6 days (Lind, 1753/1983). Those assigned two

FIGURE 1. PICOT Question for Daniel's Uncontrolled Clinical Trial

Population	Adult males (Daniel, Hananiah, Mishael, and Azariah, along with king's seed and princes)
Intervention	Diet of pulse (legumes) to eat and water to drink
Comparison	King's meat and wine
Outcome	Countenance and fitness
Time	10 days

oranges and a lemon per day showed improvement of their signs and symptoms, becoming fit for duty. Although Lind had the treatment correct and would become known as the father of modern science, his rationale was incorrect. Lind concluded that citrus fruits cured scurvy because of their action on the digestive juices. We now associate scurvy with a vitamin C deficiency, discovered in 1927 (Maxfield & Crane, 2022). May 20 is known as International Clinical Trials Day, as Lind's trial began on this day in 1747 (Lumadue, 2018).

Often left out of compendiums on clinical trials is Florence Nightingale, the first recognized nurse scientist (Mackey & Bassendowski, 2017; Stolley et al., 2000). Besides being inspired by God's calling on her life, much of Nightingale's work in the mid-1800s was pragmatic and related to the establishment of what is known today as "best practices" (Stolley et al., 2000). Her work targeted nursing standards and practice, the healthcare environment and sanitation, advocacy and training, and impacts within systems of care delivery (Florence Nightingale Museum, n.d.). Her work visually depicted the effects of infectious disease on mortality between the British hospitals in Scutari, Turkey, and other hospitals and the battlefield in her famous cox plots (also known as Coxcomb graphs or charts); these cox plots earned Nightingale's historical acceptance into the British Statistical Association in 1858 (Florence Nightingale Museum, n.d.).

The use of a placebo, defined as "an epithet given to any medicine more to please than benefit the patient," emerged during the 1800s (Bhatt, 2010, p. 7) and was first noted in *Hooper's Medical Dictionary* in 1811 (Bhatt, 2010; Lumadue, 2018), although according to Shapiro (1968), it was first noted 8 years earlier in Fox's (1803) *A New Medical Dictionary*. The first well-known U.S. trial using a placebo was Austin Flint's 1863 trial comparing a dummy remedy of an herbal extract to an active treatment for rheumatism.

Around this time, many unsupported medical claims existed (Dodgson, 2006). The 19th century was a pivotal period of drug traditions and included the invention of the hypodermic needle in the 1840s. The Victorians ingested not just alcohol and opium but cannabis, coca, and mescal (Dodgson, 2006). By 1905, more than 28,000 medicines had been patented. These were mainly useless mixtures, potions, and concoctions produced or marketed in the United States (Gandhi, 2013). Among the false claims was Clark Stanley's fake Snake Oil Liniment, which became synonymous with the peddling of fraudulent products and the term, the "snake oil salesman" (Gandhi, 2013).

This era of pseudo-medical remedies led to the passage of the Pure Food and Drug Act of 1906, the first of a series of progressive federal consumer protection laws enacted by Congress in the 20th century, which led to the creation of the Food and Drug Administration (FDA) in 1930. Congress passed these laws just in time for the birth of the modern pharmaceutical industry which emerged during the 1920s and 1930s with the discovery and mass production of penicillin and other antibiotics (Wratschko, 2009). For other important research milestone events and corresponding legislation, see Timeline of Significant Research Milestones (Table 1) as supplemental digital content (SDC) at http://links.lww.com/NCF-JCN/A104.

Clinical trials advanced significantly in the 20th century. Although a negative and potentially harmful trial, a significant milestone was the first double-blind controlled trial investigating patulin treatment (an extract of *Penicillium patulinum*) compared to nontreatment for the common cold (Bhatt, 2010; Medical Research Council, 1943/2004). This trial also was notable for its use of new statistical methods for sampling and included noteworthy statistician M. Greenwood (Bhatt, 2010). The subsequent pivotal trial investigated the use of streptomycin in treating tuberculosis (TB). Investigators included the famous researcher Sir Bradford Hill and colleagues (Treatment of Pulmonary TB, 1950). After this and related TB trials, the number of clinical trials indexed by the U.S. National Library of Medicine steadily increased (Redmond & Colton, 2001). The passage of the U.S. FDA Kefauver-Harris Act in 1962 (also known as the Drug Efficacy Act), legal requirements meant rigorous empirical testing of clinical trials in human beings to establish claims regarding drug efficacy and safety (Meadows, 2006; Redmond & Colton, 2001; U.S. Food & Drug Administration, 2018). The thalidomide disaster that resulted in approximately 2,000 child deaths and more than 10,000 children born with a congenital disability greatly influenced

the passage of this act (Kim & Scialli, 2011; Meadows, 2006). Thalidomide was used first as an over-the-counter medication for morning sickness in Germany in 1957 before spreading to 46 other countries by 1960, although its use in the United States was limited (Meadows, 2006).

Ethical considerations surrounding clinical research expanded during the mid-1900s in part as a response to the atrocities of the Holocaust and Nazi medicine, which led to the Nuremberg trials and creation of the *Nuremberg Code*, a set of 10 ethical principles for human experimentation. The 1932–1972 U.S. Public Health Service Syphilis Study at Tuskegee and the Willowbrook State School Viral Hepatitis Study of the 1950s led to further concerns about research. These studies collectively led to the 1974 National Research Act, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, and the 1979 *Belmont Report* (Krugman, 1986). The *Belmont Report* protections emphasize the three fundamental ethical principles of respect for persons, beneficence, and justice.

With ethical considerations in mind, clinical trials for interventions such as drugs are now classified by phases, paralleling a time-ordered sequence and shifting focus with clinical phase (Redmond & Colton, 2001). See Table 2, Phases of Clinical Trials, as SDC at http://links.lww.com/NCF-JCN/A104. With the advancement of statistics, due partly to the availability of powerful personal computers in the 1980s, newer trial designs evolved, including those involving Bayesian statistics to assist with drug escalation (Redmond & Colton, 2001).

TABLE 3. Principal Distinctions Between Explanatory and Pragmatic Trials

	Explanatory trial	Pragmatic trial
Aim	Efficacy	Effectiveness
Eligibility	Strict inclusion/exclusion criteria	All participants with the condition of interest are eligible, except when the safety of the participants is a concern
Intervention	Firmly standardized	The clinician has the flexibility to individualize and alter
Participants	Selected based on study-related criteria; non-adherent patients are not considered	Little or no selection criteria
Comparison intervention or care	Strictly defined and enforced	Flexibility with individualization within constraints of usual practice
Investigator expertise	Experts	A wider range of practitioners
Blinding	Usually all parties are blinded	Only independent assessors and laboratory personnel are blinded
Setting	Well-resourced, rigorously controlled	Usual clinic or public health practice setting
Follow-up	Frequent, with extensive data collection	Limited follow-up
Primary outcomes	Strictly defined	Less structured and includes adverse events
Participant adherence to treatment or intervention	Adherence is closely monitored; study-related interventions to maintain or promote adherence	Limited or no measures of adherence with no interventions to facilitate adherence
Investigator adherence to protocol	Strict adherence with documentation	Limited measurement or attempts to influence adherence
Primary analysis	Intent to treat but may also include per-protocol analysis and other types of statistics	Intent to treat

The increase in research in the 1970s and 1980s led to the EBP movement, founded by David Sackett, David Eddy, Archie Cochrane, and others (Djulbegovic & Guyatt, 2017). They highlighted the need for strengthening the empirical practice of medicine which included proposing initial evidentiary rules for guiding clinical decisions. Evidence-based practice emphasizes the education of frontline clinicians in assessing the credibility of research evidence, understanding the results of clinical studies, and determining how best to apply research results to everyday practice (Djulbegovic & Guyatt, 2017).

Evidence-based practice emphasizes the use of the most robust evidence possible. Notably, this includes using meta-analyses and systematic reviews, advanced by the Cochrane Collaboration, and grading rules to weight the strength of the evidence, such as the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria (Djulbegovic & Guyatt, 2017). This movement also led to clinical epidemiology and health services research, resulting in the subspecialty of CER (Rogers, 2013). Focusing more on real-world experience and effectiveness over efficacy, CER overcomes some limitations of traditional trials.

Bernadette Mazurek Melnyk, a nurse and editor of the journal *Worldviews on Evidence-Based Nursing*, is a leader in EBP, especially as it relates to nursing practice (Melnyk & Fineout-Overholt, 2019). Much of Melnyk's work targets improving

quality of healthcare, healthy behaviors, and patient outcomes through the implementation and sustainment of EBP. Her work includes the use of newer study designs such as CER.

ACTIONABLE INTELLIGENCE

Also referred to as patient-centered outcomes research, CER is defined as "the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or improve care delivery" (Institute of Medicine, 2009, p. 13). Each new study, rather than being definitive, adds knowledge regarding the benefits and harms (Rogers, 2013). The purpose is to assist consumers, clinicians, purchasers, and policymakers to make informed decisions that will improve healthcare at both the individual and population levels—known as actionable intelligence (Rogers, 2013).

Comparative effectiveness research has several distinguishing features (Institute of Medicine, 2009; Rogers, 2013):

1. The intent is to inform a specific clinical or health-related decision. These decisions can be at the individual or population levels.
2. It involves the comparison of viable treatments, services, or policies. Unlike clinical trials, choices are those appropriate for individuals or populations that do not include placebos or sham treatments.
3. The research focus is within the real-world setting of everyday life. The target is those with the condition seen during ordinary clinical practice accounting for the social context, not restricted to those seen within a structured research environment.
4. The outcomes are meaningful and essential to the subjects, such as quality of life and functional outcomes.
5. The research strives to be more informative at the individual level. Hence, it seeks to answer the patient-centered question: What works best for the individual?


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Comparative effectiveness research encompasses a vast array of study designs. This includes experimental or quasi-experimental designs, such as interrupted time series, designed delays, cluster-randomized trials, individually randomized trials, pragmatic trials, or adaptive trials, as well as classic and newer nonexperimental designs (Dreyer et al., 2016). In general, Dreyer et al. (2016) note that CER tends to be more pragmatic (Does it work?) compared to tightly regulated explanatory trials (Can it work?). However, this distinction occurs along a continuum, and a study may have attributes of both; see Table 3. The PRECIS tool (**Pr**agmatic-**E**xplanatory **C**ontinuum **I**ndicator **S**ummary) enables investigators to design trials acknowledging the explanatory pragmatic continuum in 10 domains (Patsopoulos, 2011).

Regardless of the type, research conduct should follow appropriate guidelines. The GRADE (Grading of Recommendations Assessment, Development, and Evaluation) criteria provide a very sophisticated rating for the hierarchy of evidence. Initially developed for meta-analyses, GRADE criteria allow not only for limitations in bodies of evidence from RCTs, but for the rating of observational studies as high, and provide a framework for the evaluation of management studies, diagnostic and prognostic issues, animal studies, and network meta-analyses. Over 100 organizations, including the Cochrane Collaboration, the National Institute for Health and Care Excellence, World Health Organization, and UpToDate, have adopted the GRADE criteria (Atkins et al., 2004). Specific to observational CER studies is the GRACE (**G**ood **R**ese**A**rch for **C**omparative **E**ffectiveness) checklist (Dreyer et al., 2016). Researchers can find other checklists for improving the design, conduct, and reporting of research on the EQUATOR (**E**nhancing the **QUA**lity and **T**ransparency **O**f health **R**esearch) website. This includes checklists for the different types of studies, such as the CONSORT (**Con**solidated **S**tandards of **R**eporting **T**rials.) checklist targeting the reporting of RCTs.

BACK TO THE BIBLE AND DANIEL

Although researchers and others often describe the Daniel trial as a rudimentary historical clinical trial, the Daniel study is modern and pragmatic upon further examination. It addresses each of the five vital distinguishing features of CER as outlined in this article. Historically, it informs Daniel, his companions, and the king's court about the effectiveness of their vegetarian diet compared to the king's meat- and wine-laden diet. Important to CER, the Daniel study was based on the real-world setting of daily life. The study outcomes were meaningful and vital not only to Daniel and his companions but also to the guard and the king. Importantly, results were informative at the individual level, as those testing the diet experienced

Web Resources

- **EQUATOR Network**
  https://www.equator-network.org
- **Florence Nightingale Museum**
  https://www.florence-nightingale.co.uk
- **GRACE (Good ResArch for Comparative Effectiveness)**
  https://www.graceprinciples.com
- **GRADE working group**
  https://www.gradeworkinggroup.org
- **PRECIS-2**
  https://www.precis-2.org

positive outcomes in their countenances and blessings of knowledge and skill in all learning and wisdom.

The study results also support the Bible's relevance, especially the applicability of the Old Testament to current-day problems. Study relevance includes the scope of the question (harm and benefits of a vegetarian versus a meat diet; water compared to wine) and its methodology.

Within the Bible, God also provides guidance on research protections. Although the *Belmont Report* (The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) remains the world's basis for human subject protection regulations, one can appreciate these principles as biblically-based tenets. This includes careful consideration of 1) informed consent, 2) risk-benefit assessment, and 3) selection of research subjects. Biblical justice sets forth that humans are to treat others fairly and to respect that all are created equal in God's image. As Jesus taught, "So in everything, do to others what you would have them do to you" (Matthew 7:12, NIV) and "Love your neighbor as yourself" (Mark 12:31, NIV). These principles can guide study design, subject recruitment, ascertainment of informed consent, and data collection processes.

CONCLUSION

The history of clinical trials over the last 2,000 years has become increasingly sophisticated and elaborate. This includes advancement in the complexity of study designs, statistics, and understanding of health and disease. Although man has never completely separated health and disease from religion, modern secular thought in general excludes the Bible as a credible source for conducting clinical research. With scientific advancements over recent years, it is remarkable that we have returned to basic research principles outlined in the Bible as advanced methods to answer pragmatic and contemporary questions regarding health and disease. In addition to acknowledging the Daniel trial as the first clinical trial, it may be time to formally recognize the Daniel trial as the first CER trial as well.

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