Chapter 1
The Beginning – Historical Aspects of Clinical Research, Clinical Research: Definitions, "Anatomy and Physiology," and the Quest for "Universal Truth"

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Scientific inquiry is seeing what everyone else is seeing, but thinking of what no one else has thought

A. Szentgyorgyi. 1873 (he won the Nobel Prize for isolating Vitamin C) [1].

Abstract To answer many of their clinical questions, health care practitioners need access to reports of original research. This requires the reader to critically appraise the design, conduct, and analysis of each study and subsequently interpret the results. This first chapter reviews some of the key historical developments that have led to the current paradigms used in clinical research, such as the concept of randomization, blinding (masking) and, placebo-controls.

Keywords Clinical research definition • Clinical research history

Introduction

As a former director of a National Institutes of Health (NIH)-funded K30 program it was my responsibility to provide a foundation for young researchers to become independent principal investigators. A part of our curriculum was a Course entitled

Hulley S, Cummings S, Browner WS. Designing clinical research. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000.

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'The Fundamentals of Clinical Research.' This course, in addition to guiding students, towards becoming research investigators, was also designed to aid 'students' who wanted to read the medical literature more critically. The importance of this latter point is exemplified by the study of Windish et al., who note "*physicians must keep current with the clinical information to practice evidence-based medicine…. to answer many of their clinical questions, physicians need access to reports of original research. This requires the reader to critically appraise the design, conduct, and analysis of each study and subsequently interpret the results*" [2]. Although aimed at physicians, this observation can and should be applied to all health scientists who must read the literature in order to place the results in context. The Windish study surveyed 277 completed questionnaires that assessed knowledge about biostatistics, and study design. The overall mean percent correct on statistical knowledge and interpretation of results was 41.4 %.

It is my belief that the textbooks currently available are epidemiologically "slanted". There is nothing inherently wrong with that slant, but I have written this book to be more specifically geared to the clinical researcher interested in conducting Patient Oriented Research (POR). In this first chapter I will provide a brief overview of the history of clinical research. The chapter will also address the question of why we do clinical research; define 'clinical research'; discuss our quest for 'universal truth' as the reason for doing clinical research; outline the approach taken to answer clinical questions; and describe (as Hulley and colleagues so aptly put it) 'the anatomy and physiology of clinical research' [3].

Future chapters will examine such issues as causality (i.e., causal inference or cause and effect relationships); the strengths and weaknesses of the most popular clinical research designs; regression to the mean; clinical decision making; meta-analysis; and the role of the Food and Drug Administration (FDA) in the clinical trial process. We will also focus on issues related to randomized clinical trials, such as the intention-to-treat analysis, the use and ethics of placebo-controlled trials, and surrogate and composite endpoints.

Definition of Clinical Research

The definition of clinical research might appear to be self-evident; however, some researchers have narrowly defined clinical research to refer to clinical trials (i.e., intervention studies in human patients), while others have broadly defined it as any research design that studies humans (patients or subjects) or any materials taken from humans. This latter definition may even include animal studies, the results of which more or less directly apply to humans. For example, in 1991, Ahrens included the following in the definition of clinical research: studies on the mechanisms of human disease; studies on the management of disease; in vitro studies on materials of human origin; animal models of human health and disease; the development of new technologies; the assessment of health care delivery; and field surveys [4]. In an attempt to simplify the definition, some wits have opined that clinical research occurs when the individual performing the research is required to have malpractice

insurance, or when the investigator and the human subject are, at some point in the study, in the same room, and both are alive and warm. So, there is a wide range of definitions of clinical research, some valid, some not. I have chosen to adopt a 'middle of the road' definition that encompasses the term 'patient-oriented-research,' which is defined as research conducted with human subjects (or on material of human origin) for which the investigator directly interacts with the human subjects at some point during the study. It is worth noting that this definition excludes in vitro studies that use human tissue that may or may not be linked to a living individual unless the investigator during the conduct of the trial has significant interaction with a living breathing human.

History of Clinical Research

Perhaps the first clinical trial results were those of Galen (circa 250 BC) who concluded that 'some patients that have taken this herbivore have recovered, while some have died; thus, it is obvious that this herbivore fails only in incurable diseases.' Galen's observations underline the fact that even if we have carefully and appropriately gathered data, there are still subjective components to its interpretation, indicating our quest for 'universal truth' may be bedeviled more by the interpretation of data than by its accumulation (more about this in Chap. 3).

James Lind is generally given credit for performing and reporting the first 'placebo-controlled' interventional trial in the treatment and prevention of scurvy. In the 1700s, scurvy was a particularly vexing problem on the long voyages across the Atlantic Ocean. The research question that presented itself to Lind was how to prevent the condition. To arrive at an answer, Lind did what every good researcher should do as the first step in converting a research question into a testable hypothesis—he reviewed the existent literature of the time. In so doing, he found a report from 1600 that stated '*1 of 4 ships that sailed on February 13th, 1600, was fortuitously supplied with lemon juice, and almost all of the sailors aboard the one ship were free of scurvy, while most of the sailors of the other ships developed the disease*.' This was not a planned experiment, however. The first planned experiment was perhaps one that involved smallpox, performed in 1721, in which six inmates of Newgate Prison were offered to have their sentence commuted if they volunteered for inoculation. All remained free of smallpox. However, in this experiment there was no concurrent control group. Returning to Lind's review of the literature, on the one hand, Lind's job was easy; there was not a great deal of prior published works. On the other hand, Lind did not have computerized searches via Med Line, Pub Med etc available.

As a result of the above, in 1747, Lind set up the following trial. He took 12 patients 'in the scurvy' on board the HMS *Salisbury*. '*These cases were as similar as I could have them.… They lay together in one place…and had one diet common to all. The consequence was that the most sudden and visible good effects were perceived from the use of oranges and lemons*.' Indeed, Lind evaluated six treatment groups:

Table 1.1 Lind's 1747 "clinical trial"

Lind's description	Modern day RCT correlate
"These cases were as similar as I could find them"	Inclusion/exclusion criteria
"They lay together in one place and had one diet common to all"	Common treatment save for the intervention of interest
"Six treatment groups were evaluated"	Parallel group design
"The rest served as controls"	Active control groups
"Two…were put under a course of sea water"	Placebo group?
"The… the most sudden and visible good effects were perceived from oranges and lemons"	Interpretation

'*one group of two was given oranges and lemons. One of the two recovered quickly and was fit for duty after 6 days, while the second was the best recovered and was assigned the role of nurse for the remaining patients*.' The other groups were each treated differently and served as controls. If we examine Lind's 'study' we find a number of insights important to the conduct of clinical trials as follows. For example, he noted that *'on the 20th May, 1747, I took twelve patients in the scurvy on board the Salisbury at sea… Their cases were as similar as I could have them. They all in general had putrid gums, the spots and lassitude, with weakness of their knees…' Here Lind was describing eligibility criteria for his study. He continues, '…They lay together in one place, being a proper apartment for the sick in the forehold; and had one diet in common to all…' '… Two of these were ordered each a quart of cyder a day. Two others took twenty five gutts of elixir vitriol three times a day upon an empty stomach,*

… Two others took two spoonfuls of vinegar three times a day
… Two … were put under a course of sea water.
… Two others had each two oranges and one lemon given them every day.
… The two remaining patients took the bigness of a nutmeg three times a day.'

By this description, Lind described the interventions and controls. To continue, '… *The consequence was that the most sudden and visible good effects were perceived from the use of the oranges and lemons; one of those who had taken them being at the end of six days fit four duty. The spots were not indeed at that time quite off his body, nor his gums sound; but without any other medicine than a gargarism or elixir of vitriol he became quite healthy before we came into Plymouth, which was on the 16th June*.' This latter description represents the outcome parameters and interpretation of his study. In summary, Lind addressed the issues of parallel-group design and the use of control groups, and he attempted to assure similarity between the groups except for the intervention (Table 1.1).

Clearly, sample size considerations and randomization were not used in Lind's trial nor were ethics and informed consent mentioned, but this small study was amazingly insightful for its time. Other selected milestones in the history of clinical research include:

- Fisher's introduction of the concept of randomization in 1926; [5]
- The announcement in 1931 by the Medical Research Council that they had appointed '*a therapeutics trials committee…to advise and assist them in arranging*

for properly controlled clinical tests of new products that seem likely on experimental grounds to have value in the treatment of disease' [6];

- Amberson and colleagues' introduction of the concept of 'blindness' in clinical trials [6], and their study of tuberculosis patients where the process of randomization was applied [7]. They noted that after careful matching of 24 patients with pulmonary tuberculosis, the flip of a coin determined which group received the study drug [7].

Further analysis of the tuberculosis streptomycin study of 1948 is regarded by many, as the beginning of the beginning of the modern era of clinical research and is instructive in this regard. In the 1940s tuberculosis was a major public health concern, and randomization was being recognized as a pivotal component to reduce bias in clinical trials [8]. As a result the Medical Research Council launched a clinical trial in which 55 patients were randomized to treatment with bed rest (the standard of care treatment at that time) and 52 were treated with bed rest alone [9].

Other significant developments include reference to the use of saline solution in control subjects as a placebo, and the requirement in 1933 that animal toxicity studies be performed before human use [8]. In the 1940s, the Nuremberg Code, the Declaration of Helsinki, the Belmont Report, and the doctrine of Good Clinical Practice (GCP) were developed, which will be discussed in more detail later. As mentioned above, In1948, the Medical Research Council undertook a streptomycin study [9] which was perhaps the first large-scale clinical trial using a properly designed randomized schema. This was followed by an antihistamine trial that used a placebo arm and double-blind (masked) design [10].

In 1954, there were large-scale polio studies—field trials of 1.8 million school-age children. A controversy regarding the best design resulted in two trials, one design in which some school districts' second graders received the dead virus vaccine while first and third graders acted as the controls (i.e. a group clinical trial); and another design in which second graders randomly received either the vaccine or a saline injection. Both studies showed a favorable outcome for the vaccine (Fig. 1.1).

In 1962, the thalidomide tragedy became widely known and resulted in the tightening of government regulations as they applied to drug development and approval (also see Chap. 6). The story behind this tragedy is instructive. By 1960, thalidomide worldwide was being sold, but not in the United States. At the time, the prevailing US law was the 1938 Federal Food, Drug, and Cosmetic Act, which required proof of safety be sent to the FDA before a medication could be approved for sale in the United States. The law did not require demonstration of efficacy for approval. It also allowed "investigational" or "experimental" use of a drug while approval for its sale was being sought, allowing a medication to be widely distributed prior to approval. The application for use of thalidomide in the USA was given to Frances Kelsey who noted a lack of teratogenicity data, and she also had other worries about thalidomide. As a result, Kelsey rejected the application and requested additional data from the company, who complained to her superiors that she was nit-picking and unreasonable. Kelsey continued to refuse to allow thalidomide for sale in the United States, and in total, the company resubmitted its application to

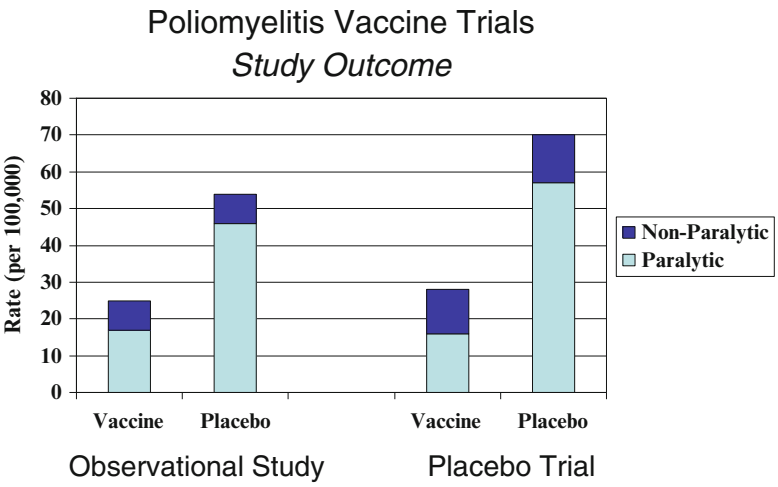

Fig. 1.1 Results from the use of polio vaccines used in both an observational trial and a placebo controlled clinical trial

the FDA six times, but with no new evidence in those applications, Kelsey refused approval. Subsequently, reports regarding a number of birth defects were reported and the drug was subsequently removed worldwide [11].

As prior mentioned, at the time of the thalidomide disaster, trials of new drugs were required to prove safety but not efficacy as described under the FDA's 1938 Act. As a result of the disaster, tightening of the regulations was instituted and trials were to have an "*adequate and well-controlled design*" before approval of any new drug. This was followed by the Drug Efficacy Study Implementation (DESI) review and the FDA's development of the four stages of clinical trials necessary for new drug approval, which set the stage for today's drug approval process (see Chap. 6).

In the 1970s and 1980s, clinical research was prospering, but by the 1990s there began a decline in the number of new clinical investigators. This trend caught the eye of a number of academicians and the NIH, which then commissioned the Institute of Medicine (IOM) to address ways to stimulate individuals to pursue careers in clinical investigation, to define appropriate curricula for training, and to ensure adequate support mechanisms for retaining clinical researchers.

The NIH also developed granting mechanisms for supporting individual clinical investigators at various levels of their careers (e.g. K23 and K24 grants) and for programmatic support of institutions that developed clinical research training programs (K30 grants), and most recently its establishment of Centers for Clinical and Translational Science (CCTS). The IOM report documented the decline in clinical investigators (particularly MD investigators), and noted that the time commitment necessary to do clinical research was underappreciated [12].

DeMets and Califf more recently noted, '*we are entering an era in which the imperative to understand the rational basis for diagnostic and therapeutic options has become a major force in medical care*.' Medical products (drugs, devices, and

biologics) are proliferating simultaneously with substantial restructuring of the delivery of health care, with a focus on evidence to support medical intervention [13].

Today, we are left with the 'good, the bad, and the ugly' regarding clinical research. The 'good' is that many experts think that sound comprehension of the scientific method and exposure to biomedical research comprise the essential core of medical education, and that the very essence of the American academic model is a balance between education, patient care, and research. The 'bad' is the increasing number of voices questioning the relevancy of research in academic health centers, as well as those concerned about the commitment to other components of training and the cost of research in a setting where the 'triple threat' (i.e., excelling in teaching, patient care, and research) may no longer be tenable given the increasing complexity of each area. The 'ugly' is that in 2003 only about 3 cents of every health care dollar was spent on medical research (more recently this has dropped to 2 cents); and, it was estimated that only 5 % of Congress could be counted on to take the initiative and be leaders in the support of clinical research; and few potential investigators were being supported to pursue careers or were given enough time to conduct research. By and large, these same issues persist today. In addition, today's challenges add even greater burdens to clinical research. It is generally believed that today's studies cost too much, fail to recruit adequate numbers of subjects/patients into trials, fail to start in a timely fashion, may not even be asking the correct questions or studying the correct endpoints, and study results are often not published (publication bias, is an issue here). In fact, Pfizer has reported that recently, 60 % of the total drug development costs go to conducting clinical trials, compared to 30 % in the 1980s. These increased costs (which are 1.5–3x higher than many other countries) are making the US less competitive worldwide.

Our Quest for Knowledge

With the above background, how do we begin our quest for knowledge? In general, research questions are generated in a variety of settings (e.g., during journal reading, hospital rounds, discussions with colleagues, seminars, and lectures). The resultant questions can then be refined into a research idea and, after further review of the literature, ultimately developed into a hypothesis. Based on a number of factors (to be discussed in subsequent chapters), a study design is chosen, and the study is then preformed and analyzed, the results of which are then interpreted and synthesized. These results add to the body of knowledge, and this may raise additional questions that will invariably generate further research (Fig. 1.2).

Of course, the primary goal of clinical research is to minimize presumption and to seek universal truth. In fact, in science, little if anything is obvious, and the interpretation of results does not mean truth, but is really an opinion about what the results mean. Nonetheless, in our quest for universal truth, Hully and colleagues have diagrammed the steps that are generally taken to seek this 'truth' (Fig. 1.3) [3].

Much of research is to explore this concept of opening ones mind. That is, *"to know that we know what we know, and that we do not know what we do not know, that is*

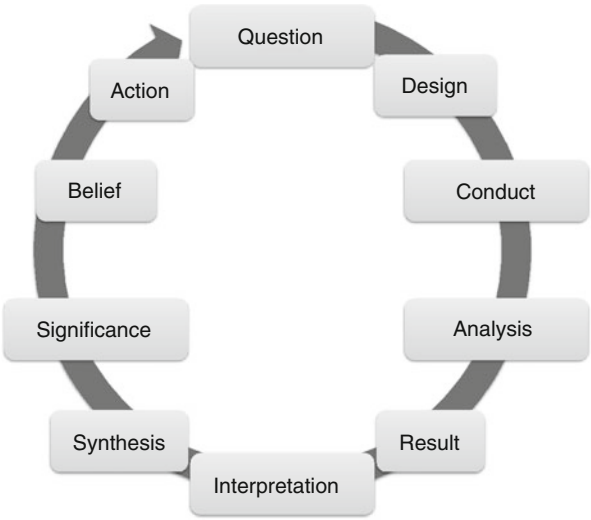

Fig. 1.2 Scientific method paradigm

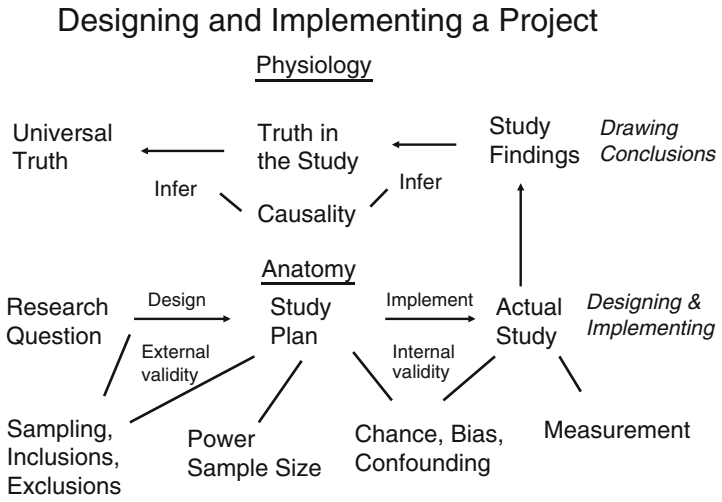

Fig. 1.3 A schematic of the design and implementation of a study

true knowledge (Henry David Thoreau (1817–1862))", or "scientific inquiry is seeing what everyone else is seeing, but thinking of what no one else has thought" (A. Szentgyorgyi. 1873 won the Nobel Prize for isolating Vitamin C). Most (perhaps all) people generally know what they know and know what they do not know. What get's most of us in trouble is that we do not know what we do not know (Fig. 1.4), and the largest "piece of the pie" falls in the last category.

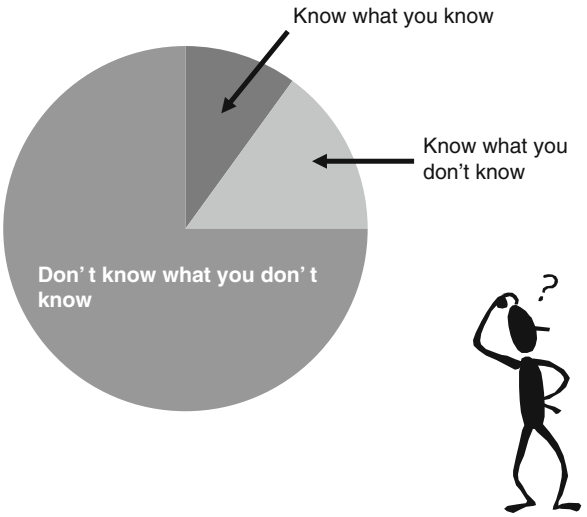

Fig. 1.4 One's universe of knowledge

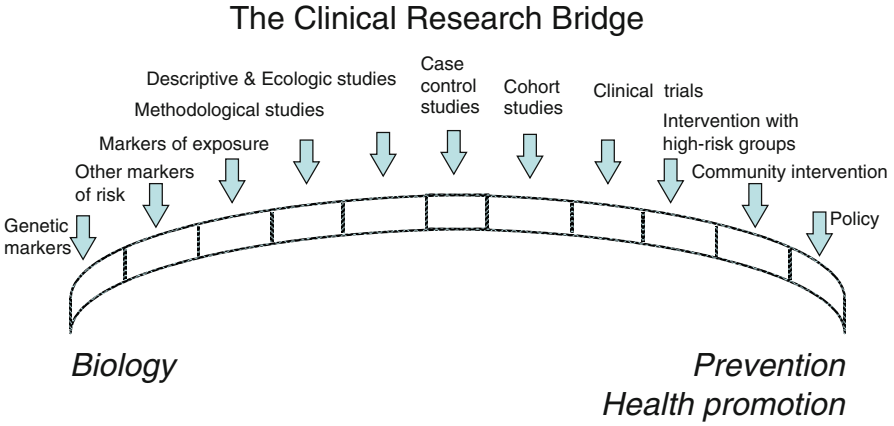

Fig. 1.5 Portrays the broad range that encompasses the term "clinical research"

This is exemplified, by considering the question of what the "experts" in the past really knew. Consider the following quotes:

"A journey such as that envisioned by Columbus is impossible. Among the many reasons that can be cited as to the folly of this enterprise is the well known fact that the Atlantic Ocean is infinite and therefore impossible to traverse"
(From a committee report to King Ferdinand and Queen Isabella, 1486)
"Who the hell wants to hear actors talk?"
From Jack Warner, Warner Bros. Pictures, 1927
"I think there is a world market for about 5 computers"
From: TJ Watson, CEO of IBM, 1943

"There is no reason for any individual to have a computer in their home."
From: Ken Olsen, President of Digital Corporation, 1977

Finally, it should be realized that clinical research can encompass a broad range of investigation as portrayed in Fig. 1.5.

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