John G. Brock-Utne

Clinical Research

Case Studies of Successes and Failures

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Springer

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Preface

The intention of this book is to highlight the many pitfalls that can occur when contemplating doing clinical research. This is based on my over 45 years of involvement in clinical research in four continents. Even though some of my mishaps have occurred over 40 years ago, I can assure you that these mistakes occur even to this day with monotonous regularity. Hence the book.

After each case history a question is posed. These are questions you may be faced with as a clinical researcher. The solutions suggested may be controversial and as such may form the basis for discussions on how best to proceed in your special circumstance.

The object of these many stories is to alert the clinical researcher and especially the El Toro researcher that there are many potential disasters waiting to happen when you embark on clinical research. But most of all the reader will hopefully understand that meticulous planning is essential for being successful in this field.

Always remember that the object is to achieve one's research goals quickly with a minimal risk of wasting time and resources.

To quote Marks (1) and to paraphrase Hippocrates of Kos (2):

(1. "The success of research project depends on how well thought out a project is and how potential problems have been identified and resolved before date collection begins" (Marks RG. Designing a research project. The basics of biomedical research methodology. Belmont: Lifetime Learning Publications: A division of Wadsworth 1982).
2. The Art is long
   Life is short
   Experiments perilous
   Decisions difficult.)

Stanford, CA, USA — John G. Brock-Utne

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Contents

Basic Premise

A. Why Is Clinical Research Necessary?

Everything we do as physicians carries a potential hazard. It could be the technique and equipment which we use, or it could be the medication which we give. We use these techniques, etc., to treat our patients, hoping that the benefits will outweigh the potential harm. Our clinical decisions are based on what we are mostly taught by our peers, tradition, and some human and many animal studies. Our experience is limited, so where do we get the knowledge to help us make the best decisions to help each patient? The answer is a properly conducted clinical research.

From the early days of medicine, doctors knew that certain treatments were dangerous. Hippocrates of Kos (born 460 BC and died 370 BC) stated: "Primum non nocere" (First, do no harm) and he also said "Desperate diseases require desperate remedies." I remember as a little boy that my father, a doctor, said: "Vondt skal vondt fordrive," which in Norwegian means: "Pain will get rid of pain." He told me this as he lanced an abscess from my finger, without using local anesthesia. (He did not have any.)

Before 1950, there were no government regulations regarding how clinical research should be performed. Most techniques or treatments were brought to the marketplace with minimal or no clinical studies to prove that they were beneficial or, more importantly, safe.

In September/October 1937, a congressional inquiry led to the beginning of the Food and Drug Administration (FDA) after the 73 deaths in the USA from a drug called "Elixir of Sulfanilame." This Elixir contained a solvent, diethylene glycol, which is toxic.

In France, an organic preparation called Stalinon (1956–1957) contained diethyltin diiodide (15 mg) and linoleic acid (100 mg) per capsule. The adult dose was six capsules a day which was a toxic dose. Two hundred and seventeen persons were severely poisoned by Stalinon, and of those, over 100 died.

Even though each country had an FDA of some sort, it was highly ineffective in controlling what was sold to the public. But all this changed with the Thalidomide

(Contergan) tragedy in 1961. The drug, when used by pregnant patients suffering from heartburn, led to the birth of deformed babies. The public all over the world was outraged. Governments decided that the pharmaceutical industry needed to be tightly regulated. As a result, governments decided that they would in the future:

1. Make sure that adequate clinical pharmacological studies would be done on new drugs prior to their release for general use. These studies should include safety testing (in both animals and humans) and clinical trials.
2. Recognize and publish any adverse effects that may arise after the release of a new drug [1].

Hence, clinical research is necessary to answer the questions:

1. How *good* are our medicines, techniques, and equipment?
2. How *bad* are our medicines, techniques, and equipment?

B. Why Do Physicians Do Clinical Research?

Physicians start doing clinical research for various reasons. Many do it because they have passion for a certain technique, drug treatment, and/or a device. They want to show that their idea is better than everyone else's. These researchers often get "bitten by the bug" and make clinical research their life's work.

Others do research purely to get promoted in the university system. The well-known phrase "Publish or Die" is alive and well in academia. An academician's quality and quantity of research output is an easy way to measure his/her academic achievements.

Some people do research to get acknowledged by their peers and to see their name in "golden lights."

Some people do clinical research because of their clinical expertise. Outside agencies recognize this and pay the researcher to conduct research in their field. This financial support can be large and may even pay for part or whole of their annual salary. In addition to the salary, the outside supporters pay the university for using its facilities (usually 35 % of the grand total). In addition, they also pay for research assistants, laboratory fees, etc. In the USA, the financial support to do a 20-patient study can amount to about $300,000.

The individual reasons for doing clinical research vary tremendously and can be one or a combination of any of the above factors. But most importantly, clinical research can be fascinating, rewarding, and fun.

So has the interest in clinical research increased, decreased, or stayed constant in the last 70 years? Take anesthesia, for example. Feneck et al. [2] have indicated that there appears to be a decline in published anesthetic articles. However, Green and Kumar [3] point out that Feneck et al. only reviewed seven journals. It is interesting to note that the first anesthetic journal, *Anesthesia & Analgesia*, came out in 1921.