

Introduction

One of the first recorded human trials was conducted by reverend Edward Stone who found in 50 patients that 1.8 g of powder of willow bark cured their fever, results that were published in 1763 (1). The active compound, salicylic acid, was synthesized only in 1860. Since then, innumerable compounds have been used to cure almost any ailment without evidence of activity. Evidence of drug efficacy was initially required in 1962 with the passing of the Food, Drug and Cosmetic Act by the United States Congress. Currently, in all countries, development and approval of new pharmaceutical entities requires controlled trials proving efficacy. In order to standardize drug registration and approval of drugs, the first International Conference on Harmonization (ICH) was held in 1990. Even if a tremendous progress has been achieved by using ICH guidelines, many aspects of human research remain controversial (2), and even for theoretically rather simple trials, such as those aiming at proving bioequivalence, specifications and study methods differ slightly from one to another in different countries (3).

Should we be concerned with refining the methodology of clinical trials? The answer is yes. Let us consider digitalis. William Withering transformed digitalis from a folk remedy to a modern drug when he transformed a "family receipt for dropsy" that contained more than 20 substances, to a single substance by assuming that foxglove was the active ingredient. Clinical observations enabled Withering to recognize the plant's narrow margin of safety and the importance of dose: just enough foxglove to cause diuresis, but not enough to cause vomiting or very slow pulse. With these observations, Withering introduced foxglove to the medical profession in 1785 (4). Despite many small trials, it took two centuries to clearly demonstrate the benefits of digoxin in heart failure, and we know now that these benefits include reduction of symptoms, improvement in NYHA class, increased exercise time, modest increased in left ventricular ejection force, enhanced cardiac output, and decreased hospitalizations, and that digoxin does not reduce overall mortality but reduces the rate of hospitalization (5,6).

How to conduct trials to demonstrate drug efficacy? Despite the fact that guidelines for drug development are rather standardized, there is less information about the design of a clinical trial. The objective of this Compendium is to provide the scientific community interested in human research with an easy-to-use reference on how to design a research protocol to assess the effectiveness of a drug in a series of pathological conditions.

The Compendium cannot cover every class of drug and condition, and thus it has primarily focused on cardiovascular and nervous system drugs. The section dealing specifically with the design of clinical trials, chapters 11 to 30, is presented according to a common template to facilitate its consultation. This section is preceded by shorter chapters dealing with general concepts that are applied to the development of almost any drug. The Compendium does not intend to constitute a guideline, but rather an easy source of information on how to design and conduct a clinical trial aiming at demonstrate drug efficacy.

The Editors

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2. Rockhold FW. Industry perspectives on ICH guidelines. *Stat Med* 2002;21:2949-2957.
3. Nakai K, Fujita M, Ogata H. International harmonization of bioequivalence studies and issues shared in common. *Yakugaku Zasshi* 2000;120:1193-1200.
4. Withering W. *An Account of the Foxglove and Some of Its Medical Uses*. Birmingham. United Kingdom: M. Swinney; 1785:2.
5. Tauke J, Goldstein S, Gheorghiad M. Digoxin for chronic heart failure: a review of the randomized controlled trials with special attention to the PROVED and RADIANCE trials. *Prog Cardiovasc Dis* 1994;37:49-58.
6. Digitalis Investigation Group, The effect of digoxin on mortality and morbidity in patients with heart failure. *N Engl J Med* 1997;336:525-533.