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Fundamentals of Clinical Trials

Third Edition

Springer

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Library of Congress Cataloging-in-Publication Data
Friedman, Lawrence M., 1942–
Fundamentals of clinical trials / Lawrence M. Friedman, Curt D. Furberg, David L. DeMets. — 3rd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-387-98586-7 (pbk. : alk. paper)
1. Clinical trials. I. Furberg, Curt. II. DeMets, David L., 1944– . III. Title.
[DNLM: 1. Clinical Trials. 2. Research Design. W 20.5F911f 1998]
R853.C55F75 1998
615.5'072—dc21 98-26138

This is a reprint of an edition published by Mosby.

ISBN 0-387-98586-7 Printed on acid-free paper.

Printed in the United States of America. (EB)

15 14 13 12 11

Springer-Verlag is a part of *Springer Science+Business Media*

springeronline.com

CHAPTER 1

Introduction to Clinical Trials

The evolution of the clinical trial dates from the eighteenth century.[10,55] Lind, in his classical study on board the *Salisbury*, evaluated six treatments for scurvy in 12 patients. One of the two who were given oranges and lemons recovered quickly and was fit for duty after 6 days. The second was the best recovered of the others and was assigned the role of nurse to the remaining 10 patients. Several other comparative studies were also conducted in the eighteenth and nineteenth centuries. The comparison groups comprised literature controls, other historical controls, and concurrent controls.[55]

The concept of randomization was introduced by Fisher and applied in agricultural research in 1926.[8] The first clinical trial that used a form of random assignment of subjects to study groups was reported in 1931 by Amberson et al.[2] After careful matching of 24 patients with pulmonary tuberculosis into comparable groups of 12 each, a flip of a coin determined which group received sanocrysin, a gold compound commonly used at that time. The British Medical Research Council trial of streptomycin in patients with tuberculosis, reported in 1948, was the first to use random numbers in the allocation to experimental and control groups.[42, 58]

The principle of blindness was also introduced in the trial by Amberson et al.[2] The patients were not aware of whether they received intravenous injections of sanocrysin or distilled water. In a trial of cold vaccines in 1938, Diehl et al.[26] referred to the saline solution given to the subjects in the control group as a placebo.

It is only in the past few decades that the clinical trial has emerged as the preferred method in the evaluation of medical interventions. Techniques of implementation and special methods of analysis have been developed during this period. Many of the principles have their origins in work by Hill.[27,46,47,48]

Because the authors of this book have all spent formative years at the National Institutes of Health (NIH), it is also pertinent to cite a series of papers that reviews the history of clinical trials development at the NIH.*

The purpose of this chapter is to define clinical trials; review the need for them; and discuss timing, phasing, and ethics of clinical trials.

*References 13, 36, 40, 43, 66

FUNDAMENTAL POINT

A properly planned and executed clinical trial is a powerful experimental technique for assessing the effectiveness of an intervention.

WHAT IS A CLINICAL TRIAL?

A *clinical trial* is defined as a prospective study comparing the effect and value of intervention(s) against a control in human beings. Note that a clinical trial is prospective, rather than retrospective. Study participants must be followed forward in time. They need not all be followed from an identical calendar date. In fact, this will occur only rarely. Each participant, however, must be followed from a well-defined point, which becomes time zero or baseline for the study. This contrasts with a case-control study, a type of retrospective study in which participants are selected on the basis of presence or absence of an event or condition of interest. By definition, such a study is not a clinical trial. People can also be identified from hospital records or other data sources and subsequent records can be assessed for evidence of new events. This is not considered to be a clinical trial since the participants are not directly observed from the moment of initiation of the study and at least some of the follow-up data are retrospective.

A clinical trial must employ one or more *intervention* techniques. These may be "prophylactic, diagnostic or therapeutic agents, devices, regimens, procedures, etc."[62] Intervention techniques should be applied to participants in a standard fashion in an effort to change some aspect of the participants. Follow-up of people over time without active intervention may measure the natural history of a disease process, but it does not constitute a clinical trial. Without active intervention the study is observational because no experiment is being performed.

A clinical trial must contain a *control* group against which the intervention group is compared. At baseline, the control group must be sufficiently similar in relevant respects to the intervention group so that differences in outcome may reasonably be attributed to the action of the intervention. Methods for obtaining an appropriate control group are discussed in Chapter 4. Most often a new intervention is compared with best current standard therapy. If no such standard exists, the people in the intervention group may be compared with people who are on no active intervention. "No active intervention" means that the participant may receive either a placebo or no intervention at all. Obviously, participants in all groups may be on a variety of additional therapies and regimens, so-called concomitant interventions, which may be either self-administered or prescribed by others (e.g., private physicians).

For purposes of this book, only studies on human beings will be considered as clinical trials. Certainly, animals (or plants) may be studied using similar techniques.

However, this book focuses on trials in people, and each clinical trial must therefore incorporate participant safety considerations into its basic design. Equally important is the need for, and responsibility of, the investigator to fully inform potential participants about the trials.[60, 63]

Unlike animal studies, in clinical trials the investigator cannot dictate what an individual participant should do. He can only strongly encourage participants to avoid certain medications or procedures that might interfere with the trial. Since it may be impossible to have "pure" intervention and control groups, an investigator may not be able to compare interventions, but only intervention strategies. Strategies refer to attempts at getting all participants to comply to the best of their ability with their originally assigned intervention. When planning a trial, the investigator should recognize the difficulties inherent in studies with human subjects and attempt to estimate the magnitude of participants' failure to comply strictly with the protocol.

As discussed in Chapters 5 and 6, the ideal clinical trial is one that is randomized and double-blinded. Deviation from this standard has potential drawbacks that will be discussed in the relevant chapters. In some clinical trials compromise is unavoidable, but often deficiencies can be prevented by adhering to fundamental features of design, conduct, and analysis.

Several people distinguish between demonstrating efficacy of an intervention and effectiveness of an intervention. The former refers to what the intervention accomplishes in an ideal setting; the latter to what it accomplishes in actual practice, taking into account incomplete compliance to protocol. As discussed in Chapter 16 and elsewhere, our preferred analytic approach emphasizes the importance of the concept of effectiveness. Only in special circumstances, will the focus of the clinical trial described in this book be on efficacy.

CLINICAL TRIAL PHASES

While we focus on the design and analysis of randomized trials comparing the effectiveness of one or more interventions with a control, several steps or phases of clinical research must occur before this comparison can be implemented.

Phase I studies

Although useful preclinical information may be obtained from in vitro studies or animal models, early data must be obtained in humans. The first step, or phase in developing a drug or a biologic is to understand how well it can be tolerated in a small number of individuals. Although it does not meet our definition of a clinical trial, this phase is commonly called a phase I trial. People who participate in phase I trials have typically already tried and failed to improve on the existing standard interventions. Most phase I designs are relatively simple. One of the first steps in

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