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Chapter 1 Introduction to field trials of health interventions

1. Scope of the book

In this book, we aim to provide a practical and comprehensive guide to the design and conduct of **field trials of health interventions** directed against disease problems in low- and middle-income countries (LMICs). Our main emphasis is on randomized controlled trials (RCTs), but many of the issues discussed are of relevance to other kinds of field research in LMICs. Published papers reporting the results of intervention trials rarely include details of the practical aspects of preparation for a trial and its conduct, yet these are crucial to the execution of a successful trial. Those conducting trials for the first time often do not have access to references detailing the many practical issues that have to be addressed in the organization and conduct of a trial. New investigators generally have to learn by experience and, as a consequence, often repeat mistakes that others have learned not to make. While 'learning by doing' can be a valuable educational method, it is usually inefficient and wasteful. We have tried to synthesize the experience of investigators with substantial experience of conducting field trials in LMICs and describe procedures and practices found to work well in LMIC settings. Thereby, we hope that new investigators will build on and extend the experience of others, rather than repeat the same mistakes.

Trials of health interventions involve the implementation of a specific health intervention and comparison of the effects of that intervention with the effects of the currently available 'best' intervention or, if there is none, comparison with what happens with no intervention (or with a placebo). In order to avoid bias in the allocation of participants to the intervention or comparison group, assignment of individuals or groups to a particular intervention should be done by randomization. The 'trial' approach is in contrast to observational studies such as cross-sectional surveys, cohort studies, and case-control studies. But many of the methods and techniques described in this book may also be usefully deployed in observational studies.

We use the term 'field trial' for trials conducted outside clinical settings, in contrast to 'clinical trial' that is used for studies carried out in health facilities. Thus, field trials generally involve participants who are living at home in their normal environment, rather than being 'captive' in hospitals or outpatient clinics. Most trials of preventive measures, such as immunizations or health education, are 'field' trials. Important differences in field and clinical trials include inclusion and exclusion criteria that may be less stringent in field trials than criteria often imposed in clinical trials, in which it may be important to have a clearly defined disease condition for treatment. To the extent that there are less stringent inclusion and exclusion criteria, there may be fewer problems with the external validity of trial conclusions than there often are for clinical trials that limit the generalizability of conclusions. Another difference is that randomization of intervention by groups (clusters), rather than by individuals, is more often necessary or useful in field trials than in clinical trials (see Chapter 4, Section 4).

Clinical trials of drugs and vaccines are commonly carried out in successive phases, as described in Chapter 2, Section 3. Phase I trials are early studies conducted in a few human volunteers to test the safety of a promising new drug or vaccine. Thereafter, Phase II trials are carried out on larger numbers of volunteers, often to gauge immunogenicity (of a vaccine) and the effect of different doses or number of doses and to monitor for any adverse reactions. When these phases are successfully completed, Phase III trials are conducted on much larger numbers of volunteers who are randomized to receive either the new product or the comparison product, in order to establish the efficacy of the new intervention. The main focus of the book will be large-scale randomized field trials. For pharmaceuticals and vaccines, these will usually be Phase III trials, though this designation by phase does not fit so well with some other important types of interventions such as behaviour change interventions or environmental modification.

We do not envisage that many readers will sit down and read the book from beginning to end! We have called it a 'toolbox', because we think this reflects how it might be used, i.e. to consult different chapters and sections to guide different stages in the planning and execution of a trial.

2. Outline of contents

The chapters of this book can be considered in three main groupings. Chapters 2 through to 13 review issues to consider and steps to be taken before starting a trial. Chapters 14 through to 20 detail the tasks to be carried out during the conduct of a trial, with a focus on data collection. Chapters 21 and 23 discuss the analysis, interpretation, and reporting of trial results. We have also included a short chapter on Phase IV studies (Chapter 22), that are usually conducted after a product has been licensed and is in, or is about to go into, public health use. Phase IV studies are usually not randomized designs, because of the ethical issues in withholding a licensed intervention from participants, and such studies are not a main focus of this book. However, we have included this chapter because many of the design, conduct, and analysis issues discussed in other chapters have relevance for Phase IV studies and also because it will often be desirable for Phase III trials, which usually measure the efficacy of an intervention delivered in a highly controlled manner, to be followed by Phase IV evaluations in 'real-life' programmes.

Before embarking on a trial, the first steps are to define the goals, objectives, and key questions for the study. As background to this, the broad array of potential types of interventions is catalogued in Chapter 2. The importance of critically reviewing essential background information relevant to a trial, including trials of similar interventions, through a systematic review of literature is emphasized in Chapter 3. The heart of the book is concerned with the design of the trial, as outlined in Chapter 4, and making it of appropriate size (Chapter 5). Many of the design details are guided by ethical concerns (Chapter 6), regulatory requirements, and governance issues (Chapter 7). A major issue in planning a trial is generating the resources to carry it out, and guidance is given in Chapter 8 on the preparation of grant applications for trials to funding agencies.

Field trials are generally based in communities, and their successful conduct is highly dependent on investigators engaging appropriately with community members at all stages in the planning and execution of a trial (Chapter 9). Before a trial starts, the target population has to be defined and registered (Chapter 10), and then the interventions under test must be allocated to individuals or communities, in an unbiased way, by randomization, with the intervention allocations being kept 'blind', if possible, to investigators and participants. Ways of achieving this are discussed in Chapter 11. Evaluation of the impact of an intervention depends upon appropriate definition of the outcomes that the intervention is expected to affect. Choice of appropriate outcome measures and unambiguous definition of these is considered in Chapter 12.

Undertaking a trial is often a major activity, involving a large trial team for several years. It is rarely possible to start a trial immediately the protocol has been written and the funding obtained. Almost always, it is necessary to have collected preliminary data to facilitate the planning of the trial and to conduct studies to test out the procedures that are proposed for use in the trial, and modifying them appropriately if they are not found to be fit for purpose. Such preliminary studies and pilot testing of procedures are covered in Chapter 13. Information about trial participants is commonly collected through the administration of questionnaires. The various forms that these might take and different methods of administering them are summarized in Chapter 14.

Most intervention trials involve some element of behaviour change, both on the parts of those administering the intervention (for example, workers in the health service) and of those taking it up—the trial participants. The extent of behaviour change required will vary, according to the intervention under test. Evaluating a new vaccine which is administered at the same time as routine vaccinations in the childhood immunization programme may require relatively little behaviour change, but implementing an intervention to reduce high-risk sexual behaviour to lower the risk of human immunodeficiency virus (HIV) infection, or promoting hand-washing to reduce the risk of diarrhoeal diseases, will involve substantial behaviour changes. Undertaking social and behavioural research to facilitate the design and implementation of interventions is reviewed in Chapter 15.

Quality control of all aspects of conducting a trial is crucial if the findings from the trial are to be used to make important public health decisions about the use, or otherwise, of an intervention, based on the trial results. These issues are discussed in Chapter 16, while Chapter 17 specifically focuses on methods and quality control in field laboratories, which are an important component of most trials.

Nothing can be done without financial support for the trial. The essentials for the preparation of budgets for grant applications are given in Chapter 8. The efficient planning and management of finances during a trial are also key to success, and a requirement of funding agencies. The necessary budgeting and accounting methods are outlined in Chapter 18. Chapter 19 affords an overview of the main methods used to assess the costs of health interventions and summarizes the types of economic analyses that can be conducted to assist decisions concerning resource allocation to health interventions.

In all but the smallest trials, substantial amounts of data are collected and have to be efficiently processed, both during the conduct of the trial and for the analysis of the results during, and at the end of, the trial. Methods of data management are summarized in Chapter 20, and an outline of methods of statistical analysis of trials is given in Chapter 21. In most trials it will be necessary to employ a statistician to oversee the analysis of the data from the trial, but the relatively simple methods summarized in this chapter should be sufficient to elucidate the main results from most trials.

Finally, Chapter 23 stresses the importance of communication at all stages of the trial, how best to communicate to the many different audiences who should be informed about the trial, and the necessary steps to translate research findings into policy and public health action.

We have deliberately not included large numbers of references, as the book is intended to stand largely on its own, without readers needing access to a well-stocked library. Referencing has been reserved for where a particular study has been described, or as a guide for readers who may require a more detailed explanation of a concept than can be included in this text. Whenever possible, we have favoured open access or relatively low-cost resources.

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