22.1: Introduction to Phase IV studies

The main focus of this book is on randomized controlled field trials of health interventions in LMICs, many of which can be classified as Phase III trials (see Chapter 2, Section 3). This chapter gives a brief overview of Phase IV studies that are often carried out after an intervention has been shown to be efficacious in Phase III trials. We give a brief description of the rationale and some of the terminology used in such studies, outline the main types of Phase IV study, discuss some key issues in the design of such studies, and give a brief description of two specific Phase IV studies.

For new drugs or vaccines, the evidence from one or more Phase III trials, taken together with the results of the Phase I and II trials, will be presented to licensing authorities to register the product for clinical or public health use. However, the total number of participants included in Phase I to III trials of a new product will often be no more than a few thousand, and there are usually important public health issues that will have been incompletely addressed at the time a product is licensed. For example, individuals included in Phase III trials will often have been a carefully selected sample of the population and will not include all of those eligible for eventual administration of the product. Particular groups may have been excluded, such as children and adolescents, the very undernourished, or pregnant women, but these groups will often receive the product when it is in general use, and it is important to collect data on both the safety and the effectiveness of the product in these groups. Also, in most Phase III trials, great care will have been taken with product supply and storage, and, if the dosing regimen requires multiple doses, care will have been taken to ensure that the interval between doses was as recommended. Rigid adherence to such intervals is much less likely once the product is in general use. For these reasons, it will be important to measure whether the effect of the product, when it is administered in a routine health system or programme, is similar to the efficacy that was assessed in the Phase III trials conducted in a research setting. Phase IV studies are conducted to assess the effectiveness of an intervention when it is in public health use, as compared to the efficacy of the intervention as assessed in a carefully controlled Phase III trial (see Section 2.1).

Most Phase III trials will not have been large enough to detect reliably important, but relatively uncommon, side effects.
For example, a serious adverse effect (SAE) of an intervention that occurs, on average, in one in every 2000 recipients may well be missed in a Phase III trial that involved only a few thousand participants. There may also be other unexpected effects when an intervention is implemented in a public health programme that were not apparent in the carefully controlled situation of a Phase III trial. For example, in a trial of a health education intervention in schools, teachers may be willing to promote condom use when they have been carefully trained, supported, and supervised, as part of the trial procedures. However, when the intervention is implemented on a widespread basis, in settings where condom use is unpopular and talking of such things with young people frowned upon, teachers might actually discourage use without the support that was included in the trial. It is important that studies are conducted to detect such adverse effects once an intervention is in routine use. Whenever possible, such Phase IV studies should be used as the basis for developing systems that persist after the study, so that routine health systems can continue to detect such events.

Historically, assessment of how interventions work in ‘real-world' public health programmes has been relatively neglected. However, presently, such Phase IV research is receiving increasing attention. It encompasses post-marketing surveillance of the effect of interventions and implementation research which investigates better ways of ensuring the successful delivery of an intervention (such as how to increase the coverage of a vaccination programme). A common goal of Phase IV studies is to provide evidence that the health intervention can be successfully and safely integrated into public health or clinical practice where ‘successful’ means that it is not only feasible to do so, but also that the intervention remains effective and its implementation is not associated with any serious adverse effects.

This chapter focuses mainly on Phase IV studies related to the introduction of new drugs or vaccines, but similar studies can be used to evaluate other types of health intervention such as surgical procedures, health education, or peer supporters to encourage adherence to treatment regimens.

Phase IV research serves three major functions:

1. to support pharmacovigilance systems in monitoring the safety of new interventions used in large populations and in specific groups who were not studied adequately in the pre-marketing phases such as children, pregnant women, the elderly, or those with co-morbidities
2. to determine the effectiveness of an intervention in a routine health system, as opposed to within a carefully controlled trial
3. to assess new strategies of use of approved products or interventions, such as the evaluation of antimalarials when used for intermittent presumptive treatment, rather than either for malaria prophylaxis or for treatment of a diagnosed malarial infection.

Furthermore, studies to seek ways of widening the coverage, ensuring a more equitable distribution or conducting an economic evaluation of an intervention (see Chapter 19) may also be encompassed by Phase IV studies. A key issue with respect to such studies is that they are conducted after a product has been licensed or is already in widespread use. Thus, placebo-controlled trials are generally ruled out for ethical reasons, and observational designs are often employed. A full description of all the potential observational study designs is beyond the scope of this chapter. However, because of the importance of Phase IV studies and the overlap with many of the field research issues covered in this book, after defining some of the key terms and concepts, Section 2 of this chapter gives a brief overview of some of the commonest Phase IV research approaches.
1.1 Efficacy and effectiveness

A distinction should be made between the effect of the intervention, as measured in a Phase III trial, called the *efficacy* of the intervention, and the effect of the intervention when it is delivered in a public health programme, called the *effectiveness* of the intervention. Generally, it is expected that the efficacy of an intervention will be greater than its effectiveness, for the reasons outlined in Section 1. However, this is not always the case. For example, when some vaccines are administered to large populations, there are at least two factors that may operate to reduce the incidence of disease. First, the vaccine may offer individual protection to recipients of the vaccine. Second, the reduction in the number of individuals who acquire the disease as a consequence of vaccination may reduce the overall level of infection in the community, and thus even those who are unvaccinated may be at lower risk of acquiring disease, simply because they are less likely to be exposed to someone with the infection. Such *herd effects* may be substantial for some person-to-person infections, for which humans are the main reservoir. If the vaccine coverage is high enough, the effectiveness of the vaccine may be higher than would have been predicted from Phase III efficacy trials, in which typically, at most, half of the eligible population is vaccinated. Fine et al. (2011) give an overview of herd effects.

The overall impact of an intervention against a disease in a population, sometimes known as the *community effectiveness* or *system effectiveness* of the intervention, will depend on the *effectiveness* of the intervention and its *effective coverage*, i.e. the proportion of the *target* population who receive it. The *target* population consists of all those who should receive (would benefit from receiving) the intervention. An example of how an evaluation of the effective coverage of a broad range of different health services was used to benchmark the performance of the health system in the various states of Mexico is given in Lozano et al. (2006).

1.2 Stakeholders

The primary audience for Phase IV studies is health policy decision makers, but other stakeholders may include regulatory agencies, industry, health care professionals, patients, community groups, media, and suppliers. Regulatory agencies and public health officials will seek to ensure the continuous evaluation of an intervention’s risks and benefits. Industry engages in Phase IV research to determine the effects of long-term use, as requested or demanded by regulatory agencies, but also to inform key strategic and operational decisions related to the marketing of their products. Governments, decision makers, and policy makers need high-quality evidence on effectiveness and cost-effectiveness in the real world, as well as in Phase III trial settings, in order to design and implement public health programmes that optimize health gains and reduce health inequity. For clinicians, Phase IV study data can guide their prescribing and the advice they give to their patients.