22.2: Types of Phase IV study

2.1 Safety/pharmacovigilance

Pharmacovigilance is defined as ‘the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other possible drug-related problems’ (World Health Organization, 2006). Pharmacovigilance studies are designed to detect and assess both long-term and short-term adverse effects of medicines (including drugs and vaccines). Regulatory agencies will often require that specific monitoring is conducted after a product is licensed (post-marketing safety monitoring or pharmacovigilance) that is designed to detect the occurrence of rare, but serious, adverse effects of the product. Similar issues apply to medical devices and prostheses.

Pharmacovigilance studies can include observational or intervention studies. Common designs include case-control studies, cohort studies (cohort event monitoring), and spontaneous (passive) reporting schemes. In some circumstances, RCTs might also be possible. The main method used in HICs is the collation of adverse drug reaction reports submitted by clinicians, which are compiled and analysed by national pharmacovigilance centres. The reports may also be submitted to the WHO Programme for International Drug Monitoring (http://www.who-umc.org>). However, this reporting system is not yet functional in most LMICs, and, even in HICs, the system is acknowledged to be an imperfect way to detect all of the adverse events (AEs) that might be associated with a particular product. However, monitoring for product safety is particularly important in LMICs, often with their overburdened health care systems and frequent polypharmacy. Other potential safety issues in LMICs include the widespread manufacture and sale of counterfeit, substandard, or expired medicines, and potentially unsafe drug donation practices. An example of how pharmacovigilance can be built into a broader Phase IV study is given in Section 4.1.
2.2 Intervention effectiveness

As discussed in Section 1, the effectiveness of an intervention may well be different in the complex and dynamic situation of a routine health system, compared to the context of a carefully controlled Phase III trial. Effectiveness studies evaluate the impact of an intervention when delivered under real-world conditions in a routine health system. Such studies are especially important when a new intervention is first introduced into a public health programme. The decision to introduce the intervention will usually be based upon the results of one or more Phase III trials, including a cost-effectiveness analysis, often using data derived from the Phase III trials. However, it is important to evaluate both the effectiveness and cost of the intervention, as used in the public health programme, and this will generally require the setting up of specific studies. For example, a series of such studies were conducted when rotavirus vaccines were introduced into public health use (Patel et al., 2011).

Phase IV studies may also be appropriate for interventions which are relatively well established in a public health programme. These may be drugs or vaccines that have been in use for a number of years already, or other interventions which may have been implemented with or without preceding efficacy trials or for which the effectiveness of the intervention is unknown, even if the efficacy had been established in controlled intervention trials. For example, controlled trials were conducted to measure the impact of introducing insecticide-treated bed-nets (ITNs) as a measure to reduce deaths from malaria in malaria-endemic areas. These showed that this intervention had a substantial impact on child mortality. A Phase IV study to evaluate the impact of such bed-nets, when implemented in a public health program, was conducted by Schellenberg et al. (2001). In this study, a programme was rolled out across two rural districts of southern Tanzania over a 2-year period, in which subsidized ITNs were made available at shops and kiosks. The proportion of young children who slept under an ITN was estimated through population-based surveys, and the impact on child mortality monitored through a case-control study, in which the prior use of an ITN was compared among children who had died from malaria and those who survived. All child deaths were identified within a demographic surveillance area. This Phase IV study confirmed that ITNs had a major impact on child mortality within a routine programme, and the study also elucidated ways in which that impact might be increased by modifications to the programme delivery system.

Phase IV studies of health system effectiveness are designed to understand reasons for the decay of the impact of an intervention that results from individual and system behaviour, including access to the intervention, diagnostic targeting, provider compliance, and patient adherence. Figure 22.1 summarizes the outcome of Phase IV studies conducted in Tanzania to determine why highly efficacious anti-malarial treatments had low community effectiveness. Controlled trials had shown that artimisinin combination treatments (ACTs) have very high efficacy for the treatment of uncomplicated malaria, with roughly 98% of patients who received treatment within carefully conducted efficacy trials cured. A community-based survey found that only 60% of those with malaria sought care from a clinic that had ACTs. Studies within the clinics showed that 95% of those who came to these clinics had an appropriate diagnostic test performed, and, in 95% of those diagnosed with malaria, the correct treatment was prescribed. Further studies in the patients who were given the correct prescription of ACT showed that only 70% of them adhered correctly to the treatment as prescribed. Taken together, this series of Phase IV studies showed that less than 40% of people with uncomplicated malaria in the community were effectively treated, despite ACTs, which had a 98% efficacy, being made available. Such Phase IV studies can not only document and measure the failings in the health system, but they can also be used to investigate the reasons behind these problems and the potential actions that can be taken to fix them (see Section 4.1).
Figure 22.1 represents what happened in the catchment population as a whole, but it is important, in such studies, to measure system effectiveness by socioeconomic status, and among specific vulnerable groups, as this may reveal substantial heterogeneity in the findings, according to these factors.

**Figure 22.1** How the efficacy of highly efficacious malaria treatments translates into low community effectiveness for the treatment of malaria due to failings in the health system.

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