22.3: The conduct of Phase IV studies

Phase IV studies should follow the general guidelines, as described elsewhere in this book, with respect to the selection of the study population and study design, sample size calculations, ethics clearance and consideration of other governance issues, and the training and supervision of study staff.

3.1 Design issues

There are multiple observational designs and evaluation schemes that can be used in Phase IV studies to assess the effectiveness, cost-effectiveness, and safety of an intervention in real-world settings. Details of these approaches is beyond the scope of this book, but the use of non-randomized study designs to evaluate interventions is discussed in Victora et al. (2004) and Bonell et al. (2011).

3.2 Study sites

Whereas Phase I to III trials are often restricted to relatively small-scale research settings with good infrastructure, Phase IV studies are typically conducted over wider areas where health care and the intervention in question are delivered through routine health systems. A variety of service providers may be involved, including public, private-for-profit, private-not-for-profit, and community-based providers. A way of encompassing this complexity is to use the district as the unit of implementation and analysis within Phase IV studies. In many countries, districts are the core administrative unit for governmental health and other programmes, and the smallest unit that includes all the major features of the health system, from a hospital down to community health workers. They are usually the lowest unit that plans and allocates budgets, manages training, and aggregates health information. They are easily identifiable and often have some level of sociocultural and economic homogeneity. Wherever possible, Phase IV studies should support and strengthen existing health systems, rather than setting up special structures that may weaken the health system in the
long term.

One of the challenges in conducting Phase IV studies in these situations is to balance the need to study the intervention in a real-world setting with the need to be able to collect reliable data. Health and demographic surveillance sites (HDSS) longitudinally monitor and register the total population living within a geographically defined area. They collect a broad array of important health-related parameters at the household and individual levels, including pregnancies, births, deaths, causes of death, socio-economic status, care-seeking behaviour, and immunization status. HDSS sometimes cover whole districts, with populations of 50,000 to more than 100,000 people, and therefore include the full range of health service providers. HDSS are increasingly being used for Phase IV studies of effectiveness and safety (see Section 4.1). Effectiveness studies involving HDSS can measure the effectiveness of the system in delivering the intervention to the whole community, as well as the effectiveness of the delivered intervention in affecting individual health status. The large numbers of exposures to the intervention that can be monitored longitudinally in HDSS make them useful for pharmacovigilance studies. The research infrastructure associated with HDSS also makes it possible to interpret results contextually and to estimate cost-effectiveness. The longitudinal history available on all residents in an HDSS provides data that makes HDSS highly valuable partners in effectiveness trials and Phase IV studies.

3.3 Ethics and governance

Planners of Phase IV studies are confronted with the need to maintain sufficient oversight of intervention delivery to ensure that the approach is as planned, while simultaneously allowing for realistic adaptation and tailoring by providers. Governance of such studies needs a balance between the requirements of routine health systems and international scientific standards. It is valuable to have a separate committee that involves donors, governments, regulators, industry, and key stakeholders who discuss the approaches used and to offer guidance as to their selection, interpretation, and use of results. Also see Chapters 6, 7, and 9.

Phase IV studies, in which any new data on people are collected, generally need ethical clearance from the relevant national and institutional bodies. Such studies pose some specific challenges, in terms of ethical considerations, as they may involve comparison of new vs old technology and expensive vs inexpensive drugs, and there may be concerns that some patients will not be receiving optimal care.

3.4 Stakeholder involvement

Mapping and involvement of stakeholders is even more important within Phase IV studies than in Phase III field trials, as described in Chapter 9. They should be part of the planning of large-scale activities that will affect policy and strategy, and they should have an active role in the selection of study sites. They should have the possibility to comment on study design, participate in the review and interpretation of preliminary results, and advise on the development of appropriate feedback mechanisms. Their active involvement will be essential for a successful translation of results into policy and programmes.

3.5 Data collection, processing, and analysis

Phase IV effectiveness studies can make judicious use of health service attendance and other data that are routinely
collected by health programmes or other sources. Possibilities for linking population data with health facility data should be explored, although systems for doing this are difficult to set up in most LMIC contexts. Prospective studies provide greater opportunities than retrospective studies to gather essential additional data. Efforts should be made to simplify data collection and management and to improve data quality by introducing real-time data collection directly onto computers or mobile devices. When using routine data sources, one issue to resolve early on, among all partners, is the question of data ownership, and it is essential to have a clear agreement of where data will be managed, stored, cleaned, and analysed, and agreed publication and dissemination policies (also see Chapter 20). Additional study data collection is usually needed to fill data gaps and address specific questions. Potential methods include health facility and household surveys, longitudinal health status studies, and qualitative research.

3.6 Contextual and confounding factors

In order to be able to adjust for confounding factors, contextual factors need to be closely monitored in observational Phase IV studies—factors that are external to the programme or intervention under consideration. These usually include socio-economic, environmental, demographic, and health system factors, as well as other locally relevant factors. Health outcomes are affected by socio-economic progress, changes in both public and private health services, and other initiatives in health or other sectors in the same geographical area. Because these changes can happen concurrently with the assessment of the effectiveness of the study intervention, they require special attention and need to be integrated in the interpretation and analysis of the data. The aim should be to collect contextual data to allow the evaluation of whether or not it is plausible that factors, other than the intervention being studied, could explain any improvements seen (Victora et al., 2004). Again, HDSS can play a central role here, as they can provide information on contextual factors and health system dynamics.

3.7 Reporting and dissemination

As for Phase III trials, a well-thought out system for reporting and dissemination of results is crucial if the results of Phase IV studies are to feed into policy and programmatic action. Whereas reporting standards for Phases I to III trials have been widely agreed (see Chapter 2), those for observational research are more recent. However, the STROBE statement (STrengthening the Reporting of OBservational studies in Epidemiology) is widely accepted and has been endorsed by a growing number of biomedical journals (<http://www.strobe-statement.org>). Efforts are also being made to develop and strengthen scientific methods for conducting comparative effectiveness research to improve the consistency, applicability, reliability, and validity of comparative effectiveness research findings for informing the health care decisions of patients, providers, and policymakers. An example is the DECIDE (Developing Evidence to Inform Decisions about Effectiveness) Network created in 2005 (<effectivehealthcare.ahrq.gov/index.cfm/who-is-involved-in-the-effective-health-care-program1/about-the-decide-network>).

3.8 Funding

Phase IV, and especially effectiveness, studies are often resource-intensive, due to large sample sizes and long follow-up periods. Also, a significant expansion of infrastructure and capacity is often required prior to the initiation of such studies, as many research groups are better placed to conduct efficacy trials than to conduct research within the health care delivery system. Raising funds for Phase IV research is challenging, but funders, including governments, have
become increasingly interested in research to check that the interventions they fund provide the best possible value for money, so opportunities are improving.