2.3: Evolution of new intervention products and sequence of study phases

Many intervention products, and especially drugs and vaccines, are likely to originate from basic research in laboratories. Such products must go through a long series of tests, before they can be considered for use in the kinds of field trials that are the focus of this book. Before any human use, a new product will be tested in the laboratory for its activity and toxicity in various *in vitro* and animal test systems. If it successfully passes through these stages, studies of safety, toxicity, and activity may be conducted in a small number of human volunteers, with careful clinical monitoring. A series of further studies, each including increasing numbers of subjects, must be carried out before a new product can be introduced for widespread use. Trials in humans usually go through a series of sequential ‘phases’ of progressively increasing size to establish first the safety and mode of action and then, in later phases, the efficacy against the target disease(s) and safety in a larger number of subjects.

3.1 Clinical studies: Phases I to IV

Phase I studies are exploratory first-in-human trials and may involve the administration of small, then larger, doses of the study product to a small number of healthy human subjects (ten to 50) to gather preliminary data on the product’s pharmacokinetics (where the product and its metabolites go within the body and in what concentrations) and pharmacodynamics (what the drug does in the body). These studies can help to establish the dosage and frequency that are safe and necessary to have an effect. These trials are designed to make an initial assessment of the safety and tolerability of the drug or vaccine in a small number of, usually healthy, volunteers.

Phase II trials are conducted for products that have shown no significant safety problems in Phase I trials. They involve progressively larger numbers of participants (for example, initially tens of subjects, but later studies may involve 100s) and are designed to assess how well the intervention works (therapeutic drugs would involve studies in patients, whereas vaccines would be assessed for immunogenicity in healthy volunteers), as well as to check for safety in a larger
number of healthy volunteers (vaccines) or in patients (therapeutic drugs). Phase II trials may also be designed to evaluate what doses and the number of doses of the intervention should be given, and what the intervals should be between doses. Usually, a product will be evaluated in a number of different Phase II trials, evaluating its performance under different circumstances, for example, a malaria vaccine might be initially trialled in adults but then tested in progressively younger groups until tested in the final target population of infants.

Phase III trials aim to provide a definitive assessment of the efficacy of the intervention against the primary outcome(s) of interest. They also provide safety data in a larger group of subjects. These trials usually involve large numbers of individuals (e.g. 1000–3000 or more) and are studies that are conducted to produce the evidence of efficacy and safety required to submit a product to a licensing authority. For this reason, they are sometimes called ‘pivotal’ trials.

Phase IV studies are conducted after the intervention has been shown to be efficacious in Phase III trials and are conducted to assess the safety and effectiveness of an intervention when used under routine health service conditions, or close to these conditions (rather than in the special circumstances of a controlled trial). Where they involve a regulated product, such as a drug or vaccine, they are usually post-registration or post-licensure studies. Safety issues that are important, but which arise in a relatively small proportion of individuals, may only become apparent through Phase IV studies, once there is widespread use of an intervention. Phase IV studies sometimes take the form of randomized trials where the safety and effectiveness are assessed by comparing the results of administering the product to some individuals or communities, but not to others (allocated at random). However, such trials may be difficult to conduct, once a product has been licensed by the national regulatory authority, and then non-randomized assessments must be made, such as through ‘before versus after studies’ or case-control investigations. Many trials of strategies of how best to use drugs or vaccines can also be considered as Phase IV studies, such as a comparison of intermittent preventive therapy (IPT) using anti-malarial drugs given to all young children, compared to teaching their mothers to recognize and treat their children if they have possible falciparum malaria.

The main focus of the book will be on large-scale Phase III trials conducted ‘in the field’ (i.e. outside clinical facilities), but there is also a specific chapter on Phase IV studies (see Chapter 22).

Although similar terms are often used for the ‘phase’ of trials conducted to test the effectiveness or efficacy of interventions that do not use an investigational product, such as behaviour change interventions or incentives, these have much less well-defined, or universally agreed, phases, and it is not uncommon for the first RCT of such an intervention to be the equivalent of a Phase III trial of a drug or vaccine.

### 3.2 Registration of new interventions

Legal registration procedures are mandated in most countries before a drug or vaccine can be put into general use, and these procedures normally require documentation of the safety and efficacy of the intervention, based on RCTs involving many hundreds of subjects. Further guidance on the rules and regulations for assessing the safety and efficacy of products for use in human beings can be found at the website of the US Food and Drug Administration (<http://www.fda.gov>).
3.3 ‘Proof of principle’ trials

The purposes of field trials may change as experience with an intervention accumulates. Sometimes, particularly in early trials of a new intervention, the purpose of the study is analytic to demonstrate an effect or to establish a principle, with little consideration as to whether the intervention is practicable at the population level for disease control. An example might be the use of a malaria vaccine that must be administered monthly to be effective. Such studies are sometimes called ‘explanatory’ or ‘proof of principle’ trials (Schwartz and Lellouch, 1967). Once an effect against the disease under study has been demonstrated, there might then be greater impetus to develop new formulations of the intervention or different schedules that would be more practicable for application in a disease control programme. Subsequent, and generally larger, trials are conducted, in which the purpose is to establish the benefit of an intervention applied under the circumstances of general use. These studies are often called ‘pragmatic’ trials (Schwartz and Lellouch, 1967).

3.4 Trials of intervention delivery strategies

Although new products developed through basic science research may serve as the impetus for field trials, some interventions or intervention strategies are developed directly as a result of field studies and experience such as a vaccine strategy for smallpox eradication and the use of tsetse fly traps for the control of trypanosomiasis transmission. Thus, trials may be needed not only of the product itself, but also of the way that product is used or delivered. Trials like these would involve intervention ‘packages’ which might include, for example, the same drug or vaccine, but provided with different educational approaches or delivery methods. Sometimes, an intervention that has been shown to be effective must be added into an ongoing disease control programme that involves other kinds of interventions. For example, it is expected that, when effective malaria vaccines become available, they will be added to other malaria control methods, based on a combination of vector control, case finding, and treatment strategies. Further studies of how best to integrate these interventions into an overall strategy will have to be worked out. In addition, policy and planning decisions about disease control will have to be guided by appropriate cost-effectiveness analyses.