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field trials of health interventions a toolbox

3RD EDITION

edited by PETER G. SMITH | RICHARD H. MORROW | DAVID A. ROSS

IEA International
Epidemiological
Association

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Table 12.1 (continued) Examples of primary and secondary outcomes for trials of different interventions

Intervention trial	Primary outcome(s)	Secondary outcomes	Comment
Cluster randomized trial to assess the impact of an adolescent sexual health intervention in Tanzania (Ross et al., 2007)	◆ Incidence of HIV infection ◆ Prevalence of herpes simplex type 2 (HSV 2) infection at end of trial	◆ Six biological measures (for example, syphilis and gonorrhoea prevalence at end of trial) ◆ Five behavioural endpoints (for example, use of condoms during sexual intercourse) ◆ One attitudinal endpoint ◆ Three knowledge endpoints (for example, how HIV is transmitted)	The intervention was designed to reduce HIV incidence through behaviour change brought about by sexual health education. A substantial number of secondary outcomes were included to facilitate understanding of the main results. This was important, as the intervention was shown to substantially improve knowledge, reported attitudes, and some reported sexual behaviours but had no consistent impact on biological outcomes.
Trial of intermittent treatment of infants for malaria and anaemia control at time of routine vaccinations in Tanzania (Schellenberg et al., 2001)	◆ First or only episode of clinical malaria	◆ Multiple malaria episodes ◆ Fever episodes ◆ Severe anaemia ◆ Admissions to hospital ◆ Outpatient attendances	This was a test of a new approach to malaria control by administering anti-malarial drugs routinely to infants attending clinics for vaccination. Clinical malaria was reduced by 59%, and severe anaemia by 50%

and there is a discussion of how the results of a trial may be influenced by poor sensitivity or specificity in the outcome measures in Section 4.2. Finally, ways of avoiding bias and maintaining quality control (QC) in case ascertainment methods are reviewed in Sections 4.3 and 4.5.

2 Types of outcome measures

2.1 Primary, secondary, tertiary

2.1.1 Primary outcomes

Primary outcomes are the most important outcomes of the study, the ones that determine its design and the study size. They represent the main reason the trial is being

conducted. Normally, a trial has only one primary outcome, so, for each main question in the development of a new drug, vaccine, or intervention, one specific trial is usually conducted. However, more than one primary outcome may be selected in some trials, provided the design and sample size allow it and if measuring them in the study does not substantially add to the cost or complicate the design or conduct of the trial. For example, Phase I or II clinical trials usually have several primary outcomes (such as the safety of a new drug or vaccine, evaluated through a series of clinical outcomes, as well as the immunogenicity of the vaccine or pharmacodynamics of the drug). Phase III or IV trials have fewer primary outcomes, and often only one. Primary outcomes need careful definition prior to the start of the trial (indicator, instrument to be used, measurement to be taken, values which will be considered as a positive or negative result, which laboratory will be used, etc.); these should be agreed upon among investigators, sponsors, and any regulatory agencies overseeing the trial.

2.1.2 Secondary and tertiary outcomes

Trials often have additional important outcomes, but these are not usually used to determine the trial design and sample size. They are included as secondary or tertiary outcomes to be measured in the trial. These outcomes may not be statistically conclusive, since the trial may not have been designed with the power to evaluate them, but they can be very useful to generate further hypotheses and guide future trials. Because of their importance in justifying future studies, these additional outcomes also need careful definition and measurement and should be fully specified in the protocol, since extra resources often are needed to measure and evaluate them.

2.1.3 Other variables which are not study outcomes

Often, trials have other variables measured in the study not directly related to the study outcomes. Variables, such as age, gender, educational or socio-economic level, and nutritional status, may be used to evaluate potential effect modifiers or confounders to the study outcomes. These variables also need to be defined and considered at the beginning of the study, so they may be included in any pilot investigations.

2.2 Clinical case definitions

2.2.1 Physician-based case definitions

In some trials, outcomes are based on a clinical diagnosis by a physician, without any type of laboratory confirmation. For example, pneumonia may be diagnosed by auscultation in a trial evaluating the impact of an intervention designed to reduce indoor air pollution. This type of outcome is subjective, and interpretation may vary among doctors, and even among experienced specialists. Nevertheless, in many clinical trials, physician-based clinical diagnosis determines the main outcome of the study, since no alternatives exist. For many diseases, standardized criteria for defining a 'case' have been established by experts. The International Classification of Diseases (World Health Organization, 2010; see also <<http://www.who.int/classifications/icd/en>>), which is revised about every 10 years, provides a basis for coding all diseases in a systematic way and is widely used for clinical and epidemiological research.