not officially required.[44] Several major organizations that run trials, such as the UK Medical Research Council (MRC) and the European Organization for Research and Treatment of Cancer (EORTC), have a policy of always considering health economics and quality-of-life implications when a new randomized clinical trial is designed. These tendencies have led to an effort to integrate economic evaluation and economic concepts throughout the clinical development process. In Japan, pharmaceutical companies have been submitting post-adoption pharmacoeconomic data to the government in recent years.[4]

Economic Studies Alongside Development of New Pharmaceutical Drugs

Both economic and clinical research have common important factors to consider in clinical trial design.[45] Good economic evaluation needs planning, pilot studies, and development of models of disease and treatment. Pharmaceutical companies will require greater coordination of these efforts to integrate clinical and economic research into clinical trials as the cost in lost sales or market share for underdeveloped economic assessments becomes more apparent. In addition, companies can consider the use of economic models in their internal planning processes.[46]

Development of new clinical therapies, especially pharmaceuticals, generally proceeds along four well-defined phases that are referred to as phase I through IV studies. Clinical economics can be integrated throughout this development process.

Phase I: Phase I studies, which are performed only after preclinical information obtained *in vitro* or in animals, evaluate the safety and dosage using a small number of (usually healthy) humans. Phase I studies determine the maximally tolerated dose (MTD), a dose just before unacceptable toxicity is experienced by patients. At this stage, economic analysis should provide a discipline to the business case based on pharmacoeconomic principles, and clearly establish the types of clinical and economic information that should be collected during the clinical development program.

During this planning phase, pharmaceutical companies should develop strategies for economic analysis for the clinical development process. They should consider epidemiologic models of disease, economic models of disease episodes, and broader economic analyses of burden of disease that include direct costs, productivity costs, and intangible costs of disease. Both assessment of the new therapy and marketing planning will be conducted using these data.

Phase II: Once the MTD is established in phase I trials, evaluation of biologic effect and adverse events is the purpose of the next series of clinical trials. Thus, phase II trials evaluate the feasibility, treatment effects including side effects, and dosage in a patient population with the disease of interest. Phase II design depends principally on the quality and adequacy of phase I trial data. The results of the phase II studies, in turn, are used to develop pilot data to help design phase III studies. During the phase II studies, variance estimates for costs, quality-of-life, and utilities for patients with a specific clinical syndrome should be assessed for sample size calculations and power determination. Evaluation of economic case report forms and clinical assessment instruments also should be performed for economic analysis at this stage. Economic investigators need to develop and refine models of disease and treatment to guide assessment of potential critical trial parameters.[45,47] The data collected in phase II studies can be used to determine which data elements are high-cost, high-frequency, or are likely to be affected by treatment. The target audience for phase I and phase II assessment is decision makers within the pharmaceutical company.

Phase III: Phase III studies are randomized trials, in which randomization can exclude the possibility of systematic bias, to assess and compare the safety and efficacy of a new therapy either with those of a placebo or those of a therapy that the new treatment will potentially replace. Phase III studies are also pivotal reimbursement and marketing studies. Economics investigators will need to address common study design issues such as required sample size, expected duration of clinical benefit, and external validity of the study population, and ensure that there is no economic bias resulting from the clinical study design.[46] For example, if a certain laboratory defined endpoint is needed for discharge of patients on a new chemotherapy regimen, the protocol may prolong hospital stays if the new treatment has less of an effect on the end discharge parameter than the existing therapy. This would result in a bias if the laboratory parameter was not correlated to the clinician's usual discharge criteria.

The time horizon, or the duration of the clinical study, is another critical parameter in the economic assessment of the therapy that clinical investigators do not always consider adequately. This parameter can have a significant effect on the estimation of clinical benefits of therapy for patients.[18] If a study assesses patients with a chronic disease, such as chronic renal failure, patient resource use may be postponed from the study period to some subsequent period. Low protein diet or angiotensin converting enzyme inhibitors may delay the progression of chronic renal failure without avoiding renal replacement therapy. In this case,