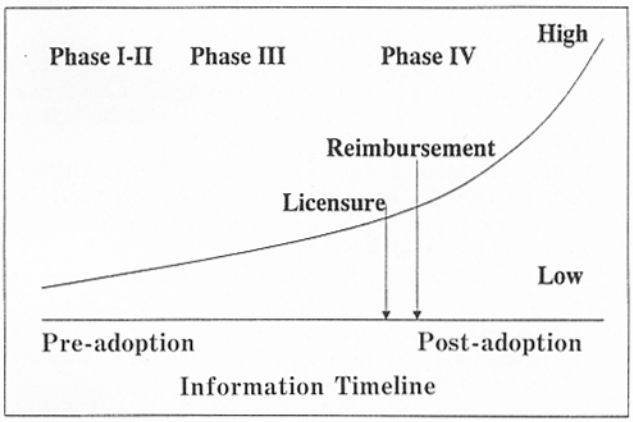

Fig. 4 Generalizability of economic data.

tems across different study countries.

Figure 4 depicts the generalizability of clinical economic data, which increases after initial adoption, and as data represent more typical patients and more typical practice uses. This means that more reliable data can often be obtained from phase IV studies that are conducted in community settings, because there are more diverse participants (in terms of factors such as age, morbidity, and compliance). However, these data are available only after decisions have been made about reimbursement for the therapy and the amount of detail available is often less than in phase III. Economic analyses have recently been included in growing number of phase III clinical trials, since these trials are the final opportunity to collect economic data prior to negotiating either drug approval or reimbursement. As a response to this concern, the design of phase III trials is being revisited to try and improve the external validity of these studies. The results of these studies can then be validated by post-marketing economic studies. These data can be used to reassess reimbursement decisions several years after a product has been adopted.

Examples of Economic Analysis Alongside Phase III Clinical Trials

An example of a prospective economic analysis as a secondary endpoint in a phase III clinical trial was reported in the FIRST study,[50] a randomized international multicenter trial which compared a continuous infusion vasodilator, epoprostenol, with the best usual care for patients with severe congestive heart failure. Prospective economic evaluation served as a secondary endpoint for the study. The clinical trial ended prematurely due to increased mortality in the epoprostenol-treated patients. In multicenter (multicountry) clinical trials, economists are concerned about the possibilities that those trials can incorporate only minimal data collection.[39] However, the economic analysis demonstrated the feasibility of incorporating economic evaluations in multinational phase III clinical trials, although the generalizability of the study was limited in that cost data were developed from a single US hospital.

Another example of an economic study alongside a phase III clinical trial is the IL-3 bone-marrow transplantation study, a multicenter (academic medical centers), randomized, controlled clinical trial.[51] The study assessed economic impact of a new cytokine therapy followed by GM-CSF that was being compared to standard therapy, GM-CSF alone as supportive care, in patients receiving autologous bone-marrow transplant (ABMT) for treatment of lymphoma. Economic analysis of this study showed no significant impact of IL-3 on the costs of care for patients undergoing ABMT for a period of up to 13 months after the procedure. Although there is a limitation that the economic study enrolled only 115 of the 206 patients enrolled in the clinical trial, this study demonstrated the feasibility of prospective economic evaluation within phase III trials of new cancer therapies.

Problems to be Solved in the Future

Reimbursement authorities are increasingly aware of the limitation of economic evaluations conducted in phase III clinical trials and are beginning to design periodic reviews to reassess product indication, effectiveness, and price at periods after the original reimbursement negotiation to validate the claims from phase III trials for wider populations and health care settings.[45] For example, unexpected side effects may be observed after clinical trials, e.g. dry cough by angiotensin-converting enzyme inhibitors, making early estimates of the costs and effects unreliable. In addition, pharmaceutical costs may change after a product has been approved and marketed. Since pharmaceutical companies do not publicize actual costs for production of a drug, the price of the drug is determined according to a price of other drugs or procedures of similar effects. But once it is accepted as standard, bulk discounts are expected and price competition will emerge.[40]

The difficulty with generalization may be more severe for quality-of-life assessments than for objective responses such as survival. Differences in quality of life seen in a trial may bear little resemblance to the magnitude of differences when patients are treated routinely.[52,53] One possible reason for this is a phenomenon of 'trial-induced benefits' where clinical trials are accompanied by better nursing support and extra attention paid to patients.[44] Further empirical evidence is needed to assess the magnitude of this issue.