

**Review Article**

Clinical Endpoints and Economic Parameters for Market Access and Value Creation

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Abstract: On the contrary to limited and shrinking health care budgets, there is an ever increasing pressure on healthcare system providers for more and newer resource-oriented health care along with significant cost constraints. Therefore, one should not be surprised if an effective new therapy does not find its way in practice within publicly funded health care systems. The influence of any therapy on health care costs and outcomes is essential important and is most often considered by decision makers, who have difficult task of making a choice whether already scarce resources should be invested in providing a the therapy or not. Usually simultaneous use of economic evaluation helps estimate the clinical benefits and costs of a therapy. Evidence of value for money is increasingly desired along with clinical safety and efficacy by stakeholders spread across formulary committees, reimbursement authorities, and national health-care systems etc. Today a variety of tools and techniques are available for conducting economic analyses of medical interventions, however one of the most common methodological approaches is to collect data on outcomes and costs alongside clinical trials. Moreover, the opportunities presented by utilizing real world evidence model in day-to-day clinical setup should be well utilized for capturing economic endpoints. Physicians, Patients, payers, providers and policy makers the 5 Ps are looking for awareness, adoption, affordability and accessibility the 4As. To achieve this Clinical-economic evaluation is critical for any new technology.

Keywords: Clinical Endpoints, Economic Parameters, Market Access, Value Creation, Evidence

1. Introduction

The health care expenditures are dramatically increasing over time throughout the world. The health care expenditures of developed countries as percentage of Gross Domestic Product have almost doubled over the past 30 years. The World Health Organization identified the following determinants of growing health care expenditures: increase in income, aging population, technological progress and type of health care system implemented in those countries. Technological progress is deemed to be the major driver of health care expenditures.

Increasing budget cuts, growing costs and inefficient deployment of current resources in the health care sector increase the necessity for economic evaluation of products brought to market. Economic evaluation plays a vital role in

the complete assessment of new medical interventions. Evidence requirement for justifying value for money is now desired more than ever along with clinical safety and efficacy by healthcare stakeholders spread across from formulary committees, reimbursement authorities, and national health-care systems and others. Today the most common methodological approach is to collect data on outcomes and costs alongside clinical trials and these data from clinical trials helps evaluate medicines, medical devices, and procedures. A rising number of clinical trials include specific data on resource use and outcome for assessment of cost-effectiveness reflecting widespread awareness in economic information for new technologies. In many countries evidence of economic value along with clinical effectiveness are considered for regulatory and reimbursement requirements and Indian landscape is also experiencing similar changes. In last several

years researchers have tried improving the methods used for the design, conduct, and analysis of data for economic evaluation that is intended to be collected alongside clinical trials however, published studies highlight that there still exists a great deal of variation in methodology and reporting of cost-effectiveness analyses (CEAs).

These provide a tangible measuring tool to decision makers who must decide whether scarce resources should be invested in providing a new therapy. Thus, the effect of a therapy on both clinical benefits and costs can be estimated simultaneously using economic evaluation.

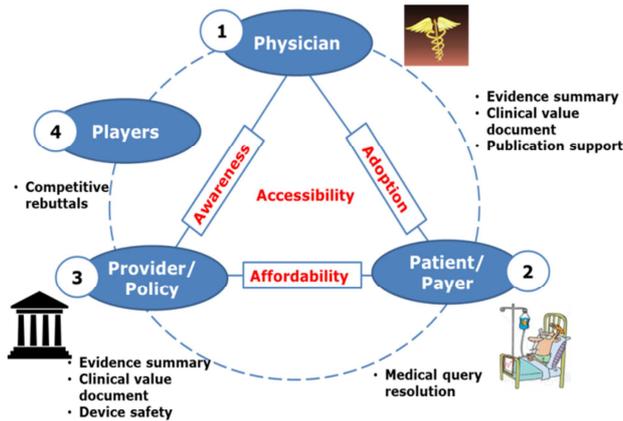


Figure 1. Clinical & Economical Study Value propositions.

Assessing whether a new drug offers not only a potential health improvement, but also that improvement comes at the expense of greater potential health gains is very essential to Governments at all levels, hospital formulary committees and prescribing doctors to help decide appropriate channelization of limited resources. For these reasons governments and other purchasers of pharmaceuticals, medical devices and health technology are increasingly interested in evidence of the cost effectiveness of new products.

The relationship between the outcomes of a clinical trial and the costs of the medical therapy under evaluation is becoming increasingly important as such analysis can more often affect reimbursement decisions for new medical technologies. For example drugs, devices or diagnostics; aid companies seeking to make claims about the cost-effectiveness of their product; allow early consideration of the economic value of therapies, which may be important to improving initial adoption decisions; or address the requirements of regulatory bodies. Economic evaluation in clinical trials usually involves use of constant set of data collected within the trial, or by forecasting from this set of data, and avoids incorporating potentially inconsistent data from many different sources.

The objective of the article is to discuss the issues of design of economic assessment in clinical trials and the appropriateness of performing the economic evaluation in these studies and the critical success factors for the same. [1-3, 9, 10] (Figure 1).

2. Collecting Economic Data Alongside a Trial

Many advantages can be listed for collecting economic data on drug/device-related resource use and health outcomes alongside clinical trials. The most primary benefit is that it offers timely collection of information on treatment/therapy costs and health outcomes specific to patients eligible for the drug/device/technology. It is important to consider that such information may not be available at any other time, and is therefore and essential to be best collected prospectively. Similar prospective measurement of costs and outcomes under the identical conditions and for the one patient population within a single study is more efficient and less expensive overall than performing it at some later point of time to estimate costs. Another important factor is that, when clinical and economic endpoints are collected simultaneously in clinical trials, it allows comparison with the cost of alternative drug/device/technology treatment(s), placebo or in some cases standard non-drug management. [4]

2.1. Definition of Economic Evaluation

“The comparative analysis of alternative courses of action in terms of both their costs and their consequences” [5] and it requires:

- a comparison of two or more alternatives
- examination of both costs and consequences

2.2. Types of Economic Evaluation

A decision tree needs to be followed for economic evaluation. We always need to start with evidence on effectiveness. If there is no evidence, we simply have a costing study. If the evidence is that effectiveness is equal, we want to compare costs and choose the least costly- cost minimization

If there is evidence that effectiveness is not equal, we need to compare the difference in cost and the difference in outcomes.

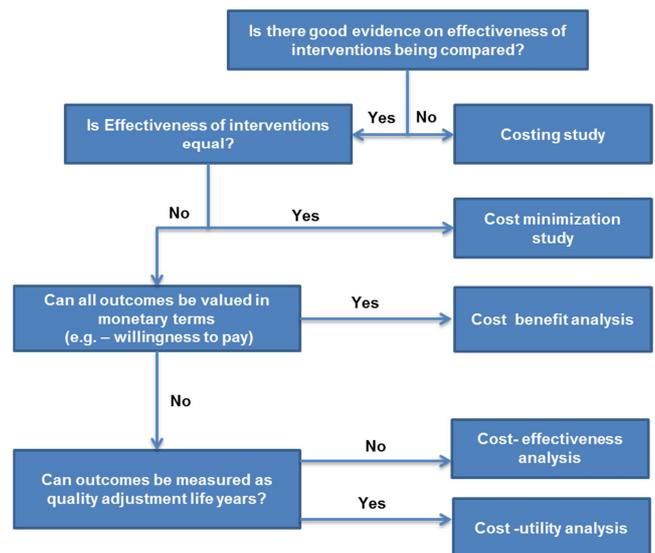


Figure 2. Decision Tree for Economic Evaluation.

The type of economic evaluation is then defined by the outcome measure used. So if everything is measured in monetary terms this is a cost benefit study.

If benefits are measure in quality adjusted life years then it is a cost utility study and if measure in other units such as cost per life year saved then it is a cost effectiveness study. [5] (Figure 2).

2.3. Economic Evaluation Alongside Trials

In a clinical trial there are (usually) two groups: a treatment group and a control group. Procedure for allocating patients randomly to these two groups should be independent.

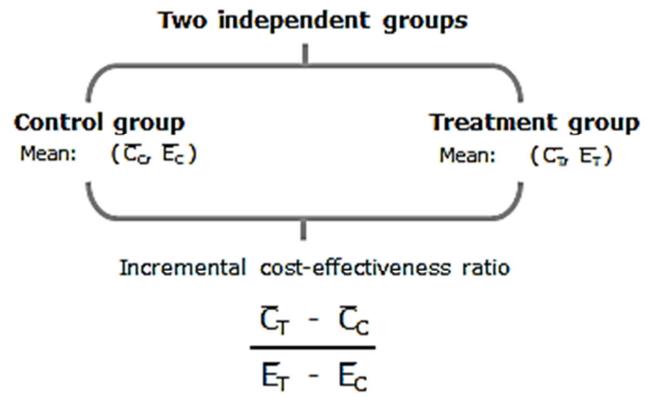


Figure 4. Two groups in economic analysis.

Control group		Treatment group	
Patient	(Cost, Effect)	Patient	(Cost, Effect)
1	(C _{c1} , E _{c1})	1	(C _{t1} , E _{t1})
2	(C _{c2} , E _{c2})	2	(C _{t2} , E _{t2})
3	(C _{c3} , E _{c3})	3	(C _{t3} , E _{t3})
.	.	.	.
.	.	.	.
n _c	(C _{cⁿ} , E _{cⁿ})	n _t	(C _{tⁿ} , E _{tⁿ})
Mean:	(C _C , E _C)	Mean:	(C _T , E _T)

Figure 3. Two groups in clinical trials.

In an economic analysis, patient level data is collected for both costs and its effects. Therefore, each patient in the trial will have a two-item vector with cost and effect for each patient. Average of both costs and effects is then done across all patients by group. As the groups are independent, there should be no covariance of costs or effects between the groups; however, covariance between costs and effects may exist within the groups. [5] (Figure 3)

Calculation is done for differences between the mean cost in each of the groups and differences in the mean effect between the groups and the incremental cost-effectiveness ratio is derived as the difference in cost over the difference in effect.

While the point estimate of the ICER is straightforward, a confidence interval is not. The variance of a ratio cannot be computed analytically since, in principle, the denominator of the ratio could take a zero value leading to an undefined (or infinite) value of the ratio. [5] (Figure 4)

3. The Cost-effectiveness Plane

The CE plane is a useful device for considering the results of CEA. We are interested in the incremental costs and effects of a new treatment compared to an existing comparator treatment. In comparison to the existing treatment, the new treatment may be more or less costly and more or less effective. Plotting incremental effect on the horizontal axis and incremental cost on the vertical axis defines four ‘quadrants’ of the CE plane which can be related to decision-making.

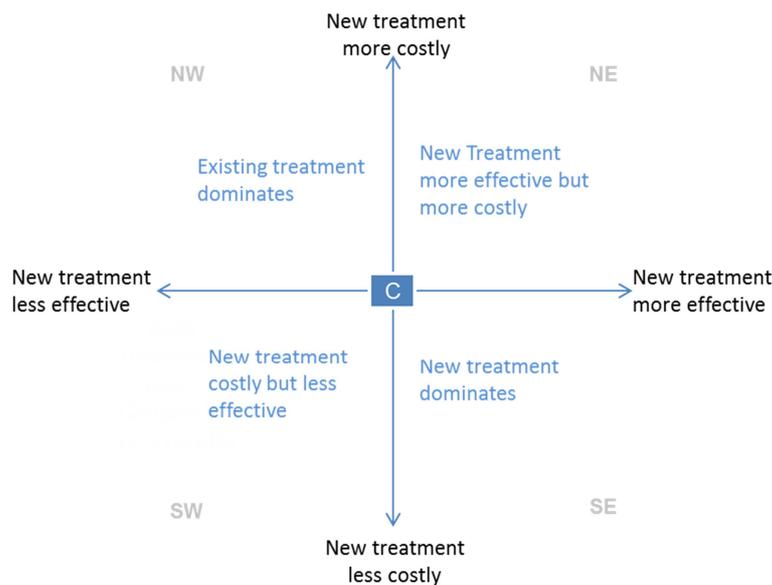


Figure 5. Cost-effectiveness plane.

Clearly, if it turns out that a new treatment is less effective and more costly than the existing treatment (NW quadrant of the plane) then the existing treatment dominates the new and remains the treatment of choice.

Conversely, if the new treatment is both more effective and less costly (SE quadrant) then it dominates the existing treatment and should replace it as the treatment of choice.

If one treatment is both more costly and more effective (NE & SW quadrants) then a trade-off between costs and effects has to be made in deciding which treatment to employ.

If we can obtain an estimate of the maximum willingness to pay by decision-makers for an additional unit of effect then we can use this ceiling ratio to make this trade-off. We can represent this decision rule on the CE plane by a line passing through the origin with positive slope equal to the ceiling ratio. [5] (Figure 5).

If we can represent the relevant decision rule on the CE plane by a line with positive slope equal to the ceiling ratio (the maximum cost per unit of effect that a decision-maker is prepared to pay) then we have effectively divided the CE plane into two halves. Interventions with a cost/effect pairing falling to the left of the line are deemed cost-ineffective, while interventions with a cost-effect pairing falling to the right of the line represent good value for money.

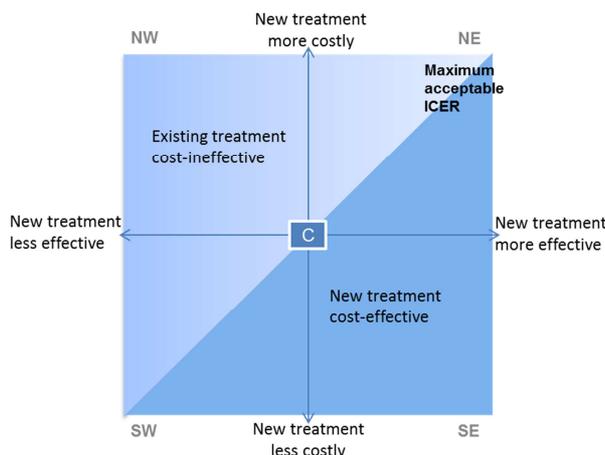


Figure 6. Cost-effectiveness plane into two halves.

This representation of the cost-effectiveness plane as falling into two-halves (rather than into four quadrants) will become important when we discuss the limitations of confidence intervals for CE ratios. [5] (Figure 6).

A Randomized controlled clinical trial has both strengths and weaknesses for economic evaluation. Economic questions in a trial are generally included either by including economic evaluation within an existing efficacy or safety trial, or through the design of a realistic trial specifically for the purpose of economic evaluation.

As it is a known fact that randomized controlled trials are the gold standard set for assessing safety and efficacy, collecting economic data within an existing clinical trial is a more feasible approach. This allows one to utilize the existing trial infrastructure and with minimal additional resources

requirement while enabling prospective collection of patient level cost and outcomes data. However trials primarily designed for clinical endpoints such as the comparison of new treatments to placebos, the use of surrogate endpoints and a lack of long term follow up can limit the ability to address economic questions.

In these cases, pragmatic trials can be designed specifically to answer economic evaluation questions. These trials minimize bias through random allocation, but aim to assess the effectiveness or cost-effectiveness of an intervention under 'real world' conditions. These have minimum restrictions on patient recruitment and follow up and allow greater generalizability of results. However, a lack of long term follow up and issues with respect to comparing more than two or three treatment options are still present in these realistic trials that need to be addressed in the design phase.

When evidence from a wide range of source is required for decision making, economic modelling is employed using data sources such as cohort studies and surveys. This can be used alongside clinical trials to obtain clinical, cost and quality of life information for use in decision analytic models. [6].

4. Designing Economic Evaluations in Clinical Trials

Economic data is collected as a primary or secondary endpoints in randomized trials are commonly used in the evaluation of the value for the cost of medical therapies.

- Short-term economic impacts directly observed; longer term impacts potentially projected by use of decision analysis

- Reported results: point estimates and confidence intervals for estimates of incremental costs outcomes, and the comparison of costs and effects

- Impact of sensitivity analysis on the comparison of costs and effects judged by its impact on both the point estimates and the confidence intervals of the ratios

There are a number of unique characteristics defining the gold standards for economic evaluations within clinical trials. Firstly, it is conducted in real life naturalistic settings, wherein a commonly used cost effective comparator therapy is studied, as it would have been used in practice.

Secondly, adequately powered sample size is necessary, to assess the consistency and validity of the results, in wide range of clinical settings and clinical indications, for which the therapy will be used. Thirdly, it is important to have an adequate length of follow up to assess and evaluate the impact of the therapy. Fourthly, it should be conducted within a specific and relevant timeframe, so the relevant findings can be used to implement decisions, and the therapy can be adopted in standard of care and disseminated.

In a gold standard evaluation, all costs of the trial participants are measured, regardless of the reasons for incurring these costs. The cost prior to randomization and continuing for duration of the follow up are calculated and measured.

Costs incurred post randomization is the cost outcome of

interest that is being studied. Cost incurred subsequent to randomization is a potential predictor of post randomization cost and may explain variability in cost.

Feasibility of gold standard studies is high when such evaluations are undertaken in hospital based studies or integrated healthcare systems. Access to administrative databases which captures the healthcare services utilized and the cost allocation enhances the feasibility of such studies. Associability to already collected data makes it easier to undertake such evaluations.

5. Appropriate Incorporation of Economic Evaluation Alongside a Trial

Economic evaluation is best performed using data on comparative costs and outcomes in 'usual' clinical practice rather than in the special setting of a clinical trial. That is to say conducting an economic analysis alongside a clinical trial is more beneficial when the trial setting is more naturalistic. However, it may be inappropriate to include an economic component to a trial if the choice of comparator is uncommon in routine practice that generalizations cannot be made. Using modelling at a later stage some of the necessary data can be grafted on to the analysis, however the closer the trial is to providing policy relevant information to clinical practice then the more useful it will be. Such data may be more appropriately collected outside the trial protocol in special circumstances. For example, specific surveys could be undertaken to collect cost or resource utilization data from patients or health care providers alongside trials.

5.1. Steps in Economic Evaluation in Clinical Trials

Table 1. Steps involved in Economic Evaluation.

Step 1	Quantify the costs of care
Step 2	Quantify outcomes
Step 3	Assess whether and by how much average costs and outcomes differ among the treatment groups
Step 4	Compare magnitude of difference in costs and outcomes and evaluate "value for costs" (e.g. by reporting a cost effectiveness ratio or the probability that the ratio is acceptable)
Step 5	Perform sensitivity analysis

5.2. Study Design Issues

Strategic planning necessary for the study

- Identify appropriate length of the follow up of the economic endpoints
- Estimate arithmetic means, variances and correlation of cost, health related quality of life, and preference
- Identifying the types of medical services used by the participants
- Pilot testing data collection instruments and procedures
- Gauging level of patient interest in the study

An investigator may have a number of objectives in mind while designing a clinical trial with an economic component; however the results of the trial may be used for multiple different purposes. These may include: regulatory approval;

formulary listing; institutional purchasing; and consumer and clinician acceptance of the drug/device/technology. Direct input from clinical investigators, economists, marketing and statisticians at the early stages of protocol development helps collect key data (eg. important cost categories) alongside the trial, or inappropriate sample size or statistical analyses being used. This is important as in the case of insufficient sample size, invalid conclusions can be drawn about important differences in treatment cost and effectiveness.

It will be essential to resolve any differences between local and global priorities especially for instance when trial is conducted for a multi-national company, (eg suitable comparator, appropriate dosage and formulation in Japan) prior to trial initiation.

6. Measurable Medical Services

- Limit data collection to disease related services
- Limit the delivery settings in which medical service use is collected
- Limit participants from whom economic data is collected

For comparative cost-effectiveness the major interest in a trial is in differences in resource use between treatment groups. This is termed the incremental cost between treatment alternatives. It is hard to know ahead of the trial whether certain unrelated costs may somehow in fact be related to the intervention and may differ between groups. If the data are not gathered this will never be known. It is important to clearly identify the full range of costs that could potentially vary between treatment alternatives. In practice, trial design is a compromise between the desire to gather information on all resource utilization no matter how seemingly unrelated to the treatment under study, and the desire to be efficient and reduce the burden on investigators and subjects by not gathering excessive amounts of irrelevant information. A Common situation is to gather all major events (deaths, hospitalizations) regardless of cause, and all other events that can reasonably be attributed to the disease under study or to the treatment. Relevant economic cost data relate to resource use associated with the drug intervention, the control therapy, any associated adverse events, and any condition-related resource use. The type of data collected will depend on the purpose of the study, the condition being treated, interventions included in the analysis, and the trial setting (eg hospital outpatients, general practice). For PBAC purposes, identification and measurement of direct costs are required. Indirect costs (eg effect on productivity) can be measured but should be included as supplementary data in a PBAC submission. Indirect costs may be more relevant for marketing purposes and for certain conditions (eg cancer, flu). It is less relevant to the overall societal perspective if days lost by a worker are easily replaced by another worker with little change in total productivity and total social income.

7. Aggregated Levels of Medical Service

Care may be necessary when pooling data on resource

utilization from different hospitals, states, or countries where disease patterns, cultures, physiological traits or medical practices differ noticeably. This is not so important for protocol-driven resource utilization, but is very relevant for the management of patient withdrawals where usual clinical decision-making applies. Different styles of medical practice may also operate in public and private hospitals compared with specialist clinics or general practice settings. If resource utilization for a particular condition is considered appropriate for pooling across several countries, it is crucial for PBAC purposes that Australian costs only are applied to all resource items. There may also be a different incidence or prevalence rate or prognosis for a condition across several countries, which may need to be considered when pooling data and analyzing results.

Measurement takes place during the trial and follow up period. Resources used should be collected in naturally occurring physical units as well as in monetary values (eg days in intensive care, and cost per day in intensive care; number and type of pathology tests ordered and the cost per unit; hours of nursing time and cost per hour). This ensures that the study can be replicated and alternative dollar costs attached at other times in other places. It is preferable to measure the direct costs associated with treatment from existing Case Report Forms (CRFs) being used for the study. Where this is not possible (eg due to constraints on CRF in multi-national companies), consideration should be given to using other data collection instruments including questionnaires (either administered at medical consultation or by telephone or mail), or patient diaries. Any data collection instrument to be used in the study should be mentioned in the protocol itself. Indirect costs refer to production (or output) losses to society due to patients and/or their family (or friends) losing time from work as a direct result of the treatment process. Measuring such indirect costs will require detailed information including number of days when employment was not possible, changes in activities of daily living, employment status of patient (or family/caregiver), number of days off paid employment, and gross wage rates. Including indirect costs is clearly relevant to a third party payer who is liable for compensation or whose customers are employers. Indirect costs are usually measured using either patient diaries or questionnaires.

8. Price Weight Estimates for the Study

Valuation of costs is usually done outside of the clinical trial since cost data on individual patients can often be estimated subsequently as long as utilization data is collected alongside the trial. The PBAC encourages the use of standardized resource costs for specific healthcare utilizations as specified in its Manual of Resources. For example, for hospital stay, the PBAC recommends that resource weights developed as part of the National AN-DRG costing study be used for specific hospital episodes of care rather than the prospective collection of costs alongside the trial. In certain circumstances, (eg when a specific DRG weight may not capture the full extent of the real cost of a hospital episode) some companies may prefer to

collect

Patient specific resource costs as part of the trial itself. General cost information on resource usage is best collected from a number of investigational sites participating in the study, to increase generalizability given the potential variation in prices unrelated to resource use variation. For example, clinician salaries may differ from state to state.

9. Realistic Study Design and Limitations

- Sample inclusion criteria
- Intent to treat analysis
- Lost to follow up
- Protocol included cost and effect

Given clarity about the analytical framework, how do randomised trials help us address cost-effectiveness questions? The short answer is that a single randomised trial will generally not, on its own, be an adequate source of data for cost-effectiveness analysis. Here is a list of the sort of limitations seen in trials as a source of data for economic evaluation. For each, an example of a recent NICE appraisal is shown where the trial data are characterised by the limitation. The first limitation is that most trial compares the new technology with the wrong comparator (e.g. the least effective existing intervention) or a partial set of comparators (e.g. one of the 6 existing therapies). The second item in the list is more a characteristic than a limitation: when more than one trial exists, then all measurements in those trials need to be synthesised. Methodologically, trial-based economic evaluation based on more than one trial (when patient-level data is only partially available) has not been extensively developed. The third item is that trial often does not provide all the parameter estimates needed for cost-effectiveness analysis (e.g. a major area of resource use has not been measured). Fourthly, trials are limited when they are undertaken in locations which are unrepresentative of routine practice in the decision makers jurisdiction – e.g. many cardiac trials are undertaken in a number of countries but clinical practice in the UK is quite different to many other developed countries. A fifth problem is that trials often do not measure ultimate end-points which relate to the measure of health gain needed for economic evaluation; rather they focus on intermediate outcomes (e.g. viral load in HIV trials). A sixth feature is that, because trials are costly to undertake, indefinite follow-up is impossible which a limitation to economic evaluations is often where a long-term time horizon is appropriate. Finally, in many instances trials simply do not exist, but it is still necessary to make a decision about cost-effectiveness.

10. Opportunity with Real World Evidence

Today Real world evidence data is becoming an increasingly important element of healthcare decision-making as HTA and reimbursement agencies and payers become more

demanding in terms of the relevance of clinical evidence and connections to the delivery of care in clinical practice computed by increased regulations and policies for conducting clinical trial.

They serve to project real time data inputs into many elements of the market access strategy, from choice of comparators in pivotal trials to development of economic models that help policymakers to direct investments in healthcare and to help obtain benefit for the patients and other end users. RWE today when synergized with appropriate statistic tool can provide treatment pattern surveys, patient selection, treatment decision drivers, and comparators in individual markets among few. The economic impact of a disease burden, also critical insight into the impact of a disease and its treatment on patients and care givers, and provide a platform to understand potential changes in treatment. Budget impact can be understood by resource utilization RWE studies. RWE offers a real-time market inputs with respect to clinical endpoints highlighting corresponding economic evaluations.

11. Pragmatic Way Forward

The collection and analysis of economic data in clinical trials is a research is emerging in response to the need for better information about the economic implications of medical and public health interventions. This research involves incorporating economic measures into the prospective data collection activities of a clinical investigation to determine the safety and efficacy or effectiveness of an intervention. Both the economic and clinical data from the trial are analyzed to provide information about economic implications or cost-effectiveness of the intervention for the use of various decision makers.

Suggested checklist for assessing economic evaluations

- Was question well-defined?
- Were alternatives clearly described?
- Were resources measured and valued fully & appropriately?
- What evidence on effectiveness was used?
- Was discounting necessary and was it performed?
- Were incremental costs and outcomes analyzed?
- Was an adequate sensitivity analysis performed?
- Are the results adequate to inform purchasing?
- Are the conclusions justified?
- Are the results applicable to the local population?

The success of clinical-economic trials in meeting the important goal of more rational and efficient use of health care resources will depend on the strengths and limitations of the research method.

Successful economic assessments within clinical trials are dependent on commitment to undertake such studies, characterized by early and meticulous planning. Clinical trial design needs to be planned in advance to integrate such data collection. Clinical investigators at the outset need to collect economic data along with the clinical data. Cooperation and collaboration between all the study team is critical in these studies.

12. Conclusion

Health care providers and financing organizations have become more aware of the resource constraints on the provision of medical services, thus increasing the importance of economic evaluations within the health care industry. With rising costs and stricter budgets, healthcare companies have to provide not only efficacy and safety data but also justify the costs of the new therapies/technologies.

Clinical trials may provide the best opportunity for developing information about a medical therapy's value for the cost early in its product life cycle.

Moreover, the opportunities presented by utilizing real world evidence model in day-to-day clinical setup should be well utilized for capturing economic endpoints. Physicians, Patients, payers, providers and policy makers the 5 Ps are looking for awareness, adoption, affordability and accessibility the 4As. To achieve this Clinical-economic evaluation is critical for any new technology.

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