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Review Article

Health economics and cost-effectiveness research with special reference to hemato-oncology

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ABSTRACT

The cost of health care is increasing globally, especially in cancer. Health economics is an increasingly important field and medical professionals should have a working knowledge of the basis for health technology assessment such as cost-effectiveness analysis, cost utility analysis and cost benefit analysis. There are limited studies on health technology assessment regarding expensive therapies, primarily from high-income countries, but these cannot be applied to countries with different gross domestic product (GDP) and cost of health care delivery. There is a need to carry out health economics related research utilizing data from India. Whereas clinical trials establish the efficacy of new drugs in controlled environments, with strict inclusion and exclusion criteria, their transferability to the “real-world” situation is not always true. With the shifting of the global cancer burden to middle-income and lower middle-income countries, this field is going to assume greater importance in the future. Health economics research conducted in India may be of benefit to other countries with similar economies. The Armed Forces Medical Services of India, with a well-established system of assessing health outcomes, and robust system of accounting for expenses, can provide the lead for these studies.

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Health care expenditure in cancer and hematology

The global cancer burden is radically shifting to low-income and middle-income countries, although they also have the added burden of significant acute, infectious, and chronic diseases.¹ Costs of health care in general and cancer care in particular are rising at a rate that outpaces inflation and consumes an increasing share of expenditures at all budgetary levels, from national to individual, in almost all countries. We are increasingly faced with the question

of whether, sometimes minor benefits of proven interventions are worth the cost to individuals or society.¹

Health economics

Economic evaluation is important as resources are scarce. It is based on the premise that individuals must give up one resource in order to get another. The “opportunity cost” (cost of what we give up to get another benefit) of health care may

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be substantial. Decisions need to be based on comparisons of costs and benefits.

Health economics is a branch of economics dealing with issues related to efficiency, effectiveness, value and behavior in the production and consumption of health and health care.

While committing resources, it is better to have an organized consideration of the factors involved in the decision to commit resources to one use instead of another. This is important for the following reasons.²

- (a) To identify clearly the relevant alternatives.
- (b) . A program which looks unattractive from one viewpoint may look significantly better from another. Analytical viewpoints may include the following: the individual patient, a specific hospital, Armed Forces Medical Services budget, Government's overall budget or societal viewpoint.
- (c) The real cost of any program is not the number of Rupees spent on that program, but rather the value of the benefits achievable in some other program that has been foregone by committing resources in question to the first program. It is this "opportunity cost" that economic evaluation seeks to estimate and to compare with program benefits.

Importance of economic evaluation

An example of the importance of economic evaluation is shown in the classical study of Neuhauser et al.³ The American Cancer Society endorsed a protocol of 6 sequential stool tests for occult blood for detection of asymptomatic colon cancer, after a study by Leffall LD Jr. (1974).³ Subsequently Neuhauser et al showed through their economic analysis that, based on the cost of the stool test and barium enema testing on all those with a positive stool test, the average cost of the cancer detection screening program went up from \$1175 for the first test to \$2451 for the sixth test. However, the marginal cost (extra cost per case detected) increased from \$1175 for the first test to a staggering \$47 million per cancer detected for the sixth stool test. The study showed that with each subsequent test the number of cases detected decreased and 99.9421% of cases were detected with the first three tests. Subsequently, the recommendation for sequential stool testing was modified for only three stool tests.³

Although this is an extreme example, this classical study nevertheless demonstrates that without measurements and comparisons of outputs and inputs, we have little criteria on which to base any judgement about the value of money and resource investment. The optimal use of a technology would be achieved when the marginal cost is equal to marginal benefit.

Economic evaluation is most useful when it is preceded by three other types of evaluation, each of which is important

- (a) Efficacy: Can a health procedure or program work?
- (b) Effectiveness: Does it work? This assesses its acceptance and usefulness when it is offered.

- (c) Availability: Is the program reaching those for whom it is intended?

Types of economic evaluation

In the health care sector, economic evaluation is used as a generic term for a range of techniques that may be used to assemble evidence on the expected costs and consequences of different procedures or programs. These include costs related to productivity, loss of time from work, loss of time of family members, time and cost of travel for therapy and quality of life. An understanding of various economic terms used in health care literature is useful to critically analyze health economic literature and for decision making.²

Cost-minimization analysis is an appropriate form of evaluation if there is reason to believe that the outcomes of the procedures under consideration are the same. Thus comparing two anti-hypertensives of the same class, with similar effectiveness, would constitute cost-minimization. If literature suggests that there is no difference in the clinical outcomes for defined groups of patients, the analysis can concentrate on the least costly option.⁴

Cost-effectiveness analysis (CEA) is suitable when the outcomes of different procedures may be expected to vary, but these outcomes can nonetheless be expressed in common natural units. It is most useful in situations where a decision maker is operating within a given budget, and considering a limited number of options within a given field.

These effects can be measures such as: "life years gained" when evaluating thrombolysis, "reduction of diastolic blood pressure (mmHg)" for anti-hypertensives, "episode-free days" for comparing asthma therapy or "cases of pulmonary embolism detected" when comparing different imaging procedures. CEA can also be performed on any alternatives that have a common effect. Thus kidney transplantation could be compared to cardiac surgery if the effect of interest is life-years saved.

Cost-effectiveness is typically evaluated using an incremental cost-effectiveness ratio (ICER) comparing the new treatment with the treatment used in the control group of a pivotal randomized clinical trial (RCT), usually a less efficacious and less costly alternative. Usually, the ICER is expressed as an incremental cost per life-year gained, and calculated as:

$$\text{ICER} = \frac{\text{Cost}(\text{new}) - \text{Cost}(\text{old})}{\text{Effectiveness}(\text{new}) - \text{Effectiveness}(\text{old})}$$

Cost utility analysis (CUA): While CEA is useful for comparing different treatments for particular diseases, it does not help in comparing different treatments for different diseases, when the units of outcomes vary. Moreover, CEA is unable to combine reductions in morbidity and reductions in mortality into a single index and thereby allow direct comparison between treatments that vary on these two dimensions. Hence, effort has gone into development of "utility" based measures of outcome. The usual measures of utility are quality-adjusted life-years (QALYs) or disability-adjusted life-years (DALYs). QALYs are calculated by estimating the total life years gained from a procedure and weighting each year to

reflect the quality of life in that year. CEA and CUA are similar on the cost side, but differ on the outcomes side. Thus, results of CUA are often expressed as cost per QALY gained.⁵

Cost benefit analysis (CBA): From the economic angle, the CBA is considered the most comprehensive and theoretically sound form of economic evaluation. It measures both the costs and consequences of alternatives in monetary terms. CBA is broader in terms than CEA/CUA. It is not restricted to comparing programs within the health care, but can be used to inform resource allocation decisions both within and between sectors of the economy.⁶

CEA/CUA is restricted to comparison of health care programs and produce similar units of outcome such as QALYs. CEA and CUA address mainly questions of *productive efficiency*, with outcomes restricted to health benefits. In contrast, CBA is broader in scope, and able to inform questions of *allocative efficiency*, because it assigns relative values to health and non-health goals to determine which goals are worth achieving, given the alternative uses of resources.² The differences in these different forms of analyses have been summarized in Table 1.⁷

Country specific programs

Countries set different thresholds (both explicit and implicit) for what is considered good value or is cost effective. In the UK, the National Institute for Health and Clinical Excellence (NICE) evaluates the clinical and cost-effectiveness of health care interventions, explicitly considering cost per quality-adjusted life-year (QALY) gained, and provides the National Health Service (NHS) with advice on which treatments should be covered.⁸ NICE is acknowledged as a world leader in health technology assessment, and is responsible for approval of drugs for the NHS. Economic analysis is a major factor in its approval process.

In Canada, the Common Drug Review (CDR) was established in 2002, to provide a national process to review and recommend inclusion of new drugs in the formulary. The CDR evaluates a drug for its cost-effectiveness, based on a systematic review of relevant published and unpublished literature and

the manufacturer's pharmaco-economic evaluation. A similar organization, Pharmaceutical Benefits Advisory Committee (PBAC) is functioning in Australia to determine if new drugs should be included in public formularies.⁸

Medical education and health economics

Medicines account for 20–60% of health spending in developing and transitional countries, compared with 18% in countries of the Organization for Economic Co-operation and Development. Up to 90% of the population in developing countries purchases medicines through out-of-pocket (OOP) payments, making medicines the largest family expenditure item after food. As a result, medicines are unaffordable for large sections of the global population and are a major burden on government budgets.⁹

Medical education is often focused on technical skills and clinical decision making, without attention to cost. There is a need to incorporate knowledge of costs and understanding of cost-effectiveness analysis into primary and continuing medical education. The communication of cost and cost-effectiveness to patients is becoming increasingly relevant as patients share an increasing burden of the cost of care.¹

Research

For establishing the efficacy and safety of a drug, randomized clinical trials (RCTs) are the gold standard for showing the efficacy, under ideal conditions, of a new drug.

Cost-effectiveness analyses provide the basis for defining affordability; they are usually based on results of RCTs, although these trials might not predict benefits and costs when a new treatment is used more widely in real world conditions. Such analyses should be supplemented by cost analyses based on health outcomes databases, so that resource utilization and longer-term toxicity are better elucidated.

Ideally, pragmatic trials would follow pivotal RCTs that have established efficacy of a new treatment in a restricted

Table 1 – Methods of analyzing health care costs.

Method	Characteristics
Cost identification or Cost-minimization analysis	<ul style="list-style-type: none"> Compares costs of 2 or more interventions with the assumption that their outcomes are similar.
Cost-effectiveness analysis (CEA)	<ul style="list-style-type: none"> Compares net costs of 2 or more interventions in monetary units with their effectiveness (e.g., survival). Incremental cost-effectiveness ratio (ICER) is calculated (ratio of difference in costs versus difference in effectiveness). Less costly and more effective intervention preferred over more costly and less or equally effective therapy.
Cost utility analysis (CUA)	<ul style="list-style-type: none"> A type of cost-effectiveness analysis that incorporates quality of life considerations in the outcomes. Results are expressed as cost per quality-adjusted life-years (QALY) gained. Survival time is adjusted using "patient-utilities" (ranging from 0 for death to 1 for full health).
Cost benefit analysis (CBA)	<ul style="list-style-type: none"> Assigns a monetary value to clinical benefit and estimates net financial impact of an intervention. Not commonly performed in health care due to the challenges in assigning monetary value to health or a disease state.
Adapted from Reference. ⁷	

population. Pragmatic trials would be simple and would assess the treatment groups under conditions that reflect daily medical practice, but they would face at least one problem. There are ethical issues in denying treatment to a control group when efficacy has been acknowledged by regulatory bodies, although equipoise might be maintained if the benefit is marginal and the new treatment increases toxicity.

It is often suggested that non-randomized comparisons based on routinely collected data may have more external validity, as these include all patients, are set in the real world and by their setting, include preferences of the patients and any influences of doctor-patient relationship.¹⁰ Differences in RCTs and pragmatic trials are summarized in Table 2.

Comparative effectiveness research

A more recent term used in pharmaco-economics is comparative effectiveness research (CER), which has been variably defined by different agencies with certain common elements. These are (a) CER would focus on clinical effectiveness, (b) it would be used to inform a wide range of decision-makers, such as patients, providers and policy makers and (c) CER would focus on a broad range of interventions and services.¹² It would be conducted in the 'realworld' setting.¹¹

CER would aim to bring together RCTs and real world evidence to form an integral framework of comparative evidence.¹³ A number of methods can be used to conduct CER, including systematic reviews, experimental studies such as pragmatic clinical trials as well as non-experimental studies including retrospective and prospective studies that leave the choice of treatment to the patients and their health care providers.¹¹

Observational studies can contribute in situations where clinical trials have not or cannot be performed for political or ethical reasons. Thus it would be unacceptable to deny access to vaccinations in the threat of an epidemic, or deliberately expose patients to less effective treatment. Other situations where observational studies can contribute are:¹¹

- (a) When adherence to treatment in the "real-world" differs from RCTs.
- (b) When providers have different levels of training.
- (c) When larger studies are needed to study the benefits of different dosing or routes (e.g. oral or inhaled steroids in asthma).
- (d) When treatment is off-label.

Defining value in cost-effectiveness

A major challenge is for countries to establish threshold values on which to base funding decisions for new interventions. The World Health Organization (WHO) has proposed using the wealth of an individual country when deciding on thresholds for economic value - specifically, multiples of a country's per-capita gross domestic product (GDP).^{14,15} New treatments with an ICER of less than or equal to the per-capita GDP would be considered very cost effective, one to three times the GDP would be cost effective, and more than three times would not be cost ineffective.

The decision to implement expensive new interventions should be based on an increase in survival or quality of life (or both) and its financial viability. This requirement involves a trade-off between the risks and benefits to the patient as well as between clinical effectiveness and limited resources.

Role of health economics and CER in India

The majority of published studies on economic evaluation are generated from the high-income countries. Most of them are not applicable to the middle-income and lower middle-income countries as the costs of drugs, hospitalization, charges for services, as well as affordability are strikingly different.

In India there is no national health service, hence payment for medical care is mainly from out-of-pocket spending for majority of the population.^{9,16} There is also a rising number of patients who are covered by state or employer funded health care or personal health insurance. For both groups of patients, health technology assessment would be required, given the constraints of budgets.

Another factor unique to India is the availability of generics at a much lower cost. Thus the cost of patent drugs in Canada, compared to the cost of generics in India is quite different. A comparison of some drugs used in hemato-oncology is shown in Table 3. Hence economic evaluations carried out in high-income countries will not be applicable for Indian conditions.

To illustrate this, literature about whether hematopoietic cell transplantation (HCT) has a favorable economic profile in chronic myeloid leukemia (CML) with the advent of tyrosine kinase inhibitors varies according to the economy of the country. Most investigators comment that the results of these studies are sensitive to the pricing of imatinib.¹⁷ These

Table 2 – Limitations of randomized clinical trials and characteristics of pragmatic trials.

Limitations of clinical trials	Characteristics of pragmatic trials
<ul style="list-style-type: none"> • Clinical trials are often undertaken in specialist centers. • The investigators are highly committed. • Patients are highly selected, without co-morbidities and with low risk of adverse events. • Patients are motivated and compliant. • Length of follow up is limited. • The comparator is usually a placebo or baseline therapy. 	<ul style="list-style-type: none"> • These are undertaken in generalizable trial setting. • Include real world patients. • Sample size is chosen to accommodate socioeconomic variability. • Comparator: either a well-defined alternative, or the physician's best alternative. • Doctor and patient not blinded. • Freedom to change therapy.

considerations are even more important in developing countries, where lifelong treatment with an expensive drug may consume more resources than a “once only” HCT procedure. Investigators from Mexico found a non-myeloablative allograft with a median cost of USD \$18,000 in their practice, a more attractive option for patients with newly diagnosed CML because that amount would be enough to cover only 180 days of treatment with imatinib 400 mg/day.¹⁸ In India, with the availability of generic imatinib, now endorsed by the Supreme Court of India, the results and conclusions may be different.

India has a large patient population and highly trained medical professionals. The country is considered a leader in information technology, and it should be possible to create reliable electronic medical records and databases needed to conduct CER. The universities in different regions have academic departments of economics, to provide support to health economics research. India is also considered the global leader in the manufacture of generic drugs. Hence, with planning and coordination, it should be possible to conduct comparative effectiveness research and health technology assessment of various patent and generic drugs in the country.

The Armed Forces Medical Services (AFMS) of India are unique in that they provide comprehensive health care to their serving personnel and families. Even after retirement, those who suffer from disabilities are followed for a long time. The pension offices have the capacity to provide data on mortality, periods of hospitalizations, low medical classifications and employability. Thus parameters such as overall-survival (the most important end-point for any trial), progression-free survival, time-to-next treatment and quality of life (full employability or fitness) can all be obtained in the setting of the “real-world”. Moreover, the AFMS would have the capability of carrying out cost analysis of drugs, hospitalizations and other interventions. As the supply of medicines is through the AFMS, at least for the serving personnel, there is uniformity in the brands supplied, whether patent or generic. Other Government or corporate organizations may also be providing similar services, but do not have the advantage of an affiliated teaching institution like the Armed Forces Medical College with its academic departments such as hospital administration and information technology services. Research is an integral part of the AFMS with annual research conferences and dedicated budgets. Whereas carrying out RCTs in the AFMS may be controversial, comparative

effectiveness research through observational studies using databases would be ethically feasible. Using these resources, health technology assessments of patent drugs (monoclonal antibodies or expensive chemotherapies) or technologies (cardiac stents) or of Indian generics should be possible. These studies would be of benefit, not only to the nation, but to other countries with similar economies as in India.

Conflicts of interest

On Advisory Board of Celgene; Speaker for Novartis.

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Table 3 – Comparison of cost of drugs in Canada and India.

Drug	Cost of patent drug in Canada	Cost of generic brand in India (approximately)
Rituximab 500 mg vial	\$2265	\$1000
G-CSF 300 mcg vial	\$181	\$25
Bortezomib 3.5 mg vial	\$1870	\$200–250
Imatinib 400 mg/month	\$3400	\$100–250
Thalidomide 100 mg/month	\$1700	\$50
Lenalidomide 10 mg/month	\$9600	\$50–100