



ISPOR India Chapter

PROPOSED PHARMACOECONOMICS GUIDELINES FOR INDIA (PEG - I)

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PROPOSED PHARMACOECONOMICS GUIDELINES FOR INDIA (PEG - I)

(Affordable and equitable medical care through informed decision-making)

Draft submitted to:

ISPOR – India Chapter, Executive Committee

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About ISPOR - India Chapter

Rising medical care costs is not only a cause of concern for patients but also for policy makers and service providers. The creation of ISPOR India chapter is a humble initiative by professionals, students and researchers interested in Pharmacoeconomics, health economics and its impact of various policies related to health care sector.

Our Mission

The mission of the Society of Pharmacoeconomics and Outcomes Research India (SPOR-INDIA) is to provide an environment for knowledge sharing among researchers, healthcare practitioners and decision-makers interested in Pharmacoeconomics and outcomes research; to serve as a bridge in bringing together Indian researchers, healthcare practitioners, and decision-makers interested in Pharmacoeconomics and members of pharmaceutical industry, health-related organizations, and academia; to act as a resource at a local level for individuals including students interested in Pharmacoeconomics and outcomes research and to provide an opportunity for India chapter members to become more familiar with the activities of ISPOR as well as participate in its activities.

Aims and Objectives

The Aims and Objectives of the society shall be as under:

- Provide an environment for knowledge sharing among researchers, healthcare practitioners, and decision-makers interested in Pharmacoeconomics and outcomes research.
- Serve as a bridge in bringing together Indian researchers, healthcare practitioners, and decision-makers interested in Pharmacoeconomics and members of the pharmaceutical industry, health-related organizations, and academia.
- Act as a resource at a local level for individuals including students interested in Pharmacoeconomics and outcomes research.
- Provide an opportunity for India chapter members to become more familiar with the activities of ISPOR as well as participate in it.
- Maintain affiliation as a component chapter of the International Society of Pharmacoeconomics and Outcomes Research (ISPOR).
- Promote research in area of policy, advocacy and public health related issues.

For further information, please visit www.isporindia.com

Abbreviations

| | |
|-------|--|
| BIA | Budget Impact Analysis |
| CADTH | Canadian Agency for Drugs and Technology in Health |
| CBA | Cost Benefit Analysis |
| CCA | Cost Consequence Analysis |
| CEA | Cost Effectiveness Analysis |
| CGHS | Central Government Health Services |
| CMA | Cost Minimization Analysis |
| CPA | Central Procurement Agency |
| CUA | Cost Utility Analysis |
| DALY | Disability Adjusted Life Years |
| DCGI | Drug Controller General of India |
| DGHS | Directorate General of Health Services |
| DHR | Department of Health Research |
| DTAB | Drugs Technical Advisory Board |
| HRQoL | Health-related quality of life |
| ICER | Increment cost-effectiveness ratio |
| IRDA | Insurance Regulatory and Development Authority |
| ISPOR | International Society of Pharmacoeconomics and Outcomes Research |
| MCI | Medical Council of India |
| NICE | National Institute for Health and Clinical Excellence |
| NPPA | National Pharmaceutical Pricing Authority |
| PABC | Pharmaceutical Benefits Advisory Committee |
| PEG-I | Pharmacoeconomics Guidelines For India |
| QALY | Quality Adjusted Life Years |

Chapter I: Prologue and Objective

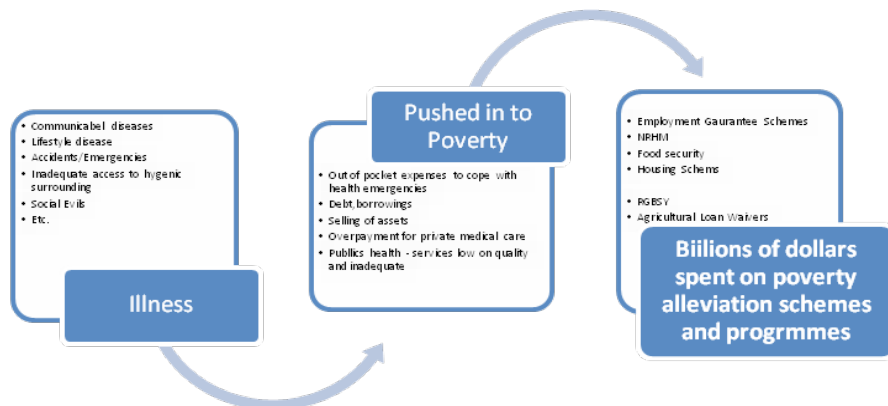
Objective of this guideline

The Primary Objective of this guideline cum working paper is to initiate India specific Pharmacoeconomics research. The pharmacoeconomic data generated from such research needs to be as per global Pharmacoeconomics research standards and principles. This will help various stakeholders to appreciate and criticise the applicability of such data as an enabler to a wiser and more informed decision-making tool.

Secondarily, the working paper intends to identify information vacuum in areas where more studies need to be conducted with experts from respective areas.

How it started?

Cost of illness and medical bills are leading over 100 million people globally into poverty every year. In some countries, 5% of the population is forced into poverty every year because they have to pay for health services. As per World Health Organization (WHO), in countries like India, people who pay for their health care services suffer "catastrophic costs". While millions suffer and die in absence of access or inability to afford medical care, many others suffer because they end up paying through borrowing debts and selling assets etc.



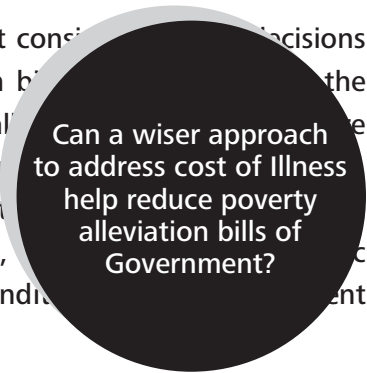
Health and medical service is a finite resource for an infinite demand which is reflected in WHO's annual World Health Report 2010, which stated that even rich countries where medical care was earlier accessible and affordable are finding it very difficult respond to people's needs. The report estimated that between 20% and 40% of all health expenditures is wasted due to inefficiency. Overpaying is a form of waste. For instance, in some countries medicine prices are up to 67 times more than the international average price, grossly affecting expenditures for other health services. This calls for

serious review of public's procurement and alignment of health policies.

Like India, in many other middle and low income countries, direct and indirect medical costs drives millions of people to poverty every year. Rising medical costs and inaccessibility to health care leads to millions of deaths many of which could possibly have been saved if health policies were better informed and equitable. Unlike developed countries, health policy formulation in developing countries encompasses far more complex areas of intervention besides direct medical care and infrastructure such as primary education, poverty alleviation, sanitation, housing, insurance etc. Unarguably the funds available for this scope of health care spending are extremely scarce and the ability to utilise them wisely and economically is absolutely necessary.

Review of Evolution of health policy of India pre and post Independence concluded that there is not much improvement in vision of equity in health.¹ It is very ironical that the vision laid by Sir Bhor Committee at the dawn of Independence is yet to be achieved, even while the problems today are much larger and disease burdens are enormous. The Indian government published their first National Health Policy 35 years post independence as a consequence of signing of Alma Ata declaration on Primary Health Care. Notably, several governments and 5 years plans later, the goal of Health for all still eludes us. Indian expenditure on health care still remains at 1.4 percent. Health Ministry has proposed a new initiative called 'Free medicine for all through Public Health Facilities' under the National Rural Health Mission (NRHM). The Cabinet has approved the setting up of a Central Procurement Agency for bulk procurement of drugs and to support in preparing Standard Treatment Protocols.

However formulary decisions by CPA's is unclear. It is not clear on what considerations decisions taken to include drugs in to free medicine distribution plan. An even bigger question for the policymakers and the people of India is whether the funds that are allocated are being rationally utilised? This is an area where Pharmacoeconomics comes in. The total allocation for healthcare must be raised to at least 2.5 per cent of GDP by 2017 and 3 per cent in the subsequent five years. This, the expert group estimates, will result in a reduction in out-of-pocket spending from 67 per cent of total health expenditure in 2011 to 33 per cent by 2017 and 33 per cent by 2022.²



In one of his speeches³ prime minister of India stated that "health issues need to be conceptualized in a framework that understands these relationships, even though a specific disease itself can be treated through a mixture of social and clinical management. Issues of health particularly in developing countries have strong links with social, economic, environmental and cultural factors. They therefore need responses that appreciate intersecting spaces".

Following the 1st International Conference of ISPOR India Chapter on 22- 23 Oct 2012 at New Delhi, it was widely felt that pharmacoeconomics research is helping decision makers globally in taking

informed decisions and India should have its own guidelines addressing the needs of the country in many interrelated domains like health policy, pharmaceutical policy, pharma pricing, health insurance and clinical prescription standards. India lacks independent and credible data in terms of health and pharmacoeconomics. So it was decided that ISPOR shall take an initiative to draft the guidelines based on study of international guidelines and ISPOR. Many countries have issued guidelines to conduct pharmacoeconomics research. Several countries like Canada and USA and UK have specific templates and directions to submit PE data for evaluation by regulatory authorities. It was observed that these guideline may vary from country to country but basic component of PE research remains same. PER is gradually progressing toward (Health Impact Analysis) HIA and (Budget Impact analysis) BIA and they make absolute sense for low and middle income countries (LMIC) with low funds to spend on health care (Appendix A).

What prompted ISPOR to draft PEG for India?

Globally PER is impacting national health policies, reimbursement decisions, formulary compositions, new drug research and drug development process. Data generated from such research is increasingly helping policy and law makers, health care administrators, and practitioners to take rational decisions.

| Type of Impact | Country | Associated Organisation |
|---|---------|-------------------------|
| Influence on Health Policy, Regulatory Impact and clinical guidance | Canada | CADTH |
| | UK | NICE |
| | France | HAS |
| | Germany | IQWiG |
| | Italy | AIFA |
| | Spain | AEMPS |

On 28 January 2013, Annual meeting National Executive of ISPOR India Chapter passed a unanimous resolution that being flag bearers of pharmacoeconomics research in India, an initiative should be taken by ISPOR India Chapter to formulate guidelines to conduct pharmacoeconomics research in India and help researchers develop India specific data. A core committee with few experts in industry and academia were entrusted with task to prepare first draft to be circulated among with public for wider consultations. Following this decision core group of experts had several meetings and deliberations and decided to place guidelines on ISPOR India website for further comment and review.

Please refer www.isporindia.com

Chapter II: Pharmacoeconomic Research Guidelines around the World

Research and methods for conducting pharmacoeconomic analysis have developed over the last several decades and many countries throughout the world are increasingly trying to generate robust data to support decision-making. Many changes exist in approach to conduct studies however; basic principles of Pharmacoeconomics remain same. Countries like UK, Canada, and Australia have come a long way in setting some global standards for conduct and reporting of pharmacoeconomic research.

The Canadian Agency for Drugs and Technology in Health (CADTH) has provided clear guidelines for the submission of pharmacoeconomic analyses. These guidelines define the methodologies behind the scope, perspective and reporting formats of the analyses, as well as providing best practices for the calculation of the costs and benefits associated with the assessed technology. The importance of the pharmacoeconomic component of review submissions has grown in direct proportion to the increased public and political pressure on health care budgets. Similarly, in UK NICE had taken up a major advisory role to legislative representatives, clinicians and many other stake holders. In Australia, guidelines for Preparing Submissions to the Pharmaceutical Benefits Advisory Committee (PBAC) (December 2008) provide manufacturers with guidance to prepare the clinical and economic data for submissions to the PBAC.

A summary of some of the pharmacoeconomic guidelines is presented in Table 1. Most of these guidelines were published during years 2004-2009, with Swiss guidelines published earlier in year 1998. All of these guidelines had policy decision makers as common target audience. Other targets included researchers, pharmaceutical companies, health departments, and stakeholders for insurance. The perspective for evaluation included in all guidelines was 'Societal' in order to include all relevant costs and outcomes. Other commonly suggested perspectives were 'Provider', 'Payer', 'Patient' and 'Employer'. The choice of comparator was primarily the most frequently used drug or closest alternative. Choice of comparator was also based on clinical practice, current practice or all relevant comparators in a given indication. These guidelines suggested using a time horizon that should be long enough to capture all the meaningful differences in costs and outcomes.

Most of the published guidelines advocate using assumptions in economic analysis, German guidelines being an exception as IQWiG tries to avoid assumptions. These guidelines specify the sources for costs in respective countries and the need for systematic review of evidence, meta-analysis and modelling. The most commonly used health economic analysis types include CEA, CUA, and CMA. Most of the guidelines had preference for effectiveness over efficacy and advocate using Health-related quality of life (HRQoL) parameters as preferred outcome measure. For modelling studies, all guidelines suggest using discount rates between 3-5% (for costs and outcomes), with few exceptions. The preferred

methods to derive utility values reported across guidelines were 'standard gamble' (SG) and 'time-trade-off' (TTO). All guidelines suggested stating the implicit and explicit equity assumptions made in the evaluation.

All guidelines suggest conducting sensitivity analysis (univariate, multivariate, probabilistic) for checking robustness of results. Incremental analysis is suggested in case of health economic analysis involving drug comparisons. Wherever applicable, increment cost-effectiveness ratio (ICER) should be calculated as it may be used as a criterion to assist in decision-making.

Table 1: Comparison of PE Guidelines for selected countries on selected key features

| | Canada | France | Germany | The Netherlands | Switzerland |
|---|--|---|--|--|---|
| Title and year of the Document | Guidelines for the Economic Evaluation of Health Technologies: Canada (3rd Edition, 2006) | French Guidelines for the Economic Evaluation of Health Care Technologies (September 2004) | General Methods for the Assessment of the Relation of Benefits to Costs (Version 1.0 dated 19/11/2009) | Guidelines for Pharmacoeconomic Research in the Netherlands (April 2006) (Dutch Version 2004) | Manual for the standardization of clinical and economic evaluation of medical technology (1998 draft) |
| Target audience of funding/author's interests | Canadian decision and policy makers who are responsible for the funding decisions regarding health technologies | Decision makers, researchers, pharmaceutical companies | IQWiG can be commissioned by Federal Joint Committee (FJC); or by the Department of Health | Who conduct PE evaluation or evaluate the PE studies (decision makers) | Federal Commission for Health Insurance Benefits (ELK) |
| Perspective | This perspective may include costs that are incurred by long-term care, social services, or community-based services | Economic evaluation studies of health care programmes must adopt the widest possible perspective in order to include all the relevant outcomes of each programme studied. | Health care sector, optional: social security (including long term nursing care and other branches of social security) or societal | Societal perspective. Report indirect costs separately. | Society, third party payer / reimbursement agency, health care provider, patient, employer |
| Choice of comparator | Single most prevalent clinical practice, current practice weighted by market share, or lowest cost but more effective than placebo, do-nothing alternative | The therapeutic strategies to be used as comparators will be chosen among those most frequently used (including non-treatment) or newer strategies which may legitimately be deemed likely to become reference strategies | All relevant comparators in a given indication | Treatment in clinical guidelines of GPs; if not available most prevalent treatment | Closest alternative technology, first choice treatment, non-intervention |
| Time horizon | The time horizon should be long enough to capture all the meaningful differences in costs and outcomes between the intervention and comparators. | Long enough that all outcomes, both positive and negative, of the treatments used and evaluated be included in the study. | Primary time horizon: Duration of RCTs, secondary time horizon: Any longer time horizon depending on the relevance for the decision maker, eg chronic diseases | Should be clearly described and appropriate to the disease and treatment. Long-term effects should be emphasized | Not specific |
| Assumptions required | Yes | Yes | IQWiG tries to avoid assumptions | Yes | Yes |
| Preferred analytical technique | The selection of the appropriate type of evaluation (CUA, CEA, CMA, CBA, and CCA) depends on the research question, the condition of interest, and the availability of data on outcomes. | Any one of CMA, CEA, CUA, CBA, and CCA. The choice must be justified. | Efficiency frontier method based on a CEA, but CUA also possible | CEA, CUA, no CMA | Any one of CMA, CCA, CEA, CUA, CBA. Refer CBA as the gold standard |
| Source of costs | CADTH Guidance Document for the Costing Process | The identification, measurement and valuation of costs should be consistent with the perspective of the PMSI. | Resource use and costs are to be reported separately. Data should come from German statutory health insurance. | Reference prices list should be used | Reimbursement rates established by health insurers, tariffs and other administratively fixed rates |
| Modeling | Yes, requires details | Yes, requires details. | Yes | Yes, requires details | Yes |

| | | | | | |
|--|---|--|--|--|--|
| Systematic review of evidences | Yes | Yes | Yes, for any health economic analysis is based on prior benefit reports by IQWiG | Yes, encourage meta-analysis | Yes, emphasize meta-analysis |
| Preference for effectiveness over efficacy | Where feasible, the outcomes and costs in an economic evaluation should be based on the effectiveness of the intervention, rather than its efficacy | Effectiveness is to be preferred to efficacy. If, however, efficacy is the sole indicator available, every effort should be made to convert this into effectiveness by means of appropriate adjustments. | See the general methods of IQWiG on efficacy vs. effectiveness. RCTs should be focusing on realistic scenarios while high level of evidence for the benefit assessment is warranted | Yes, modelling on trial data and other sources is required | Yes, the basis for technology assessment is the whole disease management process in real practice |
| Preferred outcome measure | Health-related quality of life, Quality-adjusted life years, Preferences (utilities), Willingness to pay | Final outcomes preferred. | Patient relevant outcomes (mortality, morbidity, quality of life) as indicated in social code book V relevant for statutory health insurance in Germany | Effectiveness by intention-to-treat principle, and expressed in natural units (pref life-years gained) or QALY | Life years gained or lost, health related quality of life, quality corrected life years gained or lost |
| Preferred method to derive utility | Should justify the selection | The methods most commonly used to identify preferences are the SG, TTO, and VAS methods. These methods allow for the expression of individual preferences within a strict framework. | Patient preferences about the hierarchy of endpoints are to be elicited with methods (discrete choice, analytic hierarchy process). If utilities are included in the analysis they are derived from patients and not the general public. | SG, TTO or VAS. Should justify the selection | SG, TTO, and rating scale. |
| Equity issues stated | Yes. State the implicit and explicit equity assumptions made in the evaluation. | Yes | Equity issues will be taken into account by the decision maker FJC. | Yes | Yes, issues of access, distribution and ethical questions should be considered |
| Discounting costs | Yes, standard: 5%; conduct sensitivity analyses using (real) discount rates of 0% and 3%. | For the purposes of international comparisons the rates used should be 0%, 3% and 5%. | Base case 3%, sensitivity analyses at 0,5,7, and 10%. | 4% | Most common: 2.5%, 5%, 10% |
| Discounting outcomes | Yes, standard: 5%; conduct sensitivity analyses using (real) discount rates of 0% and 3%. | For the purposes of international comparisons the rates used should be 0%, 3% and 5%. | Base case 3%, sensitivity analyses at 0,5,7, and 10%. | 1.5% | Most common: 2.5%, 5%, 10% |
| Sensitivity analysis-parameters and range | Capture the full range of variability or uncertainty that is relevant for each model input. | Maintain uncertain variables. | Sensitivity analyses are performed and respective ranges are chosen to check for robustness of results. | All key uncertain parameters, within a defined area and best/worst case scenario | The variation range accepted for key parameters should be plausible |
| Sensitivity analysis-methods | One-way, two-way, multi-way, scenario analysis, Monte Carlo simulation | A distinction is made between univariate and multivariate analysis, and also between first order and second order analysis. | Both univariate and multivariate sensitivity analyses are performed. | One-way, multi-way and probabilistic analysis | The sensitivity of study conclusions should be examined in detail. |
| Incremental analysis | Yes | Yes | Yes | Yes | Yes |
| Total C/E | Yes | Cost-effectiveness (or cost-utility ratios) must be expressed in incremental form so that they may be used as a criterion to assist in decision-making. | Efficiency frontier will be presented as a plot. Maximum reimbursable price to be recommended for decision maker will be calculated on the basis of efficiency frontier (ICERs). | Yes | Yes |

Chapter III: Need for PE Research in India – Who needs it and why?

Analysis of global case studies gives varied utilities of pharmacoeconomic research from health policy, drug evaluation, licensing, clinical prescription recommendations, insurance etc. Everyone is aware that such PER data is necessary and it will be useful in several ways in many multidisciplinary areas, but who will need it in India?

From an Indian perspective, after analysis of entire gamut of agencies and organisation engaged in pharma and healthcare sector, we have shortlisted a few that are likely to be affected by these guidelines and be important as stakeholders:

Stake holders of Pharmacoeconomics Research in India

Some of the identified & probable stakeholders for Pharmacoeconomic research in India would be:

| Roles | Institute/Organisation/ Offices |
|--|--|
| Advisory/Policy maker | National Pharma pricing authority - NPPA |
| Policy Maker | Directorate of Health Research , MOHFW, GOI |
| Advisory | Drug Consultative Committee (DCC) |
| Advisory | Drug Technical Advisory Board (DTAB) |
| Medical Research | Indian Council for medical research (ICMR) |
| Regulatory Authority | Central drugs and standards control organisation (CDSCO) and Drug controller general of India (DGCI) |
| Regulatory Authority/ Executive | Director General of Health Services- DGHS |
| Regulatory Authority | Insurance regulatory and development authority .IRDA |
| Education and research | AIIMS |
| Education and research | NIPER, DIPSAR, UIPS, PTU, UPTU, Social Research Institutes/ Various University centres |
| Education and research | NIA |
| Education and research | PHFI |
| Industry Association | IPMA |
| Global Advisory Org. | WHO India Chapter |
| Global Advisory Org. | ISPOR India Chapter |

A brief description of some of these stakeholders is as follows:

National Pharmaceutical Pricing Authority (NPPA)

Brief of NPPA:-

- NPPA is an organization of the Government of India, which was established inter alia, to fix/ revise the prices of controlled bulk drugs and formulations and to enforce prices and availability of the medicines in the country, under the Drugs (Prices Control) Order, 1995.⁴
- The organization is also entrusted with the task of recovering amounts overcharged by manufacturers for the controlled drugs from the consumers.

- It also monitors the prices of decontrolled drugs in order to keep them at reasonable levels.

The Drugs Technical Advisory Board (DTAB)

Drugs Technical Advisory Board (DTAB) is a board constituted by the Central Government to advise the Central Government and the State Governments on technical matters regarding administration of Drugs and Cosmetics act 1940 & Rules 1945, and to carry out the other functions assigned to it by this Act. DTAB is the Apex decision-making body for safety of the drugs.

Insurance Regulatory and Development Authority (IRDA)

IRDA is an autonomous apex statutory body which regulates and develops the insurance industry in India. It was constituted by a Parliament of India Act called Insurance Regulatory and Development Authority Act, 1999 and duly passed by the Government of India⁵.

Executive bodies like DCGI and DGHS

Under the Drug and Cosmetics Act, the regulation of manufacture, sale and distribution of Drugs is primarily the concern of the State authorities. The Central Authorities are responsible for approval of new drugs; Clinical Trials in the country, laying down the standards for Drugs, control over the quality of imported Drugs, coordination of the activities of State Drug Control Organizations and providing expert advice with a view of bring about the uniformity in the enforcement of the Drugs and Cosmetics Act.

Drug Controller General of India (DCGI) is responsible for approval of licenses of specified categories of drugs such as blood and blood products, IV fluids, vaccines and sera in India. The Directorate General of Health Services (DGHS), a repository of technical knowledge, is an attached office of this Ministry. The DGHS also renders technical advice on all medical and public health matters and in the implementation of various health schemes. In order to implement the policies and programmes of the Ministry in an effective manner, there are three subordinate offices located at various places in the country which function directly under the Ministry. The Ministry is also administratively concerned with 29 autonomous/statutory bodies. There are also three Public Sector Undertakings under the administrative control of the Ministry.

Central Procurement Agencies (CPA's)

The establishment of India's Central Procurement Agency (CPA) paved the way for a single procurement system for healthcare goods for the Indian government's health services and programmes. Separately, the government has scaled up its low-cost Jan Aushadhi pharmacies, with 740 outlets planned in the next two years, and at least one for each district as part of efforts to increase drug access and affordability. A single procurement system should improve the transparency of the drug-tender system,

enabling the government to negotiate better prices and streamline the current process, while expansion of Jan Aushadhi will increase access to drugs and reduce out-of-pocket expenditure, as the stores provide generic drugs at 50% less than the retail cost equivalent. As the sole national procurer, the CPA will enjoy greater bargaining power over pharma firms, while the expansion of Jan Aushadhi will mean that both innovative and generic firms can expect a push for lower pricing and larger volumes⁶.

Educational and Research Institutes

The Medical Council of India (MCI) is the statutory body for establishing uniform and high standards of medical education in India. The Council grants recognition of medical qualifications, gives accreditation to medical colleges, grants registration to medical practitioners, and monitors medical practice in India.

The main functions of the Medical Council of India are the following:

- Establishment and maintenance of uniform standards for undergraduate medical education.
- Regulation of postgraduate medical education in medical colleges accredited by it. (The National Board of Examinations is another statutory body for postgraduate medical education in India).
- Recognition of medical qualifications granted by medical institutions in India.
- Recognition of foreign medical qualifications in India.
- Accreditation of medical colleges.
- Registration of doctors with recognised medical qualifications.
- Keeping a directory of all registered doctors (called the Indian Medical Register).

Registration of doctors and their qualifications is usually done by state medical councils.

It is obvious from global literature that pharmacoeconomic evidence can be utilized at various levels in the healthcare setup to support decisions on licensing, pricing, reimbursement, and even maintenance of formulary procedure of pharmaceuticals in hospitals. For the insurance companies to give better facility at minimum cost, India must develop the platform for Pharmacoeconomics with a valid methodology and appropriate training. Pharmacoeconomics should be proposed be a part of course curriculum across various pharma colleges and universities in India.

How these stakeholders can benefit from PEG?

PEG can be useful for these stakeholders to facilitate decision making in following ways:

1. National Pharmaceutical Pricing Authority (NPPA) – National Pharma Pricing Policy
 - Prioritization and Identification of drugs/products in India, which are pharmacoeconomically more important and beneficial.
 - Creation of database by sponsoring/conduction PE studies- Pharmacoeconomic Studies and Health Technology Evaluation. Can replicate role of NICE – UK to some extent.
 - Help government in identification of areas of pharmaceutical subsidies, import, and identify the areas in research where government can incentivize the research of new drugs and health technologies
2. Health Insurance – Health policy-makers and health systems research institutions in collaboration with economic policy study institutes need to gather information about the prevailing disease burden at various geographical regions to develop standard treatment guidelines. This would help estimate the costing of health services for evolving benefit packages and to determine the premium to be levied and subsidies to be given. This will also help to map health care facilities available and the institutional mechanisms, which need to be in place, for implementing health insurance schemes.⁷
3. Government/Central/State can be guided on reimbursement under various mandatory sponsored insurance schemes like CGHS/ESIS. Department of Health Research (DHR), Government of India) is expected to play pioneering role in development of pharmacoeconomics research in India. DHR can somewhat play role similar to NICE in UK. As per the mandate given by Government of India, it states “DHR will promote and provide guidance on research and governance issues, including ethical issues in medical and health research”
4. Public hospitals Procurements: Guidance to States and Centre on free drug distribution in public hospitals.
5. Guide government on subsidy to be provided on technologies, so that medicine bills could be reduced, new technologies could be introduced in management of diseases and import

duties waived off on essential pharmacoeconomic drugs.

6. Prescription Advice to practitioners in various therapeutic domains.
7. Creation of national database on the pharmacoeconomics of various drugs and health technologies, which may help Central Bureau of Health Intelligence.
8. Universal Vaccination Programme: Pharmacoeconomic research can help prioritization of vaccine and biological to be introduced in this programme by demonstrating comparative impact of vaccines. Vaccines are considered as most pharmacoeconomic health interventions.
9. Prioritisation of clinical trial application: Drug Controller General of India/CDSCO is the competent authority to give permission for clinical trial in India. However with the advent of "Me too" drugs and large generic drug market have similar claims but before marketing they need to take approval from DCGI. However, similar to American and European drug regulators, CDSCO is also short of experts to review applications and they need to strategically prioritise. So, proposed pharmacoeconomic benefits can one of the decreasing or enable in deciding, if the clinical trials can be evaluated and prioritised. It is several times observed that globally various regulatory authorities spend lot of time to review clinical trial application of generic and "Me too" drugs, whereas those drug trials which are necessary to be conducted in larger public interest are delayed. This will also encourage pharma companies to innovate pharmacoeconomic economic medicine and health technologies.

Chapter IV: Existing scenario in India

A sincere attempt at estimating the current level of understanding and research efforts in Pharmacoeconomics across India is essential to enable identification of gaps in knowledge and maximize impact of these guidelines for various stakeholders in the healthcare chain. Systematic Literature Reviews are essential first steps to consolidate existent data into meaningful inferences on various aspects. One such review recently reported at the ISPOR Annual meeting at New Orleans, 2013⁸ has attempted a comprehensive look at PE and OR research publications from India. The full manuscript currently exists as Data on File and is under review for publication in one of the journals.

Abstract:

Background and Objectives: This systematic literature review was conducted to identify, evaluate, and characterize the variety, quality, and intent of the health economics and outcomes studies being

conducted in India. **Methods:** Studies published in English language between 1999 and 2012 were retrieved from Embase and PubMed databases using relevant search strategies. Two researchers independently reviewed studies as per Cochrane methodology; information on type of research and outcomes were extracted. Quality of reporting was assessed for model-based health economic studies using a published 100-point Quality of Health Studies (QHES) instrument. **Results:** Of 546 studies screened, 132 studies were included in the review. The broad study categories were cost-effectiveness analyses ([CEA], 54 studies), cost analyses (19 studies), and burden of illness (18 studies). The outcomes evaluated were direct and indirect costs, and incremental cost-effectiveness ratio (ICER), quality-adjusted life years (QALYs), and disability-adjusted life years (DALYs). Direct medical costs assessed cost of medicines, monitoring costs, consultation and hospital charges along with non-medical costs (travel and food for patients and caregivers). Loss of productivity and loss of income of patients and caregivers were identified as components of indirect cost. Overall, 33 studies assessed QoL, and WHO Quality of Life-BREF (WHOQOL-BREF) was the most commonly used instrument. Quality assessment for modeling studies showed that most studies were of high quality (mean [range] QHES score to be 75.5 [34-93]). **Interpretation and conclusions:** This review identified various patterns of pharmacoeconomic studies and good quality CEA studies. However, there is a need for adequate utilization of healthcare resources in India.

Some other noteworthy observations of this review include (Data on File):

1. The trend for pharmacoeconomic studies published from India has increased since 2007. Most studies from India were published in foreign journals and the authors of most model-based studies were from outside India. The model-based studies utilized appropriate model parameters and analyses and were therefore categorized to be of high quality as per the QHES instrument.
2. There is still a paucity of health economic studies conducted in India by Indian healthcare providers. Economic evaluation and QoL assessments were commonly estimated in patients with human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS), carcinomas, or tuberculosis (TB). Studies also evaluated CEA of vaccines for immunization of children.
3. The QHES scores were estimated for quality assessment of full economic studies (35 studies) and were of high quality. However, most studies that were identified could not be classified as full-fledged health economic studies. This is perhaps a reflection of the lack of understanding of the standard concepts of health economics in India.
4. Most of the model-based studies included CEA and the perspective was societal. Though

other perspectives such as that of hospital, provider or patient were also represented in some studies. This finding differs from the only other previously published literature review by Desai et al⁹ who reported that most included studies did not present a perspective.

5. An understanding of true cost measures including all direct and indirect cost components is necessary while formulating national policies. Few studies, example in TB and HIV patients used resource utilisation and costs estimates from established or state level resources such as National Institute for Research in Tuberculosis, Chennai, Y. R. Gaitonde Centre for AIDS Research and Education (YRG CARE) in Chennai, the Karnataka Health Promotion Trust (KHPT), the Andhra Pradesh State AIDS Control Society (APSACS) and National AIDS Control Organisation (NACO) (for HIV anti-retroviral therapies). However, majority did not report the source of cost data used while few others mentioned using institutional cost databases. It is clearly apparent that no centralized cost database exists in the country making temporal and inter- study comparisons extremely challenging.
6. Utilization of healthcare resources and resulting data from these health economic studies in India by policy makers, and institutions was inadequately assessed and reported. The disparity in resource availability as well as utilization that is evident in public vs. private provision healthcare; rural vs. urban spending as well as seen across states was evident in some studies and suggests the need for the policy initiatives to be relevant to the different healthcare settings in India.
7. It is therefore, a challenge at the current time for healthcare providers to promote health using improved and cost-effective modalities for the prevention, diagnosis and therapy of various diseases and ailments.

Chapter V: Proposed guidance for Pharmacoeconomic Research in India

Guideline 1: Identify target groups of audience and type of analysis to be performed

The primary target of pharmacoeconomic research is the Ministry of Health and Family Welfare, Government of India. More government stakeholders including Ministry of Chemicals and Fertilizers (Department of Pharmaceuticals) will be identified during implementation phase of the guideline. Secondary target groups include patients, prescribers, suppliers, hospitals, insurers and researchers. Pharmacoeconomic research will provide insight into the cost-effectiveness of the drug.

Guideline 2: Identify the perspective of the evaluation

Pharmacoeconomics evaluation should be performed and reported from a societal perspective, in which all costs and benefits are included, irrespective of who actually bears the costs or receives the benefits.

All studies must be reported from a social perspective. There is a broad consensus internationally, that on the grounds of welfare-theory the social perspective should form the basis for pharmacoeconomic evaluation. This social perspective means that, all costs and benefits should be identified regardless of who incurs the costs or who receives the benefits. However, the comprehensive societal perspective should be transparently disaggregated into multiple viewpoints, including that of the primary decision-maker (the decision-maker, if any, to whom the study is primarily targeted). Relevant subsidiary viewpoints could include the health care system, major third party payers such as ministries of health, and the patient and family viewpoint. No matter what the viewpoint chosen, it should obviously be consistent on both sides of the cost-outcome ratio (i.e. in both the numerator and the denominator).

Guideline 3: Justifications on choice of comparator should be provided

How and why a comparator was used in PER?

The economic evaluation of a drug is always based on comparison with another treatment. The outcome of that comparison will be largely determined by the choice of the comparator. Selecting the right comparative treatment is therefore vitally important, not only for the economic evaluation but also when evaluating the therapeutic value of the drug. In choosing the comparator, it is important to adhere as closely as possible to the current guidelines and evaluation procedures. There may be a variety of relevant comparators for a drug, and they may differ across the various subgroups of patients. Relevant comparators may include other drugs, other medical care (e.g. surgery or watchful waiting), and no treatment. In theory, all other possible treatments for the same patients are relevant comparators. In practice, studies will have to identify one, or a small number, of primary relevant comparators. The issue of relevant comparators is complicated because there are two possible questions. Is the new drug cost-effective relative to the existing drugs or treatments that it will in fact replace (local cost-effectiveness)? Or, is the new drug cost-effective relative to optimally cost-effective treatment (global cost-effectiveness)? For example, if current practice is itself unevaluated (which is often the case) and if current practice is in fact not cost-effective, the new drug can appear to be cost-effective (locally cost-effective) when in fact it is not (not globally cost-effective).

In the ideal situation, one would compare the current most cost-effective option (as reflected [theoretically] in current practice guidelines or criteria for use) to the new agent. Practically, one often cannot identify such a comparator and, therefore, will use the agent with the lowest treatment costs (i.e. the sum of drug costs, administration costs, and the costs of treating any side effects) for a given

course of therapy. This is more appropriate than using the drug with the lowest unit price as the comparator. However, even choosing the lowest cost comparator can be difficult. The selection of an appropriate comparator requires input from the decision-makers, as the choice of comparator relates to the question(s) the target audience wants answered. Thus, analysts are encouraged to obtain input from decision-makers as they develop their research protocols.

The comparative treatment can also be a non-medicinal form of treatment. A number of problems can arise in the practical application of these guidelines. The prescribing behavior of doctors and therapeutic insights can both change with time. This means that views on the most suitable comparative treatment will also change. What was considered to be a well-founded choice of comparator for Phase 3 studies may, once all the clinical studies have been concluded, or by the time the drug is being registered for inclusion on the list, prove to no longer be the most appropriate choice. It is also important that clinical research with new drugs has a markedly international character; when choosing the comparison model, a manufacturer cannot be expected to take all possible views and desires into account. The choice made may deviate from what would normally be regarded as 'standard' in India. This choice will have to be supported by arguments demonstrating a close connection with generally accepted guidelines and protocols. Since it is so important that the comparative treatment should adhere as closely as possible to the Indian situation, consultation on the choice will usually be necessary before carrying out pharmacoeconomic evaluation.

Guideline 4: Choice on use of Analytical technique to be used for PER

If the improvement in quality of life forms an important effect of the drug being assessed, then it is necessary to carry out a cost-utility analysis (CUA). If this is not the case, then a cost-effectiveness analysis (CEA) has to be carried out. If the manufacturer does not expect the drug to have an added therapeutic value, nor that it will be mutually replaceable with (a) different drug(s), then a cost-minimization analysis (CMA) can be carried out.

In the case of a new drug, research is primarily aimed at determining its therapeutic value. If the drug has a therapeutic added-value, then its costs and how these costs relate to the therapeutic added-value must be defined by means of an economic evaluation. All aspects of the treatment, such as side-effects and their costs, must be included in the evaluation. For the economic analysis of new drugs a choice can be made between a cost-minimization analysis (CMA), cost-effectiveness analysis (CEA), cost utility analysis (CUA) or cost-benefit analysis (CBA). Although there is considerable overlap among the various analytic techniques that can be used, it is useful to identify the following five methods. Not all of these approaches have been widely used, but conceptually they are distinct and the distinctions are useful in helping to clarify the field.

1. **Cost-Minimization Analysis (CMA):** Cost-minimization analysis is appropriate when the

clinical outcomes (i.e. efficacy and safety) for the drug and the comparator(s) are virtually the same. In such a case, the decision simply revolves around the costs.

2. **Cost-Consequence Analysis (CCA):** This is a disaggregated type of study that makes the least assumptions and puts the greatest burden on the decision-makers. It is a “Consumer Reports” style of study. The costs and consequences of the drug compared to one or more relevant alternatives are simply listed in disaggregated form (e.g. drug costs, hospital costs, other costs, strokes avoided, minor side-effects, major side effects, etc.). Any weighting of the component factors and aggregation is left to the user of the study.
3. **Cost-Effectiveness Analysis (CEA):** In cost-effectiveness analysis, the incremental costs are compared to the incremental outcomes as measured in physical or natural units. Natural units could range from clinical measures, such as millimeters of mercury blood pressure reduction, through disability days averted, to lives saved, or life-years gained.
4. **Cost-Utility Analysis (CUA):** Cost-utility analysis refers to a particular form of CEA where the outcomes are measured in terms of quality-adjusted life years (QALY) gained. QALYs combine changes in quantity and quality of life (QOL; mortality and morbidity) into one composite measure which is independent of program or disease. The quality-adjustment factors should reflect aggregated preferences of individuals for the outcomes. The factors have been measured directly on patients or the general public, taken from published tables or formulae, or estimated by professional judgments.
5. **Cost-Benefit Analysis (CBA):** In cost-benefit analysis, the incremental outcomes are expressed in dollar terms, usually using the contingent valuation approach of estimating benefits to elicit an assessment of willingness to pay (WTP), so that the overall analysis can be conducted entirely in dollars.

A process should be established within each disease category to agree upon standard clinical outcomes that could be used for CCA, CMA, and CEA. Moreover, the outcomes could form the basis for the preference elicitations required in both of CUA and CBA.

Guideline 5: Time horizon of a Pharmacoeconomic evaluation

Time horizon of PE evaluation must be such that it enables valid and reliable statements to be made regarding the effects and costs of the treatments being compared. This includes both intended and unintended effects and costs (e.g. side effects).

The analytic horizon of a pharmacoeconomic evaluation must be able to capture all relevant outcomes. This time horizon should provide sufficient opportunities for observing the most important outcomes of the intervention. When modeled data are needed to meet this requirement, the structure and rationale of the model must be presented. The analytic horizon for pharmacoeconomic studies should extend into the future to capture the major clinical and economic outcomes related to the treatment(s) under study. It must be emphasized that the same time horizon must be applied to both costs and outcomes. In many cases, this would mean that the analysis must follow patients for the duration of their lifetime. Frequently, the appropriate analytic horizon will extend beyond the availability of primary data. In this case, the study will consist of primary data and modeled data. The assumptions of modeling should be explicit, well-justified, and thoroughly tested by sensitivity analysis. In many studies it may be useful to analyze the data using several analytic horizons: a short-term horizon that includes only primary data, and a long-term horizon that also incorporates modeled data.

The time within which effects and costs can be anticipated depends on the treatment goal and thus on the anticipated outcome. When a decision has to be made regarding the reimbursement of a new drug, there is often insufficient information available about its effectiveness. To obtain this information, the drug needs to be used in practice. Because primary data usually provide insufficient insight into the value of a drug in the medium- and long-term, modeled data will often have to form an integral part of the dossier being submitted in application for reimbursement.

Guideline 6: Cost identification, measurement and evaluation

Cost identification

Cost identification involves identifying all the relevant resource items for subsequent measurement and valuation. A useful first step is to develop a probability or decision tree of the therapeutic pathway which describes all relevant downstream events. Then viewpoints for the analysis are selected, and resource items that are applicable to each viewpoint are identified. In the comprehensive societal viewpoint, all costs related to the therapeutic pathway should be included; however, transfer payments (e.g. sickness pay, unemployment insurance, welfare payments) should not. If subsidiary viewpoints are presented in the analysis, they should contain the subset of cost items relevant to that viewpoint but which were excluded from the primary societal analysis. This means that subsidiary analyses may include transfer payments if they represent a cost or savings from the viewpoint in question.

The following cost categories can be distinguished:

Direct costs within the healthcare system: From a social perspective, the direct costs within the healthcare system must form part of the analysis. These are the medical costs of prevention, diagnosis, therapy, etc.

Direct costs outside the healthcare system: From a social perspective, the direct costs outside the healthcare system must form part of the analysis. An example of such costs is a patient's travelling expenses

Indirect costs within the healthcare system: These are the medical costs which may arise during life-years that have been saved. It is increasingly recommended that these costs should only be included in the analysis if there is a clear relationship with the intervention. Costs of illnesses that are not related to the intervention should be omitted from the analysis.

Indirect costs outside the healthcare system: In the case of indirect costs outside the healthcare system, the focus is mainly on the costs of production losses. However, it can also involve costs in other sectors (e.g., education). One approach for determining these costs is the human capital approach (HCA). This method is controversial, however, because it can lead to extremely high outcomes (for the savings made), which raises the question of whether the results are realistic. This is because in the HCA, the potential (and, in theory, maximum) production loss is calculated by totaling the loss of earnings from the moment of morbidity/mortality to the moment of retirement.

An alternative approach to HCA is the 'friction cost method'. The period over which the production loss is calculated is limited to the friction period, i.e. the period between the initial absence and the actual moment of replacement. This period is currently estimated to be some 3 months on average.

Due to the above-mentioned overestimation, the human capital method is not the method of choice. It is preferable to use the friction cost approach. For the sake of completeness, it should be mentioned that costs incurred as a result of the research itself should not be included.

Cost measurements

The deployment of people and resources during a treatment must first be described in natural (non-monetary) units, such as hours, tasks, nursing days or daily doses. All cost data obtained from international studies must be validated for use in India. A distinction should be made between volume and price when presenting the costs. The natural units should be shown in as much detail as possible. Showing the deployment of people/resources in volume units also makes the study more easily transferable to other countries/situations.

Resources used in treatment must first be described in natural (non-dollar) units. All resource utilization data derived from international trials must be validated for Canadian practice. Costs are the product of a vector of the quantities of resources (Q) and the unit prices of resources (P). Cost measurement consists of determining the quantities, Q, of resources (i.e. health care resources, non-health care resources, informal caregiver time, patient time for treatment) used as part of a given intervention. Cost valuation consists of determining the unit costs/prices, P, of these individual resources. It is

important to separate these two concepts, in part, because of the potential to use standard costs for valuation. Where should one go to determine the resource consumption associated with a particular product? In considering drugs that go through multiple trials during their development, the later trials would more nearly match the actual therapeutic pathway of final use and would be the appropriate source for the resource quantities. In considering international trials, it should be noted that resource quantities cannot be directly imported into the Indian system; because of the major differences in the way that health care is delivered in many countries. As a minimum, resource quantities must be re-validated for Indian practice. Note should also be made regarding the methods by which one analyzes the uncertainty inherent in resource utilization versus unit price data. The former should be subjected to inferential statistical analysis, while with the latter uncertainty should be evaluated via sensitivity analysis.

Cost evaluation

Economic definitions should be used for the costs. Ideally, uniform amounts should be used for certain cost categories in order to promote the comparability and extrapolability of the results of different studies.

Guideline 7: Assessing quality of life and QALYs

The quality of life (QOL) can be measured by using generic and disorder specific questionnaires or a utility instrument. In a prospective study, if health related quality of life (HRQOL) is being included as an outcome, one instrument from each of the following three types: specific measures, generic profiles, and preference-based measures can be included. Quality of life includes many aspects of living in addition to health, for example; wealth, freedom, political system, and cleanliness of the environment all contribute to the overall QOL¹⁰.

Specific Measures

Specific instruments include those that target at specific diseases, such as the Functional Living Index - Cancer¹¹ or the Western Ontario-McMaster Osteoarthritis Index¹²; specific populations, such as the Care and Resource Evaluation Tool for the Elderly¹³; and specific functions, such as visual function measured by the Activities of Daily Vision Scale¹⁴.

Generic Measures

Generic measures are applicable to a wide range of patients and diseases¹⁵. They provide scores on a number of dimensions and typically are not aggregated into an overall summary score. Three well known instruments in this category are the Short Form 36¹⁶ (SF-36), the Sickness Impact Profile (SIP¹⁷), and the Nottingham Health Profile (NHP¹⁸).

QALYs

A QALY is calculated by multiplying the number of life years added via a program by a standardized weight (between 0.0 and 1.0) that reflects the health-related quality of life during that time (where 0.0 is the weight given to immediate death and 1.0 is the weight given to perfect health for a defined period of time). In a slight variation on this theme, some approaches to QALY weights provide for the possibility of negative weights for states considered worse than death¹⁹.

Direct Measurement

Direct measurement requires conducting of complex and costly measurement tasks using one of the three more widely used instruments: the standard gamble or time trade-off for revealed preferences; or the visual analog scale for stated preferences.

The weights can be obtained indirectly through the use of “off the shelf” preference weighted health status systems. Three well-known instruments in this category are the Quality of

Well Being (QWB²⁰), the Health Utilities Index (HUI²¹), and the EuroQol, now renamed the EQ-5D²². All of these systems have the same overall structure, whereby health status is described by multiple attributes and levels of function within each attribute. The score represents an estimate of the mean preference score that would be given to that health state by a random sample of the general public. In each indirect preference measurement system, every unique combination of levels across attributes defines a unique health state.

Guideline 8: Modelling

The use of modeling techniques is desirable in pharmacoeconomic studies. There are two different and important situations in which the modelling of data is required. The first is to obtain effectiveness data from efficacy data. The second occurs if the data originated from a study which was carried out in another country with a different healthcare system. This is of particular importance in the context of multinational studies. The modelling of data must be carried out with great care. Choices made need to be substantiated.

The translation from various other guidelines referred (Dutch and Canadian) should take into account demographic and epidemiological differences, differences in the provision of healthcare, differences in (financial) incentives for healthcare providers and differences in relative prices.

Ideally, pharmacoeconomic studies should report on drug effectiveness rather than efficacy. As effectiveness data are generally not available, appropriate modelling techniques based on sound

Pharmacoepidemiology (e.g. using epidemiologic studies to estimate patient compliance with therapy

in the real world) are permissible. All assumptions used in such extrapolation techniques must be stated explicitly and thoroughly tested with sensitivity analysis.

Guideline 9: Incremental analysis

Costs and effects must be reported in the form of incremental values (i.e. as differences between two alternatives). These incremental values must be used in the pharmacoeconomic evaluation. The study must also provide insight into the total values of the costs and effects of both treatments. From the incremental analysis one can deduce what the (net) difference in costs and effects will be when the new treatment replaces the existing one. In order to place the outcome of the incremental analysis in a broader context, the total costs and effects also need to be reported. The inclusion of total costs and effects will, moreover, improve the ability to translate the study to, for example, (future) situations with another comparative treatment.

Analytic Technique

Although there is considerable overlap among the various analytic techniques that can be used, it is useful to identify the following five methods. Not all of these approaches have been widely used, but conceptually they are distinct and the distinctions are useful in helping to clarify the field.

Cost-Minimization Analysis (CMA): Cost-minimization analysis is appropriate when the clinical outcomes (i.e. efficacy and safety) for the drug and the comparator(s) are virtually the same. In such a case, the decision simply revolves around the costs.

Cost-Consequence Analysis (CCA): This is a disaggregated type of study that makes the least assumptions and puts the greatest burden on the decision-makers. It is a "Consumer Reports" style of study. The costs and consequences of the drug compared to one or more relevant alternatives are simply listed in disaggregated form (e.g. drug costs, hospital costs, other costs, strokes avoided, minor side-effects, major side effects, etc.). Any weighting of the component factors and aggregation is left to the user of the study.

Cost-Effectiveness Analysis (CEA): In cost-effectiveness analysis, the incremental costs are compared to the incremental outcomes as measured in physical or natural units. Natural units could range from clinical measures, such as millimeters of mercury blood pressure reduction, through disability days averted, to lives saved, or life-years gained.

Cost-Utility Analysis (CUA): Cost-utility analysis refers to a particular form of CEA where the outcomes are measured in terms of QALY gained. QALYs combine changes in quantity and QOL (mortality and morbidity) into one composite measure which is independent of program or disease. The quality-adjustment factors should reflect aggregated preferences of individuals for the outcomes. The

factors have been measured directly on patients or the general public, taken from published tables or formulae, or estimated by professional judgment. Readers should beware that not everyone makes the distinction between CEA and CUA which has been made in this document. Some researchers refer to CUA studies as CEA or as cost per QALY (gained) studies.

Cost-Benefit Analysis (CBA): In cost-benefit analysis the incremental outcomes are expressed in dollar terms, usually using the contingent valuation approach of estimating benefits to elicit an assessment of willingness to pay (WTP), so that the overall analysis can be conducted entirely in dollars. Consistent with the desire to permit broad comparisons, the expression of results in cost-utility or cost-benefit terms is preferred. Cost-minimization analysis is, of course, appropriate in those rare cases where clinical outcomes across alternatives are virtually the same. The expression of results in only cost-effectiveness or cost-consequence terms is acceptable, with justification, for example, when there is no important impact on health-related quality of life (HRQOL). A process should be established within each disease category to agree upon standard clinical outcomes that could be used for CCA, CMA, and CEA. Moreover, the outcomes could form the basis for the preference elicitations required in both of CUA and CBA.

Guideline 10: Discounting future effects and costs

Future outcomes and costs should be discounted at equal rates. The current discount rate must be applied. This discount rate must be varied in a sensitivity analysis. If other percentages are used as the basic discount rate, they need to be thoroughly substantiated.

Future outcomes are required to be discounted at the same rate as costs. This rate must be varied in a sensitivity analysis, with a discount rate of 0% (no discounting) at minimum. Discussions can be made that these future outcomes must be discounted, and at the same rate as costs, to avoid paradoxical results.^{23,24} Experts also call for increased research on individuals' time preferences in order to come to a resolution regarding the differential discounting of costs and benefits. The discount rate should, however, be varied in a sensitivity analysis. At minimum, a sensitivity analysis involving a discount rate of 0% should be carried out in order to assess the impact of the above argument. In addition, it is suggested that sensitivity analysis based on a 3% rate should be considered, in order to allow comparisons with studies which will be using the 3% rate required by the Washington Panel reference case²⁵.

Identification of Cost

A probability tree of the therapeutic pathway which describes all relevant downstream events should be provided, when appropriate. Cost items that should be included are all direct health care costs, social services costs, spillover costs on other sectors, and costs that fall on the patient and family. Cost items that should be excluded are those not relevant to the therapeutic pathway such as those not

related to the treatment being evaluated, costs relevant only to the clinical trial, and transfer payments such as sickness pay, unemployment insurance and welfare payments.

When relevant, lost time should be documented and reported as part of the description of the impact of the intervention. If HRQOL is an outcome measure in the study, some lost time will likely contribute to changes in HRQOL. Depending on the viewpoint, some lost time will represent a real cost in terms of lost resources and should be included as a cost item, but should also be tested with sensitivity analysis.

Cost identification involves identifying all the relevant resource items for subsequent measurement and valuation. A useful first step is to develop a probability or decision tree of the therapeutic pathway which describes all relevant downstream events.

Future Health Care Costs

One of the important issues is that of dealing with future health care costs; that is, the costs associated with patients who live longer and consume health care resources as a result of a given intervention. Future costs should be judged by their relationship to the intervention; for example, any additional care required during “added years of life” as a direct consequence of the program in question. For instance, future costs of care for patients who survive septic shock via a new intervention should include the cost of treating the underlying condition which is now an issue as a direct consequence of giving the new therapy. Alternatively, the impact of a new drug for high cholesterol produces added years of life which occur far into the future. One would not be expected to include the treatment costs of clinically unrelated diseases (e.g. cancers) during the added life years, because these treatment costs are not a necessary and direct consequence of the specific intervention. Also, availability of data should be taken into consideration.

Cost of Loss of Productivity

Cost of lost time or indirect non-medical costs (i.e. productivity costs, formerly referred to as indirect medical costs) they relate to economic evaluations taking the societal perspective.

Patients and/or family members can lose time from work and other activities as part of illness and treatment. For family members, time may be lost in taking patients for treatment, visiting patients in hospital, or caring for patients at home. The amount of lost time, by whom, and lost from what (work, other major activity, leisure) should be recorded. At the most basic level, these data should be reported as consequences of the intervention.

Placing a value on lost time has been the focus of papers by Koopmanschap and his colleagues²⁶. They have proposed the friction cost method as an alternative to the HCA for incorporating work absence

and productivity losses into economic evaluations.^{27,28} This may be an alternative means of accounting for lost time, although it omits the value of the patient's time in the analysis (which is contrary to welfare economic theory) and is most correctly used in a non-full employment scenario.

Guideline 11: Use of expert panel

The current report describes the pharmacoeconomic guidelines in Indian scenario. A Guideline Development Committee has been set up for the development of the same. The Committee has tailored the Canadian guidelines and Dutch practice and has, where necessary, introduced certain modifications as per the Indian scenario. In addition, the guidelines have been formulated with respect to the choice of the comparative treatment. The guidelines have adopted the social perspective as their starting-point. This implies that direct costs, inside and outside the healthcare system, need to be included in the analysis. The indirect costs outside the healthcare system should be mentioned separately. A new standard cost list if required will be available for the purpose of uniformity of costs. The Committee also recognizes that differences in interpretation may occur, especially in the beginning and reconciliation may be required. The pharmacoeconomic guidelines will be evaluated and adjusted where necessary.

Chapter VI: Proposed areas of further research In India

Anticipated road map on formalisation of PEG India

- Phase 1 of PEG: Education and awareness on Pharmacoeconomics
- Phase 2 of PEG: Data generation and analysis and Meta-analysis, pilot studies.
- Phase 3 of PEG: Advisories and regulatory recommendations.
- Phase 4 of PEG: Expansion of PEG to other areas like Insurance, Clinical Prescriptions, and Policy etc.

Core committee recommends that PE studies be conceptualized and their relevance demonstrated through some of the areas enumerated below and more inputs are at present being sought from experts to further refine this list.

This will be an essential step in making these guidelines more comprehensive and adaptable to India scenario while also enhancing the understanding of PER data applicability by various stake holders.

1. Study the current policy decision making processes prevalent in health care sectors in India
2. Study on the role of PEOR in enhancing equity in health care and prioritisation of health care spending within the existing policy framework In India.

3. Study on the role of PEOR on health impact assessment in evaluation of national health programmes in India.
4. Studying the feasibility and utility of a national pharmacoeconomic database.
5. Identify the road blocks in conduct of reliable PE studies in India .
6. Encourage and train researchers on conduct of systematic reviews and meta-analysis in their respective domains to generate and build on robust data for initiation of PEA and HTA (health technology assessment) by policy makers.
7. Encourage better reporting of PE data in a user friendly manner by making use of the recent guidance for economic evaluations of health interventions- The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Checklist²⁹ (Appendix C).
8. Develop and agree on formats for Technology Assessment Reviews which can be used by Mission Directors, Programme directors, individual advisors and advising institutions to govt on various committees, ICMR, NPPA, DCGI, DGHS, industry consultants, marketing strategists. Some examples are cited below-

| Format for Technology Assessment | Perspective and audience of PER |
|----------------------------------|---|
| Policy Assessment and Review | Policy Makers, Health Secretaries, Ministers, Standing committees etc. |
| Marketed Common Drug | Pharma Co's /Brand Owners of drugs /Physicians |
| Therapeutic Reviews | Physician/Epidemiological/Medical Researchers |
| Optimal Use Review | Optimal Use review to encourage ideal prescribing, purchasing, and use of drugs and health technologies by health care providers, policy-makers, and consumers. |

Appendix A: Budget Impact Analysis (BIA)

Budget impact analysis (BIA)

Budget impact analysis (BIA) is an essential part of a comprehensive economic assessment of a health-care technology and is increasingly required, along with cost-effectiveness analysis (CEA), before formulary approval or reimbursement.

What is Purpose of BIA?

The purpose of a BIA is to estimate the financial consequences of adoption and diffusion of a new health-care intervention within a specific health-care setting or system context given inevitable resource

constraints. In particular, a BIA predicts how a change in the mix of drugs and other therapies used to treat a particular health condition will impact the trajectory of spending on that condition (see Fig. 1).

Where is it used and users?

It can be used for budget planning, forecasting and for computing the impact of health technology changes on premiums in health insurance schemes. Users of BIA include those who manage and plan for health-care budgets such as administrators of national or regional health-care programs, administrators of private insurance plans, administrators of health-care delivery organizations, and employers who pay for employee health benefits. Each has a need for clearly presented information on the financial impact of alternative health-care interventions, yet each has different and specific evidentiary requirements for data, methods, and reporting.

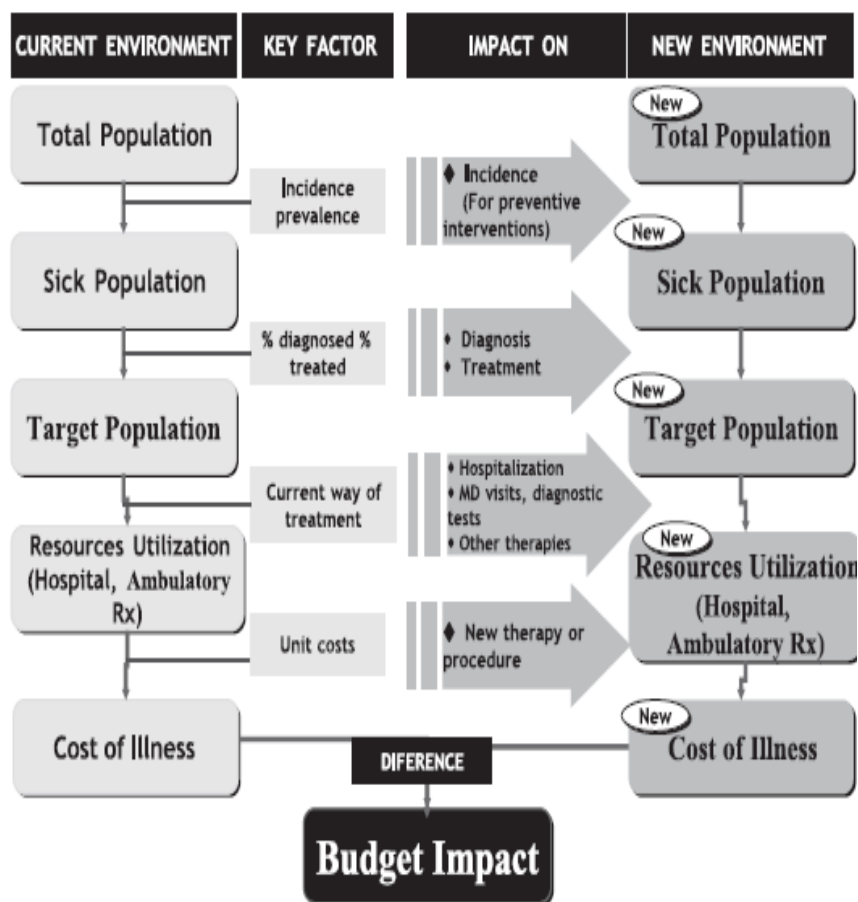


Figure 1 Budget impact schematic. Adapted from Brosa et al. [39].

Appendix B: CHEERS Checklist

Consolidated Health Economic Evaluation Reporting Standards – CHEERS Checklist 1

The CHEERS Checklist is part of the CHEERS Statement. The CHEERS Statement has been endorsed and co-published by the following journals: BJOG: An International Journal of Obstetrics and Gynaecology BMC Medicine 2013; 11:80 BMJ 2013;346:f1049 Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003) Cost Effectiveness and Resource Allocation 2013 11:6. The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print] International Journal of Technology Assessment in Health Care Journal of Medical Economics 2013 Mar 25. [Epub ahead of print] Pharmacoeconomics 2013 Mar 26. [Epub ahead of print] Value in Health 2013 March - April;16(2):e1-e5

CHEERS Checklist

Items to include when reporting economic evaluations of health interventions

| Section / Item | Item No | Recommendation | Reported on page No / line No |
|---------------------------------|---------|---|-------------------------------|
| Title and abstract | | | |
| Title | 1 | Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared. | |
| Abstract | 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | |
| Introduction | | | |
| Background and objectives | 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | |
| Methods | | | |
| Target population and subgroups | 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | |
| Setting and location | 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | |
| Study perspective | 6 | Describe the perspective of the study and relate this to the costs being evaluated. | |

| | | | |
|--|-----|--|--|
| Comparators | 7 | Describe the interventions or strategies being compared and state why they were chosen. | |
| Time horizon | 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | |
| Discount rate | 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | |
| Choice of health outcomes | 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | |
| Measurement of effectiveness | 11a | Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data. | |
| | 11b | Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | |
| Measurement and valuation of preference based outcomes | 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | |
| Estimating resources and costs | 13a | Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | |
| | 13b | Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | |

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|--------------------------------------|-----|---|--|
| Currency, price date, and conversion | 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | |
| Choice of model | 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | |
| Assumptions | 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | |
| Analytical methods | 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | |
| Results | | | |
| Study parameters | 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | |
| Incremental costs and outcomes | 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | |
| Characterising uncertainty | 20a | Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective). | |
| | 20b | Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | |

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| Characterising heterogeneity | 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | |
| Discussion | | | |
| Study findings, limitations, generalisability, and current knowledge | 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | |
| Other | | | |
| Source of funding | 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support. | |
| Conflicts of interest | 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations. | |

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The CHEERS Statement may be accessed by the publication links above.

The ISPOR CHEERS Task Force Report provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: <http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp>

The citation for the CHEERS Task Force Report is:

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We sincerely hope that this first attempt at compilation of India specific data on need, proposed application and guidance for PE research by the core committee will stimulate further refinements through constructive dialogue among stakeholders on pharmacoeconomic application and research in India. We are confident that the Pharmacoeconomic guidelines of India once finalized will go a long way in promoting research, health policy development, value-based decision making in the clinics and prioritisation of health care spending in the days to come.

Sincerely,

The Core Committee on PEG

(Dr Suresh K. Gupta , Dr Divya Mishra, Mahendra K. Rai, Richa Goyal, Javed Shaikh, Munish Duvedi)

Date: September 2013

Place: New Delhi

Declaration of Conflict of Interest

There was no conflict of interest. Dr. S.K. Gupta is President, ISPOR India Chapter. Dr. Divya Mishra is an Executive committee member of ISPOR India chapter and is an employee of SFJ Pharmaceuticals, New Delhi. Mahendra K. Rai, Richa Goyal and Javed Shaikh are employees of Capita India Pvt Ltd, Mumbai. Munish Duvedi is employee of GVK Biosciences, Gurgaon. Authors declare that they have volunteered for their contribution to PEG, ISPOR India and have received no payments for writing these guidelines.

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