PHARMACOECONOMICS

&

OUTCOMES RESEARCH GUIDELINES FOR INDIA

PEOR Guidelines

Guidelines for Pharmacoeconomics and Outcomes Research for India

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Pharmacoeconomics Guidelines:

1. Introduction

Pharmacoeconomics (PE) refers to the scientific discipline that compares the value of one pharmaceutical product or treatment mix to another. It is a sub-discipline of health economics.[1,2]
A pharmacoeconomic study evaluates the cost (expressed in monetary terms) and effects (expressed in terms of monetary value, effectiveness, efficacy or enhanced quality of life) of a pharmaceutical product. Data generated from pharmacoeconomics studies have potential to impact many domains like health insurance, reimbursement under Central and State Government schemes, health policy, import and export of pharmaceutical products, technologies, subsidies on health products and planning of future health care benefit programmes.[3] In 1993, Australia became the first nation to use pharmacoeconomic analysis as part of the process for deciding whether new drugs should be subsidized by the Federal Government.[4]

The current healthcare delivery system in India is more skewed towards private healthcare utilization. As per WHO's World Health Statistics 2012, almost 60% of total health expenditure in India was paid by the common man from his own pocket in 2009. The Report states that 39 million Indians are pushed to poverty because of ill health every year. Around 30% in rural India did not go for any treatment for financial constraints. About 47% and 31% of hospital admissions in rural and urban India were financed by loans and sale of assets.[5] Although attempts have been made by government in terms of health financing coverage in terms of Employees State Insurance Scheme (ESIS), Central Government Health Scheme (CGHS), Universal Health Insurance (UHI) Scheme etc, these have failed to cover the vast number of populations. It is mainly due to the reason that schemes such as ESIS, CGHS etc. are for formal employment sector whereas 70% of India's employed are in the informal sector, thus keeping them out of any "safety net" mechanism. Social security schemes such as UHI Scheme have failed due to lack of awareness about the scheme among the poor, inadequate social marketing efforts and its usage through reimbursement rather than "cashless" transactions. Other schemes such as the Rastriya Swasthya Bima Yojana (RSBY) are eligible for enlisted Below Poverty Line (BPL) populations and listed employment groups, such as domestic workers, street vendors, construction workers etc., and hence are not inclusive for all poor and vulnerable populations in the country.[6]

The economic boom in India has opened up commercial markets for manufacturers of healthcare products, in particular the pharmaceutical industry, cosmetic industry, vaccine manufacturers, medical device/ equipment manufacturers etc. Since health-related decision-making process is often not based on scientific evidence, commercial interests often take priority over scientific concerns, in framing and implementing health policies. In India, a strong price control mechanism is in place through the National Pharmaceutical Pricing Authority.

Most healthcare services in developing countries are provider-driven, in the sense that people have little role in their healthcare decision-making process. This is largely related to limited resources and infrastructure, and the demand-supply imbalance. Thus people in developing countries are often faced

with the difficult choice to "take it or leave it". However, this scenario is changing in developing countries where empowerment of people in terms of wealth and education, is increasing. In such countries, many people can access and afford levels of healthcare that are of high quality, and also provide value-for-money. This is changing the provider-driven systems to demand-generated systems. Insurance and employer reimbursement of health costs, is also aiding this process. A mix of social, voluntary, private and community-based health insurance plans are available in India. Although the government pays for approximately 20% of drugs used in India, private out-of-pocket expenditure in India on health-care is one of the highest in the world. Increased public funding combined with flexibility of financial transfers from centre to state can greatly improve the performance of state-operated public systems. Just by increasing public healthcare funding would not help the quality of health-care delivery unless there are strictly implemented robust pharmacoeconomics guidelines in place. In New Delhi, Mumbai, and Trivandrum, state authorities have invited the National Institute for Health and Clinical Excellence (NICE) to help in the development of clinical guidelines.[5,7]

2. Health technology assessment in India

Health technology assessment (HTA) is a rapidly growing field of interest in India. Hope this very first pharmacoeconomic guidelines in India would be a formal framework for assessing pharmaceutical products for the country. *Health Technology Assessment (HTA) is a multidisciplinary field of policy analysis, studying the medical, economic, social and ethical implications of development, diffusion and use of health technology*. HTA would ensure that public funds within India's central government, states and union territories is spent on safe, effective and value-for-money pharmaceuticals to maximize the efficiency of public pharmaceutical spending so that coverage of medicines can be gradually extended across a wider satisfied population. It is well known fact that the healthcare delivery in each country is influenced by local and global politics.[8]

Preparing pharmacoeconomics guidelines will be an important step in order to establish health technology assessment (HTA) in India. Areas in which HTA could be applied in the Indian context include, drug pricing, development of clinical practice guidelines and prioritizing interventions that represent the greatest value with in a limited budget. India is planning to be part of universal health coverage scheme by 2022. It is a big capacity building challenge for central and state governments to provide high quality health-care without financial hardship on the healthcare seekers. It is important to focus on preventive and public health strategies aimed at reducing the most important health problems in India. Recent advancements in high quality primary healthcare including maternal and child health services by the State Tamil Nadu is encouraging.

Challenges in developing and implementing pharmacoeconomics guideline could be managed by involvement of all stakeholders. Some suggestions are as follows:

- Central and state drug regulators constituting with the pharmacoeconomics advisory groups.
- Implement HTA using pharmacoeconomics guidelines.

- Concentrate on both direct and indirect services to decrease the burden of ailments such as improving nutrition, decrease poverty, develop infrastructure for healthcare and living healthy and prevent transmission of diseases by treating patients and immunizing public.
- Improve access to life-saving medicines and affordability of essential medicines.
- Implementing public-private partnership medical insurance systems linked with Aadhar card.
- Collect healthcare tax and increase spending on health budgets.
- Creating awareness in public and professionals for better resource utilization.
- Consider healthcare as a basic necessity, individual right and responsibility.
- Include pharmacoeconomics principles in medical, pharmacy, nursing, public health and other healthcare professional education.[9]

Public health system of a country is driven by many factors like modernization of healthcare services, burgeoning cost of healthcare, rapidly increasing population and rapid growth of biomedical literature databases in medical sciences. There are different reasons for conducting health technology assessments such as qualifying the product in terms of its applicability in common public, designing mechanism for healthcare reimbursement or finding pathway to integrate health technology in current health system.

The methodology of HTA differs from countries to countries. For example, NICE conducts HTA to provide recommendations to make sensible choice between available clinical interventions, where as Germany HTA agency considers it as an evidence based documentation purpose. However, main methodology remains same which includes systematic review which is synthesis of critically appraised original articles and clinical studies/trials. This systematic review is followed by cost-effectiveness analysis which is combined representation of clinical effect and coverage cost in form of ratios such as cost benefit, cost utility or cost effectiveness. The market status review is conducted by identifying demand/need, costs of same or similar technologies and patent status. Innovative health technologies not only impacts commercial environment but also sometimes mandates organizational structure changes. This may include recruitment of staff with higher skills or change in role of current personnel depending on use of technology in investigational or established diffusion phase.[8]

Health Technology Assessments have become increasingly useful, providing evidence on clinical benefit, cost effectiveness, social, legal and regulatory insights leading to identification and uptake of appropriate and safe technologies such as bio-pharmaceuticals, medical devices, implants, drugs and therapeutic practices. National Health Systems Resource Centre (NHSRC)[10], New Delhi has been interested in HTAs for various interventions. NHSRC suggests a focus on;

1. How to ensure universal access to essential medicines and devices
2. How to write specifications when processing these so that we get the best value for money

3. How to assess technologies that public health systems should adopt for increased effectiveness and those that we should avoid, due to reasons of safety or poor cost effectiveness

4. How to identify areas where new technologies appropriate to our needs are invented and to develop an ecosystem that focus on such innovations.

Structured quick assessment (SQA)

The HTA outcomes can be translated into pharmaceutical policy if authorities perform a structured quick assessment (SQA) for all pharmaceuticals which wish to receive public funding from any government program. Ideally, government-funded programs (incl. drug tenders) should only be open to medicinal products which have undergone SQA. It is equally important that all pharmaceuticals with a reimbursement history (i.e. previously reimbursed products) should also be subject to SQA, and different assessment criteria should be accepted and used for on-patent (single-source) and competing (off-patent) drugs. The evaluation process should follow a pragmatic, easy-to-execute, low-resource approach. General assessments must ensure that health technologies meet the above-stated principles by;

1) Serving the overall benefit of society by not raising barriers to access,
2) Avoiding the need for additional primary data collection and resource-intensive quantitative analysis, and
3) Minimizing the burden on state administration, maximizing the speed and quality of evaluation, as well as transparency and unambiguity in policy decisions.

In order to ensure a balanced, informed decision, assessments should also encompass multiple criteria, i.e. clinical, societal and financial aspects, and it should reference to relevant assessments available abroad. Health technologies may be further evaluated on the basis of quality of safety and effectiveness evidence in India, assessment and reimbursement history of the medicine in peer countries, therapeutic value added (e.g. high unmet need, higher effectiveness, favourable side effect profile, convenience of use, improved adherence and better quality of life), service to society (alignment with health policy, alleviation of social burden), and impact on drug budgets (direct and indirect).

For previously reimbursed drugs, assessment criteria may be different, where the quality of local safety and effectiveness evidence in India would be an important factor to consider. SQA of technologies could be undertaken in any research oriented organization with the Ministry of Health & Family Welfare. Ideally such as institution should have technical collaboration with academia and research institutes for uptake of technical inputs as well to serve nodal points for dissemination within the health system. HTA work in India should primarily be done on a response basis on the priorities that are appropriate to the various health departments with the government decision making".

In summary, structured quick assessment (SQA) of pharmaceuticals in India could be a qualification process linked to public funding to ensure safety, effectiveness, patient preferences, and value-for-money public pharmaceutical spending.

Model SQAs could be performed by a competent and independent agency under Department of Healthcare Research (DHR). States and union territories could follow the standard operating procedures developed by the DHR.[11]

PE guidelines 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 pharmaco-economically 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.

3. Central/State Governments 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 sates “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 healthcare providers, society, and 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. Drug regulatory agency and patent: Drug Controller General of India (DCGI) / Central Drugs Standard Control Organization (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 marker 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 prioritize. 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, where as those drug trials which are necessary to be conducted in larger public interest are delayed. Patent system is strict in India. This will also encourage pharma companies to innovate newer molecules and health technologies.

3. Pharmacoeconomic (PE) Guidelines

The guidelines presented below represent to the economic evaluation of pharmaceutical drugs, but can be applied to the following situations: designing and conducting an economic evaluation of a new health technology or healthcare intervention (e.g. screening).

Guideline 1. Study design

The study design for any economic evaluation should have the following framework:

- Clearly defined research question or objectives of analysis
- Audience of the evaluation
- Analysis methods
- Cost determination
- Viewpoint of the analysis
- Analytic horizon
- Intervention to be specified
- Choice of therapeutic alternatives for comparison should be specified
- Target population

Method of analysis	Measurement/assessment of costs	Measurement/assessment of outcomes	Cost-outcome comparisons
Cost-minimisation analysis (CMA)	Monetary	None	None
Cost-effectiveness analysis (CEA)	Monetary	Natural units	Costs per outcome unit
Cost-utility analysis (CUA)	Monetary	Utility values	Costs per QALY
Cost-benefit analysis (CBA)	Monetary	Monetary	Net costs
Cost- consequence analysis (CCA)	Monetary	Variety of different natural units	Cost per outcome unit

The study design could use both as prospective and retrospective study designs. The economic evaluation of the pharmaceutical drug can be carried out in parallel to a clinical study for measuring 'efficacy'. This can also be done through modelling methods for documenting 'effectiveness'. If all the data required for model calculations is not available for India, then similar parameters from other developing countries could be used, or in certain cases expert opinion can be used if such data is not available. It should be kept in mind that a high degree of transparency would need to be maintained in such cases, and the details should be provided as much as possible.

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines give a much complete framework for designing PE studies.

Guideline 2. Audience of the evaluation

The main audience of an evaluation should be the decision makers, and in the context of India, this may be different from the funders of the evaluation. This can include:

- Ministry of Health and Family Welfare
- Drug Pricing Control Authority
- Government Departments financing large-scale health insurance programs, e.g. Ministry of Labour for Rashtriya Swasthya Bima Yojana (RSBY)
- International organisations, such as World Bank, USAID etc.
- Non-government aid agencies, e.g. Medicines Sans Frontiers, Bill & Melinda Gates Foundation etc.
- Insurance companies
- Pharmaceutical companies

Guideline 3. Methods of analysis

Table 1 shows that there are different types of evaluation which can be used to answer different decision questions. However, these are classified according to the type of comparison to the costs and consequences. The choice of method of analysis will depend on the research question, and must be clearly justified.

On the basis of these methods of analysis, supplementary questions can also then be considered, such as budget impact or cost impact. This would be particularly important for public agencies such as Ministry of Health, and government departments responsible for financing health insurance programs.

Guideline 4. Viewpoints (or perspective) of the analysis

The perspective is the point of view through which the research question is examined and assessed. The choice would be based on the research question, and can have the following two types of perspectives:

a) Society

b) Decision-makers, e.g. Ministry, Insurance Companies etc.

In India, as the majority of expenditure is out-of-pocket. It would be highly useful to consider the societal perspective and opportunity costs that are appropriate should also be considered.

Guideline 5. Cost determination

The societal perspective means that the evaluations must include all the costs and benefits, no matter who actually bears the cost or gets the benefits. This means that all costs and benefits outside the health financing/health insurance payment must also be considered. Any direct or indirect cost outside the health financing/health insurance payment must be presented and calculated separately. Thus, three types of costs must be displayed:

(1) Direct costs in the health insurance/health financing payment
(2) Cost in (1) plus direct costs not paid by the health financing/health insurance payment system (i.e. health/public system perspective)
(3) Costs in (2) plus indirect costs outside the health insurance payment system (i.e. the societal perspective)

Direct costs include direct medical and direct non-medical costs. Direct medical costs arise directly from the treatment (e.g. diagnosis, drug therapy, medical care, in-patient treatment, etc). Direct non-medical costs arise from the consequences of treatment (e.g. transport costs, care services etc)
Indirect costs include losses of productivity resulting from illness and premature death. If impairment of capacity to work is to be considered together with absence from the workplace, the procedure must be presented separately.

A marginal consideration should be attempted in order to quantify the costs of an additionally consumed unit. Mean values should only be used if marginal values are not available. In order to make the whole consumption of resources transparent, unit quantities and prices should be defined. Ideally, the opportunity cost of a resource should be considered. Opportunity costs represent the value of the next best use of resources, and should represent as accurate figures as available. The calculation of the opportunity costs should consider; all identified relevant costs, measurement of amount of resources, and value (or cost) of these resources.

In a competitive market, this value is represented by market prices, e.g. drugs, medical devices etc. If there is no competitive market, then scales of charges or fees or other forms of administrative reimbursement, can be used. In other cases, substitute quantities or 'shadow prices' should be used. If there are no published data for the cost survey, calculations and individual assessments (estimates, mean values, exploration of published data) should be performed.

Losses of productivity should be quantified by the human capital approach, i.e. the period-related income of the patient group concerned. If no specific data are available for the patient group considered, average values can be used from official statistics.
Loss of productivity= Incapacity for work x Wage costs
Dependent employees x 365 days
In determining the loss of productivity; gender, age and social components must be considered, depending on the research question.

In cases where long-term absence from work or death, only the period until the workplace is filled again (by others or by colleagues) (i.e. friction period) is assessed as loss of production. However, the use of the friction cost approach must be justified.

Guideline 6. Analytic horizon

The choice of analytic horizon depends on the research question and can range from a few weeks to several years (e.g. remaining life expectancy). In choosing the time horizon, it should at all events be ensured that the chosen outcome and the resource consumption of the treatment alternatives are observable in this period.

Guideline 7. Specifying the intervention

The interventions to be analysed and the system within which it is delivered need to be described fully and with care. This will help ensure that all resources used are identified and allow others to understand exactly what was evaluated, which is important for considering the generalizability of the results.

Guideline 8. Choice of therapeutic alternatives for comparison should be specified

The aim of comparative economic analyses consists in assessing competing measures. The choice of alternatives must be appropriate to the research question and the state of science. The chosen alternatives should be described as fully as possible and comply with clinical practices in India and other developing countries. The choice of alternative(s) must be justified.

Potential range of options against which to compare interventions

1. Current practice
   a. Single principal type(s) of intervention
   b. Mix of interventions
2. Best available alternative (e.g. as represented by clinical guidelines or low-cost alternatives)
3. Do nothing
   a. Without the new intervention
   b. Without any care
4. Alternative levels of intensity for the new intervention

Source: Adapted from Castor and Ganiats (1999)

Guideline 9. Target population

The target population is the group for whom the intervention is intended, and this can vary by age, sex, disease and geography. It is also important to identify whether there are subgroups for which separate analysis should be undertaken, such as for different age groups, urban-rural, ethnic groups etc.

Guideline 10. Outcome parameters

In order to state the effectiveness of a medicine, data from clinical trials can be applied to economic models using real and clear assumption. All assumptions must be scientifically reviewed and explained in detail. The reliability and validity of important variables in the models must be examined.

Economic evaluations must be based on complete data for effectiveness and side effects, which are obtained from reviewing and obtaining the existing data of all treatments for a specific indication. Conducting a systematic review using a relevant database will be necessary, listing the databases used, key words used for the inquiry, and inclusion and exclusion criteria of literature. Moreover, unpublished reports that examine treatment conditions of indicators can also be presented.

Wherever possible, a summary table using meta-analysis of all selected literature can increase the accuracy of estimating the differences between the medicine and its comparator. Meta-analysis will also be helpful in finding some characteristics of the medicine that are of clinical importance but cannot be observed in randomized clinical trials. However, while conducting meta-analysis care must be taken to clearly describe the statistical methods adopted. Source of effectiveness data can be from experimental research or observational research. If no such research is available, expert opinion can be taken. However, the evidence of lower value data can be adopted in an economic evaluation only when the evidence of higher value data does not exist. The methods of choosing experts and collecting their opinions must be described in detail in the evaluation reports.

The values of clinical data can be ordered as follows:

A) Systematic reviews/Meta-analysis of randomized controlled trails
- Randomized controlled clinical trials
- Controlled clinical trial with pseudo-randomization
- Controlled clinical trial without randomization

B) Systematic reviews/Meta-analysis of observational studies
- Cohort prospective studies with parallel control
- Cohort prospective studies with historical control
- Cohort retrospective study with parallel control
- Epidemiological case- controlled studies retrospective
- Studies of a “before and after” type
- Expert opinion (Delphi methodology, committee later report and descriptive studies)

As the relationship between clinical outcome parameters and subjective patient well-being is only very indirect, in specific indications- particularly where the medical treatment does not hold out the prospect of either a cure or a significant prolongation of life- the health-related quality of life is the appropriate outcome indicator.

If the quality of life is to serve as an outcome variable, it must be ensured that the variable measured is also an appropriate measure for comparing the chosen treatment alternatives. Outcomes of this kind, in other words utilities, can be determined in the following way:

- specific scales (rank scales),
- game theory procedures (e.g. standard gamble, time-trade off, etc),
- psychometric scale procedures which include generic and disease-specific procedures as well as one-dimensional and multidimensional instruments.

These individual measures are suitable for combining with quantitative objective measurements such as survival time in the form of quality adjusted life years (QALYs), and can be applied to cost-utility analysis (CUA). The utilities of health states can be determined by patient themselves or the general population. If utilities are determined by the general population, the evaluations based on them are considered as "from the societal perspective". QALY is currently the most widely used and recommended outcome measure. For pharmaceutical manufactures, it is recommended that QALY be used in the main analysis and other effects be used in the secondary analysis. The World Bank & World Health Organization (WHO) suggested adopting disability-adjusted life-year (DALY) as an alternative to QALY. Using DALY world statistics on Global Burden of Diseases (GBD) are released by WHO since 1990. In other cases economically oriented outcome measures such as hospital days, days of incapacity for work etc. can also be chosen.

Guideline 11. Incremental cost-effectiveness

The incremental cost-effectiveness shows the difference in the cost-effectiveness of two alternatives or the additional costs of the net effect. Health economic analyses should include the description of the modelling techniques for calculating the incremental cost-effectiveness.

To develop models, the structure and the theoretical framework of the models should be explained explicitly, and they should be presented through diagrams (for example, decision trees, Markov models). All data sources used must be described exactly, their choice justified and their suitability and validity assessed. This involves scrutinizing both internal and external validity. In India, economic data is not systematically recorded or published. For this reason, health economic evaluations should refer primarily to data from the following sources:

- Five year Plans, Committee Reports, National Health Policy (NHP), National Sample Survey Organization (NSSO), Economic Census, National Rural Health Mission (NRHM), Public Budgets (Central and State). The new government under the leadership of Sri. Narendra Modi shall revise the planning commission system.
- Insurance Companies Annual Reports, ESIS, CGHS, Railways, Mines, Plantations, Labour Yearbook
- Primary studies on cost of illness, cost of care etc, done by organisations such as WHO, World Bank, NGOs etc.
- Data from cost calculation by hospitals
- Cost estimates from Delphi model surveys
- Empirical surveys

- Expert opinion

Epidemiological surveys performed directly in India or related to India are extremely rare. However, the data sources could be from:

- Published data or data surveys from India
- Published data from comparable developing countries (e.g. Bangladesh, Sri Lanka, Central Africa etc)
- Other available data (e.g. Global Burden of Disease)
- Expert opinion

Guideline 12. Discounting

Often, in health economic analysis, costs and/or outcomes are considered over a period of more than a year. If this is the case, the calculation of current values is necessary, i.e. long-term considerations require discounting of the costs and benefits at a particular reference point - usually the time at which the study is setup. Discounting allows two different treatment alternatives in which costs and benefits of a particular reference point generally occur at different times to be compared. As an annual discount, a rate of 5% is adopted, while a sensitivity analysis with lower and higher rates (e.g. 3% and 10%) should verify the robustness of the results. Non-monetary outcomes should be discounted in a separate calculation.

Guideline 13. Uncertainty

Data for a health economic analysis are derived from various sources (e.g. pooled data sets, meta-analyses, unverifiable assumptions). As this is to some extent incomplete and affected by uncertainties, assumptions are frequently made about certain parameter values. Stochastic approaches such as deterministic sensitivity analyses should examine the effect of uncertain and/or estimated parameters on the outcome of the evaluation. Ranges of variation are defined for the variation in exogenous parameters. The definition of the plausible range of variation is based on the following options, depending on the study design for sensitivity analyses:

- Confidence intervals from clinical studies, statistical studies,
- Assumptions from the scientific literature,
- Expert opinions, etc.

A sensitivity analysis is unnecessary if the parameters have already been presented with their dispersion. The results of the sensitivity analysis must be discussed critically.

Guideline 14. Equity

In any economic evaluations used for allocating resources, the equity is an important factor. The equity assumptions for the base case in economic evaluations means that all patients, in clinical trials, and economic evaluations, have a fair participatory opportunity and obtain the expected treatment and outcomes. For example, in the cost-effectiveness analysis (CEA), the cost per life saved or life-years gained is based on the assumption that all lives are equal, regardless of their age, co-morbidities or other states. In cost-utility analysis (CUA), everyone’s increase in QALY is of the same value, no

matter who the person is, i.e. an additional QALY of a 40-year old man and that of an 80-year old man are equally preferable.

Guideline 15. Presentation of the results

Consolidated Health Economic Evaluation Reporting Standards (CHEERS) guidelines need to be followed in publishing the PE study reports. The results and procedure of the health economic evaluation must be reproduced transparently. The results should be presented in the same way as for a publication in journals (peer review) (details of the author, sponsoring, etc). Negative results also should be published. Descriptions relevant to the research question and significant results should be presented in an aggregated and disaggregated way (e.g. according to cost components, perspectives, etc). The different viewpoints should be presented comparatively. An additional clear and brief description of the results should present the cost-effective (i.e. dominant) strategy.

4. Good Prescribing & Pharmacy Practices

Pharmacoeconomics (PE) principles are vital parts of good prescribing practices. Many of the developing economies either do not have national pharmacoeconomic guidelines or they are poorly implemented. National drug price controls shall stabilize the cost of medicines in different brands and schemes, which shall decrease confusion in prescribers for selecting medicines. Variation in price for drugs and different brands are huge.[13]

The basic purpose of separating medicine prescribing and dispensing is to ensure independence in the choice of medicines. Incentive or remuneration for prescribing should be discouraged; prescribing from essential medicines list need to be encouraged so that over prescribing or unnecessary prescribing of costly medicines could be avoided. Pharmacy and therapeutic committees could perform routine resource utilization and patient based PE studies to develop and update clinical guidelines as part of implementing good prescribing practices.13 Restrictions on reimbursement also play a major role in avoiding overprescribing and additional costs. Conflict of interest policies need to be enforced in medical education, conferences, and continuing medical education. Influence of pharmaceutical marketing shall not bias good prescribing practices. It is advisable that pharmaceutical marketing should be limited to the purchase department of health care facilities. Prescribers shall seek drug information through unbiased drug information services, so that prescribers and dispensers could have independence in their decision making on medicines in discussion with consumers, which will improve medication adherence.[14-16]

Further research and development of PE guidelines are needed in institutional and regional levels in India based on pharmacoeconomics, clinical interventions, health care delivery systems, and clinical outcomes. A combination of ethical and scientific reform could help in planning & implementation of good PE practices in India.

References

1. Mueller C, Shur C, O'Connell J. Prescription Drug Spending: The Impact of Age and Chronic Disease Status. American Journal of Public Health. 1997; 87 (10): 1626–29.
2. Arnold RJG and Ekins S, Time for cooperation in health economics among the modeling community, PharmacoEconomics. 2010; 28(8):609-613.
3. Mandal CS, Pharmacoeconomics- Regulatory perspective and its relevance in Indian Context. Pharma Times. 2013; 45(5): 18-20.
4. Birkett DJ, Mitchell AS, McManus P. A cost-effectiveness approach to drug subsidy and pricing in Australia. Health Aff (Millwood). 2001;20(3):104-14.
5. Press Information Bureau. GOI. India Embarks on Universal Health Coverage during 12th Plan. Available at: http://pib.nic.in/newsite/erelease.aspx?relid=88129 (Accessed on 27-08-2014).
6. Gerard La Forgia & Somil Nagpal. Government-Sponsored Health Insurance in India: Are You Covered? The World Bank, 2012. Available at: http://documents.worldbank.org/curated/en/2012/08/16653451/government-sponsored-health-insurance-india-covered (Accessed on 10-02-2014)
7. NICE. International projects. Available at: http://www.nice.org.uk/aboutnice/niceinternational/projects/NICEInternationalProjects.jsp?textonly=true (Accessed on 02-01-2014). 23
8. INHATA. HTA resources. Available at: http://www.inahta.org/HTA/ (Accessed on 02-01-2014).
9. Thomas D, Zachariah S, Padmanabha Reddy Y, Alvarez-Uria G. Development of Pharmacoeconomics guidelines in India. Perspect Clin Res. 2014; 5(2):54.
10. NHSRC. Healthcare technology. Available at: http://nhsrcindia.org/index.php?option=com_content&view=article&id=173&Itemid=642 (Accessed on 02-01-2014).
11. Thomas D, Danko D, Structured Quick Assessment of Pharmaceuticals in India. News Across Asia. 2013; 2(3):3.
12. ISPOR. CHEERS: Good reporting practices. Available at: http://www.ispor.org/taskforces/economicpubguidelines.asp (Accessed on 21-02-2014).
13. Fleetcroft, R., Cookson, R., Steel, N. &Howe, A. Correlation between prescribing quality and pharmaceutical costs in English primary care: national cross-sectional analysis. Br. J. Gen. Pract. J. R. Coll. Gen. Pract. 2011; 61, e556–564.
14. Thomas, D, Seetharam, G. & Alvarez-Uria, G. Essential medicines concept for quality assurance of health care facilities. J. Pharm. Bioallied Sci. 2012; 4, 172.
15. Mishra SI, Gioia D, Childress S, Barnet B & Webster RL. Adherence to medication regimens among low-income patients with multiple comorbid chronic conditions. Health Soc. Work 2011; 36, 249–258.
16. IPA. Good Pharmacy Practice Guidelines. Available at: http://www.ipapharma.org/html/GPP_Guidelines_IPA2002.pdf (Accessed on 21-02-2014

Outcomes Research Guidelines

INTRODUCTION

Outcomes research is concerned with measuring the end results regarding effectiveness of healthcare interventions and methods. It focuses on themes of Health Related Quality of Life (HRQoL), Patient Reported Outcomes (PRO) , effectiveness, quality of care, health status screening, diagnostic tests, medical treatment, procedures and practices, guidelines and healthcare policy.[1] In India more than half of the morbidity and mortality - (53%) is due to the burden of communicable and non-communicable diseases together. [2] This burden poses significant public health challenges such as safeguarding public health, expanding health care coverage and improving quality of care while controlling costs before India. In spite of its importance and relevance, the number of outcomes research studies conducted in India is less compared to many countries due to the lack of proficiency, trained staff and proper guidelines. [3]

Outcomes research data is useful for the regulators, policy makers, researchers and other stakeholders, for setting national policy, designing drug formulary and drafting pharmacoeconomics guidelines. [4] In order to encourage and facilitate the conduct of outcomes research studies, the knowledge, access and sustained support of pre-existing resources is essential.[5] There is a tremendous need to develop the outcomes research guidelines for India. The outcomes research studies are carried out in the form of randomized control trials (RCT), cohort studies, case control studies, meta-analyses and systematic reviews. [6] These studies are based on the Clinical, Economic and Humanistic Outcomes (ECHOs). For example cure, survival, etc are clinical outcomes; expenses, savings, etc are economic outcomes while role physical, emotional wellbeing, etc are humanistic outcomes.

Patient-Reported Outcomes (PRO) is the status of individual patient's health status which is directly obtained from the patients without elucidation of the patient's response by physicians or any other healthcare professionals.[7]

PRO Instruments

A PRO instrument (i.e., a ***questionnaire*** plus the information and documentation that support its use) is a means to capture PRO data used to measure ***treatment benefit*** or risk in medical product clinical trials. PRO instrument development is an iterative process and we recognize there is no single correct way to develop a PRO instrument. [7]

The different types of PRO instruments with examples are listed in the table 1. [9]

Table 1: Patients Reported Outcomes Research Instruments

Type of PRO	Example
Generic Specific	World Health Organization Quality of Life
Disease Specific	Diabetes Self-Management Questionnaire

Dimension Specific	Physical Activity Index
Region specific	Cambridge Pulmonary Hypertension Outcome Review
Individualized	Schedule for the Evaluation of Individual Quality of Life
Utility measures	EQ-5D, Major and Unipolar Depression
Survey Items	General Household Survey

The outcome can be measured in absolute terms (e.g., severity of a ***symptom***, ***sign***, or state of a disease) or as a change from a previous measure. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more ***concepts*** (i.e., the *thing* being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition).
Use of a PRO instrument is advised when measuring a concept best known by the patient or best measured from the patient perspective. The concepts measured by PRO instruments that are most often used in support of labeling claims refer to a patient's symptoms, signs, or an aspect of functioning directly related to disease status. PRO measures often represent the effect of disease (e.g., heart failure or asthma) on health and functioning from the patient perspective.

Evaluation of a PRO Instrument [7]
The PRO instrument shall be evaluated taking the following into considerations:

- The population under observation
- The design and objective of the study
- The PRO instrument's conceptual framework & measurement properties

Since the purpose of a PRO measure is to capture the patient's experience, an instrument will not be a credible measure without evidence of its usefulness from the target population of patients. Sponsors should provide documented evidence of patient input during instrument development and of the instrument's performance in the specific application in which it is used (i.e., population, condition).
PRO instruments should be evaluated for Validity (Content validity, Construct validity, Criterion validity) and Reliability (Test-retest or intra-interviewer reliability, Internal consistency, Inter-interviewer variability). [8]

A. Endpoint Model
Sponsors should define the role a PRO ***endpoint*** is intended to play in the clinical trial (i.e., a primary, key secondary, or exploratory endpoint) so that the instrument development and performance can be

reviewed in the context of the intended role, and appropriate statistical methods can be planned and applied. It is critical to plan these approaches in what can be called an endpoint model.
The endpoint model explains the exact demands placed on the PRO instrument to attain the evidence to meet the clinical trial objectives and support the targeted claims corresponding to the concepts measured.

B. Choice of PRO Instrument

Initially a search has to be made among the available instruments to find a suitable option which would provide the answer to the research question. A new PRO instrument should be developed in case there are no suitable options. A new PRO instrument can also be developed by modifying the available instruments.

Characteristics of PRO instruments that are reviewed by the FDA include the following:

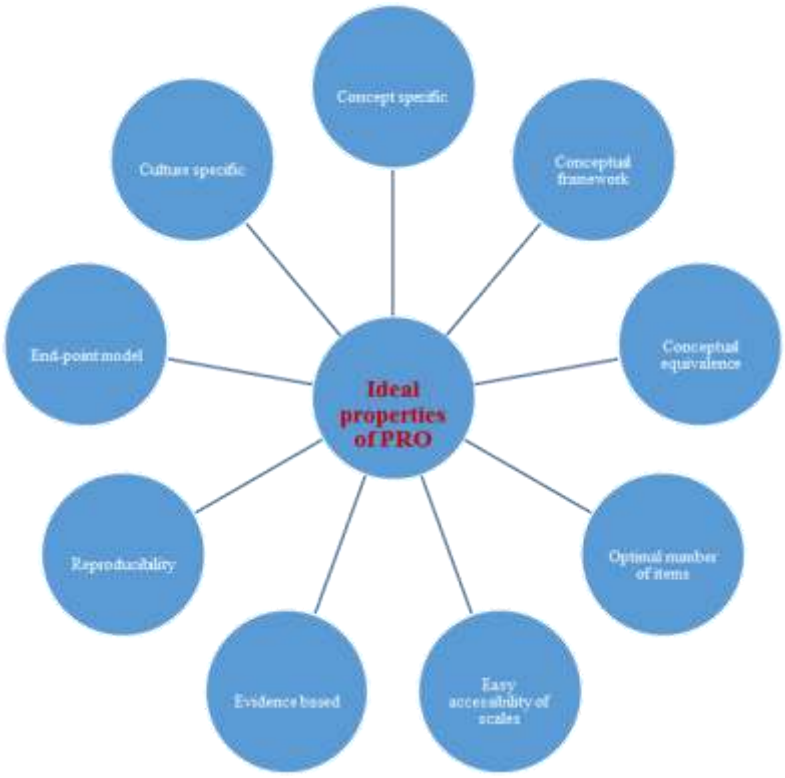

Figure 1: Ideal properties of PRO instrument [10]

When the development history of a PRO instrument is not available, the content validation should be carried out and documented including open-ended patient input from the specific population.
The sponsors should inform the regulatory bodies and start the PRO instrument development and evaluation during the early product development to ensure the measurability of the PRO instrument.

PRO instruments can be used to measure important safety concerns if those concerns represent symptoms or signs that are best captured from the patient perspective. All adverse events detected with a PRO instrument should be included in the clinical trial report.

C. Conceptual Framework of a PRO Instrument

The ability of a proposed instrument to support a claim depends on the conceptual framework of the PRO instrument. The conceptual framework explicitly defines the concepts measured by the instrument in a diagram that presents a description of the relationships between items, domain (subconcepts), and concepts measured and the ***scores*** produced by a PRO instrument.

Concepts Measured

In some cases, the question of what to measure may be obvious given the condition being treated. For example, to assess the effect of treatment on pain, patients from the target population are queried about pain severity using a single-item PRO instrument.

The conceptual framework of a PRO instrument will evolve and be confirmed over the course of instrument development as a sponsor gathers empiric evidence to support item grouping and scores. When used in a clinical trial, the PRO instrument's conceptual framework should again be confirmed by the observed relationships among items and domains.

Documentation of the instrument development process should reveal the means by which the items and domains were identified. The exact words used to represent the concepts measured by domain or total scores should be derived using patient input to ensure the conclusions drawn using instrument scores are valid.

Table 1[7]. Common Reasons for Changing Items during PRO Instrument Development

Item Property	Reason for Change or Deletion
Clarity or relevance	Reported as not relevant by a large segment of the target population Generates an unacceptably large amount of missing data points Generates many questions or requests for clarification from patients as they complete the PRO instrument Patients interpret items and responses in a way that is inconsistent with the PRO instrument's conceptual framework
Response range	A high percent of patients respond at the floor (response scale's worst end) or ceiling (response scale's optimal end) Patients note that none of the response choices applies to them Distribution of item responses is highly skewed
Variability	All patients give the same answer (i.e., no variance) Most patients choose only one response choice Differences among patients are not detected when important differences are known
Reproducibility	Unstable scores over time when there is no logical reason for variation from one assessment to the next

Inter-item correlation	Item highly correlated (redundant) with other items in the same concept of interest
Ability to detect change	Item is not sensitive (i.e., does not change when there is a known change in the concepts of interest)
Item discrimination	Item is highly correlated with measures of concepts other than the one it is intended to measure Item does not show variability in relation to some known population characteristics (i.e., severity level, classification of condition, or other known characteristic)
Redundancy	Item duplicates information collected with other items that have equal or better measurement properties
Recall period	The population, disease state, or application of the instrument can affect the appropriateness of the recall period

D. Content Validity [7]

Content validity is the extent to which the instrument measures the concept of interest. Content validity is supported by evidence from qualitative studies that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Content validity is specific to the population, condition, and treatment to be studied. For PRO instruments, items, domains, and general scores reflect what is important to patients and comprehensive with respect to patient concerns relevant to the concept being assessed. Documentation of patient input in item generation as well as evaluation of patient understanding through cognitive interviewing can contribute to evidence of content validity.

Evidence of other types of validity (e.g., ***construct validity***) or reliability (e.g., consistent scores) will not overcome problems with content validity because we evaluate instrument adequacy to measure the concept represented by the labeling claim. It is important to establish content validity before other measurement properties are evaluated. When evaluating the utility of an existing instrument or developing a new PRO instrument, sponsors are encouraged to support the adequacy of the instrument's content validity by documenting the following development processes and instrument attributes.

Data Collection Method and Instrument Administration Mode

Sponsors should consider the data collection method and all procedures and protocols associated with the instrument administration mode, including instructions to interviewers, instructions for self-administration, or instructions for supervising self-administration. We will review data quality control procedures specific to the data collection method or instrument administration mode along with case

report forms or screen shots of electronic PRO instruments. Administration modes can include self-administration, interview, or a combination of both. Data collection methods can include paper-based, computer-assisted, and telephone-based assessments. We intend to review the comparability of data obtained when using multiple data collection methods or administration modes within a single clinical trial to determine whether the treatment effect varies by method or mode. If a patient diary or some other form of unsupervised data entry is used, we plan to review the clinical trial protocol to determine what steps are taken to ensure that patients make entries according to the clinical trial design and not, for example, just before a clinic visit when their reports will be collected.

Recall Period

Sponsors should also evaluate the rationale and the appropriateness of the recall period for a PRO instrument. To this end, it is important to consider patient ability to validly recall the information requested. The choice of recall period that is most suitable depends on the instrument's purpose and intended use; the variability, duration, frequency, and intensity of the concept measured; the disease or condition's characteristics; and the tested treatment.

Response Options

It is also important to consider whether the response options for each item are consistent with its purpose and intended use. Table 2 describes some of the various types of item response options that are typically seen in PRO instruments.

Table 2[7]. Response Option Types

Type	Description
Visual analog scale (VAS)	A line of fixed length (usually 100 mm) with words that anchor the scale at the extreme ends and no words describing intermediate positions. Patients are instructed to indicate the place on the line corresponding to their perceived state. The mark's position is measured as the score.
Anchored or categorized VAS	A VAS that has the addition of one or more intermediate marks positioned along the line with reference terms assigned to each mark to help patients identify the locations between the scale's ends (e.g., half-way).
Likert scale	An ordered set of discrete terms or statements from which patients are asked to choose the response that best describes their state or experience.
Rating scale	A set of numerical categories from which patients are asked to choose the category that best describes their state or experience. The ends of rating scales are anchored with words but the categories are numbered rather than labeled with words.
Recording of events as they occur	Specific events are recorded as they occur using an event log that can be included in a patient diary or other reporting system (e.g., interactive voice response system).

Pictorial scale	A set of pictures applied to any of the other response option types. Pictorial scales are often used in pediatric questionnaires but also have been used for patients with cognitive impairments and for patients who are otherwise unable to speak or write.
Checklist	Checklists provide a simple choice between a limited set of options, such as *Yes*, *No*, and *Don't know*. Some checklists ask patients to place a mark in a space if the statement in the item is true. Checklists are reviewed for completeness and non-redundancy.

Instrument Format, Instructions, and Training

Results obtained using a PRO instrument can vary according to the instructions given to patients or the training given to the interviewer or persons supervising PRO data collection during a clinical trial. Sponsors should consider all PRO instrument instructions and procedures contained in publications and user manuals provided by developers, including procedures for reviewing completed questionnaires and procedures used to avoid missing data or clarify responses.

We recommend that the user manual provided by a developer during the PRO instrument development process specify how to incorporate the instrument into a clinical trial in a way that minimizes administrator burden, patient burden, missing data, and poor data quality.

Patient Understanding

The PRO instrument should be tested via a pilot study which should include patient cognitive interviews, readability tests, usability tests and the cognitive interviews analysis. Evidence from the patient cognitive interview studies can be used to determine when a concept is adequately captured.

Scoring of Items and Domains

For each item, numerical scores generally should be assigned to each answer category based on the most appropriate scale of measurement for the item (e.g., nominal, ordinal, interval, or ratio scales).
Equally weighted scores for each item are appropriate when the responses to the items are independent. If two items are dependent, their collected information is less than two independent items and they are over-weighted when they are treated as two equally weighted items.

Respondent and Administrator Burden

Undue physical, emotional, or cognitive strain on patients generally decreases the quality and completeness of PRO data. Factors that can contribute to respondent burden include the following:

- Length of questionnaire or interview
- Formatting
- Font size too small to read easily
- New instructions for each item

- Requirement that patients consult records to complete responses
- Privacy of the setting in which the PRO is completed (e.g., not providing a private space for patients to complete questionnaires containing sensitive information about their sexual performance or substance abuse history)
- Inadequate time to complete questionnaires or interviews
- Literacy level too high for population
- Questions that patients are unwilling to answer
- Perception by patients that the interviewer wants or expects a particular response
- Need for physical help in responding (e.g., turning pages, holding a pen, assistance with a telephone or computer keyboard)

E. Reliability, Other Validity, and Ability to Detect Change [7]

Once the instrument's content validity has been established, we should consider the following additional measurement properties: reliability, construct validity, and ability to detect change.
We should review the measurement properties that are specific to the documented PRO instrument's conceptual framework, confirmed scoring algorithm, administration procedures, and questionnaire format in light of the clinical trial's objectives, design, enrolled population, and statistical analysis plan (SAP).

Reliability

The adequacy of a PRO instrument for use in a clinical trial depends on its reliability or ability to yield consistent, reproducible estimates of true treatment effect. Test-retest is most informative when the time interval chosen between the test and retest is long enough in stable patients to minimize memory effects. Test-retest reliability can be tested over a variety of periods to satisfy different study protocols or even in different intervals between visits in the same protocol.
Internal consistency reliability tests (e.g., Cronbach's alpha) to determine agreement among responses to different questions, in the absence of test-retest reliability, may not constitute sufficient evidence of reliability for clinical trial purposes. However, as is true for other imperfections in testing, in general, flaws in reliability tend to increase the beta (Type II) error, and instruments demonstrating poor reliability are unlikely to give a false positive result.

Other Validity

In addition to content validity we should evaluate evidence of construct validity, and if appropriate, ***criterion validity***.
Construct validity is determined by evidence that relationships among items, domains, and concepts conform to *a priori* hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.

Criterion validity is the extent to which the scores of a PRO instrument are related to a known *gold standard* measure of the same concept. However, for most PROs, criterion validity testing is not possible because the nature of the concept to be measured does not allow for a criterion measure to exist. This is true for any symptom measure where the symptom is known only to the patient. If a criterion measure is used, sponsors should provide rationale and support for that criterion.

Ability to Detect Change

Review of an instrument's ability to detect change using data that compare change in PRO scores to change in other similar measures that indicate that the patient's state has changed with respect to the concept of interest should be carried out. A review of the ability to detect change includes evidence that the instrument is equally sensitive to gains and losses in the measurement concept and to change at all points within the entire range expected for the clinical trial population.

F. Instrument Modification [7]

The adequacy of an instrument's development and testing is specific to its intended application in terms of population, condition, and other aspects of the measurement context for which the instrument was developed. When a PRO instrument is modified, sponsors generally should provide evidence to confirm the new instrument's adequacy. That is **not** to say that every small change in application or format necessitates extensive studies to document the final version's measurement properties.
Examples of changes that can alter the way that patients respond to the same set of questions include:

- Changing an instrument from paper to electronic format
- Changing the timing of or procedures for PRO instrument administration within the clinic visit
- Changing the application to a different setting, population, or condition
- Changing the order of items, item wording, response options, or recall period or deleting portions of a questionnaire
- Changing the instructions or the placement of instructions within the PRO instrument

G. PRO Instruments Intended for Specific Populations [7]

As previously mentioned, if multiple versions of an instrument will be used in a clinical trial, documentation should exist that the content validity and other measurement properties of those versions are similar to each other. Measurement of PRO concepts in children and adolescents, in patients who have cognitive impairment or are unable to communicate because of serious illness, and across culture or language groups introduces challenges in addition to those already mentioned. These challenges are discussed below.

Children and Adolescents

In general, the review issues related to the development process for pediatric PRO instruments are similar to the issues detailed for adults. Additional review issues for PRO instruments applied in

children and adolescents include age-related vocabulary, language comprehension, comprehension of the health concept measured, and duration of recall. Instrument development within fairly narrow age groupings is important to account for developmental differences and to determine the lower age limit at which children can understand the questions and provide reliable and valid responses that can be compared across age categories.

Patients Cognitively Impaired or Unable to Communicate

We discourage proxy-reported outcome measures for this population. For patients who cannot respond for themselves (e.g., cognitively impaired), we encourage observer reports that include only those events or behaviors that can be observed.

Culture or Language Subgroups

As many development programs are multinational, application of PRO instruments to multiple cultures or languages is common in clinical trials. Regardless of whether the instrument was developed concurrently in multiple cultures or languages or whether a fully developed instrument was adapted or translated to new cultures or languages, we recommend that sponsors provide evidence that the content validity and other measurement properties are adequately similar between all versions used in the clinical trial.

References

1. Jefford M, Stockler MR, Tattersall MHN. Outcomes research: what is it and why does it matter? Intern Med J. 2003;33:110–118.
2. WHO Country Cooperation Strategy (CCS) 2013. Available from: http://www.who.int/countryfocus/cooperation_strategy/ccs_nga_en.pdf
3. Liu GG, Eggleston K, Hu T. Emerging health economics and outcomes research in the Asia-Pacific region. Value Health. 2008;11:S1–S2.
4. Garman L. The Dual Burden of Disease in India, What's Going on at GRAVIS. 2013. available from: https://gravisindia.wordpress.com/2013/04/15/the-dual-burden-of-disease-in-india/
5. Shah J, Pawaskar A, Kumar S, Kshirsagar N. Outcome's research resources in India: current status, need and way forward. SpringerPlus 2013 2:518
6. Uday Venkat M, Anantha Naik N. Tools for Outcome Research. The Pharma Review 2011; November – December. 189-192.
7. U.S Department of Health and Human Services Food and Drug Administration Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. U.S. FDA, Clinical/Medical. 2009 available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
8. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspectives in Clinical Research. 2011;2(4):137-144. doi:10.4103/2229-3485.86879.
9. Kozma CM, Reeder CE, Schulz RM. Economic, clinical, and humanistic outcomes: a planning model for pharmacoeconomic research. ClinTher. 1993;15:1121–32. discussion 1120.
10. Acquadro C, Berzon R, Dubois D, Leidy NK, Marquis P, Revicki D, et al. Incorporating the Patient's Perspective into Drug Development and Communication: An Ad Hoc Task Force Report of the Patient-Reported Outcomes (PRO) Harmonization Group Meeting at the Food and Drug Administration, February 16, 2001. Value Health 2003; 6:522-31

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