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REVIEW ON PHARMACOECONOMIC MODELLING METHODS IN INDIAN HEALTHCARE

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ABSTRACT

Introduction: Pharmacoeconomic modelling is an advanced method to study the effective medical therapies. This article includes the presentation and outline of various models of pharmacoeconomic modelling like decision tree, how to develop a decision tree with a diagrammatic representation, ICER, markov model, cohort simulation, half cycle, discounting, how to develop markov model in excel, sensitivity analysis and microsimulation. ***Methods:*** We searched for all the literatures on various pharmacoeconomic models from the international database PubMed. We selected the articles that explained about various models and way to compute them. We had reviewed on the types of pharmacoeconomic models, how to develop/compute various models with their pros and cons also, the software packages available for free and subscription to compute these models. ***Results:*** Decision tree contains a structure that represents all the possible clinical pathways. A markov model is used to model chronic diseases and even relapse of the disease can be modelled. Markov model without a decision tree models only for the survival (terminal node). PSA measures the impact of combined uncertainty on the model outcomes. Microsimulation is used to model the cost effective analysis. ***Discussion:*** Pharmacoeconomic modelling plays an important role because the clinical trials are done only for a short period of time because it is a way too expensive, hence a pharmacoeconomic model is developed and the patients included in the study are followed until the end point say even death. But still these modelling methods are preferred for their accuracy, reliability and moreover they're inexpensive. ***Conclusion:*** Pharmacoeconomic models provide great evidence for the cost and effectiveness of an intervention along with their risks and benefits.

KEYWORDS: Decision tree, Markov model, Markov in excel, ICER, Discounting, Cohort simulation, Probability sensitivity analysis, Microsimulation in R, Free software to compute models.

INTRODUCTION

Pharmacoeconomic study is basically a comparison of one drug therapy value with the other. Pharmacoeconomic modelling is an advanced method to study the effective medical therapies as it is a logical and practical combination of evidence based clinical outcomes, quality of life or utility data, management strategies, epidemiological data and costs and benefits. When a new drug is discovered for any particular disease prior entering the market the drug is tested for its safety in the name of *clinical trials.* If the drug passes all the phases of clinical trials it is released in the market for sale. Here pharmacoeconomic modelling plays an important role because the clinical trials are done only for a short period of time because it is a way too expensive, hence a pharmacoeconomic model is developed and the patients included in the study are followed until the end point say even death. The main demerit of the pharmacoeconomic model is that the whole process can be open to bias.[15] But still these modelling methods are preferred for their accuracy, reliability and moreover they are inexpensive. Some of the common pharmacoeconomic modelling methods are as shown in fig (a). All the pharmacoeconomic models are performed basically by developing a decision tree.[16] This decision tree will include all the possible events (like co-morbidities, common adverse reactions and events, etc.) that the disease diagnosed in the particular patient that can lead to.

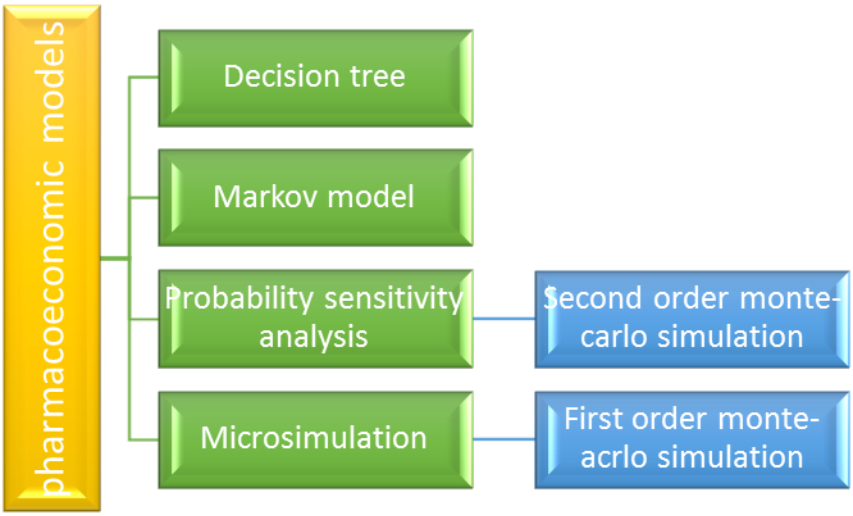


Fig: (a) Schematic representation of the various pharmacoeconomic models with their subtypes.

Decision Tree

It is a great tool for cost effectiveness analysis[28] because it is been made to show the potential actions of options and the consequences of those options.[29] Decision trees structure the analysis and guide calculations. The difference in the clinical outcomes determines the CEA results. There are three main components of decision trees- action options which show the decisions being considered, possible consequences which describes the mix of outcomes and their possibilities and the value of health and cost outcomes for each set of consequences. Once you have these in a tree then we can calculate the expected value of each action options for heath and cost outcome and we can determine the cost-effective ratios to make better decisions about health spending.

How to Compute a Decision Tree

First move is to build a decision tree with all the chances and events with their respective results. There are three nodes in decision tree- decision node (represented by a square) which shows the action options i.e. it compares two options because CEA also examines the comparison and a chance node (represented by a circle) which shows the possible consequences of each options. It is better for the chance nodes to be dichotomous in order to facilitate sensitivity analysis. The terminal node is represented by a triangle. Here we have developed a decision tree for prevention of Tuberculosis (TB) for which a camp is conducted fig (b). Here the comparison is between camp and no camp (action options) and the possible consequences of these options here is TB +ve and TB –ve. Descriptions of a population-Here assume a young man has a risk of acquiring TB infection. Suppose we have 100 such man, so n=100.

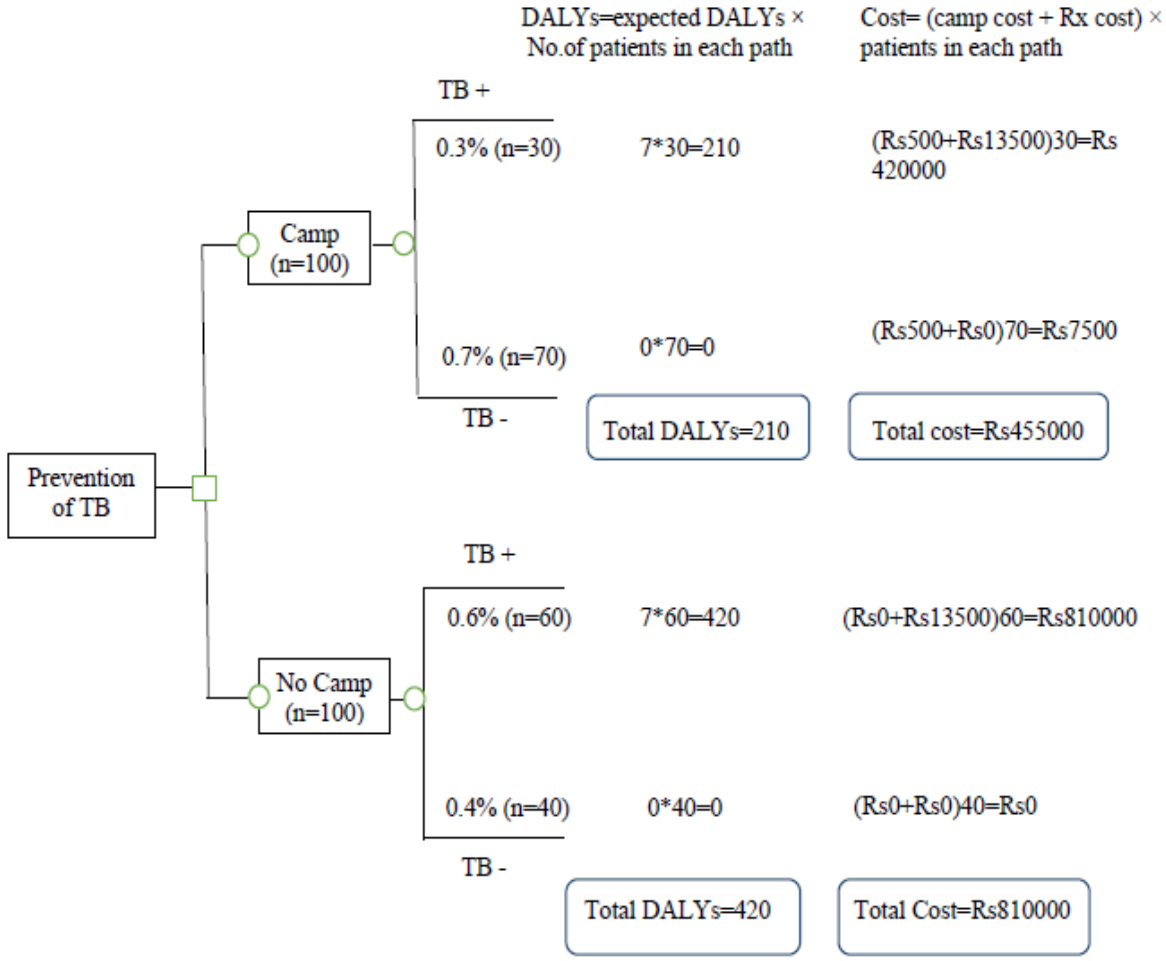


Fig. (b): Descisoin tree for the prevention of TB by conducting camp.

Secondly assign the probabilities (numbers always between 0-1) to all the chance nodes table (1). The probabilities are obtained from:

a) meta-analysis

b) trial data or observational studies.

Table 1: All possible probabilities.

Prevention of Tuberculosis	Probability of acquiring TB	Probability of not acquiring TB
With camp	0.3 (n=30)	0.7 (n=70)
Without camp	0.6 (n=60)	0.4 (n=40)

Suppose the Disability Adjusted Life Years (DALY) of TB is 7. So to calculate the expected DALYs We multiply the number of patients in each path with the DALY which is shown in table (2).

The *lower* the value of DALYs the greater the *acceptability*.

Table 2: Calculation of DALY.

Prevention of Tuberculosis	DALY	No.of patients in each path*DALY	Expected DALY
Camp with TB positive	7	7*30	210
Camp with TB negative		0*70	0
No camp with TB negative		0*40	0
No camp with TB positive		7*60	420

Calculating the cost is in a similar way- there are two types of cost i.e. program or intervention cost (cost for running the camp) and treatment cost. Suppose the cost for running the camp is Rs 500 and cost for treatment is Rs 13500. Now to calculate the cost for the path (Cost 1 + Cost 2) people table (3).

Table 3: Calculation of the total costs.

Prevention of Tuberculosis	Cost 1 + Cost 2	Total cost in rupees
Camp with TB positive	(Rs 500 + Rs 13500) *30	420000
Camp with TB negative	(Rs 500 + Rs 0) *70	35000
No camp with TB negative	(Rs 0 + 0) *40	0
No camp with TB positive	(Rs 0 + 13500) *60	810000
Thus, the camp saves Rs 355000		

Since the camp path has a lower DALYs and reduces the cost it is considered to be dominant i.e. it is better and cheaper. Suppose the camp didn't save money but decreased DALYs then we calculate the incremental cost effectiveness ratio.

$$\text{ICER} = \frac{\text{difference in total cost}}{\text{Difference in DALY}}$$

Where DALY is the disease adjusted life years.

ICER = 455000 – 810000 / 210 – 420 = Rs 1690.47. This ICER is multiplied with DALY of both camp and no camp individually (1690.4*210= 354984; 1690.4*420= 709968) and the lower value of DALY i.e. with camp is better than without camp for the prevention of TB and it will be the end result.

Limitations

Can add all possibilities (chance node) but will be inefficient.

Relapsed events are difficult to compute.

Need to asses all the possible events completely without any omissions accurately.[14]

Markov Model

Markov model is the easiest way for getting results for clinical problem with continuous risks. It is widely used for cost effectiveness studies. It usually involves three states termed as markov states as shown in the figure (c).

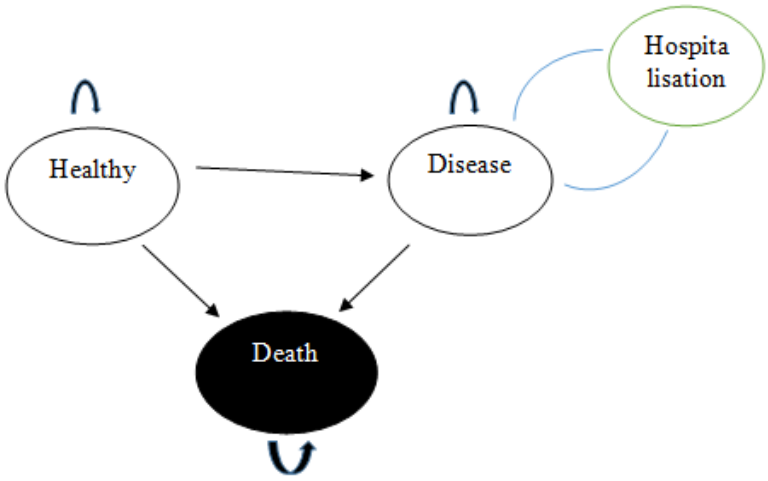


Fig. (c): A simple diagrammatic representation of all possible states in markov model.

All important events will be modeled as transitions from one state to another. Each state is allocated with a utility, this utility depends on the amount of time spent in each state for the total prognosis contribution. The time horizon of the examination is isolated into equivalent additions of time i.e. Markov cycles.[3] During each cycle transition might occur in the patients from one state to another. The Markov processes are commonly represented with state transition diagrams. For example in fig(c) circle represents state and the arrow represents transition. The arrows which lead from one state to another represent the presumed transitions, while the arrows which lead to the same state do not represent a transition i.e. the patient remains in the same state for the consequent cycles.[3] However only certain transitions are allowed such as the patient from healthy state can move to disease state, patient from disease state can move to hospitalisation state and from hospitalisation to disease state and from disease state to death state and patient from healthy state can also move to death state due to unrelated cause as any patient may die at any time due to various unrelated death causes. But it is not possible for the patient from disease state to move to healthy state. The arrow from the death state leads only to itself as it is obvious that there can be no transitions for the patient from death state to another hence the death state is termed as no transition or absorbing state.[19,20]

"The net probability of making transitions in a single cycle from one state to another is called the probability of transition." The transition risk data can be monthly, weekly, or annual. When you say annual then transitions like that depicted in table (4) can be possible.[10]

Table 4: All possible transition states in markov model.

Healthy-Disease	Annual probability of developing the disease for individuals in the state healthy
Disease- Dead	Annual probability of death for individuals in the state disease.
Healthy-Dead	Annual probability of death for individuals in the state healthy.
Hospitalisation	Annual probability of hospitalisation for individuals in the state disease.

The probability data are usually modelled with the increasing age as a 70-year-old patient has the higher risk of dying than a 60-year-old patient.

"A special type of markov process in which the transition probabilities remain constant over time" or the observable data statements are called the markov chain which is named after the Russian mathematician Andrei Andreyecich markov (1856-1922). It is boundless and only ends in the absorbing states. If it is an absorbent condition, its behaviour over time can be determined by simple matrix algebra as an accurate solution as discussed below. The dead state can be used to determine the steady death rates for execution of a markov chain.[5] In any case, the accessibility of specific programming to evaluate Markov forms and the more notable accuracy managed by age explicit death rates have resulted in a more prominent reliance on Markov forms with probabilities of time-variation. For a markov model of n states, the transition probability is n^2. When the probabilities of transition are constant with respect to time they can be represented as n × n matrix. The Probability of unallowed transitions will naturally be zero. This matrix is called as P matrix which forms the basis of fundamental markov process as explained in detail by Beck and pauker.[1] For ex, let's assume the table of p matrix table (5) for this simple model. The cycle length is picked to speak to a clinically significant time interim. For a model that traverses the whole life history of a patient and moderately uncommon occasions the cycle length can be one year. The length of the cycle is picked to speak to an interim period of clinically significant time. The interval length should be one year for a model that traverses a patient's entire life history and relatively rare occasions. If the whole life history of a patient and moderately uncommon occasions the cycle length can be one year.

Table 5: P Matrix.

		To			
		Healthy	**Disease**	**Death**	**Hospitalisation**
From	Healthy	0.7	0.3	0.3	0.6
	Disease	0	0.7	0.5	0.8
	Death	0	0	1	0
	Hospitalisation	0.2	0.5	0.3	1

If the disease has more complications or recurrent episodes then the cycle length will be longer and similarly vice versa for diseases associated with lesser complications.[9] For Example: renal or liver impairment diseases with multiple complications can have a longer cycle length and malaria (caused be P. malriae, P. falciparum and P. knowlesi) has lesser complications as does not have the chance of recurrence and curable when treated rationally and hence a shorter cycle length. The choice of the cycle length usually depends on the disease and its complications that is the probability data. Each state is assigned with an incremental utility. The time spent by the individual in each state is summed up to determine the survival period that is expected.

Expected survival or utility= $\sum_{s=1}^{n} ts$

Where t_s is the time spent in the state S. Incremental utility refers to the utility that contributes to the time spent in each of the cycles in that individual state. If the incremental utility of the healthy state is 0.5 then the time spent in that particular state is equal to 0.5 quality adjusted cycles to the expected utility.[6][17][18] The incremental utility for the complete markov process is determined by the formula given below. For each cycle spent in each of the state the patient is awarded with a utility value and that is equal to one markov cycle.

Expected utility = $\sum_{s=1}^{n}(t_s * u_s)$

Where t_s = no. of cycles spent in each state

u_s = incremental utility of that particular state

Quality adjusted life expectancy of the patient is determined to find the quality and quantity of life lived by the patient. Ex: on presuming that incremental utility of disease state was 0.5 and that of hospitalisation state 1 and if the patient spends an average of 3 cycles in disease state and 2.5 cycles in hospitalisation state then the utility would be (3*0.5) + (2.5*1) that equals to 4 quality adjusted cycle or quality adjusted life expectancy of the patient.

Cohort Simulation

It provides direct solution. It involves a group of individuals with identical characteristics modelled. Here we can assume that a group of individuals in the state healthy are diagnosed with the same disease. Cohort simulation reduces the no. of patients remaining at the end of each cycle in each state. The transition probabilities are assigned and in each of the states the patient distribution can be adjusted.[22] It is not necessary that the cycle should start from the healthy state it can also start from other states like dead for ex. In case of death after some surgery.

This simulation involves

i. No.of cycles initiating from zero
ii. In each of the states the number of cohort patients remaining at the end of each cycle.
iii. Cycle sum
iv. Incremental utility

Incremental utility is determined by the running summation. Cycle sum is calculated in the same way as the quality adjusted cycles are calculated and summed up, i.e.

$$\textbf{Cycle sum} = \sum_{s=1}^{n} (f_s * u_s)$$

Where, f_s = fraction of cohort in the state s[3].

n= number of states.

u_s = incremental utility of public s.

The Half Cycle

The half cycle is method used for the corrections of any omission in the markov modelling process.[25] In this each cycle is assumed to start from the average or half of the previous cycle and ends halfway in the succeeding cycle.[23,24] However it is not possible practically but still assumed for accuracy. This can be constructed as a histogram-line combo plot in which the line passes through the centre of each bar, where each bar represents each cycle.

DISCOUNTING

The cost of the treatment is generally taken as the baseline measure. Any discount in costs of the treatment (like insurance, etc.) given to the patient included in the cost effectiveness study should also be included if not immediately but as soon as possible.[4] The discount can be calculated using the below formulae:

N (discounted) = N (undiscounted) × [(1 (1+ d)] t.

Where N (discounted) is the discounted measure of cost or health of life.[4]

N (undiscounted) is the actual measure with no discount.[4]

t is the skipped time from the baseline.[4]

d is the rate of discount. (It usually varies but mostly is between 3-5%).

(OR)

$$U_t = \frac{U_0}{(1+d)^t}$$

Where U_t is the incremental utility at time t.

U_0 is the initial incremental utility.

d is the discount rate.

Simple steps on the basics of: How to develop markov model in excel ;

STEP 1: Construct a model of your own required disease with all the possible states. Or another way to graphically represent the model is by developing a decision tree as discussed above. Define all the possible transitions i.e. the transitions risk data (table.1).

STEP 2: Open a new excel sheet and enter all the input data or parameters i.e. cost data, quality of life data, transition risk data, and treatment effects. Cost data includes cost of treatment, administration, hospitalisation and productivity losses. Quality of life data includes utility data for all the states in the model also utility decrement for the transitional state hospitalisation, this decrement is subtracted from the utility of the state disease. Data on treatment effects ex: say the probability ratio for developing the disease modelled for the new drug compared to the old drug is 0.9 this means that whatever the risk is to develop the disease for individuals that are treated with the old drug the risk is 10% lower for individuals that are treated with new drug. So if the risk to develop the disease a certain year in simulation is 20% for an individual on the old drug the corresponding risk is only 18% with the new drug. With these decreases of transition risks the cohort being treated with new drug will develop the disease, get hospitalised and die to a lesser extent than those treated with old drug. The QUALY increases with the new drug.

STEP 3: Following the input parameter is the column of description as explained in table 1.

STEP 4: "Refer to" column which is to make any reader understand the parameter data.

STEP 5: Deterministic column to compare its value with the probability analysis.

STEP 6: Distribution column, defining distribution for each of the parameter.

STEP 7: Don't forget to include columns for the markov trace and discounted rate.

STEP 8: Enter the formulas for the transition matrix and functions to generate the data. ("=" sign should be used in respective cells to tell the excel that it should calculate that particular data and "{}" to be used to tell excel to calculate all the data mentioned within them like an array)

STEP 9: calculate the ICER and net benefit. For more detailed procedure for markov model in excel refer to building a markov cost effectiveness model in excel.[1]

Limitation

The *markovian assumption* is the main drawback of markov model. It does not include the relation of the past to the present state as the markov model assumes that the present state depends only on the future and not on the past. For e.g. for the patients in the well state they might have had some issue like jaundice in the past and now is well and similarly a patient with hepatitis is now in well state. Both does not have the same probability of developing liver cirrhosis hence two distinct states such as well with jaundice and well with hepatitis should be considered to enumerate the patient prognosis in the model. But the model forgets the past or how the patient arrived to this state and includes only the future.

Probability Sensitivity Analysis

Probability sensitivity analysis is a particular method used in developing the pharmacoeconomic models that allows the researcher to figure out the level of confidence in determining or estimating the output parameters with reference to the uncertainty in the model input and also called as *second order monte-carlo simulation*. It is different because it uses the distribution rather than a pre-determined set of values for sampling the various parameters.[7]

$$\text{ICER}[8] = \frac{\text{Cost of treatment A - cost of treatment B}}{\text{Benefit of treatment A - benefit of treatment B}}$$

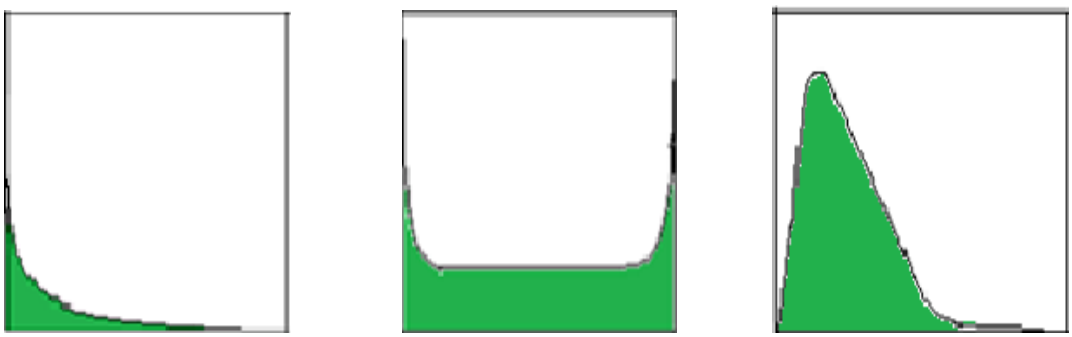
QUALY=Utility of the relevant state * No. of years lived in that year.

To be able to conduct the probability sensitivity analysis the distribution of each of the parameters should be defined. The mathematical or the computational procedure of the previous result is repeated for each of the new value randomly selected from the parameter from the distribution. The model is then recalculated by using new set of values sampled from the distribution ('single simulation vector') this is repeated many times (1000-10,000 times) automatically in the relevant software's available. And each time the model is recalculated a different set of expected

values are obtained as the output. The more often the similar or same results, the greater the accuracy of the model conclusions. Those model conclusions can also be considered as robust. Rather than changing each variable at a time as all the variables are changed simultaneously using a simulation it is called as "second order markov simulation".[21] The procedure to conduct PSA may be little complicated but simple to understand.

- Develop your relevant model or can use the example healthcare training models available in the software's.
- Define distribution for each of the variable to represent uncertainty

- Costs, utilities, life expectancies etc. are replaced with relevant probability distributions.
- Some of the common distributions usually used are shown in fig (d) i.e log normal, gamma[4], beta and etc.



GAMMA **BETA** **LOG NORMAL**

Fig: (d) Common distribution models for sensitivity analysis in Treeage.

- Randomly select or simulate numbers from any distribution (continuous).

- The software's that provide random number generators are SAS, Excel, R, and Stata.
- Calculate ICER.
- Repeat procedure 1000-10,000 times. (however it is not done manually but automated but the relevant software)
- Make the cost effectiveness plane and the acceptability curve for cost effectiveness.
- Perform the statistics i.e. the % of time ICER is below threshold.
- The scatter plot of the ICER will give the sense of overall uncertainty.

Microsimulation Model

Microsimulation model is a computerized model that is been developed by using basic details such as demographics, behaviour etc in-order to estimate the current effects and individual outcome, Micro means 'individual'.[26] Using microsimulation model we can not only predict

the prevalence of a disease by also evaluate the cost and cost effectiveness[27] of the diagnostic methods, therapy and the preventive approaches. Microsimulation models seeks to answer 'what-if' questions. Microsimulation model can be divided into two branches. Static and dynamic. Static model or Monte Carlo simulation models use probabilities in order to stimulate the individual decisions. Dynamic microsimulation models are difficult to develop and apply when compared to static models as it uses a wide range of demographic details as well as social-economic events in order to come to an outcome. In order to develop a model, the model must have a clearly stated objective. From these objectives the person can identify a process and develop a strategy for the model. In order to gauge the impact of a particular parameter on an outcome sensitivity analysis is essential. For more details on how to carry out microsimulation in R refer to Microsimulation Modelling for Health Decision Sciences Using R: A Tutorial.[2]

Limitation

The major disadvantage of this model is that it does not measure any uncertainty parameter that can be led from the disease and is called as *first order monte-carlo simulation.*

Software Packages Available for Pharmacoeconomic Modelling

Treeage is a widely used software initially assists with establishment of composite markov models, decision analysis and mote-carlo simulation too. *Excel* is widely used for decision analysis and markov models but monte-carlo simulation is not possible where as it can be made possible on installation of the macro @RISK.[4,11]

Softwares – For Free

R software is the recent widely used which allows for decision analysis, markov model and monte-carlo simulation. *Cran package- 'heemod'* is also one of the R packages. CRAN is the comprehensive R archive network.[12,13] Now there are more than 10,000 R packages available for download. Also, *popmod* can be used for cost effective analysis. A lot of cost-effective models are done in excel if you don't have excel then can go for free spreadsheet package e.g. from *openoffice*.

CONCLUSION

Pharmacoeconomic models provide great evidence for the cost and effectiveness of an intervention along with their risks and benefits. Decision trees contains a structure that represents all the possible clinical pathways. A markov model is used to model chronic

diseases and even relapse of the disease can be modelled. *Decision tree-markov model* is a combination of decision tree with markov model to model all the possible events within the markov process. Markov model without a decision tree models only for the survival (terminal node). PSA measures the impact of combined uncertainty on the model outcomes. Microsimulation is used to model the cost effectiveness analysis. A physician requires betterment of the patient and the patient requires cheap to moderate treatment. Although all these models have their own pros and cons, they are effectively used to model the cost effectiveness of the treatment thereby satisfying both the needs of the patient and the physician.

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