Original Research Article

Estimation of net benefits of a therapy: A multi-regression mathematical model

Abstract:

Introduction:

Effectiveness, adverse drug reaction, tolerability and quality of life are few parameters by which a therapy is evaluated. No method exists to measure net benefit or loss of any therapeutic option from patient or health professionals' point of view. This paper aims to measure net benefit of a single therapy or compare relative benefits of different therapeutic options.

Objectives:

To develop a mathematical equation to measure net benefit of a treatment option.

Methods:

Focus group studies conducted to identify list of variables that can measure benefits of any treatment process. Large scale sample survey conducted to develop a mathematical equation and validate it.

Results:

Cost, degree of cure, time required to cure, ease of accessibility, adverse effect, ease to use, tolerability, cure rate, improvement in quality of life, degree of pain during application are the factors that determines the net benefits of a treatment option.

Conclusions:

Degree of cure, cost of treatment and time required to cure are the most important factors towards evaluation of net benefit due to a treatment.

Key Words: Net Benefit, Regression Model, Parameters Important to patients

Highlights:

Efficacy/effectiveness, adverse events, tolerability and quality of life is measured as outcome of a treatment process.

The paper listed out parameters important to patients, their relative importances and constructed an equation which can measure net benefit of any treatment process.

Healthcare related decision makersmay prioritize the health care options estimating the net benefits using this model.

Introduction:

Efficacy and effectiveness-the ability to produce a desired outcome-are often used to measure the benefits of a medicine or any therapy. Treatment efficacy refers to intervention strength in producing an expected positive effect [1,2]. Effectiveness is measured from the patient's perspective and used in real-world conditions [3].

An adverse drug reaction (ADR) or adverse effect can be defined as 'an appreciably harmful or unpleasant reaction resulting from an intervention related to the use of a medicinal product [4]. Drug tolerability refers to the degree to which drugs' overt adverse effects can be tolerated by patients. The tolerability profile is of comparative importance to its efficacy and safety [5].

Traditionally, biomedical outcomes, not quality of life outcomes, have been the principal endpoints in medical and health research. Quality of life captures well-being at a specific point in time. However, its importance has increased [6].

Mathematical model was used in medical field and effect of treatment. It was used to find the effect of treatment on human physical activity, deciding treatment strategies, estimation of treatment cost, and influence of pandemic on dynamics social process [7,8,9,10].

Many studies have been carried out using the above-mentioned criteria to determine the different aspects and impacts of any therapy on human life. However, no comprehensive method is available to measure the net benefit of any treatment. The positive value of net benefit indicates the treatment is beneficial, negative value indicates the treatment is disadvantageous, and zero value indicates the treatment is neither beneficial nor disadvantageous. The development of such a model can evaluate the impact of any therapy or treatment option and compare it among the alternate treatment options.

Objectives:

The objective of this study is to develop a mathematical equation consisting of measurable variables that can calculate the net benefits or disadvantages (negative value for net benefit) of any treatment or therapeutic option. It will be able to compare the relative benefits of two or more treatment options.

Materials & Methods:

The research work on multivariable regression model to measure the benefits of a treatment or therapy, was carried out in two stages. In first stage qualitative study design and in second stage cross sectional study design was used.

The first step was the identification of variables through focus group studies and construction of a fishbone diagram indicating factors contributing to the to the net benefit of any treatment process, and the second step, the development of the multivariable regression model in the form of a mathematical equation, the determination of coefficients, and the validation of the developed model through a sample survey [11, 12]. During the first stage, six focus group studies were conducted in three different regions of India to generate a complete list of variables and prepare a model. Three focus group members consisted of 10 medical practitioners in each group. Another three-focus group consisted of 20 patients who were taking treatments. 10 medical practitioners for each focus group were chosen by convenient sampling from a tertiary health care facility. The group consisted of 1 each of a general practitioner (MBBS), medicine specialist, surgeon, pediatrician, dermatologist, family medicine, gynecology, orthopedics, eye, and ENT specialists. 20 patients for each focus group were chosen conveniently from a tertiary health care facility, taking 2 patients from each of the specialties from which doctors were chosen. To generate a list of variables, all the members were asked to provide the factors important to patients. Round-robin brainstorming methods are used in focus group studies. Each member is sequentially asked to provide the variables important to patients. The total identified factors were listed, factors/variables measuring the same attributes clubbed, and a final list of attributes/variables prepared. A multi-regression model is constructed using a final list of variables. The coefficients of variables were as per their relative importance [11, 12]. The coefficients were determined by a sample survey. Sample size (n) is determined by the equation $n = Z^2 * p * (1 - p) / d^2$. However, at least 30 samples need to be taken [13, 14]. The confidence level for the study was 95%, and the expected proportion of the population was 0.1 (10%). and the desired precision was 0.05. The value of Z at a 95% level of confidence is 1.96. Hence, the sample size is calculated at 138. In the second stage, 200 samples, each at three different locations (600 samples), were taken randomly from patients coming to outpatient departments of health care facilities. The samples were chosen by using a computer-generated random number table. The patient coming to the outpatient department was selected if his/her sequence is as per the generated random number. Data collected using a valid and reliable questionnaire and a 95% confidence level was taken for statistical analysis. The T-value and p-value are used to confirm the validity of the model and individual variables. The Variance Inflation Factor or interdependency of different variables was tested cross validation. Partial Least Square (PLS) was used for cross validation. The value of correlation coefficients less than 0.4 indicates poor, between 0.4 and 0.9 indicates moderate and greater than 0.9 indicates strong correlation between two variables.

Inclusion criteria: Patients given consent to participate in the survey, age >12 years.

Exclusion criteria: Patients taking any psychiatric medicine that looks mentally disturbing during the sample selection process.

Development of Model:

The final list of variables influencing benefit of treatment process is as follows:

Cost, degree of cure (extent a therapy can cure), time required to cure, ease of accessibility, adverse effect (adverse reaction), ease of use, tolerability, cure rate (% of patients got cured), improvement in quality of life, degree of pain during application. The fishbone diagram prepared from the focus group study is given in Figure 1.

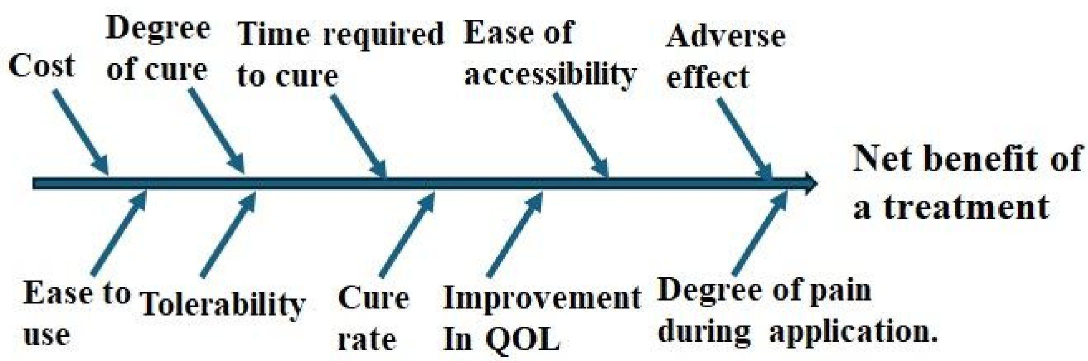

Figure 1: Fishbone diagram indicating factors contributing to net benefit of a treatment

The mathematical equation developed from the physical model is given below:

Net benefit of a treatment = C1 * Cost + C2 * degree of cure (% the therapy can cure) + C3 * time required to cure + C4 * ease of accessibility + C5 * adverse effect + C6 * ease to use + C7 * tolerability + C8 * cure rate + C9 * improvement in quality of life +C10 * degree of pain during application……………………….(1) where C1, C2, C3 etc are the coefficients which determines the relative importance of each variables.

Measurement of variables:

There are two types of variables used to measure net benefit of any treatment option: directly measurable variables and not directly measurable. Variables not directly measurable are adverse effects, tolerability and quality of life. Common Toxicity Criteria for Adverse Events (CTCAE) developed by National Cancer Institute, USA, is the standard tool to measure adverse effects. Tolerability is measured by asking patients willingness to continue the treatment based on the factors mentioned in CTCAE. The tool, WHOQOL developed by World Health Organization, measures Quality of life. As the tools to measure variables which are not directly measurable are already validated, their testing for validity is not required. Directly measurable variables are measured by asking to rate the parameters in a 0-10 scale (0 for minimum and 10 for maximum). The score can be obtained for indirectly measurable variables using above mentioned tools. Asked respondents to score in 0-10 scale against each question mentioned in those tools.

Ethical Considerations:

The personal information of participants has not been revealed. The personal information has been codified and response was recorded against these code. The code for each respondent was generated by taking the first letter of their first name; followed by first letter of their surname; age: 1 for less than 18 years, 2 for 18-40 years, 3 for 40-60 years and 4 for more than 60 years; gender: 1 for male and 2 for female; occupation: 1 for student, 2 for employed and 3 for unemployed; settlement: 1 for rural and 2 for urban; education: 1 for illiterate and 2 for below graduation and 3 for graduation and higher; income: 1 below poverty level, 2 above poverty level. The data entered in data entry sheet against these codes which is analyzed to ensure confidentiality.

Data Collection:

The research participants were asked to rate the importance of each directly measurable variables in 0 to 10 scales. Rating of importance of each construct which measure our indirectly measurable variable were also taken from participants. The importance score obtained for indirectly measurable variables are converted into 0-10 scale to maintain uniformity. The sum of score obtained for not directly measurable variable multiplied by 10 and divided by total maximum score gives the importance of the variable in 0-10 scale.

Data Analysis:

Data against is respondent is coded and the importance provided by them against each of the 10 variables (S1, S2, S3……S10) in 0-10 scale is entered in data entry form. Relative importance of each variable or the coefficients of the variables in regression equation (Ci) provided by each respondent is recoded in Data Analysis Form. Ci = Si / Sum (Si) where i = 1,2,3….10. The value of Ci is normalized to unity as their sum will be for each of the respondent. It gives the relative importance of each variable, higher the value, higher will be the importance. Average value of each Ci is the average importance of ith variable provided by all respondents. Its standard deviation gives the dispersion of each importance provided by all respondents. The respondents code and relative importance provided by them against each variable is tabulated in a data analysis form. From the data table average of weights or importance of each variable, standard deviations for each variable can be statistically calculated. From those values t-value can be calculated and from statistical table p value may be obtained. Here the average weights, standard deviations, t-values and p-values calculated from the Data Analysis Form using statistical software SPSS.

Validation of Model:

The mathematical model has been validated, and the coefficients were determined by a sample survey in the second stage of the study. The t-value > 2.262, the critical t-value for 9 degrees of freedom (10 variables), and the value of $p < 0.05$ (95% level of confidence) indicate that the corresponding coefficients are valid.

Results:

Coefficients or relative importance of variables in the equation and their validity obtained from the survey score as per the procedure mentioned in data analysis is given in Table *1*. The validated multivariable model using weights mentioned in table *1* is written as follows:

Table 1: Validation of coefficients of mathematical equation

Variables/Constructs	Weight	Std Dev	t-value	p-value
Cost of therapy	(-)0.25	0.009	556	<0.0005
Degree of cure	0.31	0.013	477	<0.0005
Time required to cure	(-)0.18	0.011	327	<0.0005
Ease of accessibility	0.01	0.0009	222	<0.0005
Adverse effect	(-)0.03	0.0012	500	<0.0005

Ease to use	0.02	0.0021	190	<0.0005
Tolerability	0.05	0.0038	263	<0.0005
Cure rate	0.09	0.0043	419	<0.0005
Improvement in quality of life	0.01	0.001	200	<0.0005
Degree of pain during application	(-)0.05	0.0017	588	<0.0005

Net benefit of a treatment = 0.31 * degree of cure (% the therapy can cure) + 0.01 * ease of accessibility + 0.02 * ease to use + 0.05 * tolerability + 0.09 * cure rate + 0.01 * improvement in quality of life - 0.25 * cost of therapy - 0.18 * time required to cure - 0.05 * degree of pain during application - 0.03* adverse effect ………….(2)

The results of cross validation determined by mutual correlation coefficients of variables is given in Table 2

Table 2: Cross Validation of Model Consisting of Coefficient of Correlation among Variable

Variables	Cost	Degree of cure	Time required to cure	Ease of accessibility	Adverse effect	Ease to use	Tolerability	Cure Rate	Improvement in quality of life	Degree of pain during application
Cost	1	0.19	0.15	0.17	0.18	0.19	0.16	0.19	0.13	0.18
Degree of cure	0.19	1	0.16	0.19	0.18	0.11	0.14	0.16	0.18	0.17
Time required to cure	0.15	0.16	1	0.14	0.11	0.17	0.13	0.18	0.15	0.17
Ease of accessibility	0.17	0.19	0.14	1	0.18	0.17	0.69	0.19	0.16	0.14
Adverse effect	0.18	0.18	0.11	0.18	1	0.15	0.13	0.18	0.19	0.17
Ease to use	0.19	0.11	0.17	0.17	0.15	1	0.19	0.17	0.13	0.16
Tolerability	0.16	0.14	0.13	0.69	0.13	0.19	1	0.11	0.13	0.16
Cure Rate	0.19	0.16	0.18	0.19	0.18	0.17	0.11	1	0.15	0.17

Improvement in quality of life	0.13	0.18	0.15	0.16	0.19	0.13	0.13	0.15	1	0.14
Degree of pain during application	0.18	0.17	0.17	0.14	0.17	0.16	0.16	0.17	0.14	1

Discussions

The coefficients of the variables signifies their relative importance. Except Adverse effect and tolerability, the results of cross validation analysis indicates the variables are independent. Though Adverse effect and tolerability are interdependent both the variables were used in the model to maintain generalizability of the model. Adverse effects are important from medical practitioners, health policy makers and researchers point of view but tolerability is important from patients point of view. The positive value of net benefit obtained from the equation indicates that the therapy or treatment option is beneficial, and the negative value indicates that the same is detrimental. The higher the positive value, the higher the benefits.

The advantage of this model is that it can be applied for any treatment process or therapeutic procedure. The model will be valid in changing scenario as well because with change in value of a parameter, responded will score the variable as per that change.

The patients undergone a therapy or received a treatment for which net benefit is to be obtained, needs to be asked to provide their scores as per the procedure described in measuring variable section and putting the values in equation 2.

The value of the coefficients may vary depending on socioeconomic positions and perception of people of the country. However, it can be used in any country by collecting the importance of the variables during data collection to measure value of the variables.

Mathematical model is being used in different medical fields as mentioned in literature review. Similar model by similar methods were developed and is being widely used in technical fields. Current research also directed to reveal different aspects of treatment processes and relative benefits of different treatment process is compared with respect to a few parameters mainly limited to efficacy and adverse events. This model is capable to find the effective outcome of single treatment or compare different treatment options.

Conclusions

Different health policy makers prioritize their investment accordingly the needs and benefits of different treatment options. As there exists no method to know the net social outcome of single treatment process, they compare the effectiveness of treatment options with respect to only limited number of parameters in the current context of research. The model developed here is general and can be used widely in any place and in any treatment process. As the model is a general one, may be used by health policy makers to prioritize their investments, medical professionals or administrators to know the net outcome of each treatment service provided by them and researchers to compare different treatment options or outcome of a single treatment option. There may be little changes in the relative importance of the parameters depending on socioeconomic and cultural behavior of different countries, the model can be used to analyze outcome of any treatment option in any country by collecting data along with importance of each factor as developed in this article. Degree of cure, cost of treatment and time required to cure are the most important factors for people of India towards evaluation of net benefit due to a treatment.

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