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Clinical Endpoint: Substitute for Prediction of Clinical Benefit

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ABSTRACT

An endpoint is a primary or secondary outcome used to judge the effectiveness of a treatment; it is a precisely defined variable intended to reflect an outcome of interest that is statistically analyzed. An endpoint usually specifies the sort of assessments made, the timing of those assessments, the assessment tools used and possibly other details, as applicable, such as how multiple assessments within an individual are to be combined. There are different types of endpoints used in clinical trials like primary endpoint, secondary endpoint, multiple endpoint and surrogate endpoint. Primary endpoint means the outcome or event that most accurately measures the benefit of the therapy or drug being studied and this is the most clinically important endpoint. Secondary endpoints are related to toxicity and undesired effects of the new therapy to demonstrate additional effects on the disease or condition. Multiple endpoints are useful in determining clinical advantage of drug depending on one illness side. A surrogate endpoint is a laboratory measure or a physical sign supposed to be used as a substitute for a clinically meaningful endpoint which in all fairness possible to predict clinical benefit.

Keywords: Clinical Endpoint, Clinical Trial, Global Assessment Variables

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INTRODUCTION:

A clinical endpoint is associate degree experiment performed by a health care organisation or skilled to judge the results of treatment against an impact in a very clinical setting. It is a prospective study to spot outcome measures that are influenced by the intervention. A clinical path is intended to keep up health, stop unwellness, or treat pathologic subjects. The safety, efficiency, pharmacologic, pharmacokinetic, quality of life, health economy, biochemical effects are measured in clinical trials.

There are two different types of clinical trials, confirmatory and exploratory trails. In confirmatory trail, the selection of hypothesis is information dependent, although this study is also have clear objectives. These trails explore the doses of resultant studies and supply is also have clear objectives. These trails explore the doses of resultant studies and supply a basis for substantiating study style. A confirmatory trail may be a well controlled study within which the hypothesis of interest is predefined and is meant to supply within which the hypothesis of interest is predefined and is meant to supply onerous proof in support of claims that have clinical edges. A confirmatory trail is a smaller amount at risk of bias and more robust. Atherosclerotic cardiovascular disorder is that the leading cause to death in ladies within the United States and in most of the developed countries. Confirmatory cardiovascular clinical trial would be a multicentre, double-blind, randomised, parallel study of 10,000 patients to check whether or not a replacement treatment compared with placebo reduces the incidence of the combined terminus of coronary death and nonfatal myocardial infraction in treatment of menoposal women in danger for coronary death.

CLINICAL TRAIL:

Objective:

Clinical trial consists of two types of objectives which are primary and secondary. Primary objective is the most crucial question to answer at the end of the trail that shows the efficiency of the study. The primary objective is directly related to hypothesis of interest in a confirmatory trail. Based on safety and efficacy of the

intervention, secondary objective deals with the other related or unrelated questions. As mentioned earlier the primary objective is compared with the effect of the treatment with placebo on secondary death and nonfatal myocardial infarction. There could be several secondary objectives like stroke, test the effect of treatment on myocardial revascularization, and long-term safety.[1]

Outcome measures:

The ultimate goal of the clinical trial is to assess the effect of treatment on the outcomes which may be direct or indirect measurement of a clinical effect in a single, adequate, well-controlled clinical trial. Generally only one primary outcome will be there for primary objects which are used to test the intervention whether it is superior or inferior when compared to a comparative agent. The outcomes should be selected prospectively.

Primary endpoint:

Primary endpoint is an outcome which is related to the selected primary objective of the study and the size of the trail is also based on that. The primary endpoint in our earlier example is combined endpoint of coronary death and nonfatal myocardial infarction.

Secondary endpoint:

The secondary endpoint is the result which may or may not relate to primary objective of the study, which is only related to secondary objectives but they support the primary variables of the study. The secondary variable can be a time to an event, incidence rate of an event or continuous variable related to efficacy or safety. The secondary endpoint in the previous example are stroke, test the effect of treatment on myocardial revascularization, long-term safety.

The primary and secondary endpoints can be clinical, surrogate, economic, global which are related to primary and secondary hypothesis. The design should be chosen adequately to reflect the objectives, appropriate primary, secondary, and global variables.

Clinical endpoint:

Clinical endpoint is a clear, appropriate outcome that can be objectively assessed without the judgement of the investigator. Nonfatal myocardial infarction is an example of an objective endpoint in contrast to a subjective endpoint, eg., relief of symptoms or severity of symptoms. The clinical endpoint is to be selected that can be reasonably and reliably assessed and can answer the primary objectives. Sometimes it is difficult to achieve both aims, so in such clinical judgement is required. Sometimes two different clinically meaningful endpoints can cross substantiate a claim for the effect of each outcome, so any definitions used to characterize the primary outcomes measure should be explained clearly.

Surrogate endpoint:

This is the endpoint that provides an indirect measurement of a clinical effect when measuring the outcome directly is not possible, as it require large sample size, long duration, and cost. Changes that are induced by the surrogate variables are expected to reflect changes in a clinical outcomes. For example surrogate variables might include biochemical markers of cardiovascular disease such as low density lipoprotein cholesterol, total cholesterol instead of myocardial infarction.[2]

Economic endpoint:

Several measurements regarding a subjects use of health care, cost of hospitilization, etc are considered as economic endpoints. The evaluation of subjects health has become more crucial in recent times. Subjective measures of health status are based on the quality of life scores of subjects performance, daily activity, mood etc. The overall score from these measurements can be analysed for treatment comparison.

Global Assessment Variables:

These variables measure the overall safety and efficacy of an intervention. These are generally based on rating scales. From these variables the idea of risk benefit profile of an intervention can be assessed, which helps the investigative physician to balance the safety and efficacy of the intervention and decide on treating subjects by weighing its risk and benefit outcomes.

Medical issues:

The outcome measures chosen to evaluate the efficacy or the primary objective depend on a number of factors, including;

- Knowledge of adverse effects of closely related drugs
- Information from non clinical or earlier clinical trails
- The types of subjects to be enrolled

Pharmacodynamic or pharmacokinetic properties of the treatment

The endpoint should be capable of unbiased assessment. To have unbiased assessment of the endpoints, studies should be blinded. The instrument used to assess the primary variable should be reliable and adequately sensitive to detect any real change in the subject. The responsible variable should be measured for all subjects. The assessments of the response should be selected as standard, widely used, and recognised.

Statistical Issues:

The sample size and power calculation for a study should be based on the primary endpoint. The endpoint could be impedance rate of an event or time to an event. Distribution of events or frequency of episodes can be occurred in this case as re-occurrence of the primary event can occur. The investigator has to follow subject for a subsequent primary variable or subsequent response variable though subject participation ends as the primary subject. The subject must be followed, because he or she is at risk for the primary variable, if a secondary variable occur first.[3]

If the subjects are lost to follow up, sometimes loss of statistical analysis for primary or secondary variables are based on the intent to treat principle of all randomised subjects, it is important to have complete information as the long term studies. Sometimes post hoc analysis based on a subject of randomised population are examined, for example the effect of an intervention for reducing the rate of occurrence of myocardial infraction in the diabetic population, in some whether the treatment is more effective in the diabetic subjects or, irrespective of the population, the treatment effect is same. To obtain odds difference in proportions,

and time to an event data, it can be analysed by using binary data.

Combined endpoints:

Large sample size or a long study needed to have adequately power to detect a treatment when primary outcome measure occurs very frequently. In this situation, combined endpoints are considered to enable the detection of treatment difference with smaller or shorter study duration. This combined endpoint has a meaningful clinical interpretation which combines more than one measurement related to practical object. Answering a question relating to the blind endpoint that only one event per subject should be counted, and also a hierarchy of each component shown be placed are improved. In addition, a combined endpoint could be considered in order to achieve more power to perform subgroup analyses.[4]

Multiple Endpoint:

Multiple endpoint are different clinical events that reflect a common mechanism of action because of the intervention. Sometimes it is important to have more than one primary variable when the investigator cannot state which of several variable addresses the primary objective of the study. Use of multiple endpoints will result in an increased probability of having false possible results. Nominal p value for each variable will be computed if more than one response variable is chosen.[5] Benferroni or similar adjustment methods can be used, if one of the multiple variables is of most importance and is most impacted by the intervention. Adjustment is not necessary if the intervention affects all the variables the same way, although the effects on the type 2 error and the sample size should be evaluated.[6]

Clinical vs Surrogate endpoints:

Clinical trials with a clinical endpoint are usually longer in duration, to determine an extended exposure of the treatment. These trails involve a large number of subjects as it drives the calculation of the sample size. The surrogate endpoint can replace the true clinical endpoint because it will often results in a shorter duration and the smaller sample size of the trail, as it is continuous nature of the data. The surrogate variables tend to change earlier in the study and the measurements can be taken at several time point, so the duration of the trail can be reduced.

While choosing the surrogate variables, there are certain important things to consider:

- Variables should be previously proven in literature to be highly correlated with the clinical endpoint.
- The selected variables should be accepted by the regulatory authorities and medical community.
- Selected variable should be reliably and accurately measured.
- Invasive procedures should be avoided because they may result in high discontinuation rates.

According to Prentice, a valid surrogate variable should be correlated with the clinical endpoint and should capture fully the treatments aggregate effect on the clinical endpoint.[7]

Statistical Consideration of Surrogate Endpoints:

Myocardial infarction is the clinical endpoint in a cardiovascular trail, LDL cholesterol is a surrogate endpoint. Comparison can be done by using change or percentage change, slopes throughout the interval and treatments based on repeated measures data are analysed at the beginning or end of the study.

Responder Variable:

When a continuous response variable is transformed to a binary or a categorical variable it can be interpreted as a responder variable. For example, the original continuous variable percentage change in LDL cholesterol can be modified to binary variables that takes two values: 1, of the percentage change in LDL is less than 0; 0, if the percentage change in LDL is greater than or equal to 0. The disadvantage in creating this responder variable is that not all the information is used in the analyses, which results in loss of power.[7]

CONCLUSION:

Clinical endpoints are regarded as a means to assess treatment in terms of feeling, functioning and survival of a patient. The endpoints reported should be clear relevant to the disease, condition, complaint or process of interest as well as the aim of treatment. Clinical endpoint should be reproducible and valid. The resultant endpoint will allow for comparisons across studies. A valid endpoint can evaluate what was intended to be evaluate. Reports of clinical endpoints should be interpreted in terms of reproducibility, validity, and statistical and clinical relevance. Endpoint evaluation by the patient, investigator or treating physician should ideally be done in a blinded fashion.

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