ELEMENTS OF CLINICAL STUDY DESIGN, BIOSTATISTICS & RESEARCH

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Bentham Books

Elements of Clinical Study Design, Biostatistics & Research

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Elements of Clinical Study Design, Biostatistics & Research

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ISBN (Online): 978-981-5123-79-1

ISBN (Print): 978-981-5123-80-7

ISBN (Paperback): 978-981-5123-81-4

First published in 2023.

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FOREWORD

It is indeed very heartening and equally gratifying that Dr. S. S. Patel, Former Dean of Jawaharlal Nehru Medical College, SawangiMeghe, Wardha, and presently the Chief Coordinator of DattaMeghe Institute of Medical Sciences (Deemed to be University), has ventured in bringing out a creative, magnificent creation in the form of this Book titled "Elements of Study Designs, Clinical Biostatistics and Clinical Research."

It is imperative and inevitable to note that the objectives of medical education are very clearly crystallized globally in the international Charter that has been worked out under the joint signatures of all the countries across the Globe, which mandate that the trained Graduate and also the specialist generated thereto should turn out to be a good clinician, an effective medical teacher, and a keen researcher. The trinity of objectives, when assessed in terms of manifestation, categorically brings out that the keen researcher part of it remains in limbo for wide and varied reasons.

It is in this very context one is required to take cognizance of a material reality that in spite of having the highest number of medical schools in India as compared to any other part of the world and thereby having the highest annual intake capacity for graduate and various broad specialties postgraduate courses whereby the highest quantum of trained, skilled health manpower is generated. Yet, the contribution of the said manpower in the domain of research output in the arena of medical sciences globally is minuscule in nature, bringing out the grossest possible mismatch.

This research output deficit is not accidental in nature. On the contrary, it is primarily because of the impoverished orientation of the learner in the domain of research principles, research methodology, and research ethics. The emphasis which is laid down at the various levels of learning on training and orientation in respect of research principles and methodology is non-existent in as much as it turns out to be an arena of least priority. Consequent to this prevailing situation, the learner as output is totally unequipped to dispense the research output expectations out of him in any manner whatsoever.

In addition, another problem that plagues the educational scenario in medical colleges in the country is the grossest paucity of reading material in the said arena, which could be availed for teaching, training, and learning purposes. The material that is availed as of now falls short with respect to the orientation of the learner emphatically in the domain of clinical research, especially in the context of clinical Biostatistics and the arena of clarity in regard to the elements with reference to study designs. More often than not, the said arena is deciphered on the required occasions through conjectural means and modes in the absence of the required clarity. Therefore, the assistance turns out to be inconsistent with the material requirement.

These vital lacunae that are operational in the system of medical education as of now need serious grappling at various levels in order to create an appropriate academic ambiance on the said count. However, the most important lacuna in regard to the paucity of the handy reading material on the said count is adequately and sumptuously dealt with by the elegant authorship that is brought out in this book.

The topics compiled in the book are vital and significant in 'general' as a whole, but the significant aspect is the emphasis that is worked out in the embodied chapters, significantly facilitatory in an analytical understanding of the requirements thereto. The topic of study designs in 'Medical research' brings out an easily decipherable depiction of understanding the

patterns of study design and the edifice of the nomenclature thereto, which is bound to go well with the learner in a huge way.

Likewise, the chapter on scales of measurements, descriptive statistics, and research data presentation brings out handy workable operational modes and modalities on the required count that is bound to give the learner enriched with clarity on the vital areas of research methodology, enabling him to grapple with the said issues on his own and emerge out successfully in the said venture.

The chapter on inferential statistics is brought out in an easy, handy, and free-flowing manner whereby the jargon depictions which otherwise baffle a learner on the said area are replaced by easily understandable modes and manners that bring out handy understanding in the learner capable of availing the same with responsibility and capacity to bring the desired outcome thereto.

The depiction of statistical methods for a relationship of variables which otherwise is tough to correlate with reference to the required ambit thereto is invoked in such a lucid manner that it is bound to equip the learner with the required capacity to work out the same on his own and thereby making him free and immune from his compulsory dependence on statisticians in a blind manner. On this count, the chapter turns out to be a beacon's light in the existing otherwise dominating darkness in the said arena of indulgence and the resultant operations thereof. The soul of inclusions in this notable book is the chapter on 'Clinical Research', which has brought out the expertise of the author in emphatic and self-speaking turns in a vociferous manner. He has poured the life long experience of his into this chapter to make any and every reader decipher the scope, meaning, and ambit of what is designated as 'Clinical research' including the manifestations that are expected out of it for the purposes of its translational accomplishments in larger societal interests. This opens genuine and wide vistas of focused understanding in the otherwise non-decipherable domain of clinical research.

It is said 'what is ethically wrong cannot be legally just and political right,' hence the paramount need for incorporation of ethicality in research in modes, manners, operations, and outcomes. The governing ethical principles of research emanating from the 'Helsinki Declaration' till the guidelines notified by the Indian Council of Medical Research and their operational utilization is the hallmark of the embodied chapter on Ethics in Clinical Research.

The vital aspect of research methodology and its resultant outcome in terms of publications and potentization also mandates that the research scholar has to be adequately equipped and armed with the much-needed armory of being an efficacious planner and writer of research projects seeking much-needed funding for the said purpose by the various statutory funding agencies including the non-governmental organizations that carter to the said cause. It categorically brings out that writing research projects is not 'an Art' but a definitive science mandating a required approach, commensurate structuring, needed inclusions, and depictions in regard to operations, outcome, expected translator component and the operational modes and manners thereto.

Speaking for the special feature of the book from beginning to end, the only expression at my disposal is that it is a 'treatise' on 'elements of study design, clinical biostatistics and clinical research' which is made easy, handy, free-flowing decipherable and usable by one and all independent of the status or the level of the user. As such, the creative writing that the author has invoked is bound to be of immense use to the user from the point of view of clarity of understanding, utility, and purpose fulfillment, but it is bound to fill in a huge void that remains unfilled all these years for wide and varied reasons. The impact it generates is unending and would turn out to be an illuminating source of light devouring the prevalent

darkness in its entirety in the true spirit of the Vedic hymn depicting 'Tamaso Ma Jyotirgamay.'

I would be failing in my duty if I did not wholeheartedly salute the diligent effort of the author whom I have known for over three decades and have always found inspiring as a mentor to all concerned. But the mentorship that is bound to be generated out of this creative manifestation of his in this book leads him to a state of 'immortality' which otherwise is the toughest and most difficult of the attainments in human life.

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PREFACE

The word statistics is derived from the Latin word **'Status',** meaning position or standing. As the skills of statistics were used by the tax assessor to assess the 'Position' or 'Standing' in society, *i.e.*, the assessment of the assets of an individual. Presently the term statistics is used for analyzing data and taking out inferences.

The theory of statistics was developed by mathematicians to predict something based on previous observations or information they proved through mathematical equations. Statistics are used even in our day-to-day activities by way of taking out averages, means, and ranges. In the field of sports, statistics are increasingly used for making predictions and in administrative decision-making. Cricket is one such example wherein statistical analysis provides strong support in team selection. Statistical formulae, if applied intelligently, can assist all types of decision-making.

For example: Calculating the number of beds required in the Intensive Care Unit of a hospital or the number of ambulances needed in the Casualty section of a hospital.

Health science researchers and clinicians who make clinical decisions based on available research inputs have got to have sound knowledge of what is known as Medical Biostatistics or Clinical Biostatistics. One of the most important uses of biostatics is in epidemiological studies. The term medical epidemiology refers to the study of health and diseases in the human population. Health professionals, especially clinicians and medical researchers, must know whether the published information is worth utilizing in decision-making. The editors of journals usually screen the research articles from the point of view of organization and analysis of the research material. Their focus is on the contents rather than methodology, including the suitability of applying the statistical tools. As such, expert statistical consultation should be sought during the planning of any research project with clarity of the research question to be answered. There is good documentation of problems with medical research articles.

Williamson *et al.* (1992) remarked that out of 4200 medical studies published in 30 Journals, which included the British Medical Journal, Journal of the American Medical Association, New England Journal of Medicine, Canadian Medical Association Journal, and Lancet, only about 20% articles met the assessor's criteria for validity.

Practitioners in medicine read the research articles to apply the results of research inpatient care for diagnostic and therapeutic purposes. The medical researchers review the research articles to find out the research gap and design a study to fill the research gap. A sound understanding of research methods and biostatics is indispensable for the interpretation of information about drugs, equipment, and diagnostic procedures, for evaluating study protocols and research articles and for participation in research projects. It is very important for a researcher, specifically in health sciences, to have skills to interpret to publish results and can make decisions on whether the statistical tests are used properly.

This title is intended to be used by researchers in health sciences, academicians, and clinicians to make them understand the basic concept of research and biostatistics so that they can make effective and efficient use in their respective fields of their indulgence.

The researcher is expected to know only which study design is best suited to answer his/her research question and which statistical test is appropriate to draw reliable inferences from the

research data. Although a good number of books are available on Biostatistics, most of them deal with core or classical parts of statistics and their application procedures in quite detail. The medical researcher finds it difficult to select the contents of his requirement suited for the application. In this work, details have been curtailed based on my experience as a learner, guide, and supervisor of research in Medicine, Dental Sciences, and the Indian System of Medicine. I hope this book will serve the intended purpose.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The author declares no conflict of interest, financial or otherwise.

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ACKNOWLEDGEMENTS

At the outset, I would like to acknowledge all my Post Graduate Scholars and Clinical Researchers who inspired me to undertake this challenging task.

I would like to thank **Prof.Ved Prakash Mishra,** Pro-Chancellor & Chief Advisor, DMIMS (DU), took painstaking efforts in the creation of an environment in DMIMS (DU), which stimulated and induced me to undertake this project. His constructive critical appraisal enhanced the quality of this work.

I thank, from the core of my heart, my wife, **Mrs.Sheela Patel,** for the care, cooperation, and encouragement rendered by her and for staying with me through all thicks and thins of life.

I will never forget the immense contribution and all the assistance I have received from **Mr.Manish Deshmukh,** Asst. Professor, in completion of this work.

I would also like to express my gratefulness and thanks to **Dr. Shraddha Patel,** Assistant Professor, Department of Oral Diagnosis & Radiology, SPDC, Sawangi (Meghe), Wardha, whom I am fortunate to have as my Daughter-In-Law, for her incessant assistance and technological support at every stage of this work.

I would like to acknowledge the kind cooperation and valuable help extended to me by **Mr.AshishTambe, Mr.Suresh Kumar,** Stenographers, **Mr. AniketPhathade,** Consultant, R&D, for his cooperation in the preparation of graphics and **Mr. Vrushabh Jain,** Personal Assistant for all the typographical assistance they provided during the process.

Satyawan Singh Patel

Date: 02.03.2020

CHAPTER 1

Study Designs in Clinical Research

Abstract: Study designs in medical research fall mainly into three categories: Observational studies, Interventional studies & meta-analyses. Further, each type of study comprises of subtypes. Each study design with its subtypes, and applicability of a specific study design, along with advantages & limitations, are discussed in this chapter.

Keywords: Blinding, Case series, Case-control studies, Cross-sectional studies, Cohort, Clinical studies, Controlled studies, Interventional study, Meta-analysis, Observational study.

INTRODUCTION

Research in general & medical research, in particular, is to be conducted to answer mainly three questions 1) Why do the researchers want to do the research, *i.e.,* research gap? 2) What the researcher wants to do, *i.e.,* the research question, 3) What will be the suitable study design necessary to answer the research question, and 4) the investigator has to decide how the research should be conducted? meaning thereby selecting the appropriate methodology to be used.

Thus, the choice of study design is a pivotal factor in finding a correct answer. This chapter deals with commonly used study designs in medical research, as knowing or familiarizing with the design of the study is very important for understanding the conclusions drawn from the research.

Understanding of Research/ Study designs will be facilitated by understanding the term “Research” from a statistical point of view. Research means a systemic way of Data Collection, analyzing, and drawing conclusions that create new knowledge. This process requires that the research plan (study design) developed by the researcher should answer the research question appropriately. Whereas Research Methodology refers to the detailed process of data collection, the tools, and the technique of Data collection [1].

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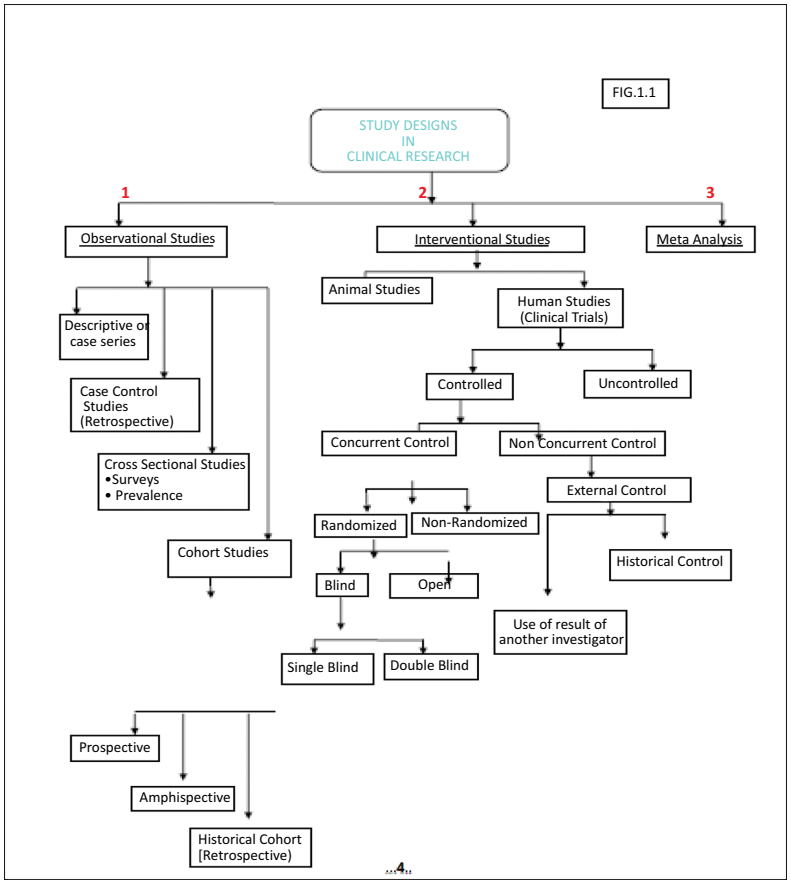

Fig. (1.1). Study Design In Clinical Research.

Classification of Study Designs: Medical research can be classified broadly into three categories (Fig. **1.1**).

1. The observational studies wherein the subjects are observed, and no specific intervention is provided.
2. The interventional studies where a specified intervention's effect is observed.
3. Meta-Analysis.

OBSERVATIONAL STUDIES

Case Series

It is the simplest of study designs in which the researcher reports interesting and curiosity-provoking observations in a small number of patient cases. Case series

studies are suitable for the generation of hypotheses. The hypotheses generated may be investigated further in case-control, cross-sectional, or cohort study designs. The power of evidence in the Case series is weak.

Case-Control Studies

These are the commonly used observational retrospective studies wherein two groups, One having an outcome and the other without an outcome, are analyzed (Fig. **1.2**). These studies differ from the case series by the presence or absence of a control group. The patient in case-control studies is selected based on some disease or outcome. These are the commonly used observational retrospective studies wherein two groups are analyzed, One having an outcome and the other without an outcome. The controls are the patients or individuals without the disease or outcome. These studies begin with the presence or absence of outcome and then look backward in time to detect the patient's possible causes or risk factors. The case-control studies are retrospective studies. Therefore, sometimes it becomes difficult to decide whether the reported study is a case-control study or a case series report. The confusion is because both types of studies are conceived and reported after the instances have happened [1, 2] (Table.**1.1**).

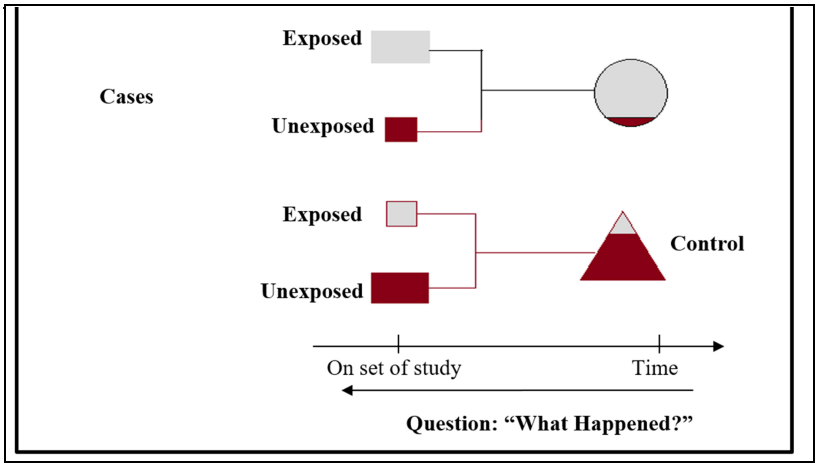

Fig. (1.2). Case Control Studies.

Table 1.1. Case Contro studies Advantages & Disadvantages.

Sr. No.	Advantages	Limitations
1)	Useful to study rare conditions or rare diseases that may not occur for many years.	Case-control studies, in general, have a lower power of evidence as compared to cohort studies.
2)	Can be completed in a shorter time than cohort studies	A good number of biasing factors can play a role

CHAPTER 2

Scales of Measurement, Descriptive Statistics & Data Presentation

Abstract: The scales of measurement could be numerical, nominal or ordinal. The measurement of data requires measurement of its central tendency and discussion. Such data can be presented, depending on its type & nature, in the form of tables & figures. The different types of descriptive statistics & the suitable form of presentation are discussed in this chapter.

Keywords: Graphs, Histogram, Mean, Mode, Median, Nominal scale, Numerical scale, Ordinal scale, Pictogram, Proportion, Range, Standard deviation.

INTRODUCTION

It has been aptly said that in research, what you say if you can measure it & express it in numbers; your information has some value. If you cannot, your information is of meager value. This chapter deals with different kinds of data collected in medical research. What is important is the type of observation & the kind of scale on which it is measured. Depending on the data type and its appropriate measurement scale, deciding which statistics are to be used for the summarization of the data is called descriptive statistics. Further, the data is to be presented in suitable tables & figures to facilitate understanding the conclusions drawn from the research [7].

SCALES OF MEASUREMENT

Commonly used scales of measurement in medicine are:

I. Nominal Scale
II. Ordinal Scale
III. Interval Scale
IV. Ratio Scale

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Nominal (Categorical Scale)

Nominal scales are used for qualitative classification. They can only determine whether the individual items belong to distinct categories. Quantifying or ranking the categories in order is not possible on this scale. Performing arithmetic or logical operations on nominal data is also not possible. Nominal variables are also called (non-ranked) categorical. The number of occurrences in each category is referred to as the frequency count for that category. The category is often dichotomous, *i.e.,* binary, where there are only two possibilities. Variables that have only two categories or levels, either the outcome occurs or does not occur. For example, a disease is cured by a drug or not cured. The evaluation of medical treatment or surgical procedure as well as the presence of possible risk factors, are often described as either occurring or not occurring.

Ordinal Scale

In the ordinal scale, inherent order occurs among the categories but is artificially converted into numbers. Ordinal data have order, but the intervals between scale points may be uneven. Due to the lack of equal distances, arithmetic operations are not possible, but logical operations can be performed. In clinical practice, ordinal scales are used to determine the number of risk factors or the appropriate type of therapy. For example, the stages of carcinoma cervix from stage 0 to 4 is an ordinal scale. Similarly, other carcinomas, like breast cancer, are also staged. Other examples of ordinal variables might include: determining the pain level of a patient (1-10 scale), Satisfaction level (very dissatisfied, dissatisfied, neutral, satisfied, very satisfied), *etc.*

Interval Scale

These metric scales have constant, equal distances between values, but the zero point is arbitrary. They can be measured on a Linear scale, and the intervals keep the same importance throughout the scale. This scale is also characterized by the fact that the number zero is an existing variable. In the ordinal scale, zero means that the data does not exist. In the interval scale, zero has meaning – for example, if you measure degrees, zero has a temperature. Interval scales can also be used to keep counts of publications or citations, Intelligence Quotient (IQ test score), Body Mass Index, age (years), *etc.*

Ratio Scale

Ratio scales are metric scales and can be the most informative scales. Ratio scales also differ from interval scales in that the scale has a 'true zero'. The number zero means that the data has no value point. An example of this is height or weight, as someone cannot be zero inches tall or weigh zero pounds, or be of negative inches or negative pounds. Examples of Ratio scales include weight, pulse rate, respiratory rate, body height, *etc.* The data is nominal and is defined by identity. It can be classified in order, contains intervals, and can be broken down into exact values.

MEASUREMENT OF CENTRAL TENDENCY

The summary of data in a research study communicates a lot of information. One of the most useful summaries of numbers is an indicator of the center of distribution of the observation. This summary is called “Central Tendency.” Three measures of central tendency are used in medicine and epidemiology. These three measures are:

- Mean
- Median
- Mode

Calculation of Measures of Central Tendency

Mean

The Mean is the arithmetic average of the observation. It is denoted by $\bar{X}$ (called X Bar). It is calculated by adding the value of all observations and dividing it by the total number of observations. The formula for Mean is written as $\bar{X} = \sum X/n$, where $\bar{X}$ Denotes mean, ∑(Sigma) means to add, “X” denotes individual observations, and 'n' denotes the number of observations.

For example (Table **2.1**). If the recorded heart rate of 18 patients is as under:

Table 2.1. Systolic blood pressure.

Subject ID	Systolic Blood Pressure (in mmHg)
A	139
B	151
C	201

CHAPTER 3

Inferential Statistics

Abstract: Probability could be objective or subjective. Byestherom is a formula to calculate conditional Probability. The sample methods of random sampling are simple random sampling, systematic random sampling, Stratified random sampling, and cluster random sampling. Use of hypothesis testing, if used as inferential statistics, definite steps are required to be followed. Using confidence intervals as inferential statistics provide more useful information in clinical research. This chapter incorporates a discussion on these aspects.

Keywords: Annova, Confidence interval, Dunnet's test, Hypothesistesting, Inferential statistics, Probability, Randomsampling, Random variables, Students test, Turkey's HSD test.

INTRODUCTION

The statistical methods discussed in Chapter 2 are called descriptive statistics as they help the researchers to describe & summarize the research data. In this chapter, we deal with the basic probability concepts to evaluate the data using statistical methods & draw inferences. In statistical methods, it is assumed that the sample selected is representative of the larger population to which the inferences are to be made applicable & selected through appropriate randomization. The statistical approach depends on the research question. In medical research, only two methods are used as inferential statistics, namely confidence interval & hypothesis testing. Caution is required while using the student t-test, particularly when it is used for nonparametric data; a good number of errors may occur. The emphasis in this chapter is placed on concept generation rather than the convenience of calculation [8, 9].

PROBABILITY

Objective Probability

Suppose an experiment is repeated many times and assume that one or more outcomes can result from each trial (Experiment repetition). In this situation, the

Probability of a given outcome is the number of times the given outcome occurs, divided by the total number of trials. If the outcomes occur every time in a trial, say in ten trials, the outcome occurs ten times, then P= 10/10 = 1. Thus, the Probability is one, *i.e.,* the maximum. If the outcome does not occur even once, *i.e.,* it occurs zero times, the P=0/10= 0. If the event occurs five times, the P=5/10=0.5, *i.e.,* 50%. The outcome can take any number.

The estimation (estimate) of Probability can be made based on the theoretical model. It can be determined empirically. For example, if we toss a coin ten times, the theoretical possibility (P) of the coming head is five times that P of Head =5/10=0.5, and that of the coming tail is also five times P of Tails =5/10=0.5. In other words, Probability of a coming head is 50%, and that of the tail is 50%, but if we repeat this experiment on ten different occasions, it may not happen regularly. In one trial, it could vary from 0 to10, taking any number on one occasion. However, in place of 10, if we repeat the experiment 100 times, the chances of obtaining 50: 50 percent are more likely. This Probability is called Objective Probability [9 - 11].

Subjective Probabilities

It is the best guess depending on the person's previous experience, for example, Provisional diagnosis in a clinical setting. Thus it is the probability estimate reflecting the person's opinion or best guess whether an event will occur or not. Subjective probabilities are important in medicine because the subjective Probability is the basis of physicians' opinions. Physician's opinion about whether a patient has specific diseases or not (Provisional Diagnosis in Clinical Practice) [12].

Understanding the concept of Probability is important for:

- Understanding and interpretation of published research data in the form of graphs and tables.
- Making predictions about the inferences of researchers' own data that how much confidence one can have an estimate like means proportions or relative risk.
- It is essential to understand the meaning of P values given in published research articles.

EXPERIMENT AND EVENT

Experiment

In Probability, an experiment is defined as any planned process of data collection.

Event

An experiment consists of a number of independent repetitions or trials under the same conditions.

Complementary Event

An event opposite to the event of interest is called a complimentary event, *e.g.,* if we want to study the cases of vivax malaria in a patient with fever, vivax malaria is an event of interest, the Complementary event is the patient of fever, not having vivax malaria.

The Probability of the complimentary event is calculated as under:

P of having Vivax + P not having Vivax = 1,

This means P not having Vivax = 1- P of having Vivax

or

P of having Vivax = 1- P of not having Vivax

Mutually Exclusive Event and the Rule of Addition

Mutually exclusive events are two or more events when the occurrence of one excludes the occurrence of the other for example, if a person has blood group A, he cannot have blood group O. Here, blood groups 'O' and 'A' are mutually exclusive events (Table **3.1**).

The Probability of two mutually exclusive events is the Probability of the occurrence of either one event or the other. This Probability is calculated by adding the probabilities of the two events. This is called the rule of addition [5, 6].

Table 3.1. Mutually exclusive event.

	PROBABILITIES		
Blood-Type	**Males**	**Females**	**Total**
O	0.21	0.21	0.42
A	0.215	0.215	0.43
B	0.055	0.055	0.11
AB	0.02	0.02	0.04
Total	0.50	0.50	1.00

CHAPTER 4

Statistical Methods for Relationship Variables

Abstract: In the language of statistics, research is a planned & systemic method of data collection, analysis, & drawing conclusions. In this chapter, a demonstration of the relationship between numerical, nominal & ordinal data & calculation of other statistical techniques applicable in critical research, is described in a nutshell.

Keywords: Anova, Ara, Bayes theorem, Correlation coefficient, Cer, Eer, Likely hood ratio, Multiple regression, Nnt, Nnt, Odds ratio (or), Probability, Regression, Roc curve, Rrr, Sensitivity, Specificity.

INTRODUCTION

Research questions that require the study of relationships between two numerical variables, Correlation, and Regression, are the statistical methods to be applied. Demonstrations of relationships amongst nominal and ordinal data require statistical treatment calculating Experimental Event Rate (EER), Control Event Rate (CER), Absolute Risk Reduction(ARR), Relative Risk(RR) & other appropriate calculations like number Needed to Treat (NNT), Absolute Risk Increase (ARI), Odds Ratio, ANOVA, Logistic Regression and Multivariant Analysis of Variance (MANOVA). The diagnostic procedure requires the calculation of Sensitivity, Specificity, Likelihood ratio & plotting of the Receiver Operating Characteristic ROC curve [17].

This chapter discusses the principles of choice of their statistics depending on the requirement of the research question.

THE RELATIONSHIP BETWEEN TWO NUMERICAL OBSERVATIONS (CHARACTERISTICS)

Correlation

Correlation and Regression are statistical methods to examine the linear relationship between numerical variables. The relationship between two numerical

observations is demonstrated by the correlation coefficient, which is also called "**Pearson Correlation Coefficient."**

The formula for the correlation coefficient is as under:

$$r = \frac{\Sigma(X - \bar{X})(Y - \bar{Y})}{\sqrt{\Sigma(X - \bar{X})^2 \Sigma(Y - \bar{Y})^2}}$$

Where *r* is the correlation coefficient, *X* is the numerical value of one variable, and *Y* is the numerical value of other observations.

The correlation coefficient ranges from -1 to +1. -1 denotes a perfect negative relationship, and +1 depicts a perfect positive relationship. A correlation of "0" (zero) means no linear relationship.

Assumptions in Correlation

The assumptions needed to draw valid conclusions about the correlation coefficient are:

i. Random selection was made in selecting the sample.
ii. Two variables are normally distributed, called a bivariate normal distribution.
iii. The normal distribution of the two variables should be in joint distribution.

It is important to remember that individually each variable is distributed normally separately. It does not guarantee that jointly they have a bivariate normal distribution. Pearson's product is unsuitable for use if one of the two variables is not normally distributed. In this situation, the Spearman Rank Correlation is suitable for statistics [5, 17].

To study the relationship, in addition to calculating the Coefficient of correlation, the scatter plots of the data should form an essential part of the analysis. A scatter plot, also known as a scatter graph or a scatter chart, is a two-dimensional data visualization that uses dots to represent the values obtained for two different variables - one plotted along the x-axis and the other plotted along the y-axis. The formula for the Coefficient of the relationship demonstrates the extent of the linear relationship between the variables (Fig. **4.1**). Without the scatter, the researcher may miss a plot-important non-linear relationship if he uses only formulae.

To understand the said statement better, let us take an example. If we record the discharges from nerve fiber and change the temperature, we know that the discharges are more at the temperature of 25^0 C. The discharges decrease both at lower than 25^0 and also at a higher temperature. In this scatter plot, there is no linear- relationship- between- the temperature- and discharges- of the nerve fiber (r = 0.0). However, there is a relationship between the temperature and discharges from nerve fiber which remains obscured if the only value of r is used to calculate the relationship.

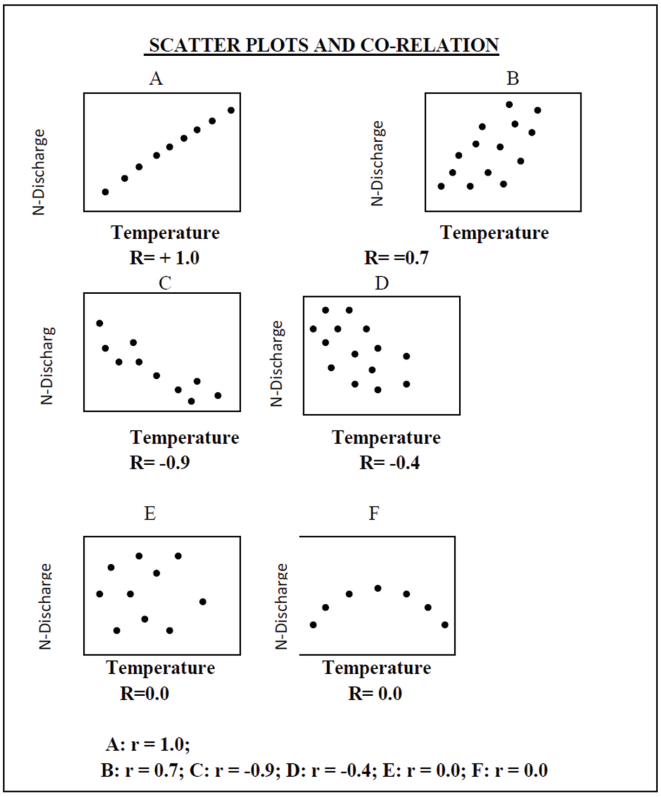

Fig. (4.1). Scatter Plots and Co- Relations.

The six hypothetical scatter plots demonstrate the usefulness of the graphical presentation of correlation. The six scatter plots, namely A, B, C, D, E, and F, demonstrate the shape of the scatter plot along with values of r.

I. Scatter plot A: r = ±1 and Scatter plot shows a straight line, indicating a complete positive relationship between increasing temperature and nerve impulse discharges.

CHAPTER 5

Clinical Research

Abstract: The clinical trial could either be an Explanatory Trial/ Randomised Control Trial (RCT) or Correlational Trial/ Pragmatic Trial. For developing new molecules as a drug, RCTs require human studies conducted in 4 phases called Phase I to phase IV of clinical trials. Pragmatic Trials are Correlational Trials. As such RCT & Pragmatic Trials are not dichotomous, there is a continuum. A PRECIS has been developed to assess the said trials. The reverse pharmacology approach is recommended to generate scientific evidence to make herbal drugs more efficacious & safe. These aspects are elaborated on in this chapter.

Keywords: Clinical trial phases precis, CONSORT, Randomized control trial (RCT), Reverse pharmacology.

INTRODUCTION

Any research wherein study subjects are human beings, is denoted as clinical research. The commonly used study designs in clinical research are discussed in Chapter 1. This chapter deals with clinical trials (RCT) in little detail as the outcome of the clinical trials have become applicable to inpatient care. Presently, the clinical research health policy decision-makers and funding agencies prefer Real World Evidence (RWE), Comparative Evidence Research (CER), and Pragmatic Trials. Now even for demonstration of cause and effect relationship explanation, trials (RCT) remains the gold standard. In the case of generating authentic, more efficacious, and safer use of herbal medicines, the approach of reverse pharmacology is considered the technique of choice.

CLINICAL RESEARCH

Clinical Research: Clinical research is defined as “a branch of health care science that determines the safety and efficacy of medications, diagnostic products, and treatment regimens intended for human use”.

Clinical research aims to find better methods to control, diagnose and treat the disease to increase overall human well-being. Clinical research generally is conducted through clinical trials.

TYPES OF CLINICAL TRIALS

Clinical trials are interventional studies conducted in humans. Clinical trials are conducted to evaluate the effectiveness and safety of drugs, devices, and therapies in human beings, healthy or suffering from the disease [24]. Clinical Trials are broadly classified into two groups:

I. Randomized Clinical trials (RCT)
II. Pragmatic Randomised Clinical Trials (pRCT)

Randomized Clinical Trials are explanatory trials wherein the cause-and-effect relationship of the intervention is evaluated under strictly controlled conditions with the application of principles of de-confounding. In contrast, Pragmatic Trials focus on the correlation between treatments (interventions) and outcomes in a real-world health system practice rather than focusing on providing a causative explanation for the outcome.

Thus this can be stated that RCTs are explanatory trials while pragmatic trials are correlation trials.

PHASES OF CLINICAL TRIALS

There are four phases of RCTs:

Phase I

The new drug, after preclinical studies, is administered for the first time to healthy volunteers. The purpose of Phase-I is to study the Pharmacokinetic and the pharmacodynamic effect of the new drug in human young adult healthy male volunteers.

Phase II

This Phase is subdivided into Phase II (a) and Phase II (b)

Phase II(a)

The drug is tested in a selected group of patients to evaluate its efficacy and safety in the patients suffering from the disease for which the drug is intended to be used. In this Phase, the appropriate doses of the drug are also determined.

Phase II(b) (Pivotal Trial)

In this Phase, the drug is administered to patients who are suffering from the disease for which the drug is to be used. The primary difference between Phase II, a, and b is that the Phase II (b) trials are more rigorously conducted to determine the new molecule's safety and efficacy in a selected group of diseased patients.

Phase III(a)

These trials are conducted after the successful completion of Phase-II trials. Only after successful completion of Phase III, (a) trials application to F.D.A. (Food and Drug Administration) can be submitted. These clinical trials are conducted in the group of patients in which the new drug is intended to be used. Phase-III clinical trial generates additional data on the efficacy and safety of the drug in a larger group of patients.

Phase-III (a) trials may be required to be conducted in the following:

- Specified group of patients, *i.e.,* renal failure, cardiac function compromised patients, or other co-morbid conditions.
- Patients suffering from specific conditions and the nature of the drug Phase III trial provide information that is needed for the packaging insert and labeling of the medicine. Trials are conducted after the medicine's efficacy is demonstrated but before regulatory submission of a New Drug Application (NDA) or other dossiers. These clinical trials are conducted in patient populations for which the medicine is eventually intended. Phase III(a) clinical trials generate additional data on both safety and efficacy in relatively large numbers of patients in both controlled and uncontrolled trials.

Clinical trials are also conducted in special groups of patients (e.g., renal failure patients) or under special conditions dictated by the nature of medicine and disease. These trials often provide much of the information needed for the package insert and labeling of the medicine [25].

Phase III Clinical trials are further designed into three sub-types:

i. Superiority Clinical Trials
ii. Equivalence Clinical Trials
iii. Non-inferiority Clinical Trials

Phase-III (a) i) Superiority Clinical Trials

When the research question is to show that one treatment is superior to another

CHAPTER 6

Survey Research

Abstract: A survey is one of the most common methods in health sciences research. As in this case, choosing a suitable study design depends on the research question, so also survey research questions also decide methods. The decision of application of scale of measurement depends on the nature of the observations, which could be numerical, nominal, or ordinal. If research develops his/her new survey instrument (survey questionnaire), its validity & reliability requires other important treatments. This forms the subject of discussion in this chapter.

Keywords: Confidentiality, Likert scale, Reliability, Scale of measurement, Validity.

INTRODUCTION

Survey Research is one of the common forms of research. Calling it the most common form of research is not inappropriate. It involves generally asking questions to people about a topic.

As is the case with any research, the research question is the most important part of the research, and survey research is no exception. Clear research questions with specific objectives help and guide in choosing a method of survey and designing an appropriate questionnaire [29].

There are three important components of survey research:

I. Designing survey tool (questionnaire)
II. Administering the questionnaire
III. Interpreting the results

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DESIGNING SURVEY TOOL

The Research Question (Framing)

As applicable to other research questions, a survey research question also requires a thorough review of the literature to know what is known on the topic and also to learn what other methods have been used earlier.

Sometimes it becomes difficult to specify the issues precisely to be addressed in a survey, even after a search by important search engines. Under such situations, a 'focused group' discussion with a small number of concerned people, about 6-10, can provide better information for the determination of the survey research question.

ADMINISTERING THE QUESTION

Survey Methods

Survey methods could be either:

- Self-administered questionnaire or structured interview.
- Self-administered questionnaires can be done by e-mail/ mail or in person. In-person administered questionnaires are considered to yield the best responses.
- Structured interviews could be conducted in person or through a Multi-Activity Device (mobile phone).
- Personal structured interviews provide a better result as compared to interviews taken on Multi-Activity Device (MAD) [30].

Developing Survey Questionnaire

Format of question close-ended or open-ended. Open-ended questions permit the subject to respond in his/her own words. These types of questions are more useful when the topic has not been studied earlier.

Close-ended questions are more difficult to write, but the main advantage is the comparatively easy analysis and reporting.

Scales of Measurements

In the case of closed-ended questions, the researcher is required to decide the level of detail required in the answer. The scale helps determine which method can be used to analyze the results. In some cases, only nominal data, *i.e.,* Yes or No, is sufficient. If the information is required to be analyzed and to be presented in

grading, an ordinal scale is to be used. If the questionnaire is in the form of open-ended questions and the subject presents information in numerical form, the numerical scale, as described in Chapter 3, is to be used. It is advisable that the researcher should collect information in detail as much as possible at the same time; too many details are to be avoided. Too much information usually leads to unreliable data.

Positive and negative categories

If data is collected in the form of ordinal responses, there should be an equal number of positive and negative responses. If there is a neutral answer question, it should be placed in the middle position between negative and positive answers [31].

Vague adjectives:

The use of qualifiers like sometimes, often, rarely, *etc.,* should be avoided. For example:

How many cold drinks did you drink last week?

☐ None

☐ A few

☐ Several

☐ Many

Making less vague:

How many cold drinks did you drink last week?

Revised balanced probe (questionnaire):

00 ☐

1-5 ☐

6-10 ☐

11-20 ☐

CHAPTER 7

Planning and Writing Research Projects

Abstract: Reading research papers/literature should be done through reviewing. It should not be not skimming. Biases in a study seriously affect the conclusion of the study adversely. While writing research reports, discrepancies in text, tables, and figures may reflect after-thought data treatment by the researchers: these and other aspects during the planning of research projects and report writing. Precautions required are the very purpose of this chapter.

Keywords: Biases, Fishing expedition, Power of study, Research gap, Study design, Sample size, Test of significance.

INTRODUCTION

Planning and developing research projects is the most important part of any research project. In medical research, the researcher must decide what he wants to do and why he wants to do it. The answer to Why requires a thorough Review of the Literature as per PRISMA Flow Chart mentioning the search strategy and search engine used. Depending on the research question, appropriate study design is chosen. All statistical methods are based on the assumption that the sample is free from bias and sample size is sufficient for accurately measuring desired effect size and reporting the research data in a concise, precise, and coherent manner in order to facilitate understanding by the readers. Depending on the type of study design, definite guidelines have been formed to bring global reporting uniformity. These are to be adhered to strictly. These issues are treated in this chapter.

PLANNING OF A RESEARCH PROJECT

Planning the research project is the most important part of any research work. At this juncture, it would be pertinent to quote Abraham Lincoln, the former president of the United States of America. He commented, “If I am given 8 hours to cut a tree, I would like to spend 6 hours sharpening my ax.” This statement is more true for research than for anything else [33, 34].

For the convenience of description and understanding, the research project can be divided into the following artificial sections, although overlapping is unavoidable.

REVIEW OF LITERATURE AND IDENTIFICATION OF THE RESEARCH PROBLEM

The common practice, more applicable to the researchers in health sciences, is that while reviewing an article, the researcher generally skims the article without going through the details of the study design, sample size, Test of significance, and power of the study. It is important to remember that the sample size for comparing the mean in three groups would differ from that of two or more groups. The said practice of skimming the research article during the literature review is not justifiable unless it is evident that the conclusions drawn by the researcher are valid and justified to be incorporated into the process of decision-making [35]. To do so, the reader (reviewer) should focus attention on the following:

Whether the study design of the concerned research project is appropriate to answer the research question/questions, it is important to remember that no statistical analysis by any expert or statistician, can compensate for shortcomings in the study design with respect to sample size, various types of biases, and poverty of observations. The research article should be reviewed and evaluated with a **critical eye** to detect the desired level of evidence.

- Whether the statistical analysis is appropriate in accordance with the data, whether numerical, ordinal, or categorical (non-parametric, dichotomous).
- Whether the results are statistically significant.
- If the results are statistically significant, whether the magnitude of change is worth it for its clinical application (application inpatient care) and for making administrative decision-making. It has to be remembered that statistical significance does not necessarily signify clinical significance; sometimes, the reverse may be true.

RESEARCH GAP ANALYSIS & FRAMING OF RESEARCH QUESTION

The clarity of the research project to be undertaken, *i.e.,* the problem to be solved or the research gap to be filled, is the most important part of any research work. In other words, it can be stated that the research question/question to be addressed is the beginning of a research project, and for framing the research question/generating a hypothesis appropriate and thorough review of the literature is required.

The researcher can test the appropriateness of his or her research question in interventional research studies on the PICO format wherein:

P - Stands for Population
I - for Intervention
C - for Comparison
O - Outcome

CHOOSING THE APPROPRIATE STUDY DESIGN TO ANSWER THE RESEARCH QUESTION

Commonly use of study designs in health science research can be grouped broadly into two groups:

Experimental/Interventional studies

It includes clinical trials or observational studies. The observational studies are cohort studies, case-control studies, surveys, case series & cross-sectional studies, as discussed in earlier chapters of this book.

Clinical trials

Clinical trials with controls and randomization, along with proper planning and properly conducted, are the study design of choice. These studies are particularly free from all biases & problems which are associated with other study designs. Therefore, RCTs provide the strongest evidence.

Cohort Studies

These are longitudinal studies. The cohort study could be prospective, retrospective, or amphispective. The Prospective Cohort Study design provides stronger evidence as compared to retrospective studies, as the researcher can exercise his control over biases. The retrospective or historical cohort suffers from biases. Hence, the evidence is weaker as compared to Prospective Cohort. The cohort studies are most suited to investigate the causes of a disease or risk factors responsible for the disease or to study the course of a disease [2].

Case-Control Study Design

It helps in the determination of whether exposure is associated with an outcome. In this study design, the cases are the individuals who suffer from the disease (Outcome), and the controls are those without the disease. Afterward, the previous clinical history of both the cases and controls is analyzed to find out the probable cause of the outcome (disease). This study design is good for the generalization of a hypothesis or for investigating a preliminary hypothesis. Case-control studies can be utilized to study rare diseases, and these studies suffer from biases.They

APPENDIX-A

ETHICAL GUIDELINES FOR CLINICAL RESEARCH

INTRODUCTION

"The Philosophy of Biomedical research is that the interest of the research subject be weighed heavier than the interest of science."

"Ethics is not definable, is not implementable, because it is not conscious; it involves not only our thinking but also our feeling" - Valdemar W. Setzer

Ethics is the moral value of human behavior and the principles which govern these values. Every profession is bound by code of ethics (Greek word Ethos meaning Custom or Character) and which dates back to Hippocratic Oath, which is a guiding principle for the physician on professional ethics and mandates. The Hippocratic oath prescribes only beneficial treatments refraining from causing harm or hurt to their patients. This ultimately puts the interests of their patients above their own interests. When the clinician assumes himself the role of the researcher, the situation becomes complicated. It was realized that a code of ethics for clinical research was needed and to address the need Good Clinical Practice (GCP) guidelines for human research were framed. The role of the ethics committee has become supremely important. Thus, knowledge about the ethics committee and its functioning is not only the administration's advantage but also important from the researcher's viewpoint.

PRINCIPALS OF ETHICS (CORE VALUES)

Ethical principles of research in the Biomedical Research are based on three core values:

- Respecting the autonomy of research subjects
- Avoiding harm
- Privacy and data protection

Respecting the Autonomy Of Research Subjects

Voluntary participation

Participation in research should be voluntary and based on informed consent. An exception from the principle of voluntary consent can be made when research is conducted on published and public information and archived materials. Research concerning official registries and documents and carried out without the consent of research subjects is governed by legislation.

Research subjects can give consent orally or in writing, or their behavior can otherwise be interpreted to mean that they have given consent to participate. For example, assenting to a polite request for an interview or responding to a questionnaire or request for a written response indicates that the subject has consented to be studied.

- In institutional settings (prisons, child protection institutions, hospitals, homes for the elderly,*etc*) it is important to make sure that consent is given voluntarily by each and every subject. In evaluating the matter, attention must also be paid to the nature of the study, *i.e* .the degree to which personal matters are dealt with (need to protect privacy). If the research intervenes in personal integrity, it is particularly important to ensure the genuineness of consent. On the whole, researchers should always take into account the constitutional rights guaranteed to each individual.
- If research intervenes in the physical integrity of subjects, consent must always be given in writing or in some other certifiable way, unless this is contrary to the interests of subjects.
- For example, a person with AIDS may not want his or her name registered on written consent.
- Consent can be specific or general. General consent applies to research use in general. General consent can include conditions regarding the form in which data are recorded and archived and conditions set for the use of data in secondary research.
- If the information obtained from subjects is combined with information in official registers, subjects must be given detailed information on the registers that will be used.
- Specific consent concerns the use of information in a particular study. Specific consent with regard to the use of data may be justified on the grounds that data cannot be anonymized and that archiving the data with identifiers for secondary research would in all likelihood be harmful to subjects.
- Subjects have the right to withdraw from a study at any stage, but this does not mean, however, that their prior input (interviews,*etc*) cannot be used in the study.

Autonomy and research involving minors

According to Indian Good Clinical Practice Guidelines and ICMR guidelines children must be treated equally and as individuals and must be allowed to influence matters pertaining to them to a degree corresponding to their level of development.

In practice, it cannot be assumed that researchers should always request separate consent from a guardian when research involves minors. First, according to the above-mentioned principles children should be able to influence matters pertaining to themselves to a degree corresponding to their level of development. Second, there are situations where there may be differences in values and interests between a guardian and a minor, and requesting the guardian's consent may endanger the collection of comprehensive research data on the conditions and behavior of minors, thus restricting the freedom of science, which is guaranteed by the Constitution. Third, there are studies that do not include risks, and where requesting consent from the guardian would be difficult.

Autonomy and Research in Schools

Many studies that are conducted in schools and institutions of early childhood education and care can be carried out as part of the normal work of the institution or school. It is not necessary to request a guardian's permission if the director of an institution of early childhood education and care or the headteacher of a school has evaluated that the study would produce useful information for the institution or school and can be carried out as part of the normal activities of the institution or school. For example, observations, broad questionnaires, and open interviews which do not collect directly identifying information(names, IDs, addresses) for research purposes can be carried out without the consent of parents or some other guardian. In other cases, they must be informed of the study.

Age

When studying minors outside an institution of early childhood education and care or school, researchers must themselves evaluate when it is necessary to ask for a guardian's separate consent or inform a guardian of the study so that the guardian can forbid the child from participating in the study. A study involving children under the age of 15 can be conducted without a guardian's separate consent or informing a guardian if this is justified from the viewpoint of:

- the age and development level of subjects
- the subject and research method or
- the need for information

If a study is to be conducted without a guardian's separate consent or informing a guardian, an ethical review must be requested for studies involving subjects under the age of 18. Researchers must always respect a minor's autonomy and the principle of voluntary participation, regardless of whether a guardian's consent has been obtained or not.

Information to subjects

The information that must be provided to research subjects depends on the nature of data collection methods. In studies based on observation, interviews, or questionnaires, subjects must be told what the study is about and what participating in the study means in concrete terms and how long it will take.

Information regarding a study should include at least the following:

1. The researcher's contact information.
2. The research topic.
3. The method of collecting data and the estimated time required.
4. The purpose for which data will be collected, how it will be archived for secondary use, and 5).
   the voluntary nature of participation.

GLOSSARY

(A).

Absolute Risk Increase (ARI)- The increase inside effect (risk) with new treatment/procedure as compared with without new therapy.

Absolute Risk Reduction (ARR)- It is the difference between the event rate in the interventional group and the event rate in the control group it is also known as absolute risk difference.

Absolute Value- It is the positive value assigned to a number iris respective of the original positive or negative value of the number.

Addition Rule- It is the rule for calculation of probability of two mutually exclusive event the probability is calculated by adding.

Alpha Error- It is wrong rejection of Null Hypothesis. Also called type I error.

Alpha Value- The level of alpha selected in hypothesis testing.

Alternative hypothesis- Alternative hypothesis it is the research hypothesis (alternative to) Null Hypothesis.

Amphispective Study- Amphispective means combination of retrospective and prospective study.

Analysis Covariance (ANCOVA)- Special type of analysis of variance used to controlled effect of confounding factor.

Analysis of Variance-It is statistical procedure determine if there is any difference among two or more groups.

(B).

Bayes'sThorem – Mathematical formula to calculate conditional probability of one event from the given probability of the other event.

Bell shaped distribution – It is a term used to describe shape of Gaussian distribution.

Beta Error – It is the error related to wrong acceptance of Null Hypothesis. Also cold type II.

Bias- Any influence that distorts the results of a research study. It is related to the ways the sample and target population or the control and the interventional group differs.

Binary Observation – observation which has only two out comes also known as nominal observation best example is gender either male or female.

Biometric- Methods of the study measures and statistical analysis in medicine and biological sciences.

Biostatistics- Research study design and application of in statistical procedure in biological sciences.

Blind Study – Study design in clinical trial to prevent bias that he researcher and the subject involved in the research presses or not aware of the treatment or interventional that a participant is receiving.

(C).

Case series – An observational study in a group of cases where in interesting features are observed.

Cases – Object are entities whose behavior or characteristics we study.

Categorical Variable- It is an observation nominal scale which false in category it is also called as qualitative observation.

Central Limit Theorem – A mathematical derivation which proves that the derivation of the mean is approximately normal if the sample size is 30 or more, provided that the character stick is normally distributed in the population.

Central Tendency – a major of centrality of a set of measurements. Three main measures of centre tendency are mean median and mode.

Chi Square Test – Statistical applied to nominal observations or proportions or characteristics which or not dependent.

Clinical Study- An experimental (interventional) study of a drug or procedure in which the study subjects are humans.

Clinical Trial – An experiment designed to test the efficacy or effectiveness of a clinical treatment.

Clinically Important Difference- A difference in a quantitative variable which will be clinically important to those in whom the variable is measure and in target population.

Closed Question- A question to which individual or required to gift own of the several answers is specified in advanced by investigator.

Cohort-A group of subjects, having common characteristics who remain together in the study over a period of time.

Cohort Study – A quantitative observational is study in which a group of individual (The Cohort) or followed of over a period of time and measurement or taken at several times.

Complementary Event – An event which is apposite to the event of the study.

Concurrent Control – Control group of subject being studied along with interventional group at the same period of time.

Conditional probability – Probability of one event calculated by the given probability of other event.

Confidence Interval – interval computed from the sample data that has a given probability that the unknown parameter, such as the mean or proportion, is contained within the interval. Commonly used confidence interval or 90%, 95% and 99%.

Confidence Limit – The limits of confidence interval. This are computed from data of the sample of the study.

Confounding Variable - A variable, other than the variables under investigation, which is not control and which may distort the results of experimental research.

CONSORT Guideline - The full form is Consolidated Standards Of Reporting Trials.

Controlled Event Rate – number of the subject in the controlled group who developed the outcome (variable) under study.

Controlled Trial – A Trial in which interventional group is compeered with a similar non interventional group or with a reference standard control group.

Correlation – The degree of association between two variables. A tendency for variation in one variable to we link to variation in a second variable.

Correlation Coefficient - A measure of degree of relationship between two variables. It is also known as Pearson's correlation coefficient.

Covariate – A confounding variable which as potential to affect the outcome.

Critical Appraisal – Interpreting the strength it weakness of the research process and applying the judgments to assts how used full the research is for practitioners.

Critical Ratio – It is used in a statistical test for Z score.

Critical Value – It is the value a test statistical must achieve for rejection of Null Hypothesis.

Cross Over Study – It is a type of clinical trial in which the control group and the interventional group or crossed over in a time sequence.

(D).

Data Analyses – Processing, interpretation and analyses of findings.

Deferential Bias – Bias that affects one group, in research study, different from another group.

Degree of Freedom – A parameter used in t in t distribution and chi square distribution for

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