ABC of Research Methodology and Applied Biostatistics

A Primer for Clinicians and Researchers

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Nithya Gogtay

Forewords
S Arulkumaran
K Sathyanarayana

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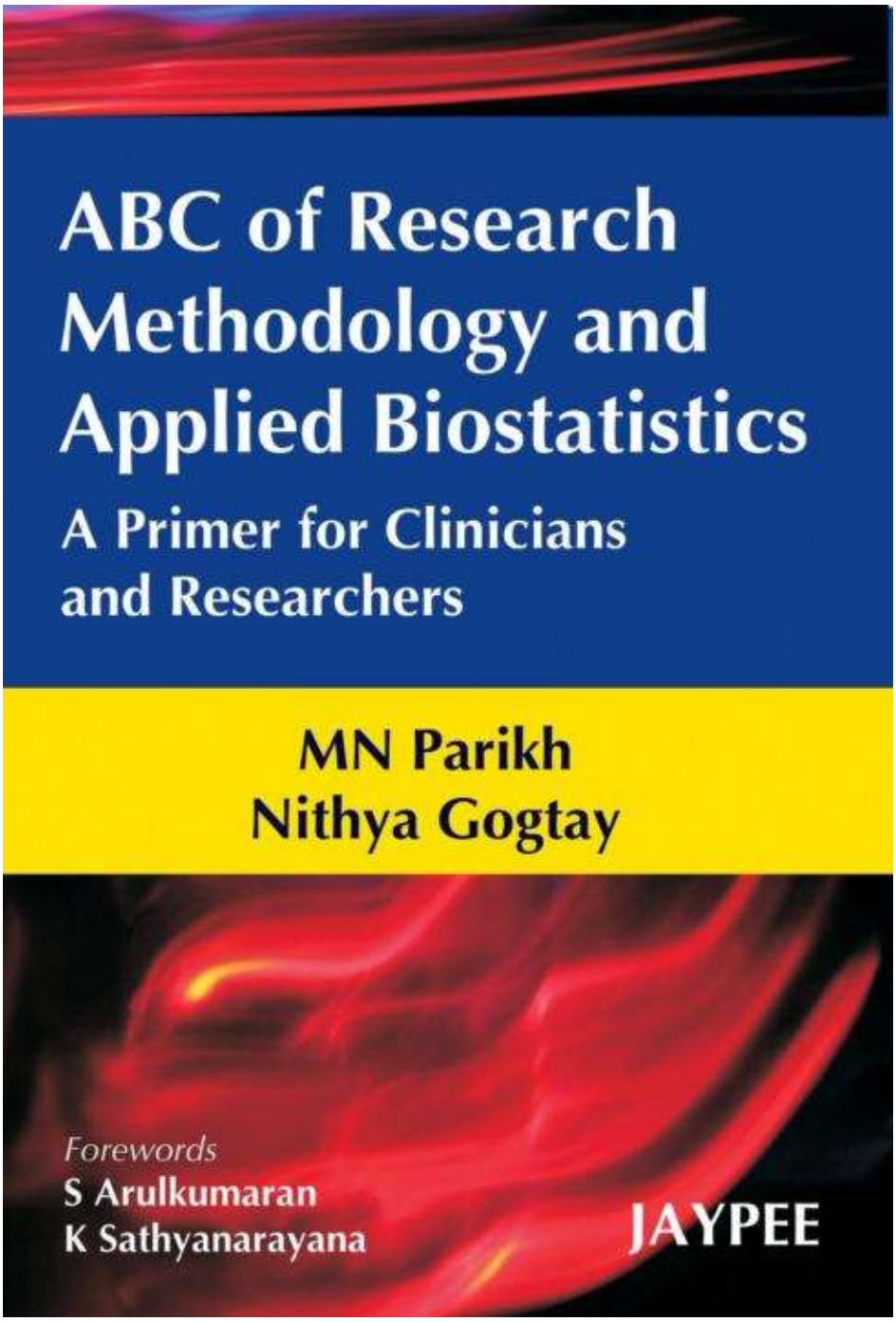
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To

(Late Smt) Shobha M Parikh

Foreword

Medical research outcome of today is clinical practice tomorrow. Hence understanding research methodology is vital for the researcher and essential for the clinician. The ABC of Research Methodology and Applied Biostatistics - A Primerfor Clinicians and Researchers is an excellent book for every clinician from beginners to those in established practice. The fifteen chapters provide a wealth of information and have been written in simple language. The chapters flow from one to the other in a format and design that will help the reader to understand research from "conception to delivery". It covers every aspect from the type of research studies to planning ethics, execution, statistics, presentation of manuscript and presentations to avoid pitfalls. The chapters on misdeeds and misconduct and historical glimpses of medical research provide interesting information.

I enjoyed reading the book cover to cover and admit that I learnt a lot about medical research. I would highly recommend it to all those involved in research and clinical practice. The authors should be commended for a truly valuable contribution to science.

S Arulkumaran
Professor and Head of Obstetrics and Gynaecology
St George's University of London

Foreword

The need for rigor in carrying out medical research that could lead to better leads and strategies for the prevention, diagnosis and management of disease is now beyond debate. This is in fact a global call. But unlike basic biomedical research with animals or in vitro systems, inherently endowed with strong experimental methodology for reliability, medical research has traditionally been handicapped to a large extent due to the involvement of human subjects. Due to this and other reasons, medical research is even accused of being `unscientific' way of putting together evidences. Yet, medical scientists have been braving along picking up nuggets of new data, painstakingly analyzing and interpreting, generating new knowledge that eventually finds way into practice. The entire process of data-information-knowledge cycle has undergone a sea change in the recent past. New evidences are currently put to most stringent testing and evaluation before applied in the clinic.

Considering the challenge, research culture among medical scientists, especially from the clinical disciplines has always been found wanting. One of our studies a few years back showed that some medical colleges in India did not publish a single paper in an indexed journal over a five year period. So unlike other disciplines in science where the adage is `publish and perish' in medical research it has been more of `publish or perish'. However, many who did publish `research papers' could not transcend journals run by their respective learned societies that did not particularly encourage excellence. So, at a time when drastic revamp was called for, our collective failure ensured perpetuation of mediocrity. Even the hesitant and tentative hesitant steps were at best ad-hoc.

But things seem to be looking up, albeit slowly, at least in major cities like New Delhi, Mumbai, Chandigarh, if the number of young doctors flocking the training workshops on biomedical communication and research methodology is any indication. A perceptible shift in the mind-set among young and middle level medical professionals to learn - learn the right (best) way of not just doing science but also publish in the best international journals is visible. In the last three years or so, even some journals published by learned societies have changed, and for better. Evidence-based medicine is slowly but steadily making

its way into clinical practice. Overall, the hunger for new knowledge that is on the rise, augers well for the medical research establishment, patients, and the country.

But the training to impart such skills has not been very widely spread being limited by the handful of committed individuals. The course material for most training workshops on research methodology and biomedical communication is largely borrowed from the west as several excellent books written by eminent experts are available. Unsurprisingly, most resource persons of workshops (being full time medical teachers) find it convenient to liberally borrow from these sources. Often, the content is not very appropriate to the Indian participants, despite `Indianization'. A good resource book on research methodology was always found wanting.

The ABC of Research Methodology and Applied Biostatistics: A Primer for Clinicians and Researchers, therefore, is a very welcome addition. What is pleasantly surprising is that the senior author Professor Mahendra Parikh is an obstetrician and gynaecologist by training, a discipline not exactly in forefront of medical research in India. Dr Parikh's passionate commitment to promote medical research, build skills and empower young medical researchers is evident by the widely attended workshops organized in various parts of India. Under his leadership, the Journal of Obstetrics and Gynecology of India has been running the very successful PICSEP (Program for Inculcating the Culture of Scientific Enquiry and Pursuit) Project since 2003. Co-authored with a young promising clinical pharmacologist Dr Nithya Gogtay, this booklet gives the elements of research methodology and biostatistics from a practitioners' point of view. Written in a very simple and easily understandable way (especially medical statistics), the booklet contains little of everything a young researcher should know - planning and designing a study, execution publication of a research paper, evidence-based medicine, application of biostatistics, ethics, research, misconduct etc.

I hope this is only the appetizer and Drs Parikh and Gogtay will dish out a comprehensive resource book in the not too distant future.

K Satyanarayana

Editor, IJMR

Preface

Progress in every walk of human activity depends upon research based on new ideas. So it is in the field of medicine too. Medical students are exposed to epidemiological research while studying Preventive and Social Medicine. During undergraduate days, they have opportunities to learn Research Methodology if they wish to. But during postgraduate training they must learn Research Methodology while working on and writing their thesis or dissertation which is an essential and integral part of the postgraduate examination. Unfortunately, thesis writing is often not taken seriously and considered a mere formality at a vast majority of universities in the developing countries. The current scientific methods of conducting research developed over the past six decades, have been refined only in the last 30 years. Even the Heads of Departments in many medical colleges are ignorant of these new methods. As a result, most published research is poorly done and there is a great need to improve the quality of research done especially in developing countries.

The Senior Author became Editor of the Journal of Obstetrics and Gynecology of India in 2003 after working in many editorial positions for three decades and having a vast teaching experience. He soon realized the need for training postgraduate students and teaching staff in Research Methodology. Hence, he initiated the project designated as Program for Inculcating the Culture of Scientific Enquiry and Pursuit (PICSEP). The project has expanded in many different directions and is showing good results benefiting students, teachers and clinicians. Clinicians must become knowledgeable about the basics of Research Methodology including the basis of Applied Biostatistics to be able to evaluate the medical literature they read. The junior author is regularly conducting training programs of 12 half-day sessions for undergraduate and postgraduate medical students since 2003 besides being part of the editorial team of the Journal of Postgraduate Medicine and Journal of Association of Physicians of India for a decade. During these activities involving training hundreds of researchers and clinicians, we realized a great need for a simple, compact and comprehensive book on this subject, written in plain language, devoid of scientific jargon and directed at clinicians and research workers. Most western books are beyond the reach of readers in developing countries due to their

prohibitive cost and complexity of writing.

This book is written keeping in mind the needs of undergraduate and postgraduate students and their teachers, junior researchers and their guides and the clinicians. The clinicians are consumers of research since they utilize it in their day-to-day practice.

It is hoped that the book will in a small way contribute to improving the quality of research done in developing countries and empower the clinicians to evaluate the quality of research that they read in journals and listen to in conferences. Suggestions and comments from the readers are most welcome.

Mahendra N Parikh

Nithya Gogtay

Contents

CHAPTER ONE

Introduction

WHAT IS RESEARCH?

Indulging in research improves every aspect in all fields of human activity. It is not easy to define research. Various definitions of research range from careful, diligent and studious scientific enquiry or examination for discovering and interpreting new knowledge, to collecting new knowledge on a chosen specific subject, to discovering new facts and verifying old ones. Research is at the core of improving human comfort and quality of life. Research in different branches of biomedical sciences is at the centre of preventing, diagnosing and treating diseases.

WHY DO WE DO RESEARCH?

The main purpose of research in medicine is to prevent sickness and improve patient care by all possible ways. Diseases can be prevented by finding out their causes or etiologies, developing immunity by vaccination, adopting healthy and nutritious diet, giving dietary supplements, changing life styles (e.g. avoiding tobacco, alcohol, unprotected sex, high cholesterol fast foods etc), improving hygiene and so on. Knowledge about all these is acquired from research studies. Diseases can be better treated by diagnosing them early by researching new diagnostic tests and imaging modalities. Research helps in improving management of the sick in various ways like developing new drugs having greater efficacy, lesser side effects, greater compliance by virtue of better taste (sugar coating to mask bitterness), convenient mode of administration (oral, rectal, vaginal and dermal in preference to injections), lesser number of dosages needed (monthly preferred to weekly preferred to daily preferred to many times a day) and developing better interventions (transverse abdominal incision preferred to vertical one, vaginal surgery preferred to abdominal one, endoscopic

surgery preferred to laparotomy) and the list goes on and on. Continuous research leads to better and better patient care which is the main purpose of conducting research.

There are other reasons why we indulge in research. Doing research gives mental satisfaction of contributing to science and society. It helps one to acquire honours and respect from peers in scientific community and in society. Good research adds meaningfully to one's curriculum vitae and leads to rise in the ladder of promotion. In fact, today, every one in academic position has to do good research for publication in good journals even for mere survival in his current position. The present culture of publish or perish is widely accepted in all good academic institutions.

Medical research also helps administrators to work out priorities for utilizing their limited funds for giving maximum benefits to maximum people. Research also helps policy makers to frame policies to improve health care. Lastly, better medical care depends on development of new drugs or new molecules of drugs by research done by pharma companies. Similarly, manufacturers of instruments and equipments contribute to better patient care by their continuous research.

We constantly strive to improve whatever we are doing. This is done by inventing a new way of doing a thing eg invention of washing machine is an improvement on manual washing. As clinicians we are perpetually trying to improve every aspect of patient care. We want simpler and more reliable diagnostic tests and investigations with greater accuracy. We invent new tests and do research to find out whether these are superior to the ones we are presently using. Pharmaceutical companies do basic research to develop new drugs or new molecules of existing drugs which, when compared to currently used ones, are more effective in fighting diseases and are more user friendly by virtue of taste, lesser frequency of dosages, and noninvasive mode of administration. So do the manufacturers of gadgets, instruments, equipments, and machines. Surgeons constantly work on developing new surgical techniques. Research studies are needed to evaluate all such new inventions to find out whether they are superior to those that are presently being used. All the new tests, drugs, devices, equipments, interventions and surgical techniques are the outcome of research in biomedical sciences. The prime and the most important purpose of research is to improve patient care in all possible ways.

CHOOSING A TOPIC FOR RESEARCH

The first step in starting a research study is to choose a topic for research. The topic must be related to the area of your interest. You should also consult your colleagues and seniors for their suggestions regarding a good topic. Attending conferences, seminars, and workshops and reading journals also gives you good ideas regarding topics for new research. In short keep your eyes and ears wide open while looking for a topic. If the topic is vast like mental depression identify important areas in that topic and choose to work on some of these areas. It is very rewarding to concentrate on controversies and/or gaps in the knowledge in your chosen topic. It is not worth while to spend energy, time and money to reconfirm universally accepted facts. But a study aimed at challenging any aspect of these accepted facts should get your top priority. Work on topics that really interest you, studies that are meant to find answers to questions you are dying to answer, and studies that aim to challenge current beliefs. One must continuously question everything that we do and ask oneself whether that is the best way of doing things and why one should not try to find a better way of doing things. A good researcher is like a child who is constantly curious, perpetually asking questions and always demanding answers. Given a choice assign priority to studies which have greater relevance to diseased people. However, for any reason you are required to work on a topic not of your choice say in the interest of your institution or department do so with all sincerity and complete dedication.

CHAPTER TWO

Types of Research Studies

RESEARCH STUDIES

Research studies are of many different types depending on the purpose of the study. One must choose an appropriate type of study, the one most suited to provide an answer to the question researcher is wanting to find an answer to.

The types of Research studies can be classified as shown in Figure 2.1.

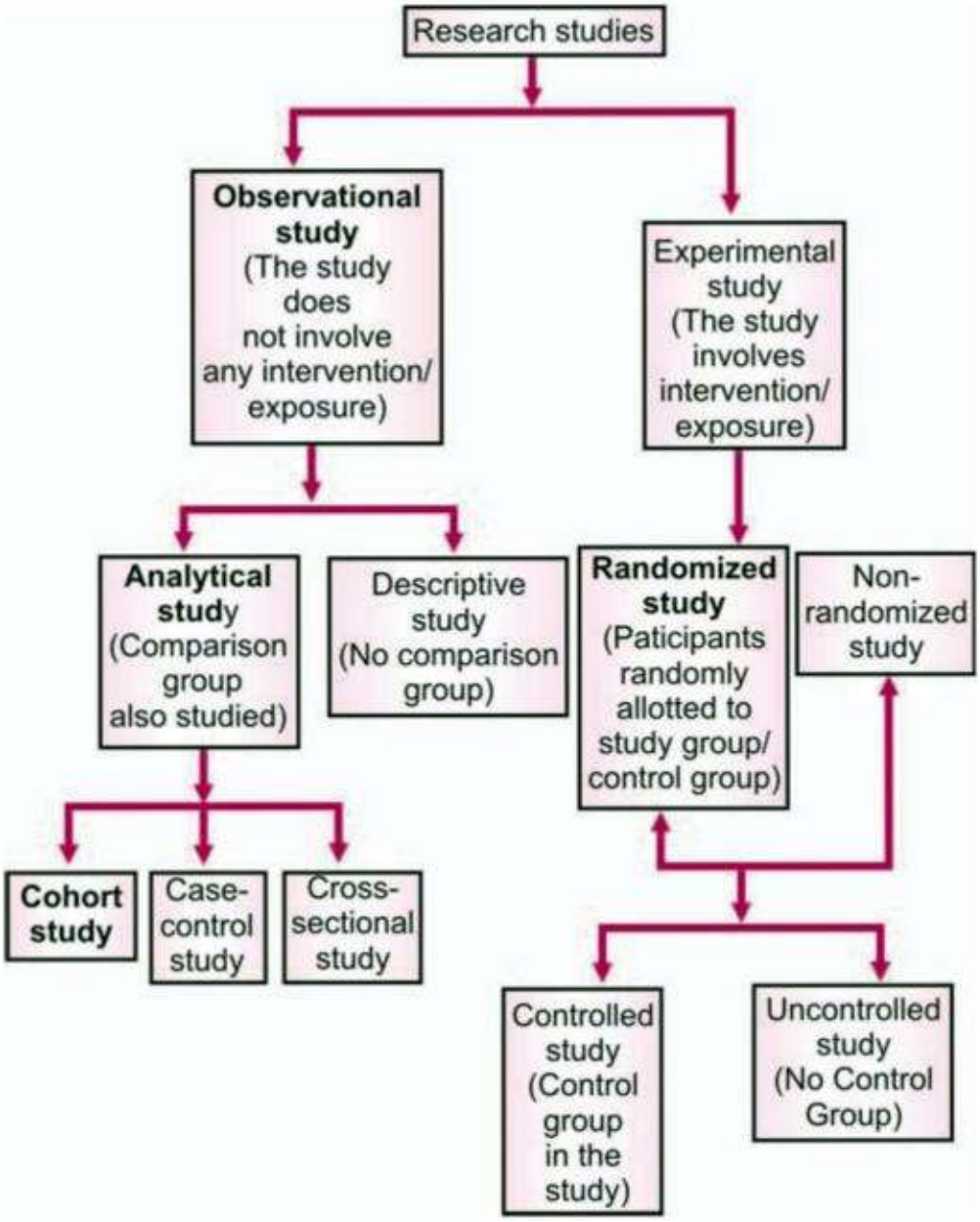


Fig. 2.1: Tree diagram showing types of research studies

COHORT STUDIES

A cohort study is a forward looking or prospective study that moves logically from exposure to outcome. Since these studies are forward looking, they enable assessment of the etiology and natural history of the disease, the incidence rates, relative risks, hazard ratios and survival curves (these terms are explained in chapter 5). For example, you can observe a group of smokers and a group of nonsmokers over a period of time and observe how many in each group develop

lung cancer. The disadvantages include greater cost, longer time and larger losses to follow up which all can introduce bias into these studies. Incidentally, the word cohort has its origin in the Roman concept of cohort to indicate an army of 500 soldiers acting as a group.

CASE CONTROL STUDIES

Case control studies establish an association between exposure and outcome, but in the opposite direction. They start with the outcome and look backwards at the exposure. For example, a case control study on association between peptic ulcer (outcome) and use of NSAIDs (exposure) will start with identification of patients with peptic ulcer as "cases" and those without peptic ulcer as "controls". The researcher will then go back in time to ascertain exposure to NSAIDs in each of the two groups to draw inference about the association between peptic ulcer and use of NSAIDs. These studies are thus retrospective or "backward" looking. They are relatively easy to conduct, are of short duration and cost less. For diseases that take a long time to manifest for example cancer or neurodegenerative disorders, a case control study presents a good study design, since doing a cohort study would take a long time. Case control studies are however susceptible to biases particularly with regard to choice of the control group and assessment of exposure. They also give an estimate of the odds ratio (OR) but not the relative risk (RR). (Refer chapter 5 for OR and RR).

CROSS SECTIONAL STUDIES

Cross sectional studies measure the exposure and outcome concurrently or at the same time. For example, a study which looks at the extent of hyperlactatemia in patients receiving stavudine can be cross sectional by studying a 1000 patients over a month's time who have received stavudine for the past 2 years. While these studies are easy to conduct and relatively inexpensive, the cause and effect relationship can become difficult to ascertain. Cross sectional studies are like still films, while case control and cohort studies are like video films.

RANDOMIZED CONTROLLED TRIAL (RCT)

Why use Controls?

When you see a pretty girl passing by, you say "Oh what a beautiful girl". When

a prettier girl follows her, you say "Wow, she is more beautiful". Here, you compare the beauty of the second girl with that of the first. The first girl is a comparator and acts as a control against whom the beauty of the second girl is compared. The situation is identical in clinical research whose main purpose is to find better ways of patient care. There is nothing better than RCT to determine whether one intervention is better than another. This invariably involves comparing a new intervention with the currently practiced one. The two interventions need to be tried on two comparable groups of patients and the results compared. The two groups must be comparable or similar in all possible features or characteristics. The group receiving the new intervention being studied is designated "treatment/intervention" group while the group receiving currently practiced best available intervention is called "control" group. The control group enables an unbiased estimate of the efficacy of the new intervention/treatment vis-a-vis the one currently in vogue.

Incidentally, it must be noted that all participants in research, whether they belong to study or control group, receive in equal measure additional benefits from better attention, greater care and more emotional and psycho-logical support than patients under routine care who are not included in the study.

The Concept of using Placebo as Control

There are situations where there is no effective treatment available. Do we still need a control group and if so, where do we get it? Yes, we do need a control group because a person receiving the drug under trial, even though it may not have worthwhile therapeutic/pharmacological action, may feel better due to the psychological effect of receiving some medicine. Two and a half millennia back, Hippocrates said that it is good remedy sometimes to do nothing. John Gaddum a British Pharmacologist (1900-1965) stated that a patient may recover in spite of drugs or because of them. What group of patients can be used as a control group? We can give placebo to a group of patients who would act as controls. Placebo is an inactive substance masquerading as drug. For practical reasons it must be made to appear exactly like the drug under trial, whether in the form of tablet, capsule, suppository or injection. To make a placebo that is exactly like the drug being studied is not always as simple as it sounds. It often taxes the pharmaceutical company's expertise, skill and resources to make a placebo identical in appearance, size, shape, weight, taste, etc. We need not discuss here the problems and difficulties involved therein.

It must be emphasized that it is unethical to use placebo when effective treatment is available since it denies treatment to patients merely because they are participating in a clinical trial and secondly because we are looking forward to a treatment better than currently in use and not just a treatment which is useful. Placebo control should be used only if no effective treatment exists for the disease - for example muscular dystrophy, inherited neuropathy and inherited metabolic disorder like lipidosis.

Do We Always Need Controls?

A good scientific clinical trial almost always necessitates a control group for comparison with new intervention. But there are exceptions. If a new intervention gives dramatic results, especially in a condition with high mortality or serious consequences (like rabies and tetanus), controls have no ethical or moral justification. When Pasteur tried rabies vaccination in 1884, or when penicillin was tried for pneumococcal pneumonia in the 1940s, controls had no justification. In general, controls are mandatory for short duration diseases having some effective treatment or spontaneous cure/remissions.

The Concept and Importance of Randomization

The basic perquisite of a controlled study is that every participant in the study must be similar to any other participant irrespective of his belonging to the treatment group or control group. He must be similar in all possible respects except in receiving the type of intervention. This is achieved by designing strict uniform criteria for recruitment, inclusion and exclusion. Having achieved this, included participants have to be allotted to either of the two groups. While doing this, one must remember that it is practically impossible to ensure that each and every participant is similar or matching in all respects. This is because there can be unknown factors affecting the course or outcome of a disease which could remain unmatched. This difficulty is overcome by adopting a process of allotment to the two groups which gives each participant a fair and equal chance to be assigned to either of the two groups. This ensures that the two groups are as similar at the start of the intervention as practically possible. This process is called randomization. The alternative of leaving the allotment to the investigator cannot be scientifically accepted since the investigator may have biased views about the efficacy of the intervention and/or the possible benefits of the

intervention accruing to his individual patient recruited in the study.

How is Randomization Achieved?

An equal opportunity/chance to enter study group or control group can be offered to every participant in varied different ways. The simplest would be tossing of a coin which gives a 50:50 chance to everyone. Uniform method of tossing the coin and a significance of head/tail showing up have to be decided in the design of a study and followed meticulously every time the coin is tossed which must be done just before starting intervention administration to a participant. In spite of its simplicity, it is a tedious process, inconvenient if sample size is large and impractical to use in a operation theater. A good method is to employ random number tables that are freely available. Alternatively computer generated numbers are used instead. Those recruiting participants and conducting the study should not be involved in the assignment of a group to a participant. This assignment is kept in sequentially serially numbered sealed envelopes one of which is opened in a sequential manner just before administration of intervention to a participant. For ensuring validity randomized assignments are done by persons not connected with research study in any way. Some research workers conveniently use simpler methods which have no legitimacy and validity. Assignment based on odd or even number of the last digit of the participant's outpatient case paper, indoor case paper, bed number, date or month or year of birth are some of them which all can be easily manipulated by some biased person involved in the study and hence not acceptable.

Types of Controlled Studies

Controlled studies vary depending upon the types of controls employed in the study. In concurrent control studies the intervention group and the control group are studied at the same time. These studies can be done with or without random allotment of the participants to the two groups.

Concurrent randomized control studies are most desirable and can be considered a gold standard in the conduct of research. But sometimes it is difficult to conduct randomized studies because the investigators or participants or both have preconceived notions that new interventions are always better (incidentally, if the new intervention is indeed better, there is no need to do the

trial) and they cannot be convinced to agree for randomization to administer or receive standard treatment or placebo therapy to some participants. In such situations, concurrent non-randomized studies are conducted. They are preferably done by using one unit in the hospital for the intervention group and another for the control group or by using patients in one hospital for intervention and in another for control. This is more readily possible if a standard treatment exists and is offered to the control group. Such concurrent, non-randomized controlled trials are quicker and cheaper to carry out than concurrent randomized controlled studies. But they carry less credibility because severity of the disease, prognostic factors, social and financial status, diet, religion, sex etc are difficult to match adequately. Sometimes, unpublished data retrieved from hospital records or data obtained from recently published literature can be used as control for comparison with data derived from intervention group study. Such non-randomized, non-concurrent studies are designated as historical control studies. These obviously have much less credibility since treatment and control groups have poor comparability. Such studies can be rapidly conducted with half the resources and cost. They are useful for pilot studies and also in diseases having poor prognosis or great fatalities (eg malignant hypertension) when the clinician investigator refuses to deny new treatment under study to his patients on ethical grounds. It can also be used when it is difficult to recruit participants because they insist on receiving only the new treatment. Historical controls have inbuilt limitations because diagnostic criteria (normal levels of serum cholesterol), new technology (automation in laboratories, digital X-rays, MRI), patient awareness (leading to early diagnosis of diabetes, hypertension, breast and cervical cancer), lifestyle changes (diet, fast food, smoking, exercise) etc would make the treatment group and control group non-comparable. Crossover study is another way of conducting randomized controlled trials. Here, every participant is used twice, once for intervention and once for control, and acts as his own control reducing problems of matching and permitting smaller sample size. It is apparent that cross over study cannot be employed for acute illnesses where cure or death results in a short period of time. In this type of study, participants are randomized to treatment and control groups. After a predetermined period of the intervention depending upon the therapeutic efficacy of the intervention both the groups are given placebo to nullify the carry over effect of the intervention and ensure their return to baseline status. This period is called "washout" or "cooling" period and its duration is decided by the pharmacodynamics of the drugs administered. After this period, the groups are interchanged and the

original control group receives the new treatment, while the original intervention group becomes the control group.

Blinding to Prevent Bias

Bias arises at various levels - participants, treatment administrators, follow-up examiners, interpreters of the findings, outcome evaluators and ancillary staff involved in the study. Bias at different levels can be prevented by hiding from people involved in the study the nature of intervention (new intervention being studied, standard intervention in use, placebo or inactive intervention). This process of hiding is called "blinding" or "masking" and plays a vital role in making the study credible and can be done at multiple levels.

Patients invariably believe that the new treatment is better than the old one and this prejudices the patient in favour of the new treatment. This can be prevented by blinding the patient alone, which is called a single blind study. Even clinicians often believe in the superiority of the new drug therapy and need to be blinded. When the clinician and the patient both are blinded, the studies are called double-blind trials. Blinding the statistician also by not revealing the blinding until the statistical analysis is completed is called triple blind study. Ideally, blinding code is revealed only after the entire study is completed.

In any trial unblinding may be necessitated in a particular participant's interest - e.g. when he develops a serious problem which the clinician suspects may be due to the adverse effect of the drug. Unblinding may also be done during the trial when a great obvious benefit or harm in one of the groups is revealed.

Limitations of Blinding

Single blind trials are simpler to design than double blind trials, which are simpler than triple blind trials. Blinding trials though not easy to execute are desirable, make the study credible and increase its validity. Everyone involved in a blinded study is curious and always looks for ways to break the blind. Participants try to study the drug they receive by assessing size, weight, color, coating, odour, taste and effect of degradation of the tablets and even the contents of the capsule. They exchange this information and their evaluation of efficacy of the drug with similar information from other participants when they

meet in the waiting room of the clinic or hospital. Blinding may thus get compromised. Even investigators and helpers are curious to try similar direct or indirect ways. In drug trial, much of the blinding depends on perfect matching of the two drugs being administered. This is not easy. Cross over studies particularly need perfect matching since every participant receives the two drugs though at different times. Trials may sometimes get unblinded because the known pharmacological effect of one of the drug may become very obvious or some serious though known side effects unexpectedly appear (eg GI tract bleeding due to aspirin). A trial of ascorbic acid for common cold published in 1975 (JAMA 1975; 231:1038-1042) can convince any researcher about the need for perfect blinding.

It is often advisable to assess the effectiveness/ soundness of blinding after the study is over but before the randomization and blinding are decoded. Participants and even the staff are asked to make a guess which should normally be correctly done by half of them. Greater the percentage of correct guess greater the suspicion of unblinding having occurred. Correct guess by much less than half the people suggests non-admittance of unblinding.

Other Types of RCTs

Cluster orgroup randomization involves randomization by groups of subjects (eg public schools in a city) or by communities (eg villages) or by religion or by ethnicity. This is simpler than randomizing each and every participant individually. Since sampling and randomization is done group wise even analysis of results is done on the basis of groups and not individuals.

Hybrid RCTs can be used when substantial data is available from hospital record or published literature about the standard intervention in use. Here only a small sample from the participants is randomized to control while the rest receives new intervention under study. Such studies lie in between concurrent RCTs and historical control studies. This enables the study with fewer participants but carries the drawbacks of historical control studies.

In Factorial RCTs the participants are randomized into one of the two different interventions and a single control group. Findings in each intervention group are analyzed comparing with the findings in the same single control group. One control group simultaneously acts as a control for two different

intervention groups. This is a device to save costs, time and resources.

LARGE SIMPLE CLINICAL TRIALS

Randomized controlled study is the gold standard study for clinical trials beyond any doubt. However, as discussed above there are situations where it is not practical to do RCT. Under these situations, a simple trial or a straight trial comes handy. Obviously, the larger the sample size of the trial, the greater the validity and reliability of the findings.

DESCRIPTIVE STUDIES

These represent the initial foray into research and are relatively easy to carry out as data is readily available and there are very few ethical issues. They may describe either individuals or populations. These aim at finding out the prevalence of a disease or of a physiological or pathological parameter. Estimating fasting blood sugar or T3 levels in a group of people or haemoglobin or blood pressure in women with second trimester pregnancy are some examples. These studies give prevalence per se without looking at causation. They are useful epidemiological tools. They are also useful for looking at associations or relationships, for example between ethnicity and obesity, hemoglobin and leucocyte count, age and ovarian cysts etc. They provide the initial information which can be used to generate a hypothesis and to perform later on rigorous controlled studies. A population survey for any parameter is a descriptive study. Case reports and case series are also descriptive studies. However, descriptive studies constitute the lowest rung of evidence.

DIAGNOSTIC TESTS

Early diagnosis of a disease or its possible/probable existence goes a long way in improving patient care. For this purpose new diagnostic tests are developed by inventors, tested by researchers and evaluated by statisticians. Efficacy of a new diagnostic test has got to be compared with that of a current gold standard test. This implies that both the new test and the gold standard test must be performed on every person or subject included in the study.

Let us say that visual inspection of cervix is to be evaluated for diagnosing cervical cancer and four quadrant cervical biopsy is the gold standard test. A

hypothetical study performing both the tests on 2000 subjects gives the results shown in Table 2.1.

Table 2.1: Results of a hypothetical study evaluating visual inspection of cervix

	Gold standard test (Four quadrant cervical biopsy)		
Visual inspection of cervix as screening test	*Cervical cancer present*	*Cervical cancer absent*	*Total*
Positive	400 (a) (True positive)	100 (b) (False positive)	500 (a+b)
Negative	200 (c) (False negative)	1300 (d) (True negative)	1500 (c+d)
Total	600 (a+c) (Affected)	1400 (b+d) (Unaffected)	2000 (a+b+c+d)

Sensitivity of a test measures the proportion of those with disease who are correctly identified by the test under study. The new test has correctly identified 400 out of the 600 affected by the disease giving sensitivity of 400 (a)/ 600 (a+c) or 66.6%.

Specificity of a test measures the proportion of those not having a disease who are correctly identified by the test under study. The new test has correctly identified 1300 out of the 1400 not affected by the disease giving a specificity of 1300 (d) / 1400 (b+d) or 92.8%.

Sensitivity and specificity of a test are independent of the prevalence of the disease and hence are an inherent property of the diagnostic test. The clinician however wants to know the probability of the disease being present if the test is positive i.e., positive predictive value (PPV) of the test and the probability of the disease being absent when the test is negative i.e., negative predictive value (NPV) of the test. In the above example the positive predictive value (PPV) of the test is 400 (a) / 500 (a+b) or 80% and the negative predictive value (NPV) is 1300 (d) / 1500 (c+d) or 86.6%. Unlike sensitivity and specificity the predictive values are dependent on the prevalence of the disease. The lower the prevalence

the lower the clinical relevance of the positive predictive value of a test. An ideal screening test should have very high sensitivity and very high specificity. Incidentally, ESR as a diagnostic test for tuberculosis and CA-125 as a diagnostic test for ovarian cancer both have low sensitivity, specificity, PPV and NPV and are of little use to clinicians as diagnostic tests.

Incidentally a clinician would often desire a trade off between sensitivity and specificity depending on the relative consequences of false positive and false negative tests. It must be noted however that consequences of false positive and false negative tests are usually not directly comparable.

META-ANALYSIS AND SYSTEMATIC REVIEWS

Often the terms systematic review and meta-analysis are used interchangeably, but there are differences between the two. A meta-analysis is a statistical analysis that puts together results from different published studies which have a similar research hypothesis and pools them to calculate a single average statistic or result. This is useful since it is often not possible for individual investigators to undertake studies with large sample sizes and many studies in literature are often "under powered" to answer a research question. A metaanalysis involves two steps viz; extraction of data from each individual study and calculation of the result of that study and secondly pooling the data to calculate an average result across the studies. Greater weightage is given to those studies which give better and more information.

A systematicreviewon the other hand is a literature review focused on a single research question which tries to identify, appraise, select and synthesize all high quality research evidence relevant to that question. It may or may not include a statistical component. A meta-analysis will necessarily include a statistical component. The best known source of systematic reviews is the Cochrane collaboration (see Chapter 7), although many other journals do publish systematic reviews. Systematic reviews and meta-analysis are generally regarded as the highest level of medical evidence by evidence based medicine professionals.

MULTICENTRIC TRIALS

Many studies need a large sample size and many others need to be completed in

shorter time period. When trials are conducted on conditions which are comparatively rare for example eclampsia, it is not possible to get all the needed patients from a single centre. Hence, the trial has to be conducted concurrently at many centers. When a new intervention expected to be effective is developed for a condition, which has no available treatment, it is desired that the study be completed in a short time so that the benefits of the intervention quickly reaches the patients. Here also, conducting a multicentric trial becomes very practical and desirable.

The most important thing about a multicentric trial is that all the centers must meticulously and precisely follow the study protocol as worked out by the sponsors of the study. All the data collected has to be sent periodically to the sponsoring body for interim analysis. It is the sponsoring body who submits the paper for publication. Individual centres cannot publish their data independently at any stage.

NEW DRUG DEVELOPMENTPHASE I-IV STUDIES

When a new drug is developed, it first undergoes animal toxicity testing. Subsequently, it is studied in four phases. Phase I studies are carried out to find the safety and pharmacokinetics in approximately 20- 80 normal healthy volunteers. Phase II studies, also called therapeutic exploratory studies or proof of concept studies, test the drug for the first time in a few hundred patients with disease. The dose to be used in actual clinical practice is also found out here. Phase III studies are called therapeutic confirmatory studies and here the drug is tested in a few thousand patients. After successful Phase III trials, the regulatory authorities permit the marketing of the drug. After marketing, the pharmaceutical companies monitor the safety in the large population exposed to the drug. This is called post-marketing studies or Phase IV studies which sometimes pay attention to special groups like children and aged people. Occasionally, post-marketing studies lead to findings of new indications for the use of the drug as was the case with vigra or sidenofil.

CHAPTER THREE

Planning and Design of A Study

HYPOTHESIS AND HYPOTHESIS TESTING

A hypothesis is usually a hunch, a reflection, a conjecture or a supposition which an investigator uses to explain his observations. When two or more groups are being compared for differences or when one is exploring relationships between groups, two basic hypothesis or presumptions are usedthe null hypothesis or Ho and the alternate hypothesis or H1. If an investigator is trying to look for a difference between group A and group B, then the null hypothesis would state that there is no difference between A and B, while the alternate hypothesis would state that a difference does exist. These hypotheses are similar to presumption of innocence (null hypothesis) of people being tried in courts of law and attempt to present proof to prove them guilty (alternate hypothesis). The alternate hypothesis if accepted shows a difference between the two groups studied. When the movement is in one direction only, the hypothesis is called one directional or unidirectional or one sided or one tailed. Several published studies in recent times use a "one directional" hypothesis. These studies are called as non-inferiority studies. An example is the use of combination vaccines in pediatrics. When vaccines are combined together (quadrivalent, pentavalent), they offer the convenience of a single injection and greater compliance. However, the antibody response after administration of the combination vaccine may not be the same as

when individual vaccines are given singly. The investigators and regulatory authorities often accept some amount of "inferiority"; the trials for which are called "noninferiority" designs meaning "no worse than" in terms of antibody response with the combination vaccine in lieu of the advantages they offer. The hypothesis in these cases is unidirectional since antibody responses are looked at only in one direction. A tail or a side simply refers to direction of movement of the variable. Most null and alternate hypotheses in medicine are bi-directional or two sided or two tailed. That is why the statistics section in published papers usually states the "two sided" or "two tailed" tests were used. This is based on the premise or presumption that biological variables are capable of bi-directional movement (eg weight as a variable can increase or decrease and a new drug can be better or worse).

STUDY SUBJECTS, PARTICIPANTS AND RECRUITMENT, INCLUSION, EXCLUSION CRITERIA

Recruiting patients/volunteers is always the most challenging aspect of any research. Since most studies have (apart from descriptive studies) inclusion and exclusion criteria that need to be satisfied prior to enrollment, finding subjects that fall within limits as specified by these criteria is crucial. The selection process usually begins by "screening" patients or volunteers for suitability and assessing parameters to see if they satisfy all inclusion criteria and have none of the exclusion criteria. Inclusion criteria are usually disease specific and often also involve laboratory parameters which must fall within a given range eg moderately anaemic with haemoglobin 6 to 8 g/dL. Exclusion criteria are those which ensure that patient safety is not jeopardized. For example, a study on Plasmodium vivax malaria will have patients whose peripheral smear is positive for vivax to be included and will exclude those with falciparum malaria and mixed infections. For most drug trials, pediatric population, pregnancy, lactation and compromised liver and renal function are often exclusion criteria.

Recruitment can become a time consuming process. The more stringent the inclusion and exclusion criteria, the more difficult it is to find acceptable subjects. Also the ability to extrapolate/generalize becomes difficult. In some countries advertisements are floated to find willing volunteers for research studies. In developing countries recruitment is most commonly done from hospital inpatients and outpatients and sometimes relatives and visitors of the patients. For epidemiological studies community leaders can help recruitments.

STATISTICAL ERRORS

When two groups are compared the null hypothesis presumes that there is no difference between the groups. The results of the analysis may have the following possibilities:

1. The results in the two groups are different and the study picks up the difference (correct)
2. The results in the two groups are different, but the study fails to pick up the difference (incorrect)
3. There is no difference in the results between the groups, but the study finds or picks up a difference (incorrect)
4. There is no difference in the results between the groups and the study also finds no difference (correct).

This means that two types of errors can occur when the study is carried out. These possibilities are depicted in Table 3.1.

Table 3.1: Type I and Type II errors

	There is a difference	*There is no difference*
Reject null hypothesis	Correct	Type I or alpha error
Accept null hypothesis	Type II or beta error	Correct

A Type I error also called the alpha error or false positive error can be defined as "finding a difference when a difference does not exist". Since this can erroneously lead to the acceptance of the new medication or new procedure, it is also called as the "regulator's error" since a new drug can get approved by the regulator based on the nonexistent difference between the two drugs. If the new drug is less safe and less efficacious it can cause harm to the patients. Hence the alpha error is kept low and 5% is an arbitrarily agreed upon low value and set at a low tolerance level of 5%. The figure of 5% is merely convention and not a magic number. It simply means that when a difference between the two groups is

seen, then the probability that the difference is a true difference is more than 95% and the probability that there is an error is less than 5%. Thus the alpha error is closely linked with the P value and when two groups are found to be different, the significance value is stated as $P < 0.05$.

A Type II error or beta error or false positive error can be defined as "not finding a difference when a difference actually exists". While this is also erroneous, it is viewed as being less serious than the alpha error and is also called the "investigator's error". Conventionally, this is set at 10% or 20%, the values higher than the alpha error. Beta error is set higher than alpha error because the consequences of beta error are less serious than those of alpha error. It is possible to set both alpha and beta errors really low but this will lead to an increase in the sample size and hence the trade off.

POWER OF A STUDY

The inability of a study to find a "difference" when it actually exists is called beta error. Conversely, the ability of a study to find a "difference" should a difference actually exist is called the "power of the study". The power of the study is inversely related to the beta error. If the beta error is 10% or 20%, then the study is said to have 90% or 80% power respectively to detect a difference.

SAMPLE SIZE CALCULATION

This is discussed in Chapter 5.

INTERVENTIONS

An intervention can be defined as that the effect of which is studied during the conduct of the study. An intervention can be a drug, a vaccine, a diagnostic test, a device, or a surgical procedure. Even mere counselling or educational sessions can be an intervention in a study on prevention of a disease like gastrointestinal infection or STD. An intervention can be studied for various purposes like treatment or prevention of a disease, safety, efficacy, utility, effect on quality of life and cost effectiveness.

BIAS AND CONFOUNDERS

Any study or research or clinical trial that is done should be "valid". Validity is

of two types-internal validity and external validity. Very simply put, internal validity is defined as the ability of the test or study to measure what it is supposed to measure. External validity on the other hand is the ability of the study to generalize or extrapolate its findings to the population since all studies are done on samples. While both internal and external validity are inter-related, internal validity is affected by "bias".

"Bias" or prejudice has several definitions. Some of them are listed below.

1. The end result of bias will be drawing conclusions which are inaccurate and erroneous or a "deviation from the truth".
2. Bias is any trend in the collection, analysis, interpretation, publication or review of data that can lead to conclusions that are systematically different from the truth.
3. Bias is a process at any stage of inference tending to produce results which depart systematically from true values.
4. Bias is a systematic error in the design or conduct of a study.

Since bias is an error, it is important to note that error itself can be of two types - (1) An error that occurs "by chance", which can happen with any study and is called "random error". (2) Bias on the other hand is a "systematic error" which must be anticipated right at the beginning of the study and minimized to the extent possible.

There are several types of biases and different authors have classified them differently. They can be broadly divided into-

1. Selection bias Selection bias may result if an investigator decides to assign sicker patients to the new medication being tested rather than to the standard therapy under the assumption that the new medication is better than the standard medication.
2. Information bias Information bias also called recall bias and results from an incorrect association between exposure and outcome. For example if a researcher were to study the association between drug X used during pregnancy and congenital heart defects in a case control study, mothers with a child with a congenital heart defect are more likely to recall the consumption of drug X than those whose children are normal. This bias

commonly affects observational studies.

3. Confounders or confounding. A confounder is a third factor or variable which is associated with the exposure and affects the outcome, thereby affecting the accurate measurement of the outcome. For example, in a study linking the association between NSAID use (exposure) and peptic ulcers (outcome), age would become a confounder since elderly people are more susceptible to peptic ulcers due to gastric atrophy. Confounding can be minimized by - 1) matching and 2) stratification. In the example of NSAIDs and peptic ulcer, cases and controls can be matched by age. Optionally, when the study is completed, stratification can be done whereby two groups of elderly and the non-elderly are analyzed separately and the effect of NSAIDs looked for. The process of randomization also ensures that confounders are equally distributed across the two groups under study. This however may not still account for unknown confounders.

END POINTS

An end point in research is a quantitative measurement which is required to fulfill the objective of the trial as determined by the research question. There are various classifications and definitions of endpoints.

1. Clinical endpoint A direct measure of how a patient feels, functions or survives eg mortality / survival or resolution of symptoms of disease.
2. Hard endpoint A clinical landmark that is well-defined in study protocol, definitive with respect to disease process and not subjective eg reaching hemoglobin 12g/dL in anaemics or serum cholesterol of 200mg/dL in hypercholesterolomics or time to metastases development in a cancer patient.
3. Soft endpoint. These are not directly related to disease process and/or may require subjective assessment by patient / physician eg., quality of life and symptom questionnaires.
4. Primary endpoint An endpoint that provides evidence sufficient to fully categorize clinically the effect of a treatment that would support a regulatory claim for the treatment.
5. Secondary endpoint Additional characterization of a treatment that could not, by itself, be convincing of a clinically significant treatment effect.
6. Surrogate endpoint: This is a laboratory measurement or physical sign used as

a substitute for clinical endpoint. It by itself may not confer direct clinical benefit to the patient. For example CD4 count in a HIV infected patient, X-ray changes and CT scan changes.

7. Composite endpoint These are used when events/ outcomes of interest are rare (eg mortality in patients with prostatic cancer) and when sample sizes become too large for timeliness of the study. Composite endpoints ensure that studies are completed in a reasonable period of time. For example, in a study of coronary heart disease, the primary end point can be a composite of mortality, duration of hospitalization, subsequent hospitalization for unstable angina, revascularization and non-fatal repeat myocardial infarction.

Primary endpoint is the single most important outcome measure in the study. It is also the outcome upon which the sample size calculation is based. Since a study can easily look at more outcomes, secondary endpoints are those which are also studied alongside but are less important than the primary endpoint. For example, in a study on the effect of a drug in myocardial infarction, death may be the primary end point and non-fatal recurrent myocardial infarction the secondary endpoint. In a study on malaria, parasite clearance time would be the primary endpoint, while gametocyte clearance would be the secondary endpoint.

Surrogate endpoints are used when it is either difficult or impractical to look at the primary endpoint. A classical example is serum cholesterol and the use of cholesterol lowering drugs. Since hypercholesterolemia is linked with heart disease, an ideal endpoint would be mortality. Since this will take a long time, reduction in serum cholesterol is taken as a surrogate endpoint.

Endpoints in general should be few so that they are easy to achieve during the study. They should also be sensitive, easily measurable and clinically relevant. Both safety and efficacy end points are equally important.

FOLLOW UP

All research studies require patients' follow-up over a period of time. The nature of the follow-up will vary with the type and objective of the study. For example, studies of analgesic efficacy of NSAIDs in toothache and dysmenorrhoea would require a short follow up of 24-48 hours. Those of febrile illnesses like falciparum malaria would need at least a month's follow up. In studies in oncology or cardiology involving survival, time to disease progression and

mortality followup is a crucial component. The duration of follow-up is usually outlined in the informed consent document and the investigator must ensure that the patients/subjects in the study are aware of this and understand it fully. Losses to follow up can occur due to a variety of reasons like adverse drug reactions, boredom, difficulty in traveling long distances, feeling better and loss of wages during follow up visits. It is thus good for the investigators to compensate subjects for travel and work days lost to ensure adequate follow-up. Loss to follow-up if substantially different between two groups being compared can lead to erroneous results and create bias which must be avoided or minimized.

DATA COLLECTION AND DATA MANAGEMENT

Data can be generated/collected by the researcher during the course of his study by some of the following ways -

- Studying patients' records
- Interviewing participants
- Studying duly completed questionnaires
- Findings of clinical examination
- Laboratory investigations/reports
- Imaging studies - X-rays, sonography, CT scans, MRI.

Data must be collected accurately and recorded honestly. The protocol of the study must be followed very strictly without any compromise.

Data can be classified as primary and secondary or quantitative and qualitative. Primary data is the one which is collected by the researcher while conducting the study. Secondary data is the one collected by somebody else which the researcher is now using in his study. This data might have been found in hospital records, published articles and unpublished studies. Secondary data may not be accurate, may be biased and may have become irrelevant with the passage of time. However, it is very useful if it is appropriate for the study and is properly used. Quantitative data is the one which can be precisely measured like blood pressure, weight, height and serum sodium. Qualitative data cannot be measured with precision and is subjective like pain or feeling of depression.

In spite of all precautions and due care, errors do occur while collecting and

recording data. Errors may be due to mix up or oversight. Errors may be apparent by gross disparities or by unrealistic information like 20 year postmenopausal lady having natural conception and delivery a year back or a 16 year old girl having a 10 year old son. Sudden changes in patients' parameters can give rise to suspicion of errors during data collection. Errors in data collection can be detected by doing periodic scrutiny of the data. Corrective measures like repeat collection where possible, and eliminating such doubtful data is called data cleaning.

Recording and Analysis of Data

Data can be recorded on a master chart and then tabulated. Alternatively, data can be straightaway recorded in preplanned tables, graphs, scatter grams etc. Modern practice is to record the data electronically on computers. One must guard against inadvertent errors during such recording that may result from illegible writing of the original data or by wrongly reading similar digits like 1 and 7 or 5 and 6 or by skipping decimals or by mistakenly pressing the neighboring key of the computer.

Finally, all the data collected must be submitted to statistical analysis.

STATISTICAL EVALUATION OF THE DATA

The data collected makes only an information. This is converted into knowledge when the data is subjected to statistical tests and appropriate conclusions are drawn. The appropriate statistical tests have to be predecided in consultation with biostatistician during planning of the study.

FUNDING FOR RESEARCH

Every research, small or large, irrespective of its nature needs money. The researcher, therefore, has to look for funding agencies to support his research. Fortunately, there are many organizations which are willing to support good research. Some of them are-

1. Institutional research committees.
2. University research grants, research fellowships and research scholarships.
3. Research allocations from state governments.

4. National organizations for medical research like Indian Council of Medical Research (ICMR), Department of Biotechnology (DBT), Department of Science and Technology (DST), Council for Scientific and Industrial Research (CSIR), and Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy department of Government of India (AYUSH). Apart from funding research projects and granting research fellowships ICMR also gives research scholarships to undergraduate and postgraduate students besides supporting postgraduate thesis.
5. Medical Research Council of UK supports research studies even outside UK.
6. National governments.
7. Non-governmental charitable organizations (NGOs).
8. Pharmaceutical companies - Trials sponsored by pharma industries must follow the International Conference on Harmonization GCP guidelines (ICH-GCP). Many pharma companies have special funds allocated for research not related to their products and grant research fellowships.
9. International bodies like World Health Organization (WHO), Co-operative for Assistance and Relief Everywhere (CARE), United Nations Development Program (UNDP), World Food Program of the United Nations (WFP), United Nations Children's Fund (UNICEF), National Institute of Health (NIH, USA), Ford Foundation, Bill and Melinda Gates Foundation and Wellcome Foundation (UK) grant funds for research.

Application for funding must comply with the requirements of the particular funding agency. By and large the following information is needed by every funding agency-

1. Title of the research study and duration of the study.
2. Details about the institution, principal investigator and his co-investigators (qualifications, experience or training in research, previous publications etc).
3. Quantum of funds needed during various time periods of the study with budgeting of proposed disbursements / expenditures and also information about funds obtained or expected from other sources.
4. Ethics committee clearance.
5. Full details about the proposed research study and its methodology.
6. Clearances from concern authorities regarding use of radioactive materials

and genetic tissues when necessary.

7. Ctri registration number is an asset.

A good research study with proper designing should not have much difficulty in obtaining necessary funds for the study.

Incidentally, it must be added that medical students can present their research work at various fora like Inter- University Research Festivals, Moving Academy of Medicine and Biomedicine, LIMSC Netherlands and National Student Research Forum (USA).

CHAPTER FOUR

Ethics in Research

EVOLUTION OF ETHICS

This is discussed in detail in chapter 12.

PARTICIPANTS' RIGHTS

Unlike in the past research participants in clinical trials have several rights today. They have a right to full information, complete privacy, and total confidentiality. They cannot be included in the study unless they voluntarily give their consent. They can decline to participate upfront. They can decline to participate even after signing the informed consent form. They can withdraw at any point of time during the study without having to give reasons for doing so. The informed consent document ensures that the fact that they withdrew from the study will not be held against them and that they will continue to receive unbiased treatment at the institute. Participants are also entitled to travel expenses, compensation for loss of pay when visiting the research site for investigations or follow-up and compensation from the sponsor for adverse effects that occur during the study.

ROLE OF ETHICS COMMITTEES (EC)

An Institutional Ethics Committee (IEC) also known as the Institutional Review Board (IRB) is any board, committee or other group formally designated by an institution to review research proposals to approve the initiation of and to conduct periodic review of biomedical research involving human subjects. Their primary objective is to ensure that the rights, safety and well being of human

subjects is protected. The role of an IEC can be divided into 3 categories-

1. Before start of research- Review and approval.
2. While the research is in progress- monitoring of study.
3. After completion of research- review study report and archiving.

As per the ICMR 2006 guidelines and the amended Schedule Y of the Drugs and Cosmetics Act the EC should be composed of 10-12 heterogeneous members from different specialties and at least one member who is a nonscientist. The member secretary should be from outside the institution. A minimum of five members should be present to form a quorum and approve projects. It is recommended that ethics committees meet at least once a month. Decision making is by a majority vote. The EC also needs to evaluate Serious Adverse Events in a clinical trial as well as the reports of interim analysis. The EC also has the power to stop a study in case they feel that patient safety is being compromised.

COMMUNITY ADVISORY BOARDS (CAB)

These are boards that are primarily composed of nonscientists who act as a liaison between trial researchers and the community. They review protocols, monitor trials, and help educate and inform the rest of the community. Historically, they developed in the late eighties and early nineties in the United States in an attempt to quickly find and approve medications for people living with HIV/AIDS. Early CABs in the United States in fact were primarily of people living with HIV/AIDS. Today, these boards are present in both developed and developing countries and have community leaders and representatives from NGOs, universities and the media. The total membership is around 20 and a trial physician usually attends the CAB meetings.

MANDATORY EC APPROVAL

No clinical trial can be started without prior approval of the EC.

CHAPTER FIVE

Applied Biostatistics

INTRODUCTION

Statistics is a branch of mathematics dealing with analysis and interpretation of collected data. Today it is a speciality science and biostatistics is a superspeciality science dealing with biomedical sciences. Statistics pervades many aspects of our life like census, averages, inflation rates etc. Incidentally, the Census ordered by Augustus Caesar 2000 years ago appears to be the earliest recorded census, though the one ordered by King Herod could be an earlier one. Use of statistics in medicine is only a few centuries old. Statistical analysis should be accurate and comprehensive but not so complex as to be beyond the grasp of clinicians, administrators, policy makers and fund providers. Misuse of statistics is the greatest ill of medical science. Hence clinicians should know the basics of statistics.

INDISPENSABILITY OF STATISTICS

As medical practitioners, we should be practicing evidence based medicine. This is getting increasingly important with growing empowerment of the patient. But, where does the evidence come from? The evidence is basically generated from the data collected by research workers during their studies. However, all such evidence must be tested on the touchstone of statistical analysis. Statistics, hence, is indispensable in clinical research and its application to evidence based clinical practice.

BIOSTATISTICS AND THE CLINICIAN

A clinician has a morbid aversion to statistics. Most clinicians are numerophobic and hate numbers, figures, equations and formulae. They even feel threatened by them. They believe that understanding statistics needs familiarity with and knowledge of advanced mathematics. Hence, while reading an article in a journal, they skip the paragraphs dealing with statistics. They are thus unable to critically evaluate the evidence claimed by the authors of the article. In reality, understanding statistics does not require any advanced mathematics; just high school level mathematics is adequate. The second problem faced by clinicians is that statisticians have abstract concepts like a 5% probability sharply dividing the research outcome as true or false. But aren't 35% marks for passing high school examinations and 50% marks for passing medical school examinations arbitrarily decided? The third problem is about the statisticians' strange language. Statisticians talk of statistical tests as statistical tools. But then don't the clinicians also talk of diagnostic tools? When statisticians talk of standard error, error does not mean a mistake but variation in the data collected. In statistics, risk does not mean danger but the probability of an event occurring regardless of its nature (death or cure) or severity (mild, moderate or complete relief). Like statisticians, all professionals have their own lingo, which those dealing with them need to learn. Research workers and biostatisticians have to work in close co-operation and the clinician should understand the basics of statistics.

HOW MUCH STATISTICS DOES A CLINICIAN NEED TO KNOW?

Statisticians have an ever increasing number of tests for the analysis of data generated by researchers. Research workers should be familiar with about three dozen of them in order to have a meaningful dialogue with their biostatistician. A clinician who reads the outcome of a research study needs to be knowledgeable about just a dozen and a half of these tests. Neither the research worker nor the clinician needs to bother about the complexity of equations, formulae and calculations involved in statistical analysis. Basic concepts in statistics are very easy to understand and the clinician only needs to know about the application and the utility of the appropriate tests.

POPULATION, SAMPLE AND SAMPLE SIZE

Human beings vary widely based on their genetic makeup, geographical

location, religion, diet, social behaviour etc. The findings of a research study cannot be applied to every human being on earth. The findings are expected or intended to be applied to a certain group of people like people living in a geographical area, pregnant women, menopausal women, people more than 60 years of age, children below 10 years, diabetics etc, depending upon the design of a study. However every person in the group cannot be studied by a researcher. One cannot study thousands of pregnant women or diabetics in an area. One can study only a small number of them designated as sample of people or subjects to be studied. The result of the study is expected to be applicable to a much larger group of people. This larger group of people is called population or universe while the subjects studied is called a sample. How scientifically reliable it can be to apply findings in the sample studied to the population from which the sample size is drawn? Commonsense says the larger the sample studied the more reliably the findings can be applied to the population. A very small sample size serves no purpose and the study becomes superfluous. If one researcher studies only 10 patients and another studies 200 patients, the findings of the latter would obviously be more reliable. But the larger the sample size to be studied greater the resources needed in terms of money, facilities, time and manpower. We should study the optimum number, neither smaller nor larger. The biostatisticians work out this optimum or ideal sample size by their calculations. Different types of studies need different methods of calculating sample size though the underline principles remain the same. Basic principles of sample size calculation are easy to understand. For an example let us say a study is comparing the difference between the effects of two treatments. The sample size needed is decided mainly by-

1. The size of the difference which is considered clinically significant. The cure rate of 60 vs 62% may not be considered significant but a cure rate of 60 vs 70% may be considered significant. The researcher has to decide upon this clinically significant difference before starting study.
2. Acceptable alpha error or type I error which is the probability of falsely rejecting a true null hypothesis. This is usually set at 5% but may be set even at a lower level by the researcher.
3. Acceptable beta error or type II error which is probability of accepting a null hypothesis when it should be rejected. Since the consequences of beta error are less serious than those of alpha error (refer chapter 3) beta error is set at a higher level of 10% or 20%.

One must remember that during the course of a study some study subjects dropout due to various reasons like change of attitude to research, finding good benefits, experiencing side effects, moving out of town, etc. To compensate for these drop-outs which are also called attritions about 20 to 25% additions are made to the sample size calculated as above. Attritions depend on the inconvenience of intervention, invasive nature of follow-up evaluation and the frequency and number of follow-up studies.

Every publication of research findings must mention how the sample size was calculated or arrived at though a reader need not understand the nitty gritty of such calculations.

POWER OF A STUDY

This is described in Chapter 3.

PROBABILITY AND ODDS

Probability or "chance" is the fraction of times you expect to see the event occurring in many trials while odds are the probability of the event occurring divided by the probability of the event not occurring. When you toss a coin, the probability of it showing "heads" is 1 in 2 or 1/2 and so also is the probability of it not showing heads. Thus the odds of it showing heads are 1 (1/2 - '/z = 1). When you throw a dice, the probability of it showing 6 is 1/6, and the probability of its not showing 6 is 5/6. Hence the odds of it showing 6 are 1/5 (1/6 - 5/6 = 1/5). Figure 5.1 makes it very clear.

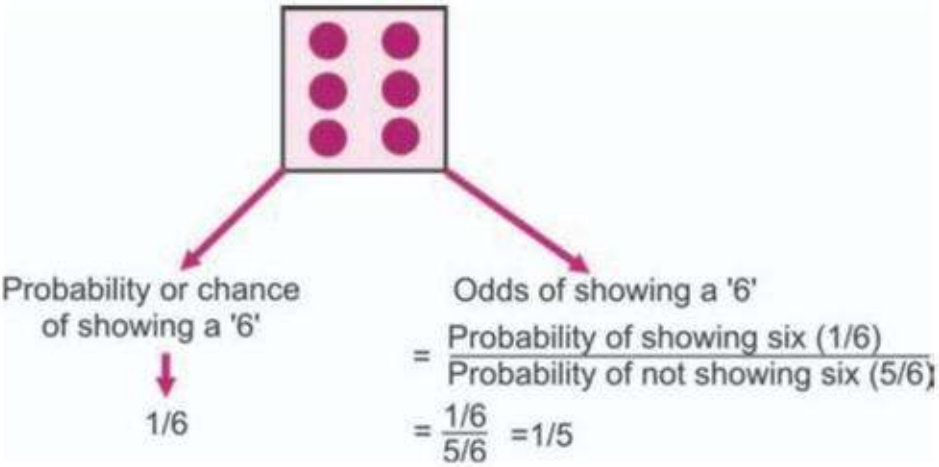


Fig. 5.1: Probability and Odds

MEAN, MEDIAN, MODE

Mean is the central value which is calculated by adding all the observations and dividing the sum by the number of observations. Median is also called the 50th percentile and is the central value when the data is arranged in an ascending or descending manner. Mode is the most commonly occurring value.

NORMAL DISTRIBUTION

Most biological values like weight, blood pressure, serum cholesterol etc differ from individual to individual. These values are distributed equally on either side of the mean value. These variable values are called "variables". For example, height is a variable. When values of several individuals being studied are plotted as a histogram, a line joining the top of the histogram columns assumes a bell shaped curve with the top of the bell curve representing the mean or average value. This distribution of variables is called "normal distribution". It is also called Gaussian distribution after the German mathematician CF Gauss, though the concept was originally developed in 1733 by the French mathematician De Moivre. Interestingly, Gauss is the only statistician in whose honour a postal stamp was released in Germany. Individual measurements are obviously greater or lesser than the mean measurement. In other words, individual measurements would "deviate" on either side of the mean which lies at the centre of the bell curve. Standard deviation (SD) summarizes how far the individual measurements are away from or "deviate" from the mean. Standard deviation as a measure of variability or dispersion was formulated by Galton in 1860s. One SD on either side of the mean includes 68% of the measured values. Two SDs include 95% of the values, while 3 SDs include 99.7% of the values (Figure 5.2). The greater the range of measured data, the flatter and wider the bell curve and greater the SD. Lesser the range the steeper and narrower the bell curve and lesser the SD (Figure 5.3 and Figure 5.4). If the mean and SD are known, the reader essentially knows as much as if he had entire data with him. As an empirical rule, large sample sizes tend to approximate normal distributions. Whether a data set is normally distributed or not can be analyzed using the Kolmogorov Smirnov test or the Shapiro-Wilk test. Data that is normally distributed is called parametric data and analyzed by parametric tests. Data that is not normally distributed is called "distribution free" data or "distribution

unknown data" and analyzed by using non-parametric tests.

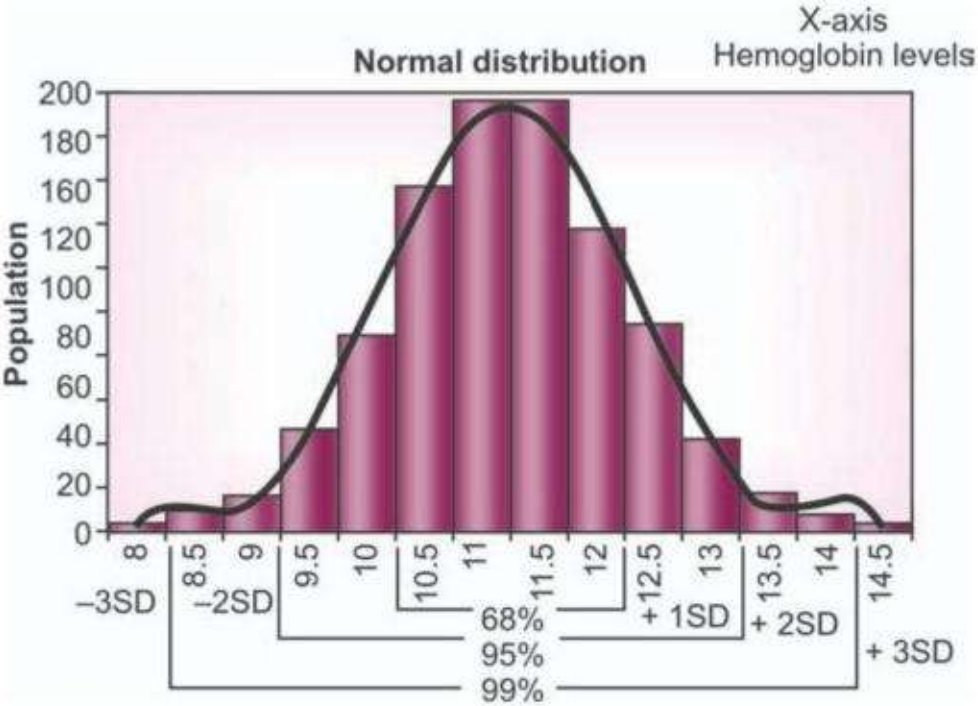


Fig. 5.2: Normal distribution showing bell curve and Standard Deviation (SD)

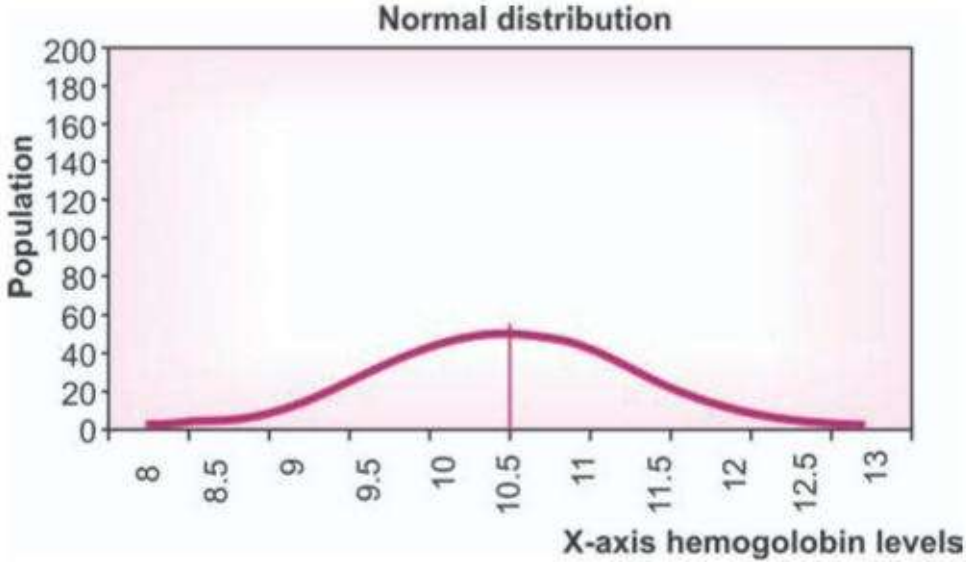


Fig. 5.3: Flatter bell curve of normal distribution

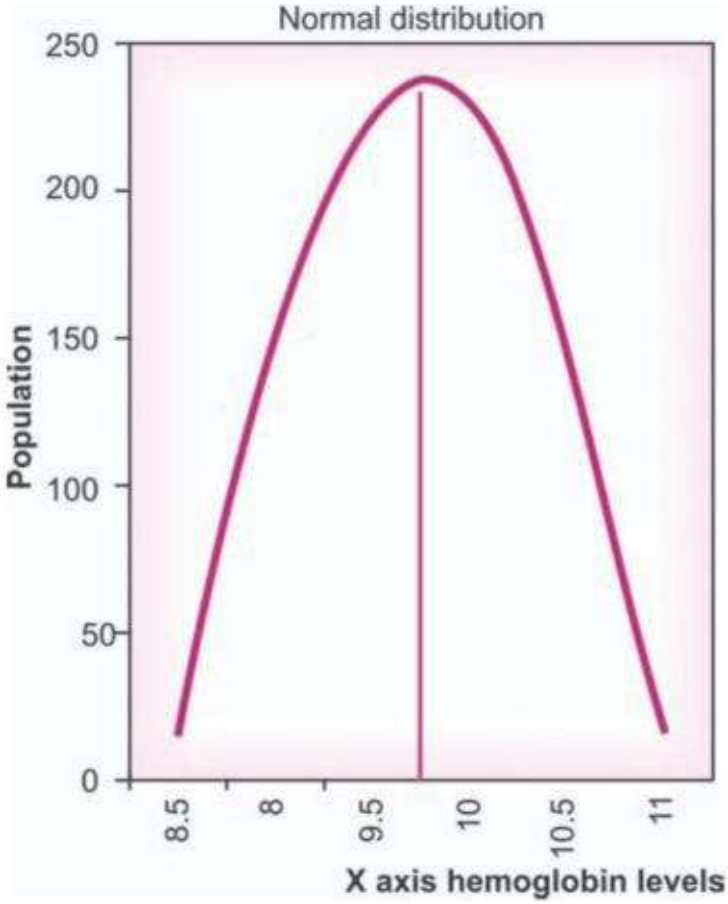


Fig. 5.4: Steep bell curve of normal distribution

STANDARD DEVIATION, VARIANCE AND STANDARD ERROR OF MEAN

Standard deviation: This is a measure of dispersion or variability in the data and was formulated by Galton in the late 1860s. Often, we want to know not just the mean, but also how far away values are from the mean. This is given by SD. When the data points are fairly close to the mean, the SD will be narrow and the bell curve will be steep. When the data points are spread out, the SD will be wide and the bell curve will be flatter.

Variance: Variance which is also the square of the standard deviation is defined as "the average of the squared differences from the mean". Like the standard deviation, it also is a measure of the variability or spread of the data. It is calculated by subtracting individual values from the mean, squaring them to remove negative signs, adding them together and then averaging them. When the square root of this value is taken, it gives the standard deviation.

Standard error ofinean: Our ultimate aim in statistics is to generalize or extrapolate to the population the research findings. We do this by drawing samples, calculating mean and SD and then extrapolating the data. When multiple samples are drawn from the same population, each sample will have its own mean and own standard deviation. All of these will be a little close or a little away from the true population mean. When all these diverse means are plotted together, it can be shown that they also follow a normal distribution and have their own SD. The SD of a population of means (i.e. SD of a number of means) is called the standard error of mean or SEM, which is in fact a misnomer.

This however does not mean that we have to repeatedly draw samples from the population to know the population mean and SD. From the SD of the sample studied by us and the number of subjects studied in the sample the statistician can calculate the SD of the population (i.e. SEM) from which the sample was drawn. The larger the sample size, smaller will be the SEM. The SEM is used when calculating confidence intervals. The SEM is used for continuous or quantitative data (height, weight, blood pressure, cholesterol). Similarly for categorical data, the standard error of proportion can be calculated by statisticians.

PERCENTILES AND QUARTILES

A percentile is defined as the value of a variable below which a certain percent of the observations fall. For example, the 40th percentile is the value below which 40% of the observations are found. A quartile is a value which divides the entire data set into four parts, so that each part represents 25% of the data. The lower quartile or the first quartile cuts off 25% of the data and is called the 25th percentile. The second quartile cuts off 50% of the data and is called the median or 50th percentile. The highest quartile cuts off the top 25% of the data or the lowest 75% of the data and is called the 75th percentile. When the data is to be divided into three parts, two tertiles are used. Similarly deciles split the data into 10 parts, while centilesspilt the data into 100 parts. It should be remembered that these terms refer to the cut off points and not the groups. A quartile is a generic term used for the cut off point. These are commonly used for quantitative or measured data.

PROBABILITY OR P VALUE

The fundamental basis of research is studying a sample and making the findings applicable to the population from which the sample is drawn. Let us presume that a study comparing treatment or intervention A with intervention B shows that intervention A is better than B. If many similar studies are done by different or even the same workers using similar samples from the same population, it is possible that purely random process or chance may produce a result showing that A is not better than B, even though in fact it is better. It is arbitrarily accepted that if 95% of such studies show that A is better than B, it should be accepted that A is truly better than B, even though 5% of studies show that it is not so. In practice, it is not necessary to conduct such large number of studies since statisticians can calculate by their tests, the probability of a result other than the one found in a particular study occurring by pure chance. This probability is indicated by P value and a P value of < 5% or $P < 0.05$ indicates that the result of the study is statistically significant or true. A researcher is at liberty to set up even a lesser P value of 2% ($P < 0.02$) or even 1% ($P < 0.01$) to bestow greater credibility or reliability to the findings of his study. In short, the reader can rely on the findings of a study carrying a P value < 0.05. Lesser the P value, the greater the reliability and hence the confidence with which he can apply the findings in day to day practice.

CONFIDENCE INTERVALS

In a study measuring the height of adult males in a sample from a population of people living in a district, the mean height was found to be 160cm. Can this be applicable to the entire population of the district? Also, would the height be 160cm if other samples were studied from the same population? Common sense says no. It could and would be different around 160 cm, but not exactly 160cm. How can we find out how different it would be in different samples? One way to do so is to carry out the same study in a number of different samples. This is tedious, taxing and not practical. It is also not necessary to do so because statisticians can calculate the range of mean height within which a specific percentage of the heights obtained in a series of studies hypothetically done on different samples would lie. This range is called confidence limits. The confidence limits would obviously be different for the different percentages of the values obtained in different samples/studies. The range of values of the confidence limits would be wider for 99% of the values, than that for 95% of values, which would be wider than that for 90% of the values. This percentage of

values for which the confidence limits is worked out is called confidence interval. Let us say that for 95% confidence intervals, the confidence limit is worked out to be 153-167cm. This is presented to the reader by the researcher as the mean height was 160cm, 95% CI [157, 163]. The reader interprets this as one can be 95% confident that the mean height of the population falls within this range of 157-163 cm 95% of the times and lies outside it only 5% of the times. A CI of 99% would carry greater reliability and validity since there would be only 1% chance that the mean height would be outside the confidence limits but the clinical situations in which such great accuracy is needed are rare. CI can be worked out for any parameters studied by the investigator like blood pressure or death rate or superiority of one intervention over another. CI can also be worked out for the difference in mean values in the two groups being studied eg, height of 12 year old boys versus height of 12 year old girls. This CI is called CI of the mean. Cl for proportions of an event like forceps delivery - 20% in nulliparous women can be represented as a range i.e., 15%- 25%, indicating that this range will contain the population proportion 95% of the times. Similarly CI can be worked for difference between two proportions. For example the incidence of caesarean section in one institute versus that in another. Similarly CI can be worked out for P value, relative risk and odds ratio. The principle for interpretation of CI and confidence limits remains the same. It is important to mention here that until recently, there was great reliance on P value. But today, the reader needs to know how much he can depend or rely on the P value. For this, the author must provide the CI, usually 95% CI for that P value.

MEASURES OF ASSOCIATION- ASSOCIATION BETWEEN TWO EVENTS, RELATIVE RISK, RISK RATIO AND ODDS RATIO

An association is the relationship between two events. Some women have fibroids, some have menorrhagia and some have both. A hypothetical study done to find out the association between menorrhagia and fibroids on 15,000 women finds out that 1000 have fibroids, 500 have menorrhagia and 100 have both (Table 5.1).

Table 5.1: A hypothetical study for fibroids and mennorhegia giving RR and OR

Outcome study	*Fibroid present*	*Fibroid absent*	*Total*
Menorrhagia present	100	400	500
Menorrhagia absent	900	13600	14500
Total	1000	14000	15000

Risk ratio or RR-

$$\frac{\text{Risk of menorrhagia in women with fibroids}}{\text{Risk of mennorhagia in women without fibroids}} = \frac{(100/1000)}{(400/14000)}$$

$= 0.100/0.028 = 3.57$

Odds ratio or OR-

$$\frac{\text{Odds of menorrhagia in women with fibroids}}{\text{Odds of mennorhagia in women without fibroids}} = \frac{(100/900)}{(400/13600)}$$

$= 0.111/0.029 = 3.83$

The association between fibroids and menorrhagia can be represented by risk and odds of the two events and the strength of the association by risk ratio and odds ratio as shown in Table 5.1. Of the 1000 women who have fibroids, 100 have menorrhagia and 900 do not have it. So the risk of menorrhagia in women having fibroids is 100/1000 or 0.1 or 10%. The odds are 100/900 or 0.11 or 11%. Similarly the risk of menorrhagia in women without fibroids is 400/14,000 or 0.028 and the odds are 400/13600 or 0.029. The risk ratio is risk of menorrhagia in women with fibroids (0.100) divided by the risk of menorrhagia in women without fibroids (0.028) viz 0.100/0.028 or 3.57. Similarly the odds ratio or OR is odds of menorrhagia in women with fibroids (0.11) divided by odds of menorrhagia in women without fibroids (0.29) viz 0.11/0.29 or 3.83. Table 5.1 explains the basic concepts of RR or risk ratio and OR or odds ratio.

RISK MEASUREMENTS

Statisticians talk of many different ways of calculating risks or occurrences of events. A clinician wonders about the need and utility of measuring so many

different types of risk. Let us say that risk of dying with the use of a statin in patients with myocardial infarction is 10% while without statin it is 15%. Table 5.2 gives the various measurements of risk in this hypothetical study.

Table 5.2: A hypothetical study of statins and placebo in myocardial infarction and risk measurements

	Risk of dying	*Risk of not dying*	*Odds of dying*
Use of statins	10	90	10/90=0.11
Use of placebo	15	85	15/85=0.18
Total	25		

$$\textbf{Odds ratio} = \frac{\text{Odds of dying with stain}}{\text{Odds of dying with placebo}} = 0.11/0.18 = 0.61$$

Measurement of risks:

- Absolute risk (AR) or absolute risk of dying -10% with statins and 15% with placebo
- Absolute risk reduction (ARR) or Risk Difference (RD) with use of statins = 15% - 10% = 5%

Thisis an index of benefit to the patient

- $\textbf{Relative risk reduction (RRR)} = \frac{\text{ARR with statins}}{\text{Baseline risk (Risk of dying with placebo)}} = 5\%/15\% = 0.33$

This is an index of efficacy ofstatins

- Number needed to treat (NNT) to benefit one patient = 5/ 100 = 20 (Note: To save the life of 5 patients we need to treat 100 patients)

This helps administrator to decide priorities

- Number needed to treat to cause harm (NNH) (death or side effect) to one patient is the other aspect of NNT
- Relative risk (RR)-

$$\frac{\text{Risk of dying with statins}}{\text{Risk of dying with placebo}} = 10\%/15\% = 0.67$$

Readers are requested to have a good look at this table. Odds ratio is by now a familiar concept with readers. Lower the absolute risk of dying and lower the odds of dying with a treatment the better for the patient while lower the odds ratio greater the superiority of the treatment. Absolute risk reduction (ARR) or risk difference (RD) measures the benefit of treatment accruing to the patient and helps the clinician counsel his patient enabling him to make a decision about opting or not opting for the new treatment considering other factors like cost, side effects and inconvenience (need for injections, hospital visits, hospitalization etc). Greater the ARR, better for the patient. Relative risk reduction (RRR) is the index of efficacy of the treatment and the clinician would choose a statin with a higher RRR if all other considerations are equal. Number needed to treat (NNT) gives valuable information to administrators for deciding their priorities. Administrators have limited funds and hence would like to use their funds to save as many lives as possible. All other factors being equal, administrators would deploy their funds in offering an intervention having a lower NNT. Number needed to harm (NNH) is the counterpart of NNT. Lower the NNT and larger the NNH, better the intervention. Lastly, given a choice, a clinician would like to treat his patient by an intervention carrying the lowest RR of an adverse event like dying or severe/serious side effects. RR of 1 makes no difference, while lower the RR below 1, the better it is.

CORRELATION AND CORRELATION COEFFICIENT

Correlation is a relationship or association between two quantitatively measurable variables. The degree of relationship between two measured values is called correlation coefficient designated by V. Statisticians calculate the correlation coefficient on the basis of data provided to them.

As the number of overtime hours put in by workers increases the extra salary earned by them increases (Figure 5.5). The two variables of overtime and extra salary are directly proportional one rising or falling with the other. This is called positive correlation. As against this as the number of children in the family increases the female education decreases. The two variables are inversely proportional (Figure 5.6). This is called negative correlation.

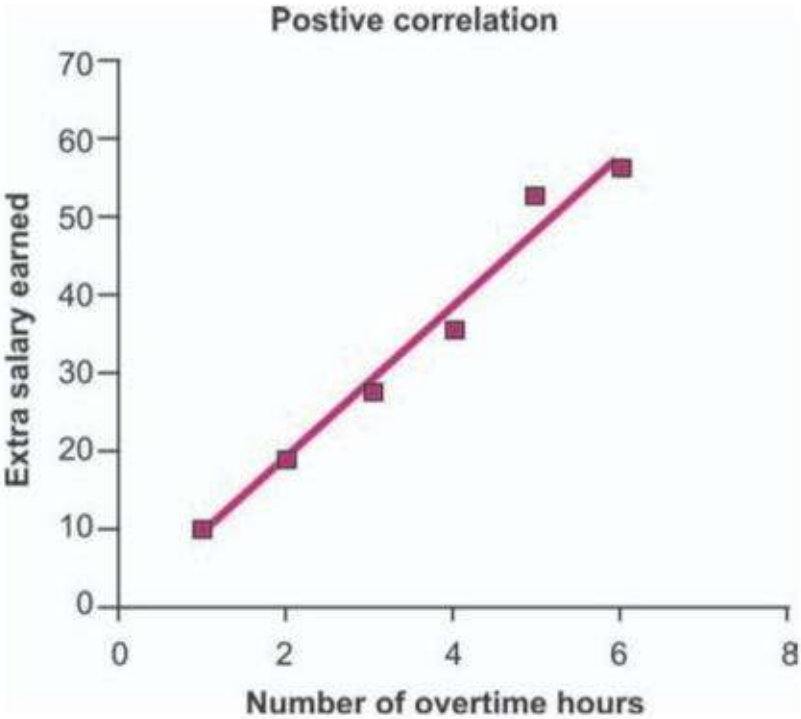


Fig. 5.5: Positive correlation

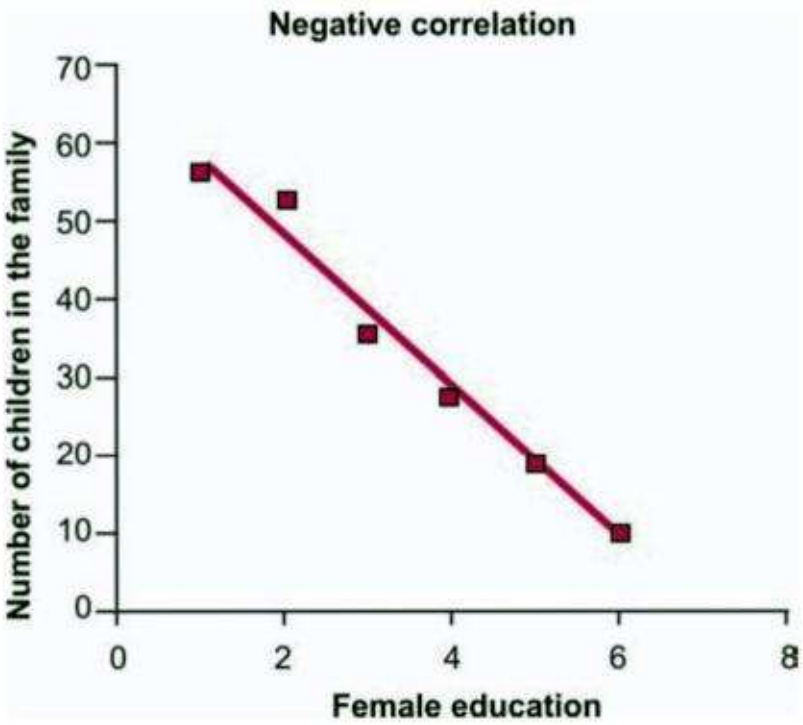
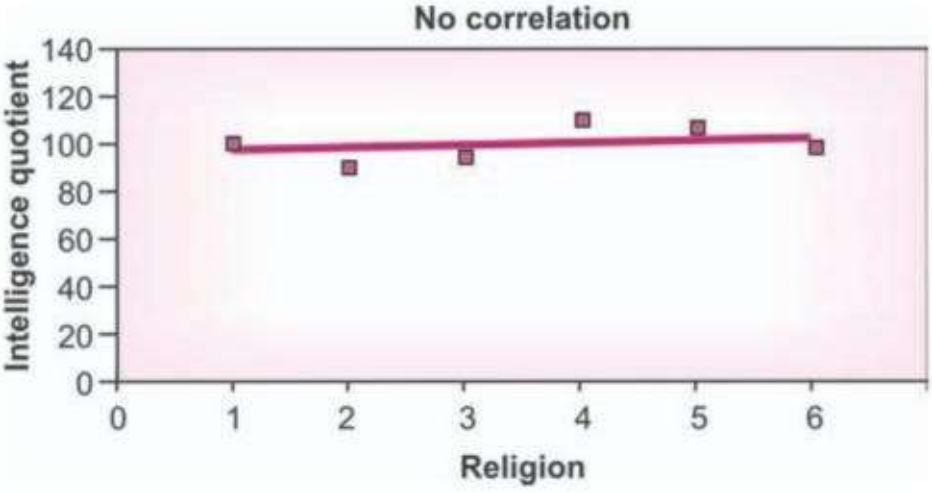


Fig. 5.6: Negative correlation

There is absolutely no correlation between the religion of a person and his

intelligence quotient (Figure 5.7).



1=Hindu, 2=Muslim, 3=Christian, 4=Jew, 5=Buddhist, 6=Atheist

Fig. 5.7: No correlation

If the value of r (Correlation coefficient) is 0 there is no correlation, value of 1 shows perfect correlation, and decreasing value below 1 shows decreasing correlation eg r = 0.7 shows strong correlation or association while r = 0.1 shows very poor correlation or association.

There is partial positive correlation between the ages of husband and wife (Figure 5.8) while there is partial negative correlation between poverty and pulmonary tuberculosis (Figure 5.9).

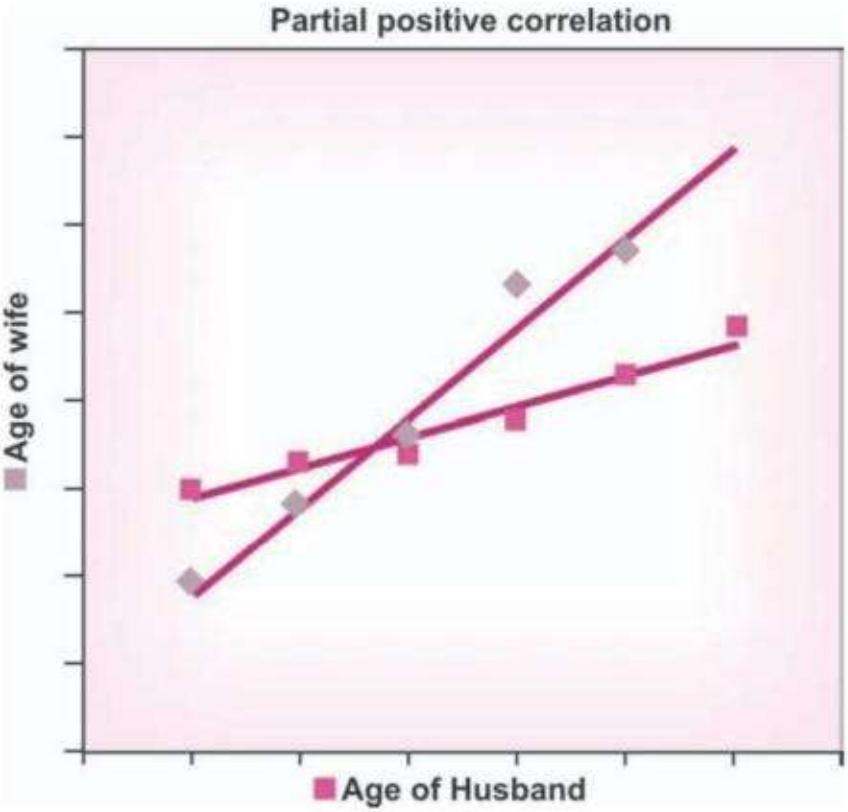


Fig. 5.8: Partial positive correlation

REGRESSION ANALYSIS

Regression is a statistical tool which uses mathematical modeling and is applied when an investigator explores the relationship between variables. The two variables used in a regression analysis are called "dependent" and "independent" variables. For example if the research question is "Does blood pressure increase with advancing age?" blood pressure is the dependent variable (y) and age is the independent variable (x). The relationship between them is described as the regression of y on x, which simply means that the average value of y is a function of x and changes with x.

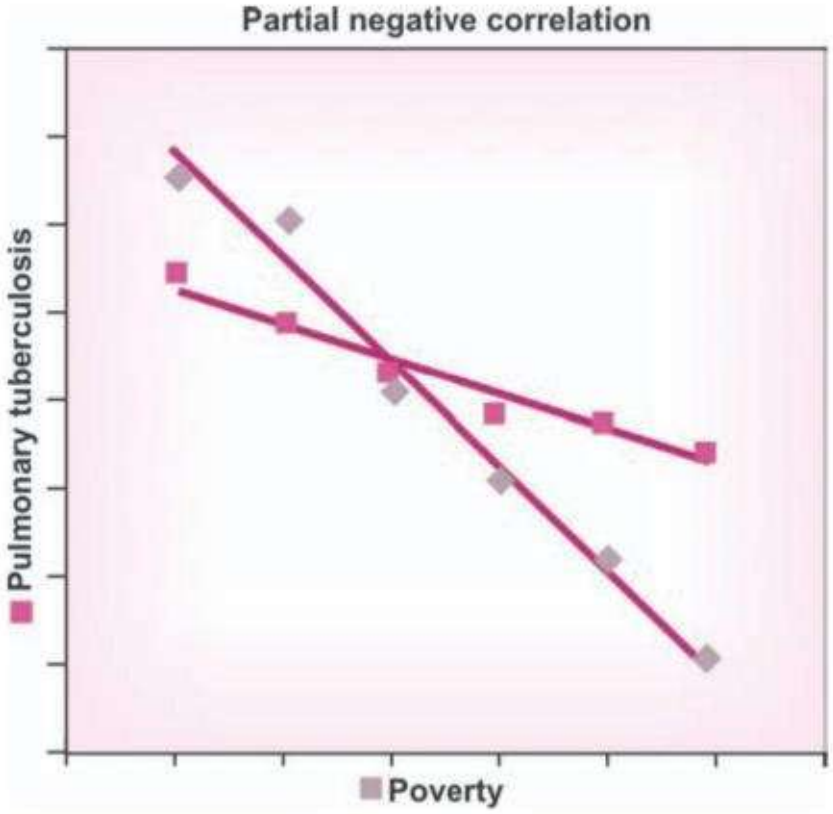


Fig. 5.9: Partial negative correlation

Note: The scatters in Figure 5.5 to 5.9 are shown around the lines representing imaginary mean values.

While correlation and regression both look at association between variables, regression is more useful since it allows prediction. For example, for a given age, one can actually predict blood pressure in a given patient. Linear regression is a technique used when the dependent and independent variables can be quantitated. Logistic regression is used when the dependent variable has only two possible outcomes - for example "dead" and "alive". When there are multiple independent variables, a technique known as multiple regression is used. This is one of the most versatile statistical techniques available.

SURVIVAL ANALYSIS

Life tables is a classical example of survival studies. Based on these Government can plan its policies concerning social security schemes and geriatric health care.

Insurance companies depend on life tables to find the mortality rates at different ages in the population and under different situations to work out the risks or hazards and the premium they need to charge for the policies they market.

Survival studies are also important in clinical medicine. Let us first clarify the concept of survival. To a layman survival is most commonly linked with death. Surviving death is the basis of life tables. In clinical medicine death is not the only event that interests physicians. There are other events like healing of a fracture, discharge from hospital and recurrent myocardial infarction that interest them. Escaping the occcurrence of an event irrespective of its nature, say good or bad, can be considered survival from that event. After a midline laparotomy some patients develop incisional hernia. Those who do not develop incisional hernia can be said to have survived the occurrence of developing incisional hernia. Here the development of incisional hernia is an event that they have survived. But all patients who do develop incisional hernia do not develop incisional hernia at a fixed interval after surgery. Some may develop within few months after surgery while some may develop it after many months or after years. Those who do not develop incisional hernia can be said to have survived the event of development of incisional hernia.

A surgeon wanting to study this problem cannot follow up his patients indefinitely nor does he have to . He has to define the duration of his study depending on its nature and facilities and finances at his disposal. Secondly it is obvious that he just cannot recruit all the study patients in one go. He may therefore decide that he will recruit patients over a period of 6 months and terminate his study 30 months after he started the study. Hence every patient will have a variable period of study duration. In essence the study becomes a `time to event analysis' i.e., analysis of time interval between entry into the study and either occurrence of the event or the predetermined termination of the study without occurrence of the event which ever is earlier. This is a unique feature of survival studies. Some other examples of survival analysis or time to event analysis studies are -

1. Time to malarial parasite clearance
2. Time to graft rejection
3. Time to healing of a wound and

4. Time to complete 100 meter walking.

Some patients may drop out from the study due to reasons like not willing to return for follow-up, death, moving out of town etc and every patient may not complete the specified months of follow-up for these reasons and also due to late entry in the study. As a result the information or data available in some patients would be only till the last follow-up or till the completion of the study. Such data is called `censored data' which simply means that the data collection stopped or ended at the last follow-up. It is obvious that the relevant patients may or may not develop the event like incisional hernia or graft rejection subsequently. Researcher should give reasons for and details about such censored data in the publication of his research. There are various ways of graphically representing the data of survival analysis. One is plotting the dots at relevant points in a graph and form a curve, the survival curve (Figure 5.10). A common way is to present the data in a step-ladder fashion which is called Kaplan Meier curve (Figure 5.11). In addition the data can be analyzed on the basis of risk ratio or hazard ratio at different times of follow up say every 3 or 6 months. The risk ratios or the hazard ratios between the two groups at different time points can be compared by Fisher's test or chi-square test as is done while comparing the risk ratios between two groups in any study.

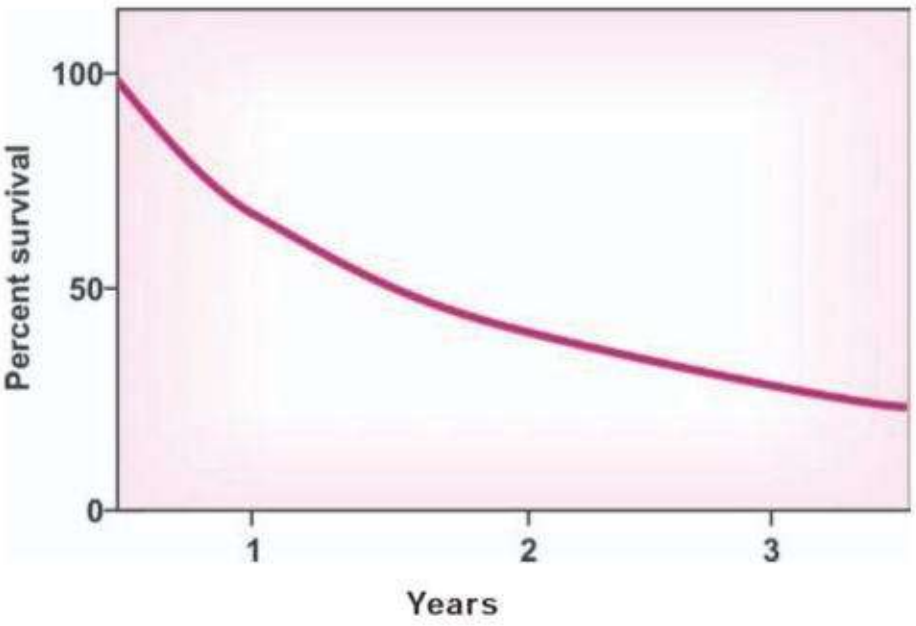


Fig. 5.10: Survival curve.

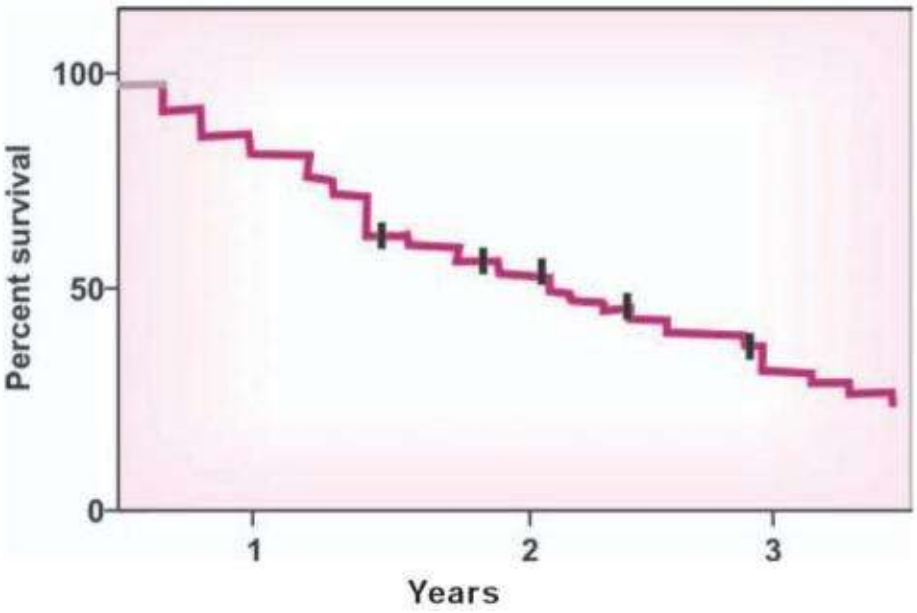


Fig. 5.11: Kaplan - Meier Graph depicting hypothetical study on incisional hernia.

A physician might want to compare the effectiveness of two drugs for acute myocardial infarction defining readmission for fresh myocardial infarction as the event over a period of 31/2 years. Figure 5.12 depicts the survival findings of this study.

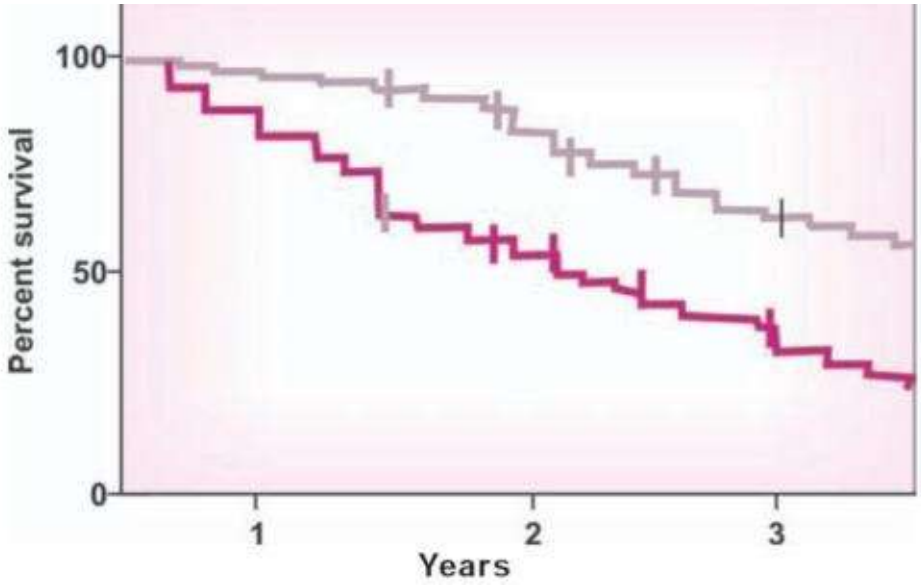


Fig. 5.12: A hypothetical survival study of two drugs for acute myocardial infarction with re-admission for fresh myocardial infarction as the study event.

Log rank test, a nonparametric test, has to be used to compare the outcome of patients in the two groups receiving drug A or B since time as a variable is not likely to be normally distributed. The test gives the P value for the difference between the survival curves of the two groups.

CHOOSING AN APPROPRIATE STATISTICAL TEST

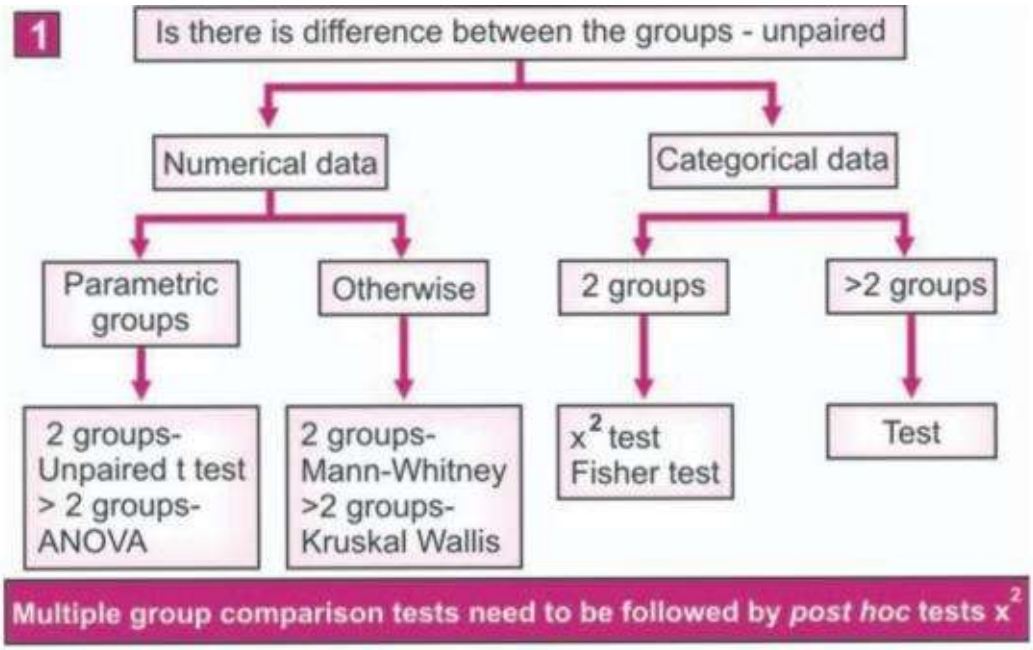
The research question in most of the studies we carry out can be broadly classified under the following five questions. Answers to these questions, understanding the type of data and type of distribution, help us understand the statistical test to be applied.

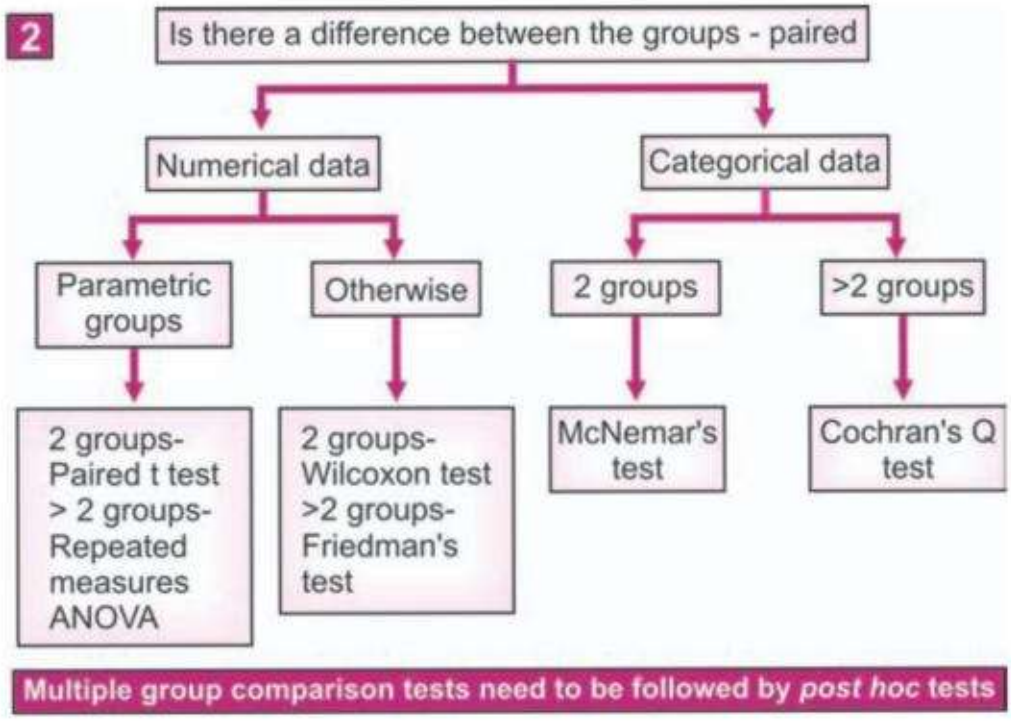
1. Is there a difference between groups - unpaired (parallel and independent groups) situation ?
2. Is there a difference between groups - paired (e.g. beforeafter, time series, cross-over) situation?
3. Is there association between two variables?
4. Is there agreement between assessments?
5. Is there difference between time (survival) trends?

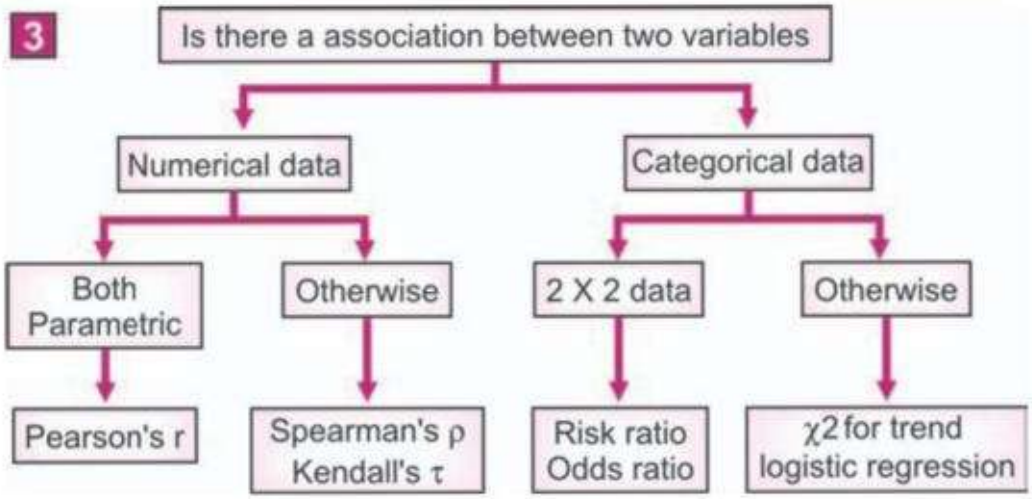
The appropriate statistical tests are described in the following five Tree Diagrams.

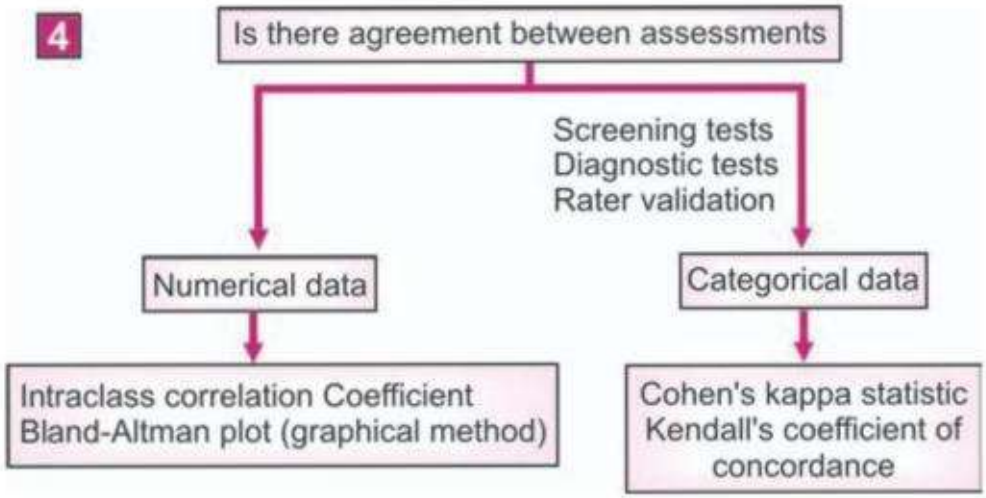
ROLE OF BIOSTATISTICIAN

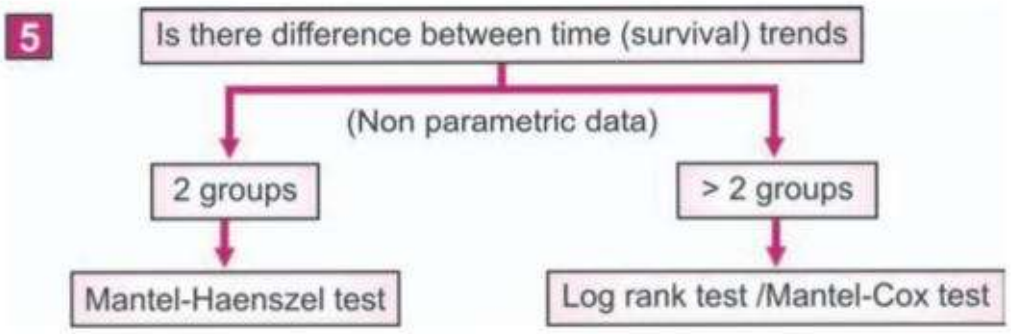
It used to be a traditional practice for researchers, especially in developing countries to complete their study and then go to a statistician for analysis of the data. This is given up long back. The researcher needs to involve a biostatistician at the very beginning of the planning and the designing of the study. The biostatistician at this stage has to calculate the sample size and the power of the study. He also makes data analysis at intervals during the study especially when the study is of long duration. At the end of the study, he statistically analyses the data obtained and arrives at the outcome of the study. In short, the biostatistician has to be an integral part of the research team. Many of the times, he becomes one of the authors of the study when it is published.


1
Is there is difference between the groups - unpaired
Numerical data
Categorical data
Parametric groups
Otherwise
2 groups
>2 groups
2 groups- Unpaired t test > 2 groups- ANOVA
2 groups- Mann-Whitney >2 groups- Kruskal Wallis
x^2 test Fisher test
Test
Multiple group comparison tests need to be followed by *post hoc* tests x^2


2
Is there a difference between the groups - paired
Numerical data
Categorical data
Parametric groups
Otherwise
2 groups
>2 groups
2 groups- Paired t test > 2 groups- Repeated measures ANOVA
2 groups- Wilcoxon test >2 groups- Friedman's test
McNemar's test
Cochran's Q test
Multiple group comparison tests need to be followed by *post hoc* tests


3
Is there a association between two variables
Numerical data
Categorical data
Both Parametric
Otherwise
2 X 2 data
Otherwise
Pearson's r
Spearman's ρ
Kendall's τ
Risk ratio
Odds ratio
χ2 for trend
logistic regression


4
Is there agreement between assessments
Screening tests
Diagnostic tests
Rater validation
Numerical data
Categorical data
Intraclass correlation Coefficient
Bland-Altman plot (graphical method)
Cohen's kappa statistic
Kendall's coefficient of concordance


5
Is there difference between time (survival) trends
(Non parametric data)
2 groups
> 2 groups
Mantel-Haenszel test
Log rank test /Mantel-Cox test

CHAPTER SIX

Submitting A Paper for Publication

SUBMITTING A RESEARCH PAPER FOR PUBLICATION

The main purpose of undertaking research is to benefit the society by its outcome. This can only be achieved by publishing and/or publicizing the research findings. Publicizing your research by presenting it at scientific meetings is very useful. But one must also publish it in a reputed peer reviewed biomedical journal so that it not only reaches a very large number of scientists and clinicians but also has longer life as it gets preserved for posterity. It is tempting to publish in the media to hog the limelight and grab the benefit of publicity. This should be avoided because unless the findings are approved and accepted by the scientific community they lack authenticity. Hence the research should be first sent to a scientific journal for publication and presented to the lay public only after its acceptance by the journal.

CHOOSING THE JOURNAL

There are tens of thousand biomedical journals publishing millions of articles every year. Choosing an appropriate journal is very important. One usually overestimates his research and sends it to a journal that publishes only far superior research. The journal rejects your paper and you waste your time. Best biomedical journals reject 85% of the articles they receive while good journals reject 65-75% and average journals about 50%. With countless number of

journals any and every research is bound to get published somewhere. A realistic maturity is required for choosing an appropriate journal. Once a journal is chosen one must study the instructions for authors that are published in that journal and follow them meticulously. Otherwise the paper will be returned for compliance of the same and your time and efforts are unnecessarily wasted delaying publication. Unfortunately authors are not blinded but often remain blind to the instructions meant for them.

THE ANATOMY OR STRUCTURE OF A SCIENTIFIC PAPER

The title of the paper should give a complete idea of all that the reader should expect in the paper. It should be short but adequate, sufficiently specific, relevant and easy to grasp. Brevity cannot be at the cost of necessity. Don't use abbreviations and don't dramatise. `Role of laparoscopy in vaginal hysterectomy for non-prolapsed uterus' (Agrawal P, Agrawal R, Chandrakar J. J Obstet Gynecol India 2007; 57:151-154) and `Innovations in attention-deficit hyperactivity disorder pharmacotherapy : long acting stimulant and non-stimulant treatments (Stein MA. Am J Manag Care 2004;10:S 89-98) are examples of appropriate title. The authorship of the paper should ideally be decided during the planning phase of the study to avoid bickerings at later stage. Only those substantially contributing to the study by way of developing methodology, giving creative inputs, rendering long term guidance, making data analysis and interpretation, doing biostatistical evaluation, preparing manuscript etc deserve authorship. Just heading the unit or department, merely allowing use of equipment, permitting the study, and giving encouragement or blessings do not merit authorship. Such undeserved or ghost or gift authorship is not tolerated. Many journals publish a capsule of the paper immediately below the title of the paper in the contents section. The capsule is not merely the conclusion of the study. It is meant to give the reader the essence of the entire study in a sentence or two. The abstract summarizes all aspects of your paper. Most journals publish a structured abstract although the number and types of headings in it vary from journal to journal ranging from background, aims or objectives, settings (teaching hospital, primary health centre, private clinic, rural set-up etc), design or methods, patients or participants, intervention, outcome measures or end points, results, statistical tools employed, and conclusions. Usually 250 words are permitted in the abstract but abbreviations are not.

Abstract is a very important part of the paper since most readers read only the abstract. It should, hence, be designed to stimulate their appetite for reading the entire paper. It is best written after the rest of the paper is written and ideally by the main author. Key words follow the abstract. These are 5 to 6 words or short phrases meant for locating the paper in various databases of indexing agencies. Avoid abbreviations and non-specific terms. Ideally MeSH (Medline Subject Headings) words should be used. It is mandatory to declare the conflicts ofinterest. These are ties with activities that could inappropriately influence judgment of the investigators irrespective of whether or not they do so. The investigators or concerned institutions may have benefited financially or otherwise by conducting the study. The pharma company sponsoring the study may have supported the authors participation in a national or international conference or given them all paid holidays or presented expensive gifts. These facts are invisible to the readers but carry the potential of introducing evil bias in the research study. The editors want their readers to know about these conflicts of interest so that they make their own judgement regarding the reliability and validity of research findings and conclusions based there on.

The basic structure of the text or body of the paper was proposed by Sir Bradford Hill in 1965 and is designated by the acronym IMRaD. It consists of -

Introduction	—	Why was the study done?
Methods	—	How was the study done?
Results and Discussion	—	What was found? What do the findings mean?

Introduction

Summarizes the current state of knowledge on the topic of the study and describes the gaps in this knowledge that are intended to be addressed by the study. The introduction should convince the readers about the need and importance of the study. It is not intended to impress readers about your scholarship by telling them everything that you know about the topic. It must be short and relevant. Usually only 2 or 3 pertinent references are permitted.

Methods

This section describes in detail how the study was carried out. All the complete details should be provided to enable the reader replicate the study in precisely the same way as done by you. The information should include location of the study, ethics committee approval, clinical trial registry number, method of arriving at the sample size, power of the study, characteristics of the participants, criteria for recruitment, inclusion and exclusion criteria, baseline characteristics of the study subjects, randomization procedure, assessment criteria, details of intervention, full details of the equipment used (type, model, manufacturer etc), criteria used for assessing the effect of the intervention, primary and secondary end points with clear definitions, methods of data collection and recording, side effects and safety assessments, yardsticks for compliance, dropouts or attritions with reasons thereof and methods of assessments at follow-ups with intervals thereof and total period of follow-up. As an example if blood pressure is recorded you should give the instrument used (aneroid, mercury, electronic, manufacturer) position of the subject (sitting or lying down), level of the instrument vis-avis the heart, rest period preceding the recording and so on. Give the statistical tools used to evaluate the results. Use past tense for this section.

Results

This section describes the findings of the study without interpreting or discussing them. Describe the findings chronologically in descending order of their importance. The results can be presented in the form of text, tables, graphs, pie diagrams, charts, diagrams, figures etc. Information should not be provided in more than one form. Data given in the text should not be replicated in tables, graphs etc. However data given in tables, charts etc can be just summerised in the text. Most reputed journals restrict the number of tables and figures. Each paragraph in the text should provide one item of information. In this section you can summarize the findings but do not discuss them nor compare them with those of other workers or draw conclusions. This section is written in past tense. References have no place in this section. Tables should give complete information without the reader needing to refer to the text. They should be serially numbered in the order of their reference in the text and have a self explanatory title. They should have no vertical lines and only three horizontal lines - one after the title, one after the column headings, and one at the bottom. Column headings should be precise and clear and should give units of measure as required. Abbreviation details, explanatory remarks and comments have to be

in the form of footnotes. Figures, graphs, pictures, photographs etc should be respectively serially numbered in the order of their reference in the text and must have an appropriate title. Pie diagrams should not be crowded with too much data and should be restricted to 5 or 6 slices. Both X and Y axis of the graph must start at zero to avoid misrepresentation and misinterpretation. Pictures, photographs, sonological and radiological images, and histomicrophotographs should have proper selfexplanatory legends. Histomicrophotographs must mention the staining methods and the magnification used. In all the above matters the instructions and conventions of the journal must be strictly observed.

Discussion

This section is very important and needs expertise and experience to write. Results should not be repeated but only summarized adequately. Mention the relevance and importance of your findings. When you give your results along with the findings of previous investigators in a comparative table it is necessary to give not only the year of their publications but also the number of cases studied by them. If authors compare their results in their small series with much larger series of previous workers without mentioning the actual numbers studied by them and by the previous workers the reader gets misguided. Needless to say that all studies mentioned in the tables must appear in the reference list at the end of the paper. If your results are different than those of others explain the reasons for the same. Describe how your findings refute currently prevailing beliefs and knowledge. Discussing the extent to which the aims of your study have been fulfilled is of crucial importance. Discuss the implications of your findings to clinicians, administrators and policy makers. Discuss the strengths, weaknesses, limitations and shortcomings of your study frankly. Mention the questions that remain unanswered and the areas to which future studies should be directed. Discussion section is written in the present tense.

Conclusions

This can be considered the final part or summary of the discussion. The conclusions must be based entirely on the findings of your study. Philosophical, political, and theoretical concepts and your views thereon should not be your conclusions. Conclusions should not be ambiguous. They must be clear, precise and strongly supported by your study.

Acknowledgements

After the discussion you must acknowledge the contributions to your study rendered by those who do not qualify for authorship. Funding agencies' financial support also must be acknowledged.

References

References made in the text to the published literature are listed at the end of the paper. Majority of the journals follow Vancouver style although some use Harvard style. One must meticulously follow the style of the journal in citing the references in the text and in formating the reference list since there are minor variations followed by journals eg some journals give the number of the last page of the article quoted while some do not. The list must be precise in every minute detail. The number of references is restricted by the policy of the journal but the references must be most recent, relevant and important. Cross references or second hand references must never by used. Don't cite your own work unnecessarily nor any unpublished work. Personal communication from other workers in the field can be cited only in the text giving the date of such communication.

SUBMISSION OF REJECTED PAPER TO ANOTHER JOURNAL

When a paper rejected by one journal is sent to another journal it must be rewritten in the style of this new journal following its instructions meticulously. Not doing so gives an impression to the editor of this new journal that he is dealing with a paper rejected by another journal and puts your paper to an avoidable disadvantage. In any case the paper bounces back to you for rewriting.

ADDITIONAL POINTS

Few other important suggestions must be remembered by authors. Writing a scientific paper is far easier than writing a piece of literature provided the author adheres to the structure and format as discussed above. Space is at a high premium in every good medical journal. Hence you must write in a scientific language and style avoiding literary verbiage. Present your work in as few words as possible without sacrificing important data. For most authors in developing

countries English is not the mother tongue nor the language of primary education. They naturally can't grasp the nuances of English language and don't realize the difference between "one out of ten " and "one out of every ten" nor the value of punctuations. Mere location of a comma changes the meaning of these two identical sentences -`A woman, without her man, is nothing' and `A woman, without her, man is nothing'. Incidentally, there were no punctuations in English language until the 15th century. Authors not conversant with the subtleties of the English language should take help of one who is proficient in English. Remember that you are writing for the readers who must precisely and clearly understand what you want to tell them. Giving your manuscript to a colleague not concerned with your research for his comments regarding clarity and ambiguity of your writing is very helpful. Once your paper is published you should carefully match your manuscript with what is published. This will improve your writing in future.

WRITING A CASE REPORT

Case reports carry good information to the readers for use in their clinical practice. Besides a case report is usually the first publication of the authors. Some journals don't publish any case reports. Most journals publish case reports only if the condition is very rare or there is some innovation in the diagnosis or management of the case. The case report should describe all important and relevant information in chronological order. All positive findings must be reported. Negative findings should be mentioned only if they are relevant. Documentation of abnormal physical characteristics, radiological and sonological images, histophotomicrographs etc is mandatory since without it the reader is left to his imagination. The journal's instructions to contributors must be followed meticulously.

CHAPTER SEVEN

Evidence Based Medicine (EBM)

IMPORTANCE OF EBM

It is mandatory that clinicians practice evidence based medicine (EBM) and not providence based medicine. Anecdotal medicine has no place in today's medical care. The essence of EBM is making judicious and explicit use of currently available best evidence in every aspect of patient care - investigative, diagnostic and therapeutic. Clinical judgment, experience, expertise and skill especially surgical are still supreme. EBM cannot displace them particularly because hard scientific evidence is not available for a great majority of what clinicians do in their day to day practice. Experience based medicine though has a place it has limitations. Experience is not what happens to us but what we do to what happens to us. Experience is the name we give to our mistakes but making the same mistakes again and again with greater and greater confidence is no experience. Unfortunately, though experts with gray hair or no hair can often be wrong they are rarely in doubt. A clinician must make the best use of his experience to improve patient care. With these reservations EBM is indispensable and has no substitute. A clinician, whatever his seniority, must be open to new ideas, new knowledge and new scientific evidence. Human minds are like parachutes. They work only when open.

SOURCES OF EVIDENCE

Where does a clinician find the new evidence? Evidence comes from good research and good research leads to EBM. There is a hierarchy of evidence in the following descending order -

1. Cochrane data base of systemic reviews - Prof Archibald Lemon Cochrane (1909-1988) innovated the idea of systemic reviews using quantitative methods to summarize the results of currently available research studies especially randomized controlled trials on a specific topic. A great merit of these reviews lies in the very strict criteria employed for inclusion of articles in the review to ensure quality, uniformity and comparability. However, these reviews are available in very few areas of patient care. Cochrane data can be presented in different ways. Figure 7.1 depicts Forest plot which is one of the ways of presenting Cochrane data.

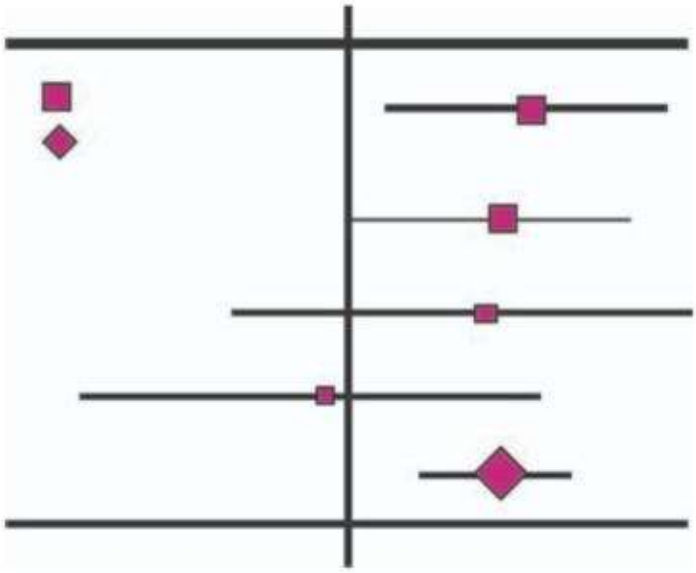


Fig. 7.1: Forest plot depicting Cochrane systemic review

The horizontal lines give 95% confidence intervals and the rectangles on the lines give the RR/OR, while the diamond summarizes the data given on all the horizontal lines depicting in a nutshell the collective OR with 95% confidence intervals of the results of all the articles reviewed. OR of 1 indicates that the intervention studied offers no benefit.

Figure 7.2. gives the famous Cochrane logo the significance and appropriateness of which is readily apparent.

(4)) The cochrane collaboration'&

Fig. 7.2: Cochrane logo

2. Other meta- analysis-These do not have the very strict inclusion criteria used for Cochrane reviews and hence have lesser strength of evidence.
3. Randomized controlled trials.
4. Randomized uncontrolled trials.
5. WHO Publication like Reproductive Health Library.
6. Cohort studies.
7. Case control studies.
8. Review articles.
9. Cross sectional studies.
10. Case series and case reports.
11. Editorials-These vary in quality and hence in the strength of evidence.
12. Clinical practice guidelines issued by professional bodies -These vary in quality and hence in the strength of evidence.
13. Data provided by indexing agencies like MedLine, medIND, SpringerLink, EmBase, etc.
14. Monographs on specific topics.
15. Text books-By their very nature they cannot provide new and latest knowledge. But they form the gold standard of basic knowledge prevalent at the time of publication of their latest edition.
15. Web resources-Quality of knowledge provided is very variable and often questionable since anybody can post any information on the web without accountability and responsibility.

EVIDENCE OF EFFICIENCY AS WELL AS OF SAFETY

A clinician must always be on the look out not only for evidence of efficacy of a new intervention but also for evidence of its safety. Before adopting a new intervention in the care of his patients he must weigh the accruing benefits and resulting hazards to his patients. The benefits must justify the possible side effects or hazards. However we should remember that there is no drug without side effects and no surgical intervention without possible complications. Paracelsus (1493-1541) said that all drugs are poisons and there is nothing that is harmless, the dose alone decides that something is no poison. In 1820 Napoleon

said "I do not want two diseases - one nature made and one man (physician) made". Michael Platt says `prescription drugs are known to be the second leading cause of death. I suspect they may actually be the primary'. It is also important to remember that no surgery is free from complications. A clinician must vigilantly be on the look out for possible side effects of drugs he intends to prescribe and complications of interventions he plans to carry out. It is obvious that when two therapies are equally effective he must choose the one with lesser and less serious side effects or complications. Notwithstanding all this, patients always demand a prescription of drugs even when they need none. Way back in 1884 William Osler wrote that a doctor's visit is not thought to be complete without a prescription. Things have not changed much over the years. Yet we must never prescribe unindicated medicines and counsel our patients accordingly.

WHY EVIDENCE BASED MEDICINE?

According to Lazarou's study conducted in the United States, adverse drug reactions are a leading cause of death. Tom Chalmers, an activist, questions why doctors kill more people than airlines pilots do and remarks that if doctors died with their patients they would take more care. Taking more care means, among other things, practicing EBM. Today patients are armed with consumer protection acts and are empowered with better information and greater knowledge, thanks to media and internet. It is estimated that 5% of all internet searches are health related. In view of these facts clinicians must practice EBM not only in the interest of their patients but also in their own interest. However, requisite sound scientific evidence is not always available. Hence clinicians have to balance evidence based care and experience based care while treating patients although EBM should always get precedence whenever sufficient evidence is obtainable.

SCIENCE OF READING A JOURNAL AND EVALUATING EVIDENCE

Every clinician must read journals to keep abreast of latest knowledge, information and developments enabling evidence based medical practice. There are over 20000 biomedical journals publishing over 6 million papers every year. According to Sacket (1997) most physicians spare only 30 minutes a week for reading journals. Clinicians must make best use of whatever time they use for

reading journals. They should read at least two journals of their specialty - one national and one international. Those practicing a superspecialty like uro-gynaecology, assisted reproduction, interventional cardiology, endoscopic surgery etc, should also read a journal relevant to their superspecialty. It is also very beneficial to read a journal in general medicine like BMJ or New England Journal of Medicine which gives new basic information across specialities. In addition spending time on internet is very rewarding.

One should first go through the contents of a journal. Meta-analysis, review articles, and editorials give useful information in a condensed form. Next, original articles should be short listed from contents based on their title and capsule and on the credibility of their authors. One should now go through the abstracts of these selected articles to decide whether it is worthwhile reading the text of these articles. In the text read the methods section first to find out whether the authors have followed proper methodology, sample size is adequate, the study has at least 80% power and proper statistical tools are employed. If the answer to any of these questions is no then one need not read any further. Otherwise one should proceed to read the results and discussion and assess the conclusions. It is important to emphasize that one must not believe all that he reads. If you believe all that you read you better not read anything. Don't believe everything nor doubt everything because this prevents you from thinking. It is wise to read but wiser to read critically. Remember that over 95% of articles published in medical journals fail to reach minimum standards of quality and clinical relevance (Haynes RB. ACP Journal Club. 1993; 119 : A 22-23). Therefore we must read intelligently, think while reading and assess, weigh and evaluate what we read. Clinicians should be knowledgeable about basics of research methodology and be conversant with applied biostatics to be able to evaluate what they read. The main purpose of writing this book is to empower clinicians to do this. One must also remember that most published research is poorly done and not sufficiently relevant in day to day practice. Hence it is of utmost importance that clinicians read intelligently and critically.

Lastly, case reports published in journals carry useful practical information provided the case is properly worked out systematically and documented adequately.

LEVELS OF EVIDENCE

Systems to stratify evidence by quality have already been developed. Given below is the one by the U.S. Preventive Services Task Force for ranking evidence about the effectiveness of treatments or screening.

Level I. Evidence obtained from at least one properly designed randomized controlled trial.

Level 11-1: Evidence obtained from well-designed controlled trials without randomization.

Level 11-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

Level 11-3: Evidence obtained from multiple series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.

Level Ill: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

Based on the above levels of evidence, recommendations are also given by the same agency as follows-

Level A: Good scientific evidence suggests that the benefits of the clinical service substantially outweigh the potential risks. Clinicians should discuss the service with eligible patients.

Level B: At least fair scientific evidence suggests that the benefits of the clinical service outweigh the potential risks. Clinicians should discuss the service with eligible patients

Level C: At least fair scientific evidence suggests that there are benefits provided by the clinical service, but the balance between benefits and risks are too close for making general recommendations. Clinicians need not offer it unless there are individual considerations.

Level D: At least fair scientific evidence suggests that the risks of the clinical service outweigh potential benefits. Clinicians should not routinely offer the service to asymptomatic patients.

Level I: Scientific evidence is lacking, is of poor quality, or is conflicting, such that the risk versus benefit balance cannot be assessed. Clinicians should help patients understand the uncertainty surrounding the clinical service.

CHAPTER EIGHT

Presenting Papers at Meetings and Conferences

One of the ways of publicizing your research work is to present it at meetings, workshops and conferences - local, national, and international. The effectiveness and impact of your presentation depends mainly on the quality of your research and equally on the skill of your presentation. Public speaking or oratory expertise is both an art and a science. A few basic things must be kept in mind. Your dress must be formal and decent. It does not necessarily have to be a suit or sari. However it should not be so gaudy and/or fashionable that the audience pays more attention to your attire and less to your talk. Avoid all unnecessary movements and actions as they too distract the audience. Stand erect while talking and maintain eye contact with your audience. Don't read but talk. Do not be monotonous as if you are singing a lullaby; vary your tone and amplitude to emphasize important points. Talk confidently and never with any hesitancy. Confidence flows from the quality of your research and your oratory skill. Saying repeatedly unnecessary words like "so" or "then" indicates your nervousness and lack of confidence. You should always speak with enthusiasm which is reflected in your attitude and gestures. It should become obvious that you are enjoying speaking to your audience. Never exceed the time allotted to you. Be willing to trunket your talk if circumstances demand it. Audience usually stops listening beyond your time. You should never need to say may I continue for a minute; it is hard for the audience to say "Oh no, don't". Never end your talk abruptly. Close your talk with emphasis on important aspects of

your work that may amount to take home messages. It is always advisable to rehearse your talk till you develop confidence. Recording your talk carefully and listening to it playing back will go a long way in improving it for effective presentation besides helping you to trim it to the time allotted to you. You should be highly knowledgeable about the topic of your presentation. Don't be reluctant to face questions from the audience as this gives a golden opportunity to show your scholarship. Answer questions with clarity and authority and always to the point. If you don't know the answer don't be ashamed to say so. Never try to bluff your way out as this exposes your ignorance. The audience is smart enough to see through your predicament.

CHAPTER NINE

Misdeeds and Misconduct in Research and Publication

MISDEEDS AND MISCONDUCT

A good researcher should always be focused on the welfare of research subjects and the science of medicine. To this end, he must undertake the research study with the aim of advancing medical science and conduct the study with total dedication, honesty and transparency. Not all researchers are so devoted to their research. Many make compromises during the conduct of the study and its publication to the detriment of science and of their ethical responsibility towards the study subjects. This is generally done for the advancement of their personal interests and benefits. Such behavior is called misdeed or misconduct. Misdeed is a wicked or illegal act while misconduct is an intentional wrong knowingly undertaken. Joint Consensus Conference on Misconduct in Biomedical Research (1990) defines misconduct, intentional and unintentional, as one that falls short of good ethical and scientific standards.

Misconduct nullifies the great efforts put in by everyone involved in the research study whose publication damages medical science and adversely affects patient care. There are many aspects of such misconduct viz; -

1. Employing faulty study design - This is often done to complete the study easily and speedily and also to help pharma companies and funders.
2. Fabrication of data - This involves inventing imaginary or cooked up data and is brought to light for personal reasons by people involved in the research or by those knowledgeable about the study, the so called whistleblowers.
3. Falsification - This is distortion or tampering of data during the study or its publication.
4. Nonpublication of the study - This is usually done to oblige pharma companies who desire to keep unfavorable outcome of the study out of the reach of medical profession. A far worse practice is to omit adverse data from the publication misguiding the medical profession.
5. Not publishing conflicts ofinterest- Conflicts of interest may or may not have affected the researcher's judgement misguiding him. Reader must always know about these conflicts so that he can draw his own conclusions about reliability of the data.
6. Duplicate publication - Some authors get their study published in more than one journal hoodwinking the unsuspecting editors. This is done to add the number of publications in ones curriculum vitae. However this damages medical science because the same paper gets included more than once during meta-analysis, distorting the findings of the meta-analysis and misguiding the medical profession.
7. Salami publication - This is another way of increasing the publications to ones credit. In this data obtained from a single study is split in pieces to make more than one publications.
8. Plagiarism - This is common to any type of publication - scientific or literary. In this the author copies the ideas, sentences and even paragraphs from others' publications without giving credit to the original authors. In simple words it amounts to literary theft or robbing others' intellectual property protected or unprotected by copyright.
9. Misconduct by peer reviewers and editors - This is done in more than one ways. They can hold on to the papers entrusted to them, delay reporting their assessment and postpone decision making till similar paper of their own or from their department or colleagues is published meriting priority. Secondly they can unnecessarily insert references to their own publications without the authors consent with the aim of improving the value or impact factor of their

publications.

PREVENTION OF MISCONDUCT

Misconduct during scientific research is detrimental to and can adversely affect the science of medicine, patient care and health care policies. Misconducts usually go unnoticed and remain undetected. It is sometimes brought to light by experienced editors, suspecting peer reviewers, alert readers and disgruntled colleagues. When it comes to light it can have disastrous consequences for the culprits. Their paper can be rejected if not yet published. If published it can be withdrawn and considered unpublished and hence would have to disappear from authors' curriculum vitae and from data of indexing agencies. The editors may black list the authors and not entertain their papers in future. Their institution and university can take disciplinary actions resulting in their losing all academic positions. Professional organizations can withdraw their membership and regulatory bodies can revoke their licenses to practice their profession. Such consequences are a strong deterrent but for the fact that detection rate is low and severe punishment very uncommon. Lastly, the menace of non-publication of research data would be countered to some extent when registration of clinical trials is made mandatory by law giving universal access to negative findings though unpublished.

CHAPTER TEN

Registry of Clinical Trials

REGISTRY

In developing countries clinical trials can be conducted at half the cost than in developed countries. Hence, with globalization, conducting clinical trials has become a booming business in developing countries. Countries like India provide ample patients, willing volunteers, and highly competent investigators. Poor regulatory mechanism is an additional temptation for pharma companies to locate their clinical trials in developing countries. More than 60% of all clinical trials are sponsored by pharma companies which spend a billion US dollars on research and development to put a new drug in the market. Inevitably, they have great stakes in positive outcome of clinical trials. Participants voluntarily submit themselves to risks, even death, for the benefit of the society. They are entitled to good clinical practices. At the All India Institution of Medical Sciences, pediatricians conducted 42 clinical trials on 4142 babies of whom 49 or 1.18% died. In England, during a clinical trial of TGN1412, a monoclonal antibody for treatment of leukemia, 12 participants had to be hospitalized for multi-organ failure. Merck had withheld critical data from investigators conducting clinical trials on Vioxx. Many pharma sponsored trials are unethical and methodologically poor and proclaim wrong conclusions based on selective reporting with exclusion of cases having unpalatable outcome and employing convenient statistics. Negative findings and uncomfortable data remain unpublished and unpublicized.

There are three pillars of good clinical trials - flawless ethics, sound methodology and brutally honest statistics. The entire business of clinical trials

desperately needs much greater transparency and total accountability. To achieve this properly functioning ethics committees and registration of clinical trials prior to recruitment of the first participant should be made mandatory. Ethics committee should demand clinical trial registration number before giving final approval for the study and no journal should publish any study that does not have clinical trial registration number. Some developing countries like India have started their own clinical trial registry (ctri). These registries should be non-profit making, funded by governments and unconditionally by pharma companies, universally accessible to anybody - even the public at large - free of cost, and easily searchable. Registration of clinical trials should be mandatory or obligatory but very few countries like USA and Spain have legislation making it compulsory. Investigators should periodically report to the registry about progress of their trials. Not all trials are reported in the journals and negative findings are almost never published. The registry cannot and does not force publication of trials but all the findings of the trials, even negative ones, are posted on the registry and are readily accessible to one and all. On line registration simplifies the registration process. Compulsory registration of clinical trials will make trials transparent, accountable and universally accessible.

REGISTRATION OF A STUDY

A study in India can be easily registered in the registry online on www.ctri.in by providing information on the following aspects of the study-

Indian Clinical Trials Registry (www.ctri.in) Requires-

0 Public title of study

0 Scientific title of study

• Secondary identification

• Name and contact details of the Principal Investigator

• Contact person in case of a scientific query

• Contact person in case of a public query

• Source of monetary support

• Primary sponsor

• Secondary sponsor

- Countries of recruitment
- Name of ethics committee and approval status
- Status of regulatory approval
- Problem studied
- Study design
- Nature of intervention and control
- Key inclusion and exclusion criteria
- Method of generating random sequence
- Method of allocation concealment
- Nature of blinding and masking
- Primary and secondary outcomes
- Target sample size
- Phase of the trial
- Date of first enrollment
- Estimated trial duration
- Status of trial
- Brief summary

Many of the items in the clinical trials registry of India are those mandated by the WHO. These are marked on the website with a red asterix. Over and above this, we are also required to send a copy of the ethics committee and regulatory approvals to the ctri office in New Delhi.

CHAPTER ELEVEN

Good Clinical Practices (GCP) and Good Manufacturing Practices (GMP)

Physicians take the Hippocratic Oath before launching their professional career. The fundamental principle of clinical practice is to do no harm to persons under your care. Progress in patient care is achieved by clinical research aimed at developing new diagnostic tests, new drugs, new procedures and new technologies. This involves much greater complexities than merely treating sick people. Research studies carry potential risk to research subjects - both patients and healthy volunteers. No research should be undertaken if the benefits do not justify the risks. All possible precautions must be taken to minimize the risks to the maximum extent possible. In the first place the researcher must meticulously follow all the ethical guidelines ensuring patients life and safety in toto as dictated by the Declaration of Helsinki. Secondly, the methodology must be beyond reproach. The design of the study, the actual conduct of the study, the collection, documentation and analysis of the data, the statistical evaluation of the data obtained, the conclusions drawn from the study and reporting and publication of the study must all follow sound scientific principles. Only this

will render credibility to the results of the study. Haphazard and non-scientific research not only ends up with untrustworthy findings and unreliable conclusions but also amounts to avoidable waste of manpower, time, money and resources. Worse still the study subjects are unnecessarily submitted to risks involved in these unproductive futile studies. Compliance with safe and scientific standards during research constitutes Good Clinical Practice (GCP). The ministry of Health and Family Welfare, Government of India has published the guidelines for Clinical Trials on pharmaceutical products constituting Good Clinical Practices. It also defines the qualifications, roles and responsibilities of everyone involved in the research study including the sponsor, researcher or investigator, funder, ethics committee, monitoring persons, data handlers, bio-statisticians etc. Similar GCP guidelines have also been designed by various other agencies like ICMR, WHO, ICH and US-FDA. Ethics committees ensure Good Clinical Practices.

Good Manufacturing Practices (GMP) - Good Manufacturing Practices (GMP) are practices which must be followed by manufacturers of drugs, devices, instruments, equipments etc.

CHAPTER TWELVE

Historical Glimpses of Research in Medicine

EVOLUTION OF RESEARCH METHODS

When humans evolved there were myriad number of animals on earth and so were diseases. Early humans fought diseases by their immunological faculties and helplessly waited for nature to heal them. They also resorted to prayers and offerings to the divine powers as per the beliefs of their times. As civilizations developed, human societies evolved their medical systems like Herbalism, Ayurveda, Chinese medicine, Arabic medicine, Unani medicine, etc. Man's fight against diseases has led to ingenious and methodological development of current therapies. This fight against diseases seems eternal and search for newer and better drugs and treatment modalities goes on and on.

The methods currently employed in finding out new cures were not developed in recent times only. It is surprising that some of these methods were employed centuries back perhaps infrequently. Roman Emperor Frederick II (1192- 1250) conducted a clinical trial to find out the effect of exercise on digestion. He recruited two of his knights for the trial, fed them identical meal and sent one of them for hunting and the other to sleep. When the hunting knight

returned after hours he killed both the knights to study their stomach contents. He found that the sleeping knight showed more advanced digestion. This seems to be the first ever recorded controlled research study, albeit ethically horrible. In the 16th century Emperor Akbar had a research query. Are the faculties of hearing and speech inborn or do they develop later due to social interaction? He rounded up 30 babies born in his capital city on a particular day and kept them totally isolated for two years except for minimal emotionless and expressionless handling only for feeding and toileting. At the end of two years all the 30 babies were found deaf and dumb. A good observational study though totally unethical. In the 17th century, John Baptista van Helmont, a physician, proposed the first ever multicentric randomized controlled study with good sample size and numerical or statistical analysis to evaluate the benefits of phlebotomy. He planned to recruit 500 poor sick people (nothing has changed and even today the burden of research is shouldered by the poor) to be assigned to two groups by casting lots, one group to have as much blood letting as its physicians desired and the other not to have any phlebotomy. His end point was hard and clearly defined as the number of funerals in each group. This study with a very good design was not done due to unknown reasons. It was more than two hundred years later that Pierre-Charles-Alexander Louis (1787-1872) statistically proved that blood letting does no good and is, in fact, harmful. It was only in the 17th century that hospitals in Europe started permitting research studies. In the 18th century James Lind (1716-1794), an English Naval physician carried out the first ever comparative study on record. In this study done on a long naval expedition half of the sailors were given lemon juice daily and the other half were not given. Only the latter developed scurvy proving that lemon juice prevents scurvy. However, the routine use of lemon juice for preventing scurvy had to wait many long years. Knowledge comes but wisdom lingers! John Hunter, the famous surgeon who turned barber surgeons into gentlemen inculcated research attitude in men of medicine. He famously said why think, why not research?

The use of statistics in medicine is comparatively recent. Census was the earliest collection of numerical data of populations and the first recorded census was carried out 2000 years back by Augustus Caesar. In 16th century some health and vital statistics were being collected. In England in early 17th century records of christenings, marriages and burials were regularly passed on to the king by local parishes weekly or yearly. In 1629 these so called `bills of mortality' were expanded to include fatal diseases excluding plague. Medical

men took no interest in these statistics considering them of no use in the treatment of patients. All this changed when John Graunt (1620-1674) a tradesman cum politician published in 1661 a book "Natural and political observations made upon the Bills of Mortality". The book analyzed the bills over a 60 year period. This impressed the medical fraternity so much that it honored Graunt, a layman, by admitting him as member of the Royal Society. Sir William Petty (1623-1687) who had helped Graunt in producing the book believed that a large population was a national asset and proposed many excellent public health measures which being well ahead of his times were not paid any attention. Christiaan Huygens (1669) and Edmund Halley (1693) produced tables of life expectancy which were later used by life insurance companies. Incidentally, the concept of average originated in primitive insurance. When sea voyages were dangerous ships had to throw overboard some of their cargo to survive storms. Those whose cargo was thus lost had to be compensated by those whose cargo was saved as agreed before the voyage started. The loss of cargo in transit was called `havaria', a Latin term, which was also used to designate the compensation amount paid by each one. From havaria comes the word average. In the 17th century statisticians made a descent living by advising gamblers on the odds of their winning at the gambling tables. Nevertheless, the gamblers often went by their instincts in preference to the rules of the statisticians! Roulette, father of Blaise Pascal is believed by some to have discovered the Roulette wheel. He is considered the father of the theory of probability. His son Blaise, the famous French mathematician, was fond of gambling. He is said to have developed the theory of odds to enhance the chances of his winning at the gambling tables. The advent of statistics in the scientific of research is rather recent. Ronald Fisher, a geneticist, enunciated the principles of numerically based experimental design in 1920s. But it was Austin Bradford Hill (subsequently knighted for his contributions) who convinced clinicians to use statistical analysis and initiated the first ever published randomized trial on streptomycin for pulmonary tuberculosis (BMJ 1948; ii : 769-782). Incidentally, randomization helped using the then limited supply of streptomycin optimally in a fair manner. Interestingly, the trial on whooping cough vaccine was started earlier following Hill's principles but it was completed and published later. Today the use of statistics in medical research is universal. Universal acceptance of good study design in medical research is thus six decades old.

EVOLUTION OF ETHICS IN RESEARCH

Charak Samhita is the oldest written code of medical ethics dating back to some 30 centuries. Hippocrates (5th century BC) enunciated the now universally accepted ethical basis of medical practice. Ethical conduct of medical research is very recent although some attention was drawn to ethical research in USA in 1895. After the 2nd world war the entire civilized world was shaken up to learn about the ghastly studies conducted on Jew prisoners by Hitler's physicians. Incidentally, Germany had good research ethics in earlier years. To try these cruel physicians by the military tribunal the Nuremberg code having 10 basic principles was developed in 1948. This led to the formation of current concepts of ethical conduct of medical research. Belmont report came in 1976. The 18th World Medical Assembly held in Helsinki in 1964 announced the Declaration of Helsinki which formed the foundation of present ethical research. The successive World Medical Assemblies modified these ethical requirements till the 2004 assembly. In 1932 the US Public Health Service began the American medical research project to study the natural course of syphilis. Impoverished black sharecroppers from Macon County in Alabama were recruited for the study without their consent and even knowledge. They were denied any treatment even when effective treatment was later available. Surprisingly, ignoring all the subsequent developments of ethical research the study merrily went on till 1972 when, thanks to the media, it got exposed and a scandal developed leading to litigation which culminated in US Government paying compensation to the victims of this research or to their descendents. Hard to believe but the study had resulted in 28 deaths, 100 disabilities and 19 cases of congenital syphilis. As a corollary to the ethical codes of medical research Ethics Committees have now been formed or are being formed in all institutions where medical research is being conducted. All the same the developing world has a long way to go towards achieving the high standards in conducting medical research ethically.

CHAPTER THIRTEEN

Abbreviations

A

AR- Absolute risk or attributable risk
ARR- Absolute Risk Reduction
AYUSH- Ayurveda, Yoga and Naturopathy, Unani, Siddha and Homoeopathy department, Government of India

C

CAB- Community Advisory Board
CARE- Co-operative for Assistance and Relief Everywhere
CSIR- Council for Scientific and Industrial Research
ctri- Clinical trials registry - India

D

DBT- Department of Biotechnology
DST- Department of Science and Technology

E

EC-Ethics Committee
EBM- Evidence Based Medicine

G

GCP- Good Clinical Practices
GMP- Good Manufacturing Practices

H

H_0- Null Hypothesis
H_1- Alternate Hypothesis

I

ICMR- Indian Council of Medical Research
ICH- International Conference on Harmonization
IEC- Institutional Ethics Committee; Independent Ethics Committee
IRB- Institutional Review Board

N

NGO- Non-governmental Organization
NIH- National Institute of Health
NNT- Number Needed to Treat
NNH- Number Needed to Harm
NPV- Negative Predictive Value

O

OR- Odds Ratio

P

PPV- Positive Predictive Value
P-value- Probability value

R

RCT- Randomized Controlled Trial
RD- Risk Difference
RR - Relative Risk
RRR- Relative Risk Reduction

S

SD-Standard Deviation
SEM-Standard Error of the Mean

U

UNDP- United Nations Development Program
UNICEF- United Nations Children's Fund
US- FDA- United States- Food and Drug Administration

W

WFP- World Food Program of the United Nations
WHO- World Health Organization

CHAPTER FOURTEEN

Demystification of Technical Jargon

A

Absolute risk reduction or risk difference- It is the reduction of risk as a result of treatment.

Alpha error - It is finding a difference when a difference dose not exist. Also called Type 1 error.

Alternate hypothesis- This states that there is difference between the effects of the treatment given to the two groups.

B

Beta error or type II error- It is not finding a difference when difference exists.

Bias- It is a belief or prejudice in the mind of patient or investigator who considers one treatment in the research study to be better than another treatment which is being compared in the study. The bias is nullified by blinding.

Blinding- It is a process of hiding the nature of treatment being administered to a study participant.

C

Case control study- In this retrospective study people with outcome (lung cancer) are looked for exposure (tobacco use) in the past.

Clinical endpoints- Predefined benefit of the treatment being looked for eg resolution of symptoms, survival from a disease.

Cluster or group randomization- In this randomization is done not on the basis of individuals but on the basis of groups of individuals or subjects eg randomization done school wise in a city, or village wise in a district, or occupation wise in an area.

Cohort study - In this prospective study people with exposure (tobacco use) are followed till the outcome of exposure (lung cancer).

Composite endpoint- Combination of more than one endpoints.

Concurrent control trials- The study group and the control group are studied at the same time.

Confidence interval- This is the percentage of values for which the confidence limit is worked out (See confidence limits) .

Confidence limits- It is a range of mean values found in a number of samples studied from a population. The confidence limits would be different for the different percentages of the values obtained in different samples.

Confounders- Additional factors or variables associated with exposure that affect the outcome.

Control group- A group of participants used for comparing with a group of study subjects.

Cross sectional study- A study where exposure and outcome are studied concurrently.

Correlation- Is a relationship or association between two quantitatively measurable variables.

Correlation coefficient- It is the degree of relationship between two quantitatively measurable variables.

D

Descriptive study- In this parameters (height, weight, hemoglobin, etc) are studied in a number of individuals.

Double blind study- In this both the participant and the researcher are kept ignorant of the type of treatment (for example drug or placebo) being given to the participant in the research study.

E

Endpoint- It is a measurement which is required to assess the outcome of a trial (for example death, cure, improvement in hemoglobin, etc).

External validity- It is the ability of a study to generalize or extrapolate its findings to the general population.

F

Factorial RCT- In this one single control group is used for two different study groups.

G

Gaussian or Normal distribution- When values of several individuals are plotted as a histogram, a line joining the top of the histogram columns assumes a bell shaped curve with the top of the curve representing the mean value.

H

Hard endpoint- This is well defined in the study protocol for example reaching hemoglobin of 12g/dL.

Historical control studies- Study group is compared to another group studied or published in the past.

Hybrid RCT- In this a small sample is randomized while the rest in the study are not randomized.

Hypothesis- This is a premise or supposition based on which the investigator conducts his study.

I

Information bias or recall bias- This is incorrect association between exposure and outcome on the part of the patient while remembering exposure in the past.

Internal validity- Internal validity of a study is its ability to measure what it is supposed to measure.

Intervention- It is defined as that (drug, vaccine, diagnostic test, etc) the effect of which is studied during the conduct of the study.

M

Mean- When all values are added and divided by the total number of values, we get the mean which is also called average.

Median- It is the central value when the data is arranged in an ascending or descending order.

Meta-analysis- This is a statistical analysis of the results of different published studies on the same research topic.

Mode- It is the most commonly occurring value in the data.

Multi-centric trial- A research trial sponsored by one organization but conducted at many research centers in precisely identical method with their data pooled together and evaluated as a single study.

N

Negative correlation- In this two variables are inversely proportional; when one rises the other falls.

Negative predictive value- This is the probability of the disease being absent when the diagnostic test is negative.

Normal or Gaussian distribution- When values of several individuals are plotted as a histogram, a line joining the top of the histogram columns assumes a bell shaped curve with the top of the curve representing the mean value.

Null hypothesis- This presumes that there is no difference between the effects of the treatments given to the two groups.

Number needed to harm- This is the number of persons while being treated results in side effects in one.

Number needed to treat- This is the number that needs to be treated to benefit one patient (eg to save the life of one patient you may need to treat 20 patients).

0

Odds- It is the probability of the event occurring divided by probability of the event not occurring.

Odds ratio- It is odds of one disease occurring in patients having another disease divided by the odds of its occurring in patients not having that another disease.

P

Phase I study- This evaluates the safety and pharmacokinetics of a drug in normal, healthy volunteers.

Phase II study- This evaluates the efficacy of the drug for the first time in patients with disease.

Phase III study- This evaluates the efficacy of a drug in a large number of patients and these studies are usually multicentric.

Phase IV study- Also called post marketing study in which safety of the drug when used in the general population is studied. Traditionally this is carried out by the pharmaceutical industry.

Placebo- An inactive substance used as drug in a control group.

Positive correlation- In this two variables are directly proportional one rising or following with other.

Positive predictive value- This is the probability of the disease being present when the diagnostic test is positive.

Power of a study- This is ability of a study to find a difference when a difference exists.

Primary endpoint- The main endpoint as defined in the study protocol.

Probability- It is fraction of time you expect to see the event occurring in many trials.

R

Randomization- It is a process that gives equal opportunity or chance to a participant to enter in a study group or a control group.

Recall bias or information bias- This is incorrect association between exposure and outcome on the part of the patient while remembering exposure in the past.

Relative risk- It is risk of one disease occurring in patients having another disease divided by the risk of its occurring in patients not having that another disease.

Relative risk reduction- This is absolute risk reduction with treatment divided by the risk without treatment.

Risk- This is occurrence of event irrespective of the nature or severity of the event.

Risk difference or Absolute risk reduction- It is the reduction of risk as a result of treatment.

S

Secondary endpoint- Additional clinical endpoint.

Selection bias- This is bias on the part of the investigator in assigning patients to the study or control group.

Sensitivity of a diagnostic test- This measures the proportion of those with disease who are correctly identified by the test under study.

Soft endpoint- Subjective assessment like quality of life.

Single blind study- In this the participant is kept ignorant of the type of treatment (for example drug or placebo) being given to him in the research study.

Specificity of diagnostic test- This measure the proportion of those not having a disease who are correctly identified by the test under study.

Standard deviation- This summarizes how far the individual measurements deviate from the mean.

Standard error of the mean- It is the standard deviation of the mean values of a number of samples studied from a population.

Surrogate endpoint- A laboratory measurement or subjective feeling used as a substitute for clinical endpoint.

Systematic review- This is a review of high quality research studies focused on a single research question.

T

Triple blind study- In this the participant, the researcher and the statistician all are kept ignorant of the type of treatment (for example drug or placebo) being given to the participant in the research study.

Type I error or alpha error- It is finding a difference when a difference dose not exist.

Type II error or Beta error- It is not finding a difference when difference exists.

V

Variance- It is a measure of the variability or spread of the data. The square root of the variance gives the standard deviation.

CHAPTER FIFTEEN

Bibliography

1. Bhaskara Rao T. Research Methodology. 2nd Ed. Hyderabad. Paras Medical Publisher 2005.

2. Duley L, Farell B, Clinical Trials. lst Indian Ed. New Delhi. Viva Books Pvt Ltd. 2003.

3. Friedman LM, Furberg CD, DeMets DL. Fundamentals of Clinical Trials. 3rd Ed. New York. Springer-Verlag. 1998.

4. Hulley SB, Cummings SR, Browner VS, Grady D, Hearst N, Newman TB. Designing Clinical Research. An Epidemiological Approach. 2nd Ed. Philadelphia. Lippincot Williams and Wilkins. 2001.

5. Indrayan A. Basic Methods of Medical Research. 2nd Ed. Delhi. AITBS Publishers. 2008.

6. Swinscow TDV, Campbell MJ. Statistics at square one. 1st Indian Ed. New Delhi. Viva Books Pvt Ltd. 2003.

7. Riegelman RK. Studying a study and testing a test. How to read the medical literature. 3rd printing. Boston. Little, Brown and Company. 1981.

Index

B

C

D

E

F

G

Q

R

S

T

V

W