INSTITUTIONAL ETHICS COMMITTEE

NRI MEDICAL COLLEGE,
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IEC NRIAS Chinakakani Guntur(AP),
http://www.nrias.net/iec.php
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Some useful Hints

- Action without a vision just passes time.
- Vision without action is just a Dream.
- Action and Vision can change the world

Ethics

- It is a mistake to view ethics as an external, authoritarian imposition of regulations or possibly arbitrary constraints on the process of clinical research.
- It is a practice of philosophy in day-to-day life and way of thinking and behavior – a matter of self-consistency and self-governance.

When do Ethics come in?

- Before : Is the study needed and if so is it well planned?
- During : Protection of the subject’s dignity.
- After : Monitoring and Results, Publication.

★ No one / study is above ethics.
★ All studies involving human subjects / Animals.
  - Prospective / retrospective
  - Volunteers / patients
  - Ayurvedic / modern
  - Drugs / procedures
  - Marketed / new drugs

★ WHO estimate that
  ➢ 65-80% of the world population use traditional medicine as their primary health care.
  ➢ Traditional therapies based on Intuition or Experience of Experiment?

★ Quackery needs research
  ➢ A scientific a treatment may not hold its place in the market, if there is no demand for it.
  ➢ Grossest quackery cannot be kept out of market if there is demand.

Traditional Medicine Needs Documentation
(In English modern scientific literature)
  ➢ It is not written, it did not happen?
  ➢ Document what happened as well as what did not happen.

***
To
The Convener, IEC-NRIAS,
Chinakakani, Guntur,

Project Title:
Department:
(Place of study)
Purpose of the study:-  *Dissertation/ Paper/ STS

The application form is to be neatly typed with Times New Roman, 12 font size. The original is to be signed in each page by the investigator and properly numbered for page as shown. A soft copy of the proposal in word format to be mailed to iecnri@gmail.com & iec@nrias.net.

Principal Investigator
Name :
Affiliation : ___ Year Post Graduate student*/ Asst*/ Assoc.* Professor,
Department of ___________________________.
NRI MEDICAL College & GH
Email :
Mobile .No :

Co-Investigator(s)* / Guide* (in case of Dissertation) (*Strikeout which is not applicable)
Name :
Affiliation :
Email :

Duration of the study :

Sponsors (if any with details) :

Approval from any other ethics / regulatory committee (if required) :

I/We shall follow the Good Clinical Practice guidelines and the approved protocol in conducting the research project. Further I/We declare that any sort of inclusion of text or Pictorial material which amounts to Plagiarism will be avoided.

Signature of the Investigator(s)

The proposal has been verified as per the requirement mentioned in the information broacher and forwarded to the IEC, NRIAS for approval. Synopsis of the project, Informed consent form, Case record form and Study flow chart are enclosed.

Signature of the Guide for dissertation (With full name and rubber stamp)

Signature of the HOD (With full name and rubber stamp)

(For IEC office use) Proposal No. Date:

Not to be typed in the application
To be submitted to Dr. Muralidhar Reddy, Professor, Anatomy Dept. NRIMC & GH.
(1) Original copy signed by PI in each page with 9 sets of Photostat copies
(2) A soft copy in MS word format to be mailed to iecnri@gmail.com & iec@nrias.net
SYNOPSIS

Title:

Principal Investigator:

Department & Institution

INTRODUCTION :

*Briefly introduce the topic in 5 to 6 lines.

*Specific aim and objective of the projects.

REVIEW OF LITERATURE:  The review should not exceed one page.

Briefly review the relevant earlier studies in running text with citations. A list of reference is to be included in Vancouver style at the end of the synopsis.

MATERIALS & METHODOLOGY DESCRIBING THE POTENTIAL RISKS AND BENEFITS:

*Describe the source of the subject,

*Sample size / duration

*Inclusion and exclusion criteria point wise.

*The procedures to be followed in the study.

*Mention the potential risk in the study and the probable benefits of the study.

STATISTICAL ANALYSIS:

* Outline the parameter to be studied.

* Mention the type of data to be collected.

* Exact statistical tests to be employed for analysis.

* Mention the level of significance.

REFERENCE :

*Mention at least six references already cited in review in Vancouver style to support your project.
**STUDY FLOW CHART**

**TITLE:**

**PRINCIPAL INVESTIGATOR:**

**PLACE OF THE STUDY:**

*Recruitment of the subject & Enrollment*

↓

Selection of patients as per the inclusion-exclusion criteria

↓

*Making study groups*

↓

*Study Procedures*

↓

Data collection

↓

Statistical analysis

↓

Conclusion

*Recruitment & enrollment of patient or volunteer require advertisement and payment. Is it true for your study? If not omit these points.*

Not to be typed

Can be modified to suit your objective.

*Consider if these points are required for your protocol*
INFORMED CONSENT FORM (ICF)

TITLE:

PRINCIPAL INVESTIGATOR:
PLACE OF THE STUDY:

I, --------------(Name)------------, aged about ------Years, a resident of ---------------------- village of ---------------------- district, have been detailed about the procedure. I know the benefit and risk of the said research project. I on my own will, agreed to participate in this study. I understood that my identity will not be disclosed and I can withdraw from the study at any point of the time without assigning any reason. My withdrawal from the study will not affect my ongoing treatment.

---------------------------------------------     ---------------------------------------------
Signature of the witness if necessary   Signature of the participant or Guardian

IN LOCAL LANGUAGE

I, --------------(Name)------------, aged about ------ Years, a resident of ---------------------- village of district, have been detailed the procedure. I know the benefit and risk of the said research project. I on my own will agreed to participate in this study. I understood that my identity will not be disclosed and I can withdraw from the study at any point of the time without assigning any reason. My withdrawal from the study will not affect my ongoing treatment.

---------------------------------------------     ---------------------------------------------
Signature of the witness if necessary   Signature of the participant or Guardian

The meaning of English and Telugu version of consent form must be same.

Not to be typed

The IFC form can be modified to suit your objective.

The IFC form may contain all the information like: Mob. No.; address of the patient; Bed No.; IP or OP No.; Admission date; Medico legal Case No and other details of the patient but required for the study; as it is confidential.
CASE RECORD FORM (CRF)

ID No. ______

TITLE:

PRINCIPAL INVESTIGATOR:

PLACE OF THE STUDY:

Design the rest of the form as per your plan of study to include all the necessary data for your project keeping the following points in mind-

It must be brief and tailor made.

No disclosure identity of the subject by any means.

---

**Not to be typed**

- Must be designed to suit your study.
- Preferably expected to be brief & objective.
- No disclosure of participants detail which may lead to disclosure of identity.
- Instead of address you may think of- Urban/ rural/ Semi-urban
- It must be more objective and study related e.g
- Family H/o or educational status is vague term. Instead you may consider:-
- Family H/o – DM - Present / Absent / Not known
- Educational status – Illiterate / Literate / Graduate / Professional
- Family H/O - DM → Yes/No/Don’t know
- BP- ____ / ____ mm of Hg
- Pulse___/Min

---

Signature of the person collecting the data
The proposal is to be scrutinized by the Guide and Head of the Department on the following points before it is forwarded to the IEC.

As per the SOP (standard operating procedure) of the Institutional Ethics Committee NRI Academy of Sciences (IEC NRIAS), the project has been reviewed for the following elements:-

1. Scientific design and conduct of the study.
2. Approval of appropriate scientific review committees.
3. Examination of predictable risks / harms.
4. Examination of potential benefits.
5. Procedure for selection of subjects in methodology including inclusion / exclusion, withdrawal criteria and other issues like advertisement detail as required.
6. Management of research related injuries, adverse events.
7. Compensation provisions, if any
8. Justification for placebo in control arm, if any.
9. Availability of products after the study, if applicable.
11. Protection of privacy and confidentiality.
12. Involvement of the community, wherever necessary.
13. Plans for data analysis and reporting.
14. Adherence to all regulatory requirements and applicable guidelines.
15. Competence of investigators, research and supporting staff.
16. Facilities and infrastructure of study site(s).
17. Criteria for withdrawal of patients, suspending or terminating the study if required.

**Ethics committee will take these points to be already scrutinized.**
Protocol is the blueprint of a clinical research project. Protocol designing is the most critical step in the entire clinical research process. Protocol is a document, definitely required by IEC, for approval of any research to be conducted in this institution. It is a written document to ensure transparency in Medical research. It should describe how an experiment would be implemented. After the protocol is finalized and approved, the Researchers should stick to the approved protocol. Any change must be re-approved through same process and is time consuming. So ‘write what you want to do & do what you have written’. Hence it is important that protocol is written after carefully planning the research project.

Protocol planning process must take into consideration the following

- Why? (Relevance of study)
- What questions will be answered? (Aim & Objectives)
- How will these questions be answered? (Plan of Study / Method)
- Measures to avoid bias and error? (Study design)
- How will the results be measured any analysed? (Outcome and statistically analysis).
- Possible difficulties and how to deal with them?
- Practical considerations-Resources-time available, budget vs. cost of study, availability of patients, trained investigators and appropriate facilities?

CRITICAL ELEMENTS OF PROTOCOL (Use this as check list)

1. TITLE
   Name of the trial (title)
   Name and designation of :
   - Principal / Chief Investigator
   - Guide
   - Co-investigator (s) if any
   - Sponsor’s medical expert
   - Sponsor’s trial monitor
   - Trial site/s
   - Table of contents of protocol (if protocol is elaborate)

2. INTRODUCTION
   Background information
   - Name and description of the investigational product.
   - Summary of findings from nonclinical studies that potentially have clinical significance and from relevant clinical trials.
   - Summary of known and potential risks and benefits to human subjects.
   - Justification of route of administration, dosage, regimen, treatment period.
   - Description of the population to be studied.
   - References to literature.
   - Disease condition/ Standard therapy limitations.
   - Likely advantages of new therapy.
3. OBJECTIVES

Formulation and expression of the study objective/s is the foundation of protocol development. This will determine type and design of study, sample size, interventions, methods of analysis. Objectives should be

- A clearly defined, Single main question / hypothesis (primary objective/s)
- Secondary questions may be included. But are subordinate (Secondary objective/s)

4. DESIGN

- Prospective or retrospective, Cross sectional or Horizontal
- Randomization ensures comparability of test groups minimizes selection bias.
- Blinding—subject, evaluator, investigator-minimizes biased outcomes.
- Control group—placebo, no treatment, comparative treatment and different doses of test drug.

5. SELECTION OF SUBJECTS

- Who? Healthy volunteers, patients? Age & Sex?
- How many? Sample size?
  - Sufficient number to get valid results
  - Not more that necessary to avoid wastage of resources
  - Influenced by
  - Disease to be investigated—common, rare
  - Objective/s of the study
  - Study end points
  - Expected magnitude of the treatment effect
  - Variability of the data
  - Specified (small) probability of error (power of the study)
  - Subsets of population or secondary end points
- From where will subjects be recruited? Hospital out-patients, in-patients, G.P.Practice?

Criteria for eligibility:- To ensure enrollment of right type of subjects (target population for the therapy).

a) Inclusion criteria – Define medical status with regard to condition / disease under study.
  - Patient characteristics
  - Disease Characteristics
  - Previous administered treatment
  - Environment and other factors
  - Screening results

b) Exclusion criteria – Based on safety considerations, anything else that will interfere with measuring effect of therapy.
  - Concurrent illness
  - Concomitant therapy
  - Pregnancy and Lactation
  - Contra-indication to therapy
  - End organ damage
  - Noncompliance
6. OUTCOME MEASURES
Includes efficacy assessment as well as safety assessment
- Study and points chosen to assess drug effects e.g., BP, Quality Of Life (QOL), Pain relief.
- Study should be clinically relevant and based on principle objective of the study
- Should be defined prospectively
- Methods of observation and quantification must be specified
- Objective/subjective methods of observations should be validated accurate, specific, sensitive, reproducible.
- Procedure for documentation of ADRs and intercurrent illnesses
- Follow up of adverse events

7. WITHDRAWAL CRITERIA – in case of RCT or drug trial
- Rules for withdrawal must be pre-defined and applied without bias
- Define procedures to handle protocol violators and dropouts, withdrawals, therapy failures.

8. STUDY PLAN / INTERVENTIONS
- Procedures and schedules for treatment, examination, investigation should be clearly stated.
- Dosage, formulations, schedules, duration of drug treatments. Must be specified.
- Under what circumstances drug administration will be modified/discontinued
- Concomitant therapy permitted must be specified

9. STATISTICAL ANALYSIS - Prospective plan for data analysis must be specified in protocol. Specific test to be followed must be mentioned.
- Choice of statistical tests depends upon type of data/study objective
- Level of significance of outcomes must be stated
- Plans for interim analysis, if any should be specified
- Patients who will be excluded from analysis must be pre-defined.

10. ETHICAL REQUIREMENTS
- Informed consent form in writing both English & local language
- Protection of safety and rights of human subjects
- Voluntary withdrawal
- Patients information sheet about trial (Optional)
- Procedures for written informed consent (Optional)

11. CASE RECORD FROM (CRF)
Must capture required, relevant, accurate and analyzable data
- It is tailor-made to suit the data collection
- Should not contain Name, OP/IP/Regd No or bed number, address, date of admission/discharge, which reveals identity of patient.
- Address can be included as Rural/semi-urban/Urban etc..
- Confirms to protocol requirement
- Checks protocol adherence
- Facilitates data transfer and processing
- As per regulatory requirements

12. ADMINISTRATIVE PROCEDURES (If required)
   - Medication storage and dispensing
   - Packaging, labeling and coding for drugs and placebo
   - Accounting procedures
   - Protocol amendments
   - Early trial discontinuation
   - Insurance, compensations and reimbursements
   - Publication policy-matters of newspaper advertisements for patients’ recruitment of trial must be approved by IEC, press release for interim results should be carefully evaluated
   - Specific circumstances for code breaking and further management
   - Audit

13. SPONSORSHIP / FUNDING DETAILS – self sponsored or by any institution or applying for any sponsorship must be mentioned

14. Reference- Minimum six & maximum of ten, most relevant references should be given in Vancouver style with proper citation.

ENCLOSURES: (MUST ATTACH)
   - Patients information sheet (Optional for dissertation & paper work)
   - Study flow chart
   - Informed consent form (ICF) in English / Telugu (See the Specimen copy)
   - Case record form (CRF)
   - Newspaper publication matter for subjects recruitment (if any)
   - Funding details of Sponsor (if any)
   - Permission letter of other institutes (if any)

SPECIAL CONSIDERATIONS (CLINICAL TRIALS ON TRADITIONAL MEDICINE).
   - Define treatment/s and indication/s clearly so that other researchers can produce them reliably.
   - Ensure quality control and standardization of study drugs
   - When active principle is known prepare formulation as per GMP standards
   - Make all trial supplies at the beginning to take care of batch-to-batch variation.
   - Involve Traditional Medicine Doctor as co-investigator.
Informed Consent Form (ICF)

INSTITUTIONAL ETHICS COMMITTEE
NRI MEDICAL COLLEGE, Chinakakani.(AP)

Confidential

“Title of Project_______________________________________________________”

“Investigator’s Name___________________________________________________”

I_______________________________ aged______ years resident of _________________ fully aware of the work and the procedures of the research, in my Free will; without any pressure or incentive in any kind; hereby give my consent (as well as consent on behalf or patient Named ___________________ Aged years as his/her_______ relative) to be included as subject in the said clinical study. I have clearly understood that I have the right to withdraw from the study at any time without assigning any reason. My information and identity will be secret.

I acknowledge the receipt of “patient’s Information sheet” and also the doctors have informed me about this research project suitably and sufficiently to my satisfaction. I agree to let my X-ray. Other investigations, photographs and blood samples be drawn as required. I agree to take necessary medicines regularly as per this trial doctor’s instructions and shall not mix any other treatment during the period of this trial. I shall report to hospital or other place where called on given appointment dates and time. I shall inform the doctors for any adverse effects or unusual symptoms noticed by me. I shall co-operate with doctors and paramedical staff in all respects. I permit to publish the results of my participation in this study. I shall not be given any reimbursement of compensation. I have been informed of my right to opt out of his research project at any time without giving any reason for doing so.

I hereby record my consent for participation in the said trial.

1._______________________  ___________________  ____________  _________
   Patient’s Name               Signature/Thumb print     Date    Time

Or_________________________  _____________________  _____________  __________
   Name of the person providing consent    Signature/Thumb print     Date    Time

2.____________________________   _______________________  ______________  ___________
   Witness Name                    Signature/Thumb print     Date    Time

3.____________________________   _______________________  ______________  ___________
   Investigator’s Name         Signature/Thumb print     Date    Time

PLEASE RECORD THE PATIENT’S ID BELOW AFTER RANDOMIZATION

PATIENT’S ID :    ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐ ☐

Center No.          Randomization No.

* strike out matter in bracket if not applicable.
CASE RECORD FORM (CRF)

“Effectiveness of Lisinopril versus Losartan in left ventricular hypertrophy”

Investigator_____________________

Department_____________________________ Mob.No______

NRI Medical College & General Hospital, Chinakakani, 522503

Age In years___ Sex – M/F

Diagnosis_________________________ Drug and dose______________________________

<table>
<thead>
<tr>
<th>Date</th>
<th>Clinical findings</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st visit</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adverse events monitoring

<table>
<thead>
<tr>
<th>Efficacy parameters</th>
<th>Safety parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective</td>
<td>Subjective</td>
</tr>
<tr>
<td>Lab. Tests</td>
<td>Lab. Tests</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

- You may use separate case record form for each visit to avoid bias findings of earlier visit.
- Design detail case record form to fulfill the needs of your protocol.

* Design the CRF to suit the data you want to collect.
* Be specific and include those points absolutely required for your work
* No details of patient in CRF like case No, IP No or OP NO.
* All these details can be recorded in Consent form (ICF).
Before requesting an individual’s consent to participate in research, the investigator must provide the individual with the following information in the language he/ she is about to understand which should not only be scientifically accurate but should also be sensitive to their social and cultural contexts:

i. Title of the research project
ii. The identity of the research teams with address and phone number of contact person/s
iii. The aims and the methods of the research
iv. The expected duration of the subject’s participating
v. The benefits that might reasonably be expected as an outcome of research to the subject or to others
vi. Any alternative procedures of courses of treatment that might be as advantageous to the subject as the procedure or treatment to which she/he is being subjected
vii. Any foreseeable risk or discomfort to the subject resulting from participation in the study
viii. Right to prevent use of his/her biological sample (DNA, Cell-line, etc) at any time during the conduct of the research
ix. The extent to which confidentiality of records could be maintained
x. Responsibility of investigators
xi. Whether free treatment for research related injury be the investigator/institution will be provided
xii. Whether any compensation / reimbursement/insurance cover for participation or risk involved
xiii. Freedom of the individual to participate and to withdraw from research any time without penalty or loss of benefits which the subject would otherwise be entitled to
xiv. Foreseeable extent of information on possible current and future uses of the biological material and of the data to be generated from the research and if the material is likely to be used for secondary proposes or would be shared with others., clear mention of the same
xv. Risk of discovery of biologically sensitive information
xvi. Publication if any including photographs and pedigree charts

Each participant of clinical trial should be given patients information sheet. However in ordinary research one may combine patients information sheet and informed consent form in one format (In both English & Oriya). If the patient demands informed consent form please prepare second original patient.
Reference in Vancouver style


Basic biostatistics

- Observations are known as data.
- Only grouped data are to be compared.
- Isolated event or a single value can not be compared.
- Real and chance error can be differentiated.

Objectives

- Appreciate the importance of statistics in research
- Understand the principles of selecting a statistical test
- Gain insight into the necessity for eliminating bias in experimental work
- Use and apply some of the commonly used statistical tests and methods
- Report statistical methods correctly in scientific publications

Basics in Experimental Research

Continuous changes in Nature with change in time bring uncertainty and variability in each and every sphere of Science. Even well known and tested principles and laws do fail with test of time. We can not control or over-power the factor of uncertainty but can measure it in
terms of probability. This will differentiate a real variation from accidental or chance variation.

Data (observations) one record in experiment may be dependent, independent or derived. BP depends on drug used, BMI. So BP is a dependant data. Weight, height and number of family members are independent data. BMI is calculated from height and weight. So BMI is a derived data.

Data can be further divided as primary data which is collected directly by the observer. It can be secondary data, when the observation is not collected directly but indirectly. Observations of one researcher are used by another. Data published can be used. Hospital records are used for secondary data.

Error and Bias

No experimentation or observation can be totally free from errors and escape from bias. But we must identify and recognize them for their elimination as far as possible or to control and minimize the effect. Measurements even being valid, if lack in precision and accuracy, irrespective of the magnitude or quantity of deviation from the intended measurement, are called errors. One sided repeated errors or systematic errors are called bias. Selection or allocation biases, measurement bias, instrument bias, inter & intra investigator or observer’s bias, misclassification bias etc. are some of the frequently encountered bias. We know that the techniques of blinding, randomization, replication, standardization, selection of controls and to a great extent the experimental designs do help us to overcome some of them.

- The clarity in knowing the variables of interest to be considered in a particular study helps a lot in recruitment of research tools, techniques and methods to be used during experimentation and use of statistical tests at the end of the study.

Measurement Scales
Each variable has its own limitation of measurement. A suitable **nominal scale** can just classify most of the qualitative variables. Whereas, only for a few of such characteristics it may be practical to put the classification in an ordered sequence by using an **ordinal scale**, still the distance between two points is not the same. But numerical or quantitative variables can always be measured either by **interval scale** or **ratio scale**. The interval scale is valid for certain interval of the possible measurement, as in case of temperature the freezing and boiling points of water have been the basis of scaling in absence of the knowledge of absolute zero temperature. However ratio scale has an absolute zero such as weight, height, and pulse rate etc. How sensitive we are at measurements or in making observation determines precision in inference. A neonate can hardly differentiate between the father and mother but an infant does. It is the wisdom and the sensitivity in measurement, which reveals that even the atoms of an element are all different if we consider the flow of electrons. If we go to that degree of sensitivity in measurement we find that even Nature is incapable of reproducing two exactly similar objects or subjects. If we were in a position to utilize the information, increasing the sensitivity in measurement would certainly be more revealing. But the approach to exhaust all resources for having Nano-sensitivity in measuring the input variables in contrast to Pico/micro-sensitivity used for measuring the output variables is wasting resources without any gain.
**Scale of measurement and Type of data**

**Continuous measurement** → Height in cm, Weight in Kg, Time in seconds is continuous
- Ht may be 155, 155.2, 155.8, 160
- Weight in kg 55.5, 57.0, 57.8 etc
- BP in mm of Hg
- Thyroid status → T3, T4 or TSH level

**Discrete measurement** → Family size, Number of live birth, Number of patients cured
- Family size can be 2, 4, 6 etc;
- Height can be Tall, short, medium,
- Weight can be normal, obese, over weight etc
- BP → Normotensive, Hypertensive, Hypotensive etc
- Thyroid status → Euthyroid, Hypothyroid, Hyper thyroid etc

**Central tendency, Variation, Confidence intervals**

Central tendency – Mean, Median
- Find out the mean for the interval data
- Median is used for scores and ranks

Variation - SD, SE, Range
- SD will be appropriate only if data are normally distributed (symmetric distribution).
- Range includes the lowest and the highest values (eg. Dose of a drug : 10-25 mg/kg)

Confidence interval – CI or fiducial limits
- Confidence limits are two extremes of a measurement within which 95% of observations (values) would lie.

**Analysis**

**Continuous data**
- (Parametric test)
  - t-test
  - Z-test
  - Anova
  - Co-relation
  - Regression

**Discrete data**
- (Nonparametric test)
  - Chisquare-test
  - Sign rank test
  - Kruskalwalis oneway ANOVA
The Chi Square Test

The Chi square test is a non parametric test of proportions. It is used to test a hypothesis. If the association between two variables is to be tested this test is commonly used. If the sample size is small a corrective test -the Fisher’s Exact test can be used. The limitation of this test is that it does not test the strength of association.

To compute this test a 2X2 table or contingency table has to be made. These tables are made to test the association between a treatment and an outcome. The variables used for this table are usually dichotomous e.g. death/survival; adverse effect present/absent. In case they are not, the investigator can transform the values into dichotomous data by specifying a particular threshold value and then computing what proportion of subjects fit above or below this threshold. These tables are made to present data from cross sectional studies, case control studies, diagnostic tests, RCTs etc.,

How to make a 2X2 table?

In a contingency table you must enter raw data, that is the exact number of subjects / animals etc., – not percentages, means or fractions. The groups (treatment/control; exposure/no exposure) are entered on the left side as rows, with the treatment group in the top row and the control group in the second row. The outcome is entered as columns on the right side with the positive outcome as the first column and the negative or no change outcome as the second column. The columns and rows are also mutually exclusive. A particular subject or patient can be only in one column not in both.

The following is a template of a 2X2 table

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Example: Patients with symptoms of viral upper respiratory tract infection were divided into two groups and given placebo or antihistaminics (AH). The result was recorded as improvement or no improvement after 48 hours.

<table>
<thead>
<tr>
<th></th>
<th>improvement</th>
<th>no improvement</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug / Intervention</td>
<td>58</td>
<td>442</td>
<td>500</td>
</tr>
<tr>
<td>Placebo/No intervention</td>
<td>67</td>
<td>423</td>
<td>490</td>
</tr>
<tr>
<td>Total</td>
<td>125</td>
<td>865</td>
<td>990</td>
</tr>
</tbody>
</table>
Student’s ‘t’ test

Student’s ‘t’ test is probably still the most popular of all statistical tests. The test compares two mean (average) values to judge if they are different or not. The Student’s ‘t’ test is the most sensitive test for interval data, but it also requires the most stringent assumptions. The variables/data are assumed to be normally distributed.

The following ‘t’ tests are commonly used:

1. One sample t test → the mean (test) of a single group is compared with a hypothetical value (control).
2. Paired t test → when the ‘paired design’ is used, paired t-test is applied (eg. BP measured before (control) and after (test) a drug administration in a single group of subjects)
3. Unpaired t test → for comparing two individual groups (eg. Height of two groups of subjects each)

The conditions for applying t test are as follows:

1. The sample must be chosen randomly
2. The data must be quantitative (measurable e.g. height, BP)
3. The data should follow normal distribution
4. The size is ideally <30 in each group
5. Populations should have equal SD. (SD of one group should not be more than twice higher or half lesser than the other)
6. The t test used must be appropriate for the design. Paired t for the paired design and Unpaired t for comparing two group means

What if the above conditions are not met?

1. If the SDs are very different Welch correction can be used.
2. If the distribution of data are non-normal or skewed, use transformation techniques before applying a t test. Else go for a non-parametric test.
3. If you are not sure of the normality of the data, use a non-parametric test.
4. If the size in each group >30, go for normal test.

**‘t’ test will give unreliable results if the above conditions are not met.**

Random Allocation

http://www.random.org/integers/

To allocate subjects or animals to different groups, randomization is followed so that each eligible individual in the population has the same chance of being allocated to a group. This eliminates selection bias. Haphazard allocation cannot be called random. Random number tables or computer programs can be used for random allocation. Simple randomization using
computer generated random numbers are used commonly. Sometimes simple randomization may pose problems. For example, randomly allocated two groups may have a different male:female ratio. If it is important to have equal number of males and females in all groups, then one of the slightly complex randomization procedures such as block, stratified or cluster randomization should used.

**Significance Testing**

Null hypothesis (statistical hypothesis) states that there is no difference between groups compared. Alternative hypothesis or research hypothesis states that there is a difference between groups.

e.g. New drug ‘X’ is an analgesic - (Research hypothesis)

Null hypothesis $\Rightarrow H_0$ (A $\equiv$ B) New drug ‘X’ is not better than a placebo (no difference between the drug and placebo)

Alternative hypothesis $\Rightarrow H_1$ (A $\neq$ B $\Rightarrow$ A > B or B > A) New drug ‘X’ is better than a placebo

Alpha is type 1 error and the acceptable limit is to be set. It is generally set at 0.05 (5%) and not above. If the P value is less than this limit then null hypothesis ($H_0$) is rejected and alternate hypothesis ($H_1$) is accepted i.e. the difference between groups is by chance but real.

If statistical test is a judge. The accused (= drug under investigation) is not guilty (= null hypothesis) until the charges are proved. The judge’s decision depends on evidences (= data). Calculation of the chances (P) of the evidence presented by the investigator (= researcher) being false (= probability of difference observed between groups being spurious). If this is < 0.05, then the accused is guilty (the difference between groups is significant). If $P > 0.05$, the benefit of doubt to the accused (=the difference is not significant and the drug is thrown out).

**Choosing an appropriate statistical test**

There are various statistical tests. The characteristics of data will determine a suitable test. The p value is calculated indirectly from a statistical table.

**The following details may help - choosing a suitable test.**

Significance tests can be divided into Parametric and Non-parametric tests. The former includes t test, ANOVA, linear regression and Pearson correlation co-efficient whereas the later includes Wilcoxon, Mann Whitney U, Kruskal-Wallis ANOVA, Friedman ANOVA and Spearman rank correlation. Those variables which follow normal distribution can be subjected to parametric tests and those which do not are suitable for non-parametric test. If the aim is to find out the association between variable, correlation or regression tests should be chosen; the difference between means or medians can be found out using other tests. If
more than two groups/means are compared ANOVA should be used. Significance test to be used must be decided at the beginning of the study.

- A study may need more than one test depending on the number and characteristics of the parameters studied.
- Always spend enough time and brain to choose a right test
- Inappropriate test will lead to invalid conclusions.

**Factors to be decided:-**

- **Aim of the study** –
- **Parameter to be analysed** -
- **No. of groups to be analysed** -
- **Data type** - [Continuous, Discrete, Rank, Score,]
- **Analysis type** - [Comparison of means, Quantify association, Regression analysis]
- **Design** - [paired or unpaired]

With the above information, one can decide the suitable test using the table given.

**Calculating and Interpreting P**

When the data are subjected to significance testing, the resulting value is called statistic. This can be t (t test), chi (chi square), F (ANOVA) etc depending on the test used. This statistic is used to find out the P value available from tables (statistics software can automatically calculate the P value). If the P value is less than the cut off value (level of significance i.e alpha error), it is considered that the difference between the groups is statistically significant. When P is <0.05, it indicates that the probability of obtaining the difference (between groups) purely by chance (i.e. when there is no difference) is less than 5%.

If P>0.05, the difference is considered statistically non-significant and it is concluded that there is no difference between the groups or the difference is not detected.

Non-significant result can be due to two reasons:

1. There is really no difference between the groups.
2. The study is not powerful enough to detect the difference.

Hence, one should calculate the power to conclude whether there is no difference or the power is inadequate. If the power is inadequate (<80%), the conclusion is “the study did not detect the difference” rather than “there is no difference between groups”
Critical Values of the $\chi^2$ Distribution

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* * *
Standard Operating Procedures (SOPs) for Institutional Ethics Committee (IEC) of ICMR’s Headquarters Office, New Delhi, INDIA

1. Objective:

The objective of this SOP is to contribute to the effective functioning of the IEC at the Indian Council of Medical Research, Headquarters Office, New Delhi, India, so that a quality and consistent ethical review mechanism for health and biomedical research is put in place for all proposals dealt by the Committee.

2. Role of IEC

ICMR Headquarters IEC will review research proposals involving human subjects submitted by scientists of ICMR Headquarters Office, New Delhi to various funding or other agencies for grant of funds or technical collaboration at the ICMR Headquarters office at New Delhi. All the 26 Institutes under ICMR have their own institutional ethics committees to review the projects undertaken by them for research.

ICMR Headquarters IEC will review and approve all types of research proposals involving human participants with a view to safeguard the dignity, rights, safety and well being of all actual or potential research participants. The goals of research, however important, should never be permitted to override the health and well being of the research subjects.

The IEC will take care that all the cardinal principles of research ethics viz. Autonomy, Beneficence, Non-maleficence and Justice are taken care of in research protocols. For this purpose, it will look into the aspects of informed consent process, risk benefit ratio, distribution of burden and benefit and provisions for appropriate compensations wherever required. It will review the proposals before start of the studies as well as monitor the research throughout the study until and after completion by examining the annual reports and final reports. The committee will also examine whether all regulatory requirements and laws are complied with or not.
3. **Composition of IEC**
   1. Chairman
   2. A Basic Scientist
   3. Two Clinicians
   4. A Lawyer
   5. A Social Scientist
   6. A Philosopher
   7. A lay Person
   8. Member Secretary.

4. **Authority under which IEC is constituted:**

   The Director-General of ICMR, New Delhi, constitutes ICMR’s Headquarters, IEC.

5. **Membership requirements:**

   a. The members are appointed by the DG, ICMR.
   b. The members are drawn from different Institutes, and specialties to give a multisectorial, multidimensional structure.
   c. The duration of appointment is initially for a period of 3 years.
   d. At the end of 3 years, the committee is reconstituted, and 50% of the members will be replaced.
   e. A member can be replaced in the event of death or long-term assignments outside the country or for any misconduct deemed unfit for a member.
   f. A member can tender resignation from the committee with proper reasons to do so, which should be acceptable to the DG, ICMR.
   g. All members should maintain absolute confidentiality of all discussions during the meeting.

6. **Quorum requirements:**

   The minimum of 50% + 1 member are required to compose a quorum. All decisions should be taken in meetings and not by circulation of project proposals.
7. Offices

The Chairperson will conduct all meetings of the IEC. If for reasons beyond control, the Chairperson is not available, an alternate Chairperson will be nominated by the DG from the members present, who will conduct the meeting. The Member Secretary is responsible for organizing the meetings, maintaining the records and communicating with all concerned. He/she will prepare the minutes of the meetings and get it approved by the Chairman before communicating to the researchers with the approval of the DG, ICMR.

8. Independent consultants

IEC may call upon subject experts as independent consultants who may provide special review of selected research protocols, if need be. These experts may be specialists in ethical or legal aspects, specific diseases or methodologies, or represent specific communities, patient groups or special interest groups e.g. Cancer patients, HIV/AIDS positive persons or ethnic minorities. They are required to give their specialized views but do not take part in the decision making process which will be made by the members of the IEC.

9. Applications Procedures:

a. All proposals are to be submitted in the prescribed application form, the details of which are given under Documentation
b. All relevant documents to be enclosed with application form
c. 12 copies of the proposal along with the application in prescribed format to be submitted duly forwarded by the Head of the Division.
d. The date of meeting will be intimated to the researcher, to be present, if necessary to offer clarifications.
e. The decision will be communicated in writing. If revision is to be made, the revised document in 12 copies to be submitted before the next meeting.

10. Documentation:

For a thorough and complete review, all research proposals to be submitted with the following documents:

1. Name of the applicant with designation
2. Name of the Institute/ Hospital / Field area where research will be conducted.
3. Approval of the Head of the Division
4. Protocol of the proposed research
5. Ethical issues in the study and plans to address these issues.
6. Proformae, questionnaires, follow up card, etc.
7. Patient information sheet and informed consent form in local language.
8. For any drug / device trial, all relevant pre-clinical animal data and clinical trial data from other countries, if available.
9. Statement describing compensation for study subjects for participation and/or study related injuries.
10. Curriculum vitae of all the investigators with relevant publications in last five years.
11. Any regulatory clearances required.
12. Source of funding and financial requirements for the project.
13. An agreement to report any serious side effects or adverse drug reactions to IEC.
14. Statement of conflicts of interest, if any.
15. Any other information relevant to the study

11. Review procedures:

   a. The meeting of the IEC will be held as and when the proposals are received for review. However, if need be, meetings can be held at scheduled intervals when large number of proposals are to be reviewed.
   b. The proposals will be sent to members at least 3 weeks in advance.
   c. Decisions will be taken by consensus after discussions.
   d. Researchers will be invited to offer clarifications if need be.
   e. Independent consultants/Experts will be invited to offer their opinion on specific research proposals.
   f. The decisions will be minuted and Chairperson’s approval taken in writing.

12. Element of review

   a. Scientific design and conduct of the study.
   b. Approval of appropriate scientific review committees.
   c. Examination of predictable risks/harms.
   d. Examination of potential benefits.
   e. Procedure for selection of subjects: Exclusion/ Inclusion criteria
   f. Management of research related injuries, side effects, ADRs.
   g. Compensation provisions.
   h. Justification for placebo in control arm, if any.
   i. Availability of products after the study, if applicable.
j. Patient information sheet and informed consent form in local language.
k. Protection of privacy and confidentiality.
l. Involvement of the community, wherever necessary.
m. Plans for data analysis and reporting
n. Adherence to all regulatory requirements

13. Expedited / Interim review

All revised proposals, unless specifically required to go to the main committee, will be examined in a meeting of identified members convened by the Chairman to expedite decision making. Such expedited review may also be taken up in cases of nationally relevant proposals requiring urgent review.

14. Decision-making

a. Members will discuss the various issues before arriving at a consensus decision.
b. Decisions will be made only in meetings where quorum is complete.
c. Only members can make the decision. The expert consultants will only offer their opinions.
d. Decision may be to approve, reject or modify the proposals. Specific suggestions should be given for modifications.
e. Modified proposals may be reviewed by an interim review through identified members.
f. Negative decisions should always be substantiated by appropriate reasons.

15. Communicating the decision

a. Decision will be communicated by the Member Secretary in writing.
b. Suggestions of IEC, if any, should be sent for modifications.
c. Reasons for rejection should be informed to the researchers. There is no need to communicate the name of the specific expert or member who made the review.

16. Follow up procedures

a. Regular reports should be submitted for regular review.
b. Final report to be submitted at the end of study.
c. Any serious side effects, adverse drug reactions and the interventions undertaken to be intimated.
d. Protocol deviation, if any, to be informed with adequate justifications.
e. Any new information related to the study should be communicated.
f. Premature termination of study should be notified with reasons and summary of the studies done so far.

17. Archiving/Record keeping

a. Curriculum Vitae (CV) of all members of IEC.
b. Copy of all study protocols with enclosed documents, annual reports, side-effects/ADRS etc.
c. Minutes of all meetings with due signature of Chairperson.
d. Copy of all existing national and international guidelines on research ethics.
e. Copy of all correspondence with members, researchers and other regulatory bodies.
f. Final report of the approved projects.

18. Updating IEC members

a. All relevant new guidelines to be brought to the attention of the members.
b. Members should be encouraged to attend national and international training programs in research ethics for maintaining quality in ethical review and to be aware of the latest developments in this area.
A) For NRI MC&GH:
All documentation and communication of an IEC are to be dated filed and preserved according to written procedures. Strict confidentiality is to be maintained during access and retrieval procedures. Records to be maintained for the followings:

a. The constitution and composition of IEC (decided by Principal)
b. The curriculum vitae of NRI MC members
c. Standing operating procedures of the IEC
d. National and international GCP guidelines including IEC guidelines (may be kept in library or the WebSite)
e. Copies of protocols submitted for review
f. All correspondence with IEC members and investigators regarding application, decision and follow up
g. Agenda of all IEC meetings
h. Minutes of all IEC meetings with signature of the chairperson
i. Copies of decisions communicated to the application
j. Record of all notifications issued for premature termination of a study with a summary of the reasons
k. Final report of the study including microfilms, CDs and Video-recordings.

It is recommended that all records must be safely maintained for at least a period of 15 years if it is not possible to maintain the same permanently.

B) For Departments:
a. Principal’s circular for composition of NRIMC &GH and changes done from time to time.
b. National and international GCP guidelines including NRIMC&GH guidelines may be department.
c. All applications of your department with copies of protocols and its annexure submitted to NRIMC &GH for review.
d. Copies of NRIMC &GH decisions communicated to applicants of your department.
e. Record of all notifications issued for premature termination of a study with a summary of the reasons.
f. Final report of research studies of your department including microfilms. CDs and Video-recordings.
g. Case record forms an informed consent forms and other documents of all research projects conducted by students and members of your department.

It is recommended that all records must be safely maintained after the completion or termination of the study for at least a period of 15 years if it is not possible to maintain the same permanently.
Further Reading on Ethics

7. Office for protection from research risks (OPRR), NIH. Institutional review board guidebook. United states : Department of Health and human services ; 1993
12. Psychology department. Ethical guidelines for research with human subjects. UK: University of hertfordshire;1994

* * *