SOP 14

PROCEDURE FOR REVIEWING PROPOSALS REGARDING CLINICAL EVALUATION OF DRUGS/ VACCINES/DEVICES/ DIAGNOSTICS/ HERBAL REMEDIES

PURPOSE:

To review research proposals by investigators involving clinical evaluation of drugs/vaccines/devices/ diagnostics/ herbal remedies

SCOPE

Applicable to IGIDS

RESPONSIBILITY

All members of IEC and investigators are responsible for implementing this SOP

PROCEDURE:

For the clinical evaluation of proposed research intervention, the framework of guidelines is provided for the following areas:

1. Drug trials
2. Surgical procedures / medical devices
3. Diagnostic agents - with special reference to use of radioactive materials and X-rays
4. Trials with herbal remedies

SOP:

1. The Pl has to submit the annual report of the trial on prescribed format along with comments to the office of the Ethics Committee.
2. The final report should be submitted at the end of the study on prescribed format, including a copy of the report which has been sent to sponsoring agency
3. All SAEs and the interventions undertaken should be intimated immediately to IEC.

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4. The Pl should submit the SAEs reported by other centers from time to time to the member secretary for information to IEC along with comments if any action is required in the current study.

5. Protocol deviation, if any, should be informed with adequate justifications

6. Any amendment to the protocol should be submitted for approval

7. Any new information related to the study should be communicated to IEC

8. Premature termination of study should be notified with reasons along with a summary of the data obtained so far

9. Change of the investigator should be done with the approval of IEC.

GENERAL PRINCIPLES

- All the research involving human participants should be conducted in accordance with the four basic ethical principles, namely autonomy or respect for person/participant, beneficence, non-malfeasance and justice
- An investigator is the person responsible for the research trial and the detection of the rights, health and welfare of the participants recruited for the study.
- She should have qualification and competence in clinical trial research methods for proper conduct of the trial and should be aware of and comply with all requirements of the study protocol as enumerated under the General Principles

SPECIFIC PRINCIPLES

I DRUG TRIALS

Clinical trial of drugs is a randomized single or double blind controlled study in human participants, designed to evaluate prospectively the safety and effectiveness of new drugs/ new formulations.

- The new drug as defined under the Drugs and Cosmetic Rules 1945 (DCR), and subsequent amendments include:

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i. a new chemical entity (NCE);

ii. a drug which has been approved for a certain indication, by a certain route, in a certain dosage regimen, but which is now proposed to be used for another indication, by another route, or in another dosage regimen; iii. a combination of two or more drugs which, although approved individually, are proposed to be combined for the first time in a fixed dose combination (FDC).

- The proposed trial should be carried out, only after approval of the Drugs Controller General of India (DCGI), as is necessary under the Schedule 'Y' of Drugs and Cosmetics Act, 1940.
- The investigator should also get the approval of Ethical Committee of the Institution before submitting the proposal to DCGI. All the guiding principles should be followed irrespective of whether the drug has been developed in this country or abroad or whether clinical trials have been carried out outside India or not.
- Throughout the drug trials, the distinction between therapy and research should be maintained.
- A physician /investigator who participates in research by administering the new drug to consenting patients should ensure that the patients understand and remember that the drug is experimental and that its benefits for the condition under study are yet unproven.
- Each such protocol using placebo requires careful consideration before approval. Denial of the available treatment to control (placebo) group of patients is unethical.
- Trials of drugs without the approval of the Indian Regulatory Authority and appropriate agencies should be dealt with according to the law of the land.
- After the clinical trial is over, if need the drug is found effective, it should be made mandatory that the sponsoring agency should provide the drug to the patient till it is marketed in

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the country and thereafter at a reduced rate for the participants whenever possible. A suitable a priori agreement should be reached on post trial benefits.

- The criteria for termination of a trial must be defined a priori in the proposal of the trial and plan of interim analysis must be clearly presented. This is important when on interim analysis the test drug is found to be clearly more effective or less effective than the standard drug. The trial can be discontinued thereafter and better drug should be given to patient receiving less effective drug.
- For new drug substances discovered in India, clinical trials are required to be carried out in India right from Phase I through Phase III and data should be submitted as required under items 5, 6 and 7 respectively of Appendix I of revised Schedule 'Y' of Drugs and Cosmetics Act. In case of amendment or deviation in the protocol not only the approval of may be obtained but also the Licensing Authority has to be notified of the same.

Phases of Clinical Trials

- All phases require approval from EC.
- The first three of the following four phases of clinical trials of drug require DCGI's clearance: -

Phase I (Human Pharmacology) - This is a non-therapeutic trial and the objective is to determine the safety of a new drug and determine the maximum tolerated dose as also to determine the nature of adverse reactions that can be expected. In healthy adults of both sexes. Healthy female volunteers could be included provided they have completed their family or do not intend to have a child in the future. These studies include both single and multiple dose administration and should ideally be carried out at a site that is adequately equipped.

Combined Phase I and Phase II - Such trials are conducted on populations for whom the therapeutic options are exhausted, as in the case of HIV/AIDS and cancer. Toxic drugs like anti-

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retroviral or anti-cancer drug, cannot be tested in normal healthy volunteers as in Phase I studies as the risk far outweighs any benefit. Hence such studies are planned in patients suffering from

the disease so that the risk-benefit ratio is more favorable. Since here the patient population is a vulnerable group and trial on them has to be planned very carefully.

The role of ethics committee assumes great importance here as the weighing of the risk-benefit ratio influences the decision and participation in terminal stages may be considered to be inducement.

The researcher also has to consider very carefully the risks involved

Phase II (Therapeutic Exploratory Trials) - These are controlled studies conducted in a limited number of patients of either sex to determine therapeutic effects, effective dose range and further evaluation of safety and pharmacokinetics in patients. Generally due to selection of patients with narrow inclusion criteria to find effective dose the study population is more or less homogenous. The dose used is lesser than the highest dose used in phase 1

Another objective of this Phase II is evaluation of potential study endpoints, therapeutic regimens including concomitant medications and target populations, and mild versus severe disease, for further studies in Phase II or III. These objectives may be served by exploratory analyses of subsets of data and by including multiple endpoints in trials. Normally 20 - 25 patients should be studied for assessment of each dosage. These studies are usually limited to 3 - 4 centres. It is advisable to include a clinical pharmacologist as a co-investigator in such studies.

Phase III (Therapeutic Confirmatory Trials) – The purpose of these trials is to obtain adequate data about the efficacy and safety of drugs in a larger number of patients of either sex in multiple centres usually in comparison with a standard drug and / or a placebo if a standard drug does not

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exist for the disease under study. This is to validate efficacy and safety found in Phase II. On successful completion of phase III trials permission is granted for marketing of the drug.

Phase IV - The Phase IV studies should have valid scientific objectives. After approval of the drug for marketing, phase IV studies or post marketing surveillance is undertaken to obtain

additional information about the risks and benefits resulting from long term usage of drug. It is an important aspect of drug trial on the long term effects of the drugs and the adverse reactions induced by drugs, if any, should be brought to the notice of the Ethics Committee. There is a need to correlate the adverse events reported during Phase IV trials with the toxicity data generated in animals, to draw markers for future warnings of potential adverse events likely to occur with other drugs.

These trials may not be necessary for approval of new drug for marketing but may be required by the Licensing Authority for optimizing its use.

1. Multicentric Trials

A multicentric trial is conducted simultaneously by several investigators at different centres following the same protocol. Ideally, these trials should be initiated at the same time at all the centers

- All the Investigators should give a written acceptance of the protocol provided by the sponsor which may be modified to suit the local requirements and should be followed for the trial duly approved by the ethics committee of the host institutes.
- Meetings should be organised at the initial and intermediary stages of the trial to ensure uniform procedures at all centres.
- Training should be imparted to research staff at the participating centres to familiarize them with the uniform procedures, data entry in the case record forms, ethics and GCP.

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- Standardisation of methods for recruitment and evaluation/monitoring of laboratory procedures and conduct of trial should be carried out.
- There should be monitoring of adherence to protocol including measures to terminate the participation of some centres, if necessary.
- A Central monitoring committee could be set up for this purpose, which could include ethics committee members too.

- Specific role of coordinators and monitors should be defined
- Centralised data management and analysis should be planned as per WHO's Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards".
- Drafting of a common final report and publication procedure should be decided at the outset. No individual centre should publish any data till appropriate authorities accept the combined report.
- The code of the administered drug could be broken in the event of a severe adverse reaction occurring during the conduct of a double blind trial necessitating such a step.
- It is advisable to establish communication between ECs reviewing multicentric studies in India to discuss ethical concerns of the trial. This is particularly important if any EC does not grant approval for a study at a site for ethical reasons

3. Randomised Controlled Trial (RCT)

- RCT reduces considerable bias but can also creates ethical problems when the comparative arm has placebo. Hence a proper justification should be provided for using the placebo. In keeping with the Declaration of Helsinki as far as possible standard therapy should be used in the control arm.
- In the following situations placebo can be used:

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i. self limited disease;

ii. where no proven prophylactic, diagnostic or therapeutic method exists

Superiority and Non – inferiority trials –

- When a trial is conducted to test if a new drug is superior to the existing one such a trial is termed superiority trial.

- When the trial is conducted to examine if the drug is as good as the existing one then it is called non-inferiority or active control equivalence trial (ACET).

Such a concept evolved due to pitching of clinical reasoning against statistical thinking which earlier gave an indeterminate result when clinically small difference in beneficial effect was expected.

- In superiority trials one of the arms can be placebo or active control but in equivalence trials use of placebo arm will be unethical as the drug's efficacy will have to be tested against a proven therapy.
- CONSORT guidelines need to be followed for reporting of RCTs

III. CLINICAL TRIALS WITH SURGICAL PROCEDURES / MEDICAL DEVICES

Device : "An instrument, apparatus, implement, machine, contrivance, implant, in vitro agent, or other similar or related article, including a component, part or accessory,

- intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or
- intended to affect the structure or any function of the body of man, and
- which does not achieve any of its primary intended purposes/ uses

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- through chemical action within or on the body of man, or
- by being metabolized within the body."

Medical devices: A medical device is defined as an inert diagnostic or therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body.

Medicated devices: These are devices that contain pharmacologically active substances which are treated as drugs. Medical devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic

accessories. Their purpose varies from being used primarily for specific affected parts of the body to being used as adjunct to primary therapies, for e.g. lithotripsy with drug therapy for kidney stone. Depending upon risks involved the devices could be classified as follows:-

a. Non critical devices - An investigational device that does not present significant risk to the patients e.g. Thermometer, BP apparatus.

b. Critical devices - An investigational medical device that presents a potential serious risk to the health, safety or welfare of the participant - for example, pace markers, implants, internal catheters.

- All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. As for the medicated devises, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained before

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pre-market certification. The duration of the trial and extent of use may be decided in case-to-case basis by the appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects :

- Safety data of the medical device in animals should be obtained and likely risks posed by the device should be considered.
- Clinical trials of medical devices are different from drug trials, as they cannot be conducted in healthy volunteers. Hence Phase I trials are not necessary for trial on medicated devices.

- Medical devices used within the body may have greater risk potential than those used on or outside the body, for example, orthopedic pins vs crutches.
- Medical devices not used regularly have less risk potential than those used regularly, for example, contact lens vs intraocular lenses.
- Safe procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patient.
- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information on follow-up procedures to be adopted if the patient decides to withdraw from the trial.
- Study design of the intra body devices like implants can be very challenging and should have adequate protective safeguards. The study should be long enough to detect if there are any late onset ADRs.
- If full assessment of safety is not complete, the Phase III could extend to Phase IV.

IV. DIAGNOSTIC AGENTS - USE OF RADIO - ACTIVE MATERIALS AND XRAYS

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- Informed consent should be obtained before any diagnostic procedures.
- Information to be gained should be gathered using methods that do not expose participants to more radiation than exposed normally.
- In the event of death of a participant with radiological implant, due precaution as per radiation guidelines may be taken not to expose the relatives or the close co-habitants to radiation till safe.
- Research should be performed on patients undergoing the procedures for diagnostic or therapeutic purposes.
- Safety measures should be taken to protect research participants and others who may be exposed to radiation.

- The protocol should make adequate provisions for detecting pregnancies to avoid risks of exposure to the embryo.
- Information must be given to participant about possible genetic damage to offspring.
- Non-radioactive diagnostic agents are considered as drugs and the same guidelines should be followed when using them.
- Ultrasound should be substituted wherever feasible.

V. CLINICAL EVALUATION OF TRADITIONAL AYURVEDA, SIDDHA, UNANI (ASU) REMEDIES AND MEDICINAL PLANTS

• The recognized traditional systems in India are Ayurveda, Siddha and Unani besides Yoga and Naturopathy and Homeopathy.

• The two unique features of herbal products used in the traditional Indian medical systems are that they are mostly used in compound forms and are multi-component mixtures including

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minerals in some of the formulations, and that substantial information is available regarding their prior human use vouchsafing safety and efficacy of these formulations.

• Therefore, an approach different from that for evaluation of synthetic drugs is required which concerns two groups, namely, clinical investigators evaluating the benefits and risks of herbal products and the regulatory authorities.

• For the herbal remedies and medicinal plants that are to be clinically evaluated for use in the Allopathic System and which may later be used in allopathic hospitals, the procedures laid down by the office of the Drugs Controller General of India for allopathic drugs should be followed. This does not pertain to guidelines issued for clinical evaluation of Ayurveda, Siddha or Unani

(ASU) drugs or formulations by experts in those systems of medicine, which may be used later in their own hospitals and clinics.

• All the general principles of clinical trials described earlier pertain also to herbal remedies.

• However, when clinical trials of herbal drugs used in recognized Indian Systems of Medicine and Homeopathy are to be undertaken in Allopathic Hospitals, association of physicians from the concerned system as co-investigators/ collaborators/ members of the expert group is desirable for designing and evaluating the study.

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