SOP

INSTITUTIONAL ETHICS COMMITTEE

Lata Mangeshkar Medical Foundation's

DEENANATH MANGESHKAR HOSPITAL AND RESEARCH CENTRE (DMHRC),

Erandawane, Pune 411004, INDIA.

THE WORK DOCUMENT

(Inclusive of Standard Operating Procedures)

This is the working document of INSTITUTIONAL ETHICS COMMITTEE (IEC) (Version: 09 Effective from 20th February 2014.)

For Private Circulation Only:

IEC DMHRC acknowledges SOP version 8 and the revised version V 9 of SOP to be effective from 20th February 2014

Disclaimer:

These rules have been compiled from national and international documents on related subjects. These are rules of guidance for our institution and may be added/amended/altered as and when deemed necessary. These guidelines have never been meant as a treatise or a reference book for another Body/institution.

Please note:

The IEC Work Document is for reference with regard to submission of Protocol/Study for approval. It can be copied and used as it is. No changes in the text whatsoever are permitted. Changes in the document, if any, shall be done by the Member Secretary, IEC, DMHRC, only after IEC approval.

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Message by the Medical Director

A great treatment offers benefit to an individual patient and a good hospital should provide such good treatment to multitude of patients.

A good research offers solutions to millions of patients across the globe and is a far more powerful tool for serving patients than just good treatment alone.

A great hospital must offer quality research and hence contribute towards improvements in treatment options.

Deenanath Mangeshkar Hospital is committed to make this transition to a great hospital by undertaking Clinical Research.

As a part of management of Deenanath Mangeshkar Hospital we are firmly committed to this research endeavor.

SD/-

Medical Director
Deenanath Mangeshkar Hospital and Research Centre

Foreword by the Chairperson

India offers unique opportunities for conducting cost effective clinical trials in view of the large patient pool, competent researchers and premiere medical institutes available in the country.

Good Clinical Practice can be traced back to the oldest tradition of medical science: The Hippocratic Oath, the guiding ethical principle of which is to do no harm to the patient. However in the current scenario of modern medical research involving many complex issues there is need for elaborate guidelines addressing ethical and scientific responsibilities of the various stakeholders.

Clinical research is crucial to the discovery of latest methods and drugs for treatment of diseases and includes design, conduct, monitoring, analysis, reporting, termination and documentation. Trials involving human subjects thus need stringent ethical and scientific standards at each stage to ensure protection of rights, safety and well being of the patients involved as agreed upon by International Convention.

The interest of science should not take precedence over the considerations of the well-being of the subjects. The trials should thus produce authentic research data and protect the rights of the human subjects. There is thus need to prepare guidelines and procedures for maintenance of proper quality of clinical research.

These guidelines also need to be reviewed and amended periodically to address the emerging issues associated with new developments in the biomedical sciences.

It gives me immense pleasure to present here the modified SOPs for undertaking clinical trials and the painstaking efforts of all the members, who contributed to the formulation of the SOPs, are gratefully acknowledged. I am confident that these will be immensely useful to further strengthen the research efforts in the Institution.

SD/-

Dr Avinash Joshi
Chairperson
IEC, Deenanath Mangeshkar Hospital and Research Centre

Research Department revisited - an overview from the Department Head

DMHRC is a super-specialty consultative tertiary-care hospital with its own Research Department to encourage and initiate in-house basic and translational research projects as well as sponsored clinical trial protocols related to a battery of human anomalies and diseases. Various health-related projects have been completed from DMHRC - and data has been published in peer reviewed journals since it's inception in 2002. We are (now) pleased to announce that the Phase II of DMHRC was inaugurated on November 1st of this year and - we are planning to expand our research efforts and endeavors beyond the Phase I plan.

There are 3 main arms of the Research Department under which biomedical/health research is initiated, coordinated and implemented.

● SPONSORED CLINICAL TRIALS:

The first arm focuses on conducting national and sponsored/global Clinical Trials, which include studies related to a battery of human metabolic, physiological and chronic conditions including cancer. The sponsor invited trials are first assessed for feasibility by the Physicians/Clinicians at DMHRC. The relevant protocols are then reviewed by Scientific Advisory Committee (SAC) of DMHRC - and are allowed to be implemented only after the approval of Institutional Ethics Committee of DMHRC. As per the regulatory requirements, the Institutional Ethics Committee of DMHRC has been registered with DCGI, under the Central Drugs Standard Control Organization (CDSCO).

(DCGI Registration No.: ECR/15/Inst/Maha/2013)

● IN-HOUSE PROJECTS:

The second major arm of the Research Department is to encourage and invite in-house basic and translational research projects in diverse fields. The investigator- initiated projects are first reviewed by biomedical and scientific experts of CCPR committee (Core Committee for Promotion of Research) and are implemented only after the approval of IRB of DMHRC. These investigations

usually have the basic objective of describing and quantifying disease problems and of examining correlation, if any, between serological, tissue biomarkers, underlying conditions - with disease etiology, diagnosis, progression, prognosis and patient outcome.We mention herein some of the broad areas of research covered by investigators at DMHRC: Cataract and Uveitis, Respiratory infections, Gastro-intestinal conditions, management of patients in ICU, Cytogenetic studies for assessing pre-natal conditions and anomalies, Maternal and Child health related issues, Renal, Musculo-skeletal disorders. Epidemiological studies/surveys are also undertaken, when appropriate.

● **RESEARCH PROJECTS UNDERTAKEN UNDER DNB PROGRAM:**

The third arm of the institute includes investigator-initiated projects undertaken by DNB (Diplomate of National Board) students under the supervision of investigators of DMHRC. We have ~ 25-30 students enrolled in the DNB program annually. After successful completion of the project(s), DNB degree is awarded by the National Board of Examinations (NBE)- an autonomous academic body under the Ministry of Health and Family Welfare, Government of India.

Biomedical or health research projects carried out under all the above three arms is subject to approval by DMHRC Ethics Committee. For questions or concerns, please contact – research@dmhospital.org

As well, I take this opportunity to thank all those who have contributed to revision of the SOP_v7 (March 2013) for DMHRC. I would like to thank all my department members, in particular -
Dr. Shweta Chittaranjan and Mrs Varada Bivalkar for preparing the initial drafts including all GR updates, wherever appropriate. Thanks also to the Chairman Dr. Avinash Joshi and Member Secretary Col.J.C.Pendse,VSM (Retd) - and all EC members for their time and recommendations towards this SOP review.

Last but not the least, I am grateful to the Medical Director - Dr. Dhananjay S. Kelkar for offering me this position at this esteemed health care institution - and giving me an opportunity to contribute to enhancement of research enterprises and activities at DMHRC.

Sd/ ----------

Dr. Vaijayanti V. Pethe
Assistant Director
Department of Research
Deenanath Mangeshkar Hospital and Research Center
Pune, Maharashtra, India
www.dmhospital.org

"*Leading the way to the future of personalized medicine through meticulous health research - and best practices at DMHRC"*

IEC Registration Certificate- Registration number- *ECR/15/Inst/Maha/2013*

File No.-ECR/48/Deenanath/Inst/Maha/2013

From:
The Drugs Controller General (India)
Directorate General of Health Services

FDA Bhawan, Kotla Road,
New Delhi – 110 002
Dated : 01 APR 2013

To
The Chairperson
Institutional Ethics Committee
Deenanath Manageshkar Hospital & Research Centre
Erandawane, Pune 411 004

SUB: - Ethics Committee Registration No. **ECR/15/Inst/Maha/2013** issued under Rule 122DD of the Drugs & Cosmetics Rules 1945.

Dear Sir/,

Please refer to your application no. Nil dated 27/3/2013, FTS No. 14998 dated 8/3/2013 submitted to this office for the Registration of Ethics Committee.

Based on the documents submitted by you, this office hereby Registers **Institutional Ethics Committee** situated at **Deenanath Manageshkar Hospital & Research Centre Erandawane, Pune 411 004** with Registration number **ECR/15/Inst/Maha/2013** as per the provisions of Rule 122DD of the Drugs and Cosmetics Rules, 1945 with the following composition:

1. This Registration is subject to the conditions specified under Rule 122DD and Appendix VIII of Schedule-Y of Drugs and Cosmetics Act, 1940 and Rules 1945.
2. The Ethics Committee shall review and accord its approval to a clinical trial at appropriate intervals as specified in Schedule Y and the Good Clinical Practice Guidelines for Clinical Trials in India and other applicable regulatory requirements for safeguarding the rights, safety and well being of the trial subjects.
3. In the case of any serious adverse event occurring to the clinical trial subjects during the clinical trial, the Ethics Committee shall analyse and forward its opinion as per procedures specified under APPENDIX XII of Schedule Y.
4. The Ethics Committee shall allow inspector(s) or official(s) authorised by the Central Drugs Standard Control Organization to enter its premises to inspect any record, data or any document related to clinical trial and provide adequate replies to any query raised by such inspectors or officials, as the case may be, in relation to the conduct of clinical trial.
5. The licensing authority shall be informed in writing in case of any change in the membership or the constitution of the ethics committee takes place.
6. All the records of the ethics committee shall be safely maintained after the completion or termination of the study for not less than five years from the date of completion or termination of the trial (Both in hard and soft copies).
7. If the Ethics Committee fails to comply with any of the conditions of registration, the Licensing Authority may, after giving an opportunity to show cause why such an order should not be passed, by an order in writing stating the reasons therefore, suspend or cancel the registration of the Ethics Committee for such period as considered necessary.
8. This registration shall be in force for a period of three years from the date of issue, unless it is sooner suspended or cancelled

Yours faithfully

(Dr. G.N.Singh)
Drugs Controller General (I)
& Licensing Authority

About this document

This Work Document is developed primarily, if not exclusively, to facilitate the transaction of business of IEC at its meetings per SOPs. These pages, therefore, represent the core part of the Work Document. It is followed by related appendices grouped in to two categories: (1) Essential ones concerning submissions of protocol/study (appendix III & Guide) and (2) Additional information (I to x) and References. However, in passing, it also attempts to make the members aware of their responsibilities and duties that they have consented to discharge, by adding some relevant information in appendices.

For the sake of brevity, only the acronyms are generally used throughout the text. Their details are given in Appendix I.

The standard supporting works, the literature that could be available and the discussions held at workshops have been referred to. This has been done either by adaptation and/or inclusion as compilation and inserted, with due acknowledgements, as appendices (as mentioned above).

IEC members are not directly involved with the details of routine, mandatory work of the Sponsor, Investigator/s and the Regulatory Authorities and therefore with their SOP's. However, it is necessary in the interest of their functioning that they should be generally in the know of the responsibilities of these stakeholders. These are, therefore, included, albeit briefly, in the said appendices. In an exercise of this nature some repetition is inevitable. This has been done wherever essential.

The document can be modified by addition/deletion or can be amended as and when necessary only after IEC approval. No circular can be issued without IEC approval. Such an amended/updated version shall be the official document, in current use at any given point of time. Those referring to the document are requested to ensure that they refer to the latest version, in vogue.

A certain part of this document can be used/quoted with due written acknowledgement to IEC-DMHRC, only for academic, administrative or research reference purposes.

The pages to follow deal with IEC and its SOPs in particular. The Work Document is divided into four (4) parts indicated by three end-separators.

1. Introduction

Clinical research happens to be a highly critical and specialized area of medical research. Added to the complexity there is an inherent aspect of responsibility in it. Currently in India, due to progressive implementation of powerful conceptual changes such as liberalization at the global level and privatization, there is a direct positive impact on Clinical research. It is on the threshold of emerging as a powerful, knowledge-based industry, involving investment of trillions of rupees, and employment opportunities to skilled, trained personnel. As a sequel, there is also the need for close co-operation between Pharma industries and hospitals. Needless to add, this must be done taking into account patient's safety and adherence to ethical principles, both before and after a drug / device is launched, and this should be the prime concern of the IEC.

This is so, because it is imperative that in clinical research an investigational substance / product/ 'molecule' has to be tested and tried at a certain developmental stage of a clinical trial on human subjects, for ascertaining its efficacy and safety, before and if at all, it gets baptized for introduction in the market as a 'drug'/'device'. The clinical research thus, also has an extremely important ethical dimension. This makes clinical research a demanding business, involving various operational stages and requiring specific skills. These can be attained through rigorous training and refined by acquiring maturity through sustained efforts and experience.

Teams involved in clinical research hold specific responsibilities. Such teams are generally grouped as:

- Sponsor/s
- Contract Research Organizations (CROs)
- Investigator/s and Assistants
- Institutional / Independent Ethics Committee (IEC) or Review Board (IRB)
- Regulatory Authorities

The historical account of the evolution and standardization of Clinical research just cannot be complete without reference to horrendous instances of the darker and deceitful side of the human mind, the saga of the participants, the pitfalls and so on. Yet it is also a shining example of the conscientious, careful, critical and collaborative organizational efforts of the caring human minds especially from European Community, the Scandinavian countries, United States of America, particularly the Food and Drug Administration (FDA) of USA, Japan, Australia and World Health Organization (WHO) that have made landmark contributions. These resulted into the development of very important documents such as the Nuremberg code, World

Medical Association's (WMA) Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS), giving directives for Human experimentation. Similarly, the FDA reference books and the European GCP document are the results of these efforts. The concern for safety and dignity of human life has been the basis for all this co-operation. These efforts eventually have resulted in the development and final adoption on 17th January 1997. The acronym stands for the full form: International Conference on Harmonization of Technical Requirements for The Registration of Pharmaceuticals for Human Use (ICH) that formulated the Tripartite Guideline for Good Clinical Practice (GCP). Since then these define the one, uniform common standard that the clinical researchers, throughout the world are required to adhere to. In a way, today these guidelines are the very bible of Clinical Research.

1.1 Institutional Ethics Committee (IEC)

Ethics deals with moral principles. The landmarks in the evolution of Good Clinical Practice (GCP) indicate that the infamous "Doctor Trial" identified the necessity of consideration of ethical issues in medical research. Thus was born the Nuremberg code, the first ever international instrument on ethics of medical research. This code, promulgated in 1947, aimed at (i) protection of the integrity of the research subject, (ii) setting out conditions for the ethical conduct of research in which human subjects are involved (cf. biomedical research), and (iii) Stressing the need for their voluntary consent for required participation in the research.

In India, the Indian Council of Medical Research developed "Ethical Guidelines for Biomedical Research on Human Subjects", in the year 2000, also called "ICMR CODE" 2000 which was subsequently followed by Ethical Guidelines for Biomedical Research on Human Participants, issued in 2006.

The body that is primarily constituted and concerned with the ethical issues of human subjects in medical research is called Ethics Review Board (ERB). Different institutions name this body differently. Thus ERB is also called Institutional Ethics Committee (IEC); Independent Ethics Committee (IEC); Institutional Review Board (IRB) or simply Ethics Committee (EC). The names are interchangeable or synonymous. Whatever the nomenclature used, the responsibilities remain the same.

In DMHRC the term used is Institutional Ethics Committee (IEC), which is equivalent to IRB/ERB. It works within the institutions framework but is an independent body as regards the decisions taken. However, it does not function as an "Independent Ethics Committee". The IEC-DMHRC is competent to consider properly formatted bio-medical and socially relevant research proposals generated at Lata

Mangeshkar Medical Foundation's group of hospitals.

The basic responsibility of IEC, per ICH-GCP guideline is: (i) to safeguard the dignity, rights, safety and well-being of all trial subjects. (ii) Special attention needs to be paid to trials that may include vulnerable subjects. (iii) To ensure and verify that universal ethical values and international scientific standards are followed in deference to local community values, customs and traditions to the extent possible.

The Institutional Ethics Committee has to weigh the suitability of the following points while assessing a certain trial or proposal recommended by the Scientific Advisory committee and placed for its consideration.

- Qualifications and experience of the Investigator, supporting staff and facilities available at the site.
- Protocol with reference to the objectives of the study, potential for reaching the set-out objectives and their soundness with the smallest possible exposure of the clients/subjects participating in the study, and to weigh the possible risks and inconveniences with possible benefits to the patient and others, or (i) importance of subject vis-à-vis effort and expense (ii) safety and interest of participants, and (iii) freedom of principal investigator.
- Patient information and consent forms, means of recruitment and other procedural matters.
- Provision for compensation and/or treatment in the event of injury or death of a subject because of the clinical trial; indemnity and insurance to cover the liability of the Investigator and sponsor.
- Extent to which Investigator/s and subjects may be rewarded and or compensated for participation in the study.
- To take into account the principle of conflict of interest.

For smoother and effective functioning of the IEC, it needs to have its own standard Operating Procedures (SOPs). Adhering to those strictly after adoption, is imperative.

The SOP's to follow deal with composition, functional modalities and such other matters for the internationally acceptable, scientifically sound working of IEC-DMHRC, enshrining the principles of morality and confidentiality.

1.2 Standard Operating Procedures (SOPs)

ICH-GCP guideline defines SOPs as "Detailed, written instructions to achieve uniformity of the performance of a specific function". SOPs provide the essential link between the guideline on one hand and the actual practice on the other. It is but natural therefore that, all the individual participants, performing their primarily required duty or a specific job and belonging to each and every category of the stakeholder has not only to have a well defined SOP but also to observe/follow it very carefully. It goes without saying, therefore, that each stakeholder has to have separate SOPs and IEC is no exception to the rule.

SOP is for the methodical functioning of any important work to be undertaken, a proper, stepwise, work procedure is necessary.

In general, in any SOP the steps given should be reproducible, e.g. in the case of clinical trials, it will be neither proper nor acceptable to have an SOP that can be applied to just one or specific clinical trial. Broadly speaking SOPs can be in four different areas covering (i) organization of study in general, (ii) prior to study, (iii) actual or during, and (iv) end of the study.

The SOP should have the following general outline.

a) Must have a number with title or checklist. A set SOP need not have a checklist, but if included it should be sub-numbered, incorporating the corresponding SOP number.
b) Reference, if any, to other related procedures.
c) Person/Personnel i.e. who carried out / who all carry out the procedure.
d) When and how the procedure is carried out (Note: These are especially required for other stakeholders in clinical trials, as compared to the IEC.)
e) Date of version in use; date of revision/ amendment/ replacement/ automatically replacing the previous version / name of the person or body responsible for the change.
f) The process of review and revision of SOP should usually be a regularly done exercise, say every few months. A team should preferably do it. The old version should be archived after approval and implementation of the revised version. This is necessary because Regulatory Authorities may want to know some relevant answer to the question that might arise.

Some benefits of SOP are:

a) It provides a written record of the process.
b) Processes used by several individuals are applied (more) consistently.
c) Team member confidence is increased and performance is enhanced.
d) It helps with the training of new staff
e) Reduces supervisory time/effort.

However, these can also be generally applicable to other stakeholders.

As far as this IEC-DMHRC related Work Document is concerned, a properly constituted IEC, functioning regularly and following its own Standard Operating Procedure is a must. Then alone the studies approved by the IEC stand a good chance of the global acceptability of the outcome of their quality results.

2. SOP ON SOP

1) It should be a neat presentation of pre-established written procedures to be followed by any organization, establishment, institution, a constituted body or committee, set up for a specific purpose and concerned with stipulated aim(s) and/or objective(s).

2) It should cover matters related to the said committee's
    a) Composition.
    b) Conduct or functioning.
    c) Documentation.
    d) Supervisory/Inspectional or Regulatory role related to the issues resulting out of its decisions.
    e) Accountability.

3) The procedures could be laid down to suit local needs and conditions but should not be at variance, or be in utter disregard to the universally accepted and followed written or conventional norms / guidelines.

4) It should be periodically reviewed, up-dated and amended to be able to discharge more effectively the purpose for which it is written and followed.

5) DMHRC EC SOP is reviewed and revised periodically as necessary:

3. Institutional Ethics Committee (IEC/ IRB)

Appointment, Composition, Tenure and Retirement, Resignation, Replacement, or Discontinuation, Need to sign agreement and according consent, Special Invitee's.

Name to be referred as:

Institutional Ethics Committee (IEC) [also meaning Institutional Review Board (IRB)]. In the text to follow it is referred to as IEC. IEC is registered with DCGI. Registration number- ***ECR/15/Inst/Maha/2013***

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3.1 Appointment:

The Medical Director shall be the sole authority to appoint the Member belonging to a certain category, by a written invitation. The basis for the invitation would be the composition given below.

The Medical Director shall be one of the members of the committee, as an ex-officio member. However, if he/she deems it necessary the responsibility as a Member of IEC could be delegated to another person by sending a suitable written communication under his/her signature to the Member Secretary. The procedure for appointing the new members after tenure shall start two months prior to the expiry of the term of the incumbent members. The Medical Director can reappoint a member / members of the sitting committee taking into account contribution or can appoint/invite new member or members (other than himself/ herself being an ex-officio member) by invitation.

3.2 Composition:

The IEC will have 08 to 12 members. It shall have a fair representation of medical, non-medical, scientific and non-scientific persons with appropriate gender representation. There shall be at least one each of lay person and legal expert. (Ref. ICMR Guidelines 2006/Indian GCP-2001, Schedule Y CDSCO 2005 Appendix VIII ,GSR dated 8th Feb 2013). Considering the overall importance of accepted responsibility, every appointed member/ special invitee is expected to remain present and participate in the discussion / decision making process.

The **Chairman / Chairperson** shall be from amongst the members but shall not belong to the Institution. In other words he / she shall not be a staff member appointed in the institution but shall be an outsider in order to be able to function independently, i.e. without any institutional influence. The **Member**

Secretary shall belong to the Institution. A Joint member Secretary from the Institution can also be appointed by the Medical Director, if required.

Generally, the representation on the IEC shall be:

Chairperson/Vice Chairperson	**1**
Basic Medical Scientists	**1**
Clinicians	**1**
Legal Expert	**1**
An eminent person conversant with social needs/ problems i.e. a Social Scientist or representative of a Non-Governmental Voluntary Organization	**1**
An Ethicist or Philosopher or Theologian	**1**
Lay-person	**1**
Member Secretary	**1**
Joint Member Secretary	**1**
A member can be added, if necessary	

A member can cast a dissenting vote or abstain by stating the reason for the same in writing and the Member Secretary should make a note of the same.

Absenteeism should be avoided. For some reason, if a member wishes to remain absent, he/she should inform the same in writing to the Member Secretary, well in advance of the meeting. However, in the event of an emergency, a telephonic notice to the Member Secretary will suffice.

3.3 Membership requirements-

Member/s should be sufficiently qualified through the experience and expertise and sensitive to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. In addition to possessing the professional competence necessary to review the specific research activities, the member/s should be able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards or professional conduct and practice. (Ref 21 CFR part 56.107) A member of IEC can be a part of any other IRB/IEC

3.4 Tenure:

The tenure for Members of the IEC is for a period of three (3) Years.

3.5 Retirement:

. The retiring members are eligible for reappointment The eligibility for reappointment of the retired IEC member will be decided by The Medical Director in consultation with other IEC members, IEC Chairman, and. Member Secretary.

The Member Secretary, in consultation with the Chairperson, shall intimate the Medical Director about members completing tenure and the need to appoint new members from the same background. However the directives of the Medical Director in the matter shall be followed.

3.6 Resignation:

A member can resign by stating the reasons thereof, after giving one-month's advance notice addressed to the Chairperson and delivered to the Member Secretary.

3.7 Replacement or Discontinuation:

The Medical Director may as and when deemed necessary, replace or discontinue a sitting member if his/ her contribution is deemed to be inadequate or on account of non-availability of his/her expertise.

3.8 *Need to sign agreement and accord consent*:

Every member shall sign the declaration and confidentiality agreement concerning his/her activities in the IEC and submit an updated copy of his/her C.V. (Biodata). He shall accord consent to any revision/amendment to be approved by IEC under signatures of Chairman/ Chairperson

3.9 Special Invitee(s):

Depending upon the need, there is provision to invite one or two additional members as special invitee(s), belonging to the area/topic of the trial/study, and/or having experience in the matters with which the IEC is/or likely to be seized, for seeking an expert opinion. The special invitee/s can be from within the institution or from other Institution/s.

Such a member, if present, shall sign the attendance sheet and have the right to participate in the deliberations during the meeting, but shall not have a right of voting. If unable to attend the meeting she/he may send in writing, opinion in the matter, for the consideration of the IEC.

3.10 Training:

Training will be imparted to all newly appointed members about ICH GCP, EC SOPs and other regulatory guidelines by member secretary/ Chairperson. In addition continuous training sessions will be arranged for all IEC members and the supporting staff the schedule for this will generally be as given below

- Duration of Training-One day
- Frequency- at every 6 months or whenever required.
- Faculty- In house as well as outside experts will give the training

Record of such training will be maintained in EC office as well as by giving certificate to participants

4. IEC (IRB) - Functions

4.1 The primary function of the IEC shall be:

a) Maintaining records of its activities, such as Agenda and Minutes of the meetings.

b) Complying with ICH GCP and other regulatory guidelines.

c) Adhering to applicable regulatory requirements.

d) Making its decisions at announced meetings.

e) Including only those members in the voting process, who are independent of the trial process and who are actually present at the meeting called for considering/reviewing the proposal/s.

f) Paying special attention to the considered opinion, of members appointed with a specific purpose, such as, the legal advisor, social scientist, Ethicist, lay-person, especially when different opinions or views are expressed in a meeting.

g) Proposals are evaluated by committee as per the assessment forms attached in Annexure in terms of full/ expedited /exempted review.

4.2 Issues and principles to be addressed and discussed at the meeting/s:

a) Ethical justification and scientific validity of biomedical research involving clinical drug/device trials, bioavailability (BA), bioequivalence (BE) and safety evaluation studies involving human subjects or biological material of human origin at an appropriate phase of the study. Of these, the BA and BE may need some different consideration while reviewing and approving such protocols. The committees could, therefore, make special reference to and follow, to the extent possible procedure in vogue.

b) Instituting a committee with proper composition when deemed necessary to consider extra ordinary ethical issues.

c) Observance of Informed consent process, which shall include details on essential information for obtaining informed consent as well as the obligations of sponsor/s or Investigator/s in Informed Consent Documentation (ICD) or Informed Consent Form (ICF).

d) Choice of control in clinical trials.

e) Research involving vulnerable persons/groups and children.

5. Roles and Responsibilities of IEC members

5.1 Role:

a) To review and arrive at appropriate decision on the submitted clinical Trial/Study/Research Proposal and to intimate it in writing.

b) To take all steps such as enquiring into a particular issue, monitoring the on-going study, seeking progress and reports from the P.I. in the interest of the study as well as the' site'/Institution.

c) To recommend all the relevant matters to the Head of the Institution (cf. Medical Director), especially in furtherance of cause of research.

d) In addition to its primary domain, viz. review and concern about ethical issues, the committee is also entitled to consider:

- How the Patient/subject/client is going to be benefited?
- How the Society is going to be benefited?
- What are the benefits to the Hospital?
- How the Investigator and the Hospital are going to be benefited (by way of contribution and credit respectively, in a research paper, etc.)

5.2 Responsibilities of the Chairperson/officiating Chairperson/Vice Chaiperson:

a) The committee meeting shall be presided over by the Chairperson who shall lead all deliberations and discussions pertinent to review of the study/research proposals, office matters, etc. in accordance with the agenda.

b) The Chairperson may permit any item for review/discussion/ decision aside from the agenda during the meeting. Such an item, when permitted by the Chair shall be deemed to be part of the agenda and any decision on the included item shall have the same effect and be as binding as any other original item on the agenda.

c) If there are any financial or administrative matters or matters that will have impact on the efficient functioning of the IEC and/or SAC, or matters that are in the interest of the institution, that the members deem it necessary to be brought to the notice of the Medical Director, the issue/s will be discussed and a suitable communication shall be sent by the Chairperson to the Medical Director. However, it is not obligatory for him/her to do so. It is to be remembered that decisions related to any administrative aspect of the trial/study is the domain of the Administration Department of Institution/site.

d) The chairperson is concluding authority in IEC voting and final decisions, he/ she will sign the minutes.

e) The chairperson will review all onsite SAEs, External SAEs CIOMS/ SUSARS and other safety updates, after reviewed by SAC , compensation details etc Regarding on site SAEs IEC opinion

will be sent to licensing authority duly signed by the chairperson

f) The Chairperson is empowered to assign any specific matter/s to the members of the IEC for smooth & efficient functioning of the IEC.

5.3 Responsibilities of the Members Secretary

In consultation with Chairperson, the Member Secretary shall discharge the following functions.

a) Receive all correspondence related to research proposals.

b) Forward those proposals/matters which are in conformity with the Proforma/ application/ guidelines for review by members of respective sub-committee such as SAC / CCPR / SAC-IR for the review and then to IEC. Incomplete proposals will not be accepted. The P.I. on his own or for the Sponsor can justify in writing the reason/s for the incomplete proposals. The Member Secretary may place such justifications for consideration of the members of SAC/IEC. The committee's decision shall be final. Furthermore, without compliance of the conformity of the proposal and the receipt of the letter of approval, the P.I. shall not enroll the subjects or start the study

c) Refuse the proposal/ matter that is not in conformity of the approved format.

d) The Member Secretary may recommend to the Chairperson to call for an extra-ordinary meeting, even at a short notice, in the interest of the trials/ study/ research proposal for review, however, in that case the Member Secretary in writing thereof shall record the reasons.

e) Preparation and posting of the Agenda for the meeting/s to the members, around four to eight days prior to the stipulated date of the meeting.

f) Invite the P.I./ Co-Investigator/ Special Invitee(s), when necessary, for the scheduled meeting.

g) Preparation and placing the minutes of the previous meeting for confirmation by the members at the current meeting.

h) Communication of review outcome of the clinical trial protocol/ research project/ study recommendation/ approval/ non-approval/, suggested modification/ re-submission or repeat review incorporating the suggestions/ advice of the committee, to the Principal Investigator. This will be done in consultation with the Chairperson or jointly with other IEC members, whatever is applicable.

i) With reference to Clinical Trials/Study, the approval shall be accorded as per Schedule 'Y' and more specifically therein as per the format for Approval of Ethics Committee as the basis (Ref. The Gazette of India: Extraordinary I Part II – sec. 3(i) Pg. 109-110. (Pl. See Appendix III), and as per Good Clinical Practice – guidelines for decision making by the IEC [Specific item 2.4.2.6.1]. The Member Secretary shall communicate the decision in writing. The practice of according approval per requirements and format given by the Sponsor is therefore discouraged.

However, in the event of specific request, if any, the procedure laid down under topic "Transaction of Business" shall be followed.

j) All correspondence shall be in writing. The IEC shall be deemed to be responsible for retention of the same and safe keeping of all records, for a period recommended as per the latest regulatory guidelines after completion of the Study. The same shall be made available for the audit. Maintenance and safe keeping of the said records shall be the responsibility of the Members Secretary. The Member Secretary should be provided with all the necessary facilities, and co-operation by the 'Administration' section of the Institution, failing which he will not be held responsible for the outcome.

5.4 Responsibilities of Joint Member Secretary

a) To assist member secretary in day to day business of IEC

b) In absence of Member Secretary will take over all roles and responsibilities of Member Secretary including signing of approval letters.

5.5 Responsibilities of other IEC members

a) To protect and safeguard the dignity, rights, safety and well-being of volunteers /subjects /patients/clients and others as actual or potential research participants.

b) To distribute the benefits and burdens of research fairly among all groups and classes of the Society, taking into account age, gender, economic status, culture and ethnic considerations, based on the principle of justice.

c) To advise the researchers on all aspects of the welfare and safety of participants in research and to encourage them to ensure scientific soundness, technical excellence and ethics involved in the proposed/ undertaken research.

d) To encourage all members of the IEC and persons concerned with research, to attend workshops /seminars/ training program to acquire proper insight, and to enhance decision making skills.

6. IEC- Related Operations

6.1 Meeting:

The IEC shall meet generally on the 3rd Thursday of every month. As an item on the Agenda, the date, time etc. of the next meeting is given for consideration, confirmation or change, if necessary, for specific reason. In the month of May there will be no sub-committee and IEC meetings. The meeting in the month of November shall be a business meeting only. Therefore, no protocols/amendments /study related documents will be considered for discussion.

6.2 Quorum:

Quorum is constituted by 5 members in attendance (Reference- Schedule Y CDSCO 2005 Appendix VIII, GSR dated 8th Feb 2013) Legal Adviser and Lay Person attendance is must in the 5 member quorum. However, these five members should not be from the same profession (cf. Medical), as also not be from the same institution. There should, at least be one member appointed in a non-medical capacity and from other institution, and that the Chairperson must be one of the five members. In the absence of the Chairperson, there shall be a member, who is not on the staff of the institution, duly officiating as the Chairperson. For want of a quorum, the meeting can be adjourned once, for fifteen minutes. In the resumed meeting appropriate decision could be taken.

6.3 Transaction of Business:

a) The business transacted in the meeting shall be recorded as the minutes of the meeting.
b) These shall be placed for consideration, confirmation and record as an opening item on the Agenda of the next month's meeting.
c) The Chairperson or a person in chair if the chair person is absent shall accord confirmation to the minutes by signing the document on behalf of self and the members. Thereafter, the trial/study proposals on which the SAC has expressed its opinion in writing shall be taken up for review by the IEC.
d) The Study is required to be discussed with the Scientific Advisory Committee (SAC) first, and upon its recommendation it shall be referred to the IEC for its consideration.
e) The IEC shall pay special attention to the informed consent documents and implications of its contents, to safety, compensation of research subjects and other ethical considerations.
f) In the event of disapproval of a trial/study/proposal under review of the IEC, the IEC shall record detailed reasons thereof.
g) The decision for the trial/ study/ amendment/ sub-study, etc. shall be by majority vote only. In the case that equal number of members is for and against the project proposal, the Chairperson shall

exercise his/her power of casting vote.

h) After the consideration of the study proposal/s, the expert views on the Serious Adverse Events (SAEs) shall be noted. Please note that a special format for reporting SAE has been provided (Ref. Onsite and Periodic SAE reporting formats). An IEC opinion letter will be issued for every onsite SAE received. Additional details related to a SAE could be sought from the PI for the review.

i) Then the office matters shall be taken up for consideration.

j) If need be, the Chairperson can take up any item for consideration of the IEC out of turn.

k) When deemed necessary, an Extra-ordinary meeting can be held, in addition to or in lieu of the regular meeting.

l) Whenever deemed necessary, the meeting can be held to transact business related to office matters only.

m) There is no provision to transact business by resorting to decision making through circulation of proposals.

n) By proposing thanks to the Chair, the meeting shall be concluded.

o) If a member is absent for a meeting he/she is welcome to know about the business transacted in the said meeting from the Member Secretary. However such a member is welcome to communicate his/her views on the protocol/s to the Member secretary, who would then table the same at the time of the meeting.

6.4 Expedited review :

There is specific provision for an expedited review of a study proposal/ amendment/ administrative matter, the procedure is followed on an expedited basis, for arriving at a decision. Such an expedited review shall be at the discretion of the Chairperson and the Member Secretary, and for which the Sponsor shall pay additional emergency fee as applicable. The P.I. is advised to contact the Member Secretary to check whether or not the study proposal qualifies for an expedited review. The submission regarding expedited review should go through a review by scientific advisory committee before sending it to the IEC chairperson and member secretary.

IEC will have the final authority to decide whether or not a study proposal should be accepted for expedited review.

6.5 Exemption from review :

Chairperson and an Expert from relevant field can decide if the research protocol needs criteria of exempt review. PI should mention in the protocol his conflict of interests, collaboration and contribution by other departments in terms of use of facilities and provision of incidental expenses. At every meeting, the members present shall sign the attendance sheet for the purpose of record keeping.

6.6 Presentation/Defense of the study by the Principal Investigator:

a) The Principal Investigator (P.I.) shall be invited for the meeting. The P.I. / Co. P.I. shall sign the attendance sheet.

b) He / she is required to present and defend the new study protocol or monitoring review report or amendments and SAEs as per SAC committee members' recommendations as the case be. If he/she remains absent, the issue will stand automatically postponed. In a certain situation the P.I. can depute a colleague, officially participating in the study but not below the designation of Co- Investigator, to present/defend the study or the amendment at the meeting. However, the P.I. in such an eventuality will have to send a written authorization in that respect to the Member Secretary, in due time, so as to know the decision from him about the request.

c) If a member of the IEC is the Principal Investigator of the study under discussion, he/she will only present/defend it, but will not participate in the decision making process and/or the voting of the committee.

d) If there are more than one protocols/ studies, the respective P.I. or Co-Investigator is expected to adhere to a certain time-table for presentations. He/she shall be informed about his/her time of presentation, which to a reasonable extent is an approximate one. In exceptional circumstances, the Chairperson is authorized to allow the P.I. to make the presentation "out of turn".

e) The P.I. or Co-Investigator is expected to excuse himself or herself after the presentation is over and while the committee is taking decision on hi/her study.

6.7 Communication of IEC decision

a) All the submitted basic protocols and amendments will be reviewed in the next upcoming IEC meeting. Queries and concerns raised by the IEC will be communicated to PI within 7 working days. However, in case of approved protocols / amendments **"In Principle Approval"** letter will be issued within seven days based on IEC decision and the **"Final Approval"** letter will be provided within 7 working days after all the documents are complete (including IEC fees, DCGI approval, signed CTA, etc.)

b) To withhold the approval for non-compliance of any specific requirement, e.g. if the Clinical Trial Agreement with financial disclosure/agreement/or exhibit is not a tripartite one and not duly signed by the authorized signatory of the Institution, and a copy of the same received by the Member Secretary.

c) The IEC has adopted the format (contained in Appendix III) for giving its approval. In the event that a sponsor requires documents/approval in a format other than the one adopted by the IEC e.g. (i) Original copy of the study documents duly stamped and signed by the Member Secretary, (ii) Approval letter from the IEC in a format other than the one given by the IEC etc., the IEC may opt to issue the same in a varied format, suggested by the Sponsor. However, it shall always be the responsibility of the sponsor to

make available the said and/or other documents at its own cost. Further, in the event the sponsor fails to provide the same, the IEC shall issue documents in its regular format. Thereupon, it shall be deemed to have fulfilled its responsibility towards the protocol/study of the said sponsor.

d) IEC decision will be informed to PI in writing duly signed by Member Secretary or Joint Member Secretary. The PI is advised to initiate the study only after a written approval is obtained from the IEC. Any document related to the study submitted to the IEC for review (including notification) can be used only after it has been reviewed by the IEC.

e) Final approval letter will be issued only after submission of DCGI approval letter, EC fees, copy of final & signed CTA, and CTRI registration number

f) The trial/study must not be initiated prior to the date of issue of the approval letter

6.8 Duration of approval:

a) The study/trial can begin on the date of issue mentioned in the letter of approval. The duration of approval is one year from the date of "Final approval" unless stated otherwise. Any studies continued outside the approved duration of the project will be deemed invalid and fresh application will have to be made along with supporting documents for the consideration of the IEC.

b) In case of approval for any other study related document/s, approval would start from the date of issue and is effective only till the basic protocol approval remains valid.

c) If the study/trial is not completed within this time frame, application needs to be made for renewing approval for the study at least two months prior to the end of approval period. No fees will be levied for such a renewal. Failure to obtain the renewal during the stipulated period will be considered a violation of the SOPs and the project/study will have to seek fresh approval including all supporting documents or it may be discontinued.

6.9 Pharmacogenomic studies

a) Regarding approval of clinical trials wherein samples are to be sent abroad for pharmacogenomic testing – Trial shall be approved by the IEC subject to receiving clearance from the responsible body of the Indian Government. Investigators willing to undertake such studies are requested to follow the guidelines as listed below-

b) Consent- Written consent mentioning all the necessary details in respect of Pharmacogenomic studies shall be explained to the subject undergoing Pharmacogenomic studies at DMH. Consent also shall mention which tests would be conducted on samples collected from subject. It shall also mention that no other tests/procedures would be carried out on the samples of subject except mentioned in the consent form.

c) Confidentiality and secrecy- Special measures to be taken in respect of giving uttermost and paramount importance to the Confidentiality and secrecy of information pertaining to subject undergoing Pharmacogenomic studies at DMH. Undertaking/Agreement between PI and sponsors shall specify this clause in much detail.

d) Details of the Laboratory wherein genomic investigations/process would be carried out should be specified in the Undertaking/Agreement entered between PI and sponsors.

e) Sponsors shall give undertaking to the Principal Investigator in respect of preservation/ destruction/ disposal/treatment of remaining samples. Sponsors shall also give undertaking to the Principal Investigator that other than the tests mentioned in protocol shall not be conducted/performed/processed on sample.

f) Sponsors shall give undertaking to the Principal Investigator in respect of following and observing the Biomedical Waste Disposal & Management Laws/Rules of concerned country while destruction/ disposal/treatment of remaining samples.

6.10 Retrospective studies

a) The use of existing records requires IEC approval and approval from concerned PI as well as the Institution when the records are private and identifiable. "Identifiable" includes direct identifiers, such as names, addresses, dates of birth and clinical information etc., and indirect identifiers, such as ID codes (e.g., student ID, case numbers, etc.). Depending on the records to be obtained, other regulations may apply. The IEC would consider requirements of these regulations for research using educational or medical records before giving approval.

b) If the data is not available in the public domain, IEC approval number should be available to receive the data. This data should be submitted to the Research department after completion of the study.

c) All the retrospective studies will be initiated only after receiving written approval from IEC.

d) Regular updates pertaining to data entry must be submitted to IEC every 6 months.

e) After the data entry is complete the data should be submitted to IEC and the copy of the same will be retained in Research Department.

f) In case of collaborative projects, separate approval must be taken from IEC before sharing the data with outside agencies or Institutions.

g) In case of collaborative projects, full data from other participating centers should be made available to Research Dept, DMHRC.

h) All the relevant documents related to retrospective studies should be maintained by the PI and made available for the monitoring done by IEC, before, during or after the study.

i) In case of collaborative projects appropriate MOU from DMHRC needs to be signed.

j) If in a study, there are not enough participants or if the study has the necessary number of participants but the study has to be terminated, the participants already enrolled in the study should receive standard care of treatment according to ICH-GCP guidelines till completion of the study unless there is termination of the study due to safety concerns from the study drug.

k) Each patient related hospital file should have a fluorescent pink sticker attached to it along the sleeve with protocol number, Principal investigator's name and years for which the data is to be archived at the site typed on it.

6.11 Studies involving Vulnerable population-

Definition- Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate.(ICH GCP 1.61) These include individuals who are minors, prisoners, pregnant, physically handicapped, mentally chalanged, old, economically disadvantaged, educationally disadvantaged, or subordinates in hierarchical groups (e.g. a soldier). (45 CFR 46, Subparts A-D). IEC, DMHRC does not allow studies on vulnerable population except pediatric, geriatric and psycheatric studies. Special care is taken reviewing these protocols to protect safety and wellbeing of such population. Subject experts from the relevant faculty will be invited as and when necessary while evaluating such protocols

6.12 Policy to monitor and prevent conflict of interest-

A conflicting interest can be broadly defined to refer to any interest of the investigator or immediate family (includes spouse and each dependent child) that competes with the investigator's obligation to protect the rights and welfare of research subjects. Financial Interest- Significant Financial Interest means anything of monetary value , including but not limited to , salary or payments for services (e.g. ,stocks, stock options or other ownership interests);intellectual property right (e.g., patents, copyrights and royalties from such right) , and board or executive relationships. it is understood, that in the event any member of the IEC has any conflict of interest as defined hereinabove, then such member shall desist from partaking in any activity related with the said trial/protocol be decision making and/or monitoring of the subject trial/protocol, until its conclusion. *It will be monitored by the management that no Ethics Committee members have any conflict of interest at any point of time.*

6.13 Policy for Phase IV or Post Marketing studies:

Phase IV / PMS studies will be allowed only if there is a certain benefit to patient as-

a) Travel allowance must be paid (Min Rs 500)
b) For drug trials, study treatment must be provided free of cost
c) In case of device study or studies including surgical intervention subsidy / concession should be given
d) All study related investigations should be done free of cost to patients
e) Compensation to SAE as per GSR 53-E (or any other latest applicable regulatory guidelines) must be given
f) NOC from the regulatory authorities is obtained (as per latest applicable regulatory guidelines)

6.14 The committee is empowered:

a) To allow/ approve advertisement/ holding of camps, etc. for enrolment of the volunteers/patients for the approved project, based on the specific written request by the P.I./ Sponsor or provision for the same in the protocol under review. Prior permission of any such promotional activity from the IEC is mandatory.
b) To take special care of ethical issues to interpret/decide on the issues related to bias or inducement resulting out of it.
c) To initiate, if deemed necessary, an investigative procedure to review any aspect of the on-going study at this or any other approved site where the study is being undertaken and to opine upon the working of the study personnel and accordingly intimate the P.I. or Sponsor. Such an act shall not be construed to mean violation of confidentiality.
d) To withdraw the approval of an on-going trial/study/research proposal and intimating the P.I./Sponsor accordingly stating in writing the reasons there for, and to re-approve the project as and when deemed appropriate.
e) There is no provision for an "appeal" by the P.I. on the decision of the IEC.
f) In the event a member of any committee is interested in beneficial participation in the study/trial under scrutiny of the IEC, the member shall make a prior written disclosure of intent to the Member Secretary. When the subject study/trial is under active consideration of the committee, the said member shall excuse himself/herself by remaining outside the meeting hall and the same shall be specifically recorded in the minutes of the meeting. In the event a member of any committee wishes to participate in a study/trial after the trial was approved by the IEC, he shall request prior permission to do so from the IEC. The member shall abide by the decision of the committee in this regard. In the event that the member neglects or fails to make such disclosure to the committee before participating in the trial, the same shall constitute a ground for his/her expulsion from the committee.

7 Submission of documents for IEC review

a) All the correspondence should be addressed to the Member Secretary, IEC-SAC, DMHRC.

b) The documents for IEC review are typically submitted in the last week of the month.

c) The dates for the entire year are published on the 1st of January of the ongoing year on the Intranet.

d) The documents should be submitted in a particular format published on the Intranet at DMHRC and in required number of copies as mentioned.

e) The covering letter signed by the Principal Investigator requesting acceptance of the protocol/ study for approval of the SAC/IEC should be secularly stating the documents submitted or not submitted along with the reason/s for the same.

f) The covering letter shall be treated as an undertaking by the Principal Investigator towards fulfillment of the procedural requirements of the protocol/study submitted for consideration of IEC.

g) The Protocol/Study shall be accepted only if it is complete in all respects. The complete sets of documents as mentioned in annexure II are required.

h) A copy of draft CTA should be submitted at the time of basic protocol submission. However in case of approved protocols, approval letter will be issued only after the copy of final tripartite CTA, duly signed by all the three stake holders is submitted.

i) Basic protocol, and amendments will be reviewed after receiving EC fees and a copy of Fees receipt should be submitted to Research Department.

j) Protocol amendments should be ideally submitted for approval If amendments are submitted for notification, covering letter should clearly justify the reason for notification, and relevant correspondence with licensing authority should be provided. Acknowledgement of the notification will be given only after SAC members have reviewed and recommended the same.

k) A protocol will not be accepted unless a copy of the DCGI approval and other regulatory approval (if any) is enclosed. If the approval of the DCGI is awaited a complete set of application made to DCGI (Submission document, including name of participating sites) should be submitted, or If DCGI has taken a certain stand and communicated accordingly, copies of the related correspondence must be submitted. In case the DCGI approval is not received in time, a written communication, giving the status must be sent.

l) A copy of CTRI registration document including name of study site must be submitted before final approval letter is issued

m) Upon approval, the covering letter shall tantamount to mean that the P.I. has signed declaration of privacy and confidentiality.

n) Any matter/ item related to the clinical trial should be submitted with a covering letter addressed to the Member Secretary, IEC-DMHRC, signed by the P.I., giving Code Number, Title of Protocol, and full details of the issue. If a team member signs on behalf of the P.I., name and designation should be legibly written.

o) The Principal Investigator is requested to keep a copy of all the submitted documents with him/her for personal record.

p) A copy of every Publication of research project and research data of in-house studies should be provided to DMHRC for every DMH approved project.

q) All Publications, Presentations & Reports of research findings are subject to approval from IEC-DMHRC.

7.1 ICF requirements

a) Site Specific Informed Consent Form is Mandatory and Local consent form to be submitted, if required.

b) For Biosimilar studies a local ICF explaining in detail nature, risk and benefits of the study must be submitted.

c) ICFs must cover all the required points as per Appendix V of schedule Y. ICFs along with translation in regional languages (Hindi and Marathi) is mandatory.

d) For all ICFs related to sponsored drug/ device trials following information is mandatory.

- Date of Birth/ Age-
- Qualification-
- Occupation- student/self employed/service/house wife/ others
- Annual income of the subject-
- Name and address of the nominee(s) and his relation to subject-

e)ICF should have well defined "**compensation details"** in terms of when and how much patient will get the compensation. Travel Allowance should be minimum Rs 500

f) Contact details of IEC Chairperson should be printed on patient related documents (ICF, Patient information sheet, ID card etc.). as - Name with Designation- Institutional Ethics Committee, DMH&RC, Contact No- 020 – 66023000, Extn. 1150/1652/1671 Mobile No. of Chairperson 9822252985.

g) As per the office order issues by DCGI, dated 19/11/2013 Audio Video consent is mandatory for all

clinical trials including global clinical trials. As per directions given by management of DMHRC Audio Video Consent Procedure to be followed as mentioned in AppendixXVI of EC SOP

h) ICF s should be amended in timely manner to include all the revision as per Gazette Rules/ Amendments in Schedule Y or any other regulatory notifications

i) ICF amendments should be ideally submitted for approval. However administrative changes (as mentioned below) can be submitted for notification provided that the basic ICFs are reviewed and approved by IEC earlier .

j) Administrative changes in ICF

- IEC/ sponsors name and contact details
- Typographical errors
- Grammatical corrections
- Answers to IEC query e.g. – Travel Allowance should be Rs 500
- Purely administrative changes and points those are covered in SOP.

7.2 Periodic updates to be submitted to IEC

a) All amendments in protocol/ ICF/ IB or any new information available related to IEC approved protocols must be submitted to IEC.

b) The investigator/Sponsor is responsible to supply ongoing safety updates, progress reports (periodic) of trial status report, re-approvals (if required) to the IRB/IEC.

c) PI is required to inform IEC in writing after the site is initiated

d) Half yearly progress report to be submitted in the last week of every December and June. PIs are requested to submit 3 copies of each report to IEC, one to be given back to PI, one for IEC record and one will be given to accounts dept.

e) After receiving IEC approval , even if site is not initiated half yearly report must be submitted mentioning reasons for not initiating the site

f) The P.I. will be required to intimate the name/s designation and nature of work/ responsibilities entrusted to all the members of his/her team in the said protocol. This information will have to be submitted by the P.I. along with the submission letter addressed to the Member Secretary. Change/s in such a job /responsibility profile will be immediately intimated to the Member secretary.

g) If an assistant whose name is not intimated is entrusted the said job/ responsibility, it will be considered as a breach and the SAC/ IEC will take appropriate action in the matter and this decision shall be final.

h) The Principal Investigator and the said team shall abide by **privacy and confidentiality** when the study is approved by the IEC.

7.3 Safety Reporting-

a) The investigator/Sponsor is responsible to supply ongoing safety updates, onsite SAEs and outside site CIOMS, SUSARs PSURs to the IRB/IEC.

b) In the case of site related serious adverse event, the Initial SAE report along with copy of SAE form Appendix XI (as defined by Schedule Y amendment 30 Jan 2013) is to be submitted within 24 hours.

c) In case of public holidays a scanned copy of SAE report should be sent to iec@dmhospital.org . Hard copy of the same should be submitted on the next working day

d) . PIs are requested to submit 4 copies of each report to IEC, two to be given back to PI as acknowledged copies, one for IEC Chairperson and one for the Institution head.

e) While submitting follow up SAE reports a photocopy of EC acknowledged copy of Initial SAE must be attached along with the follow up report.

f) For all the onsite SAE reports a copy of analyzed report from sponsor should be submitted to IEC within the time lines as specified by applicable regulatory guidelines

g) All the onsite SAEs will be reviewed by "SAE Committee" which consists of one of the SAC members, legal expert, chairperson and member secretary. Committee will give it's detailed remarks on causal relation, compensation, risk benefits assessment etc. Committee will meet on every 2nd and 4th Tuesday If any SAE member wants to remain absent he/she should inform department of Research in writing. Each member of SAE committee should write his /her remarks and sign the document with date

h) Final opinion regarding onsite SAEs will be sent to the licensing authority, duly signed by the chairperson within 21 calendar days

i) Compensation amount will be estimated by IEC as specified by applicable regulatory guidelines and recommend it to DCGI The cheque for the compensation (as conformed by the DCGI office) should be drawn in favor of "Deenanath Mangeshkar Hospital and Research Centre."

j) PI and his or her study team members are requested to ensure that such cheque is submitted to Finance Dept along with the cover letter from sponsors (mentioning all the relevant details about SAE)

k) As per the written information provided by PI Finance Dept will issue the cheque to the patient or his/her nominee

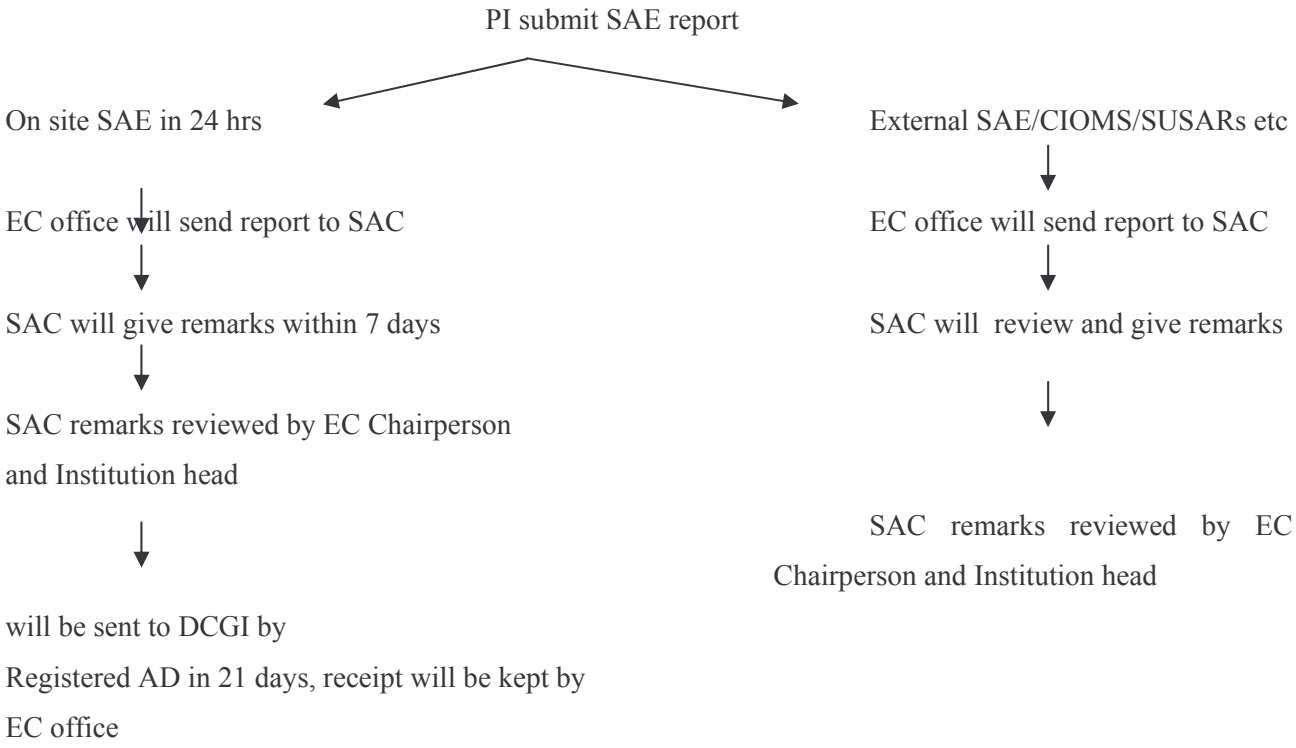
l) It is the sole responsibility of PI to ensure that all the legal aspects are taken care of during this process

m) A receipt must be obtained from the patient or his/her nominee in the format as per Appendix XV of EC SOP. A copy of the same should be submitted to IEC

n) SAE report for any external SAE/CIOMS/SUSARs etc of a protocol should be submitted to IEC as per the applicable regulatory guidelines All these reports should be submitted in DMHRC defined format with PI comments for each SAE. A copy of CIOMS/ SUSARs forms provided by sponsors should be

attached along with. PIs are requested to submit 2 copies of each report to IEC, one to be given back to PI, one for IEC

Flow chart of SAE submission



7.4 Document submission and collection (To/ From Research Department) guidelines-

a) All the documents (other than IEC approval) will be reviewed in 7 working days from the date of submission.
b) All complete and correct documents- signed copy will be issued in 7 working days from the date of submission.
c) In case of queries or incomplete documents, you are requested to collect both the copies from department, cancel the entry from register and resubmit the corrected documents later as fresh submission.
d) You are requested to collect all the documents from the department within 15 working days from the date of submission.
e) For unresolved queries and documents or other IEC acknowledged documents not collected within in 90 days, the documents will be considered as void. PI will be required to resubmit the documents freshly in order to get IEC approval / notification.

f) When approval letters not collected and if revisions are done in SOP, approval letter will be issued only after the revisions are approved in the next IEC meeting.

8 Advisory Committees

SAC (Scientific Advisory Committees)
CCPR (Core Committee for promotion of research)
SAC-IR (Scientific Advisory Committee for Integrated Research)

SAC is also called Scientific Review Committee (SRC), Scientific Review Board (SRB), or Research
Committee (RC). The terms are synonymous.

For Scientific review of the studies IEC-DMHRC has appointed 3 Advisory committees as follows:

a. SAC: For sponsor clinical trial.
b. CCPR (Core Committee for promotion of research): For in-house projects involving single pathy.
c. SAC-IR (Scientific Advisory Committee for Integrated Research): For In–House projects involving more than one pathy.

DNB monitoring committee: This committee reviews scientific aspects of the projects submitted by DNB students (Diploma of National Board), Medical superintendent (Academics) is the in-charge of the committee. The projects approved by this committee are sent to IEC for approval.

Appointment, Tenure, Retirement, Resignation, Special Invitee(s) is the same as in SOP.

8.1 Composition of Advisory Committees:

SAC: Although there is no specific stipulation for the total number of members for the SAC, it shall, as far as possible, be a small one, with number of members ranging from 4 to 8.

At a site like this hospital, some members of the SAC are required to be members of the medical fraternity (quasi-medical, paramedical) and necessarily attached to the hospital. However scientists

in basic sciences can be also be invited to be the members with a view to strengthening basic research in the fields of medicine and health care. There should be no age or gender discrimination. The representation shall, as far as possible, cover various categories of medical specialists such as surgeons, physicians, etc.

The SAC shall consist of the Medical Director who is the *ex-officio* member and Chairman of the committee (SAC). However, if he/she deems it necessary the responsibility as a Member of IEC could be delegated to another person by sending a suitable written communication under his/her signature to the Member Secretary. The Member Secretary of the IEC shall function as the Member Secretary of the SAC as well. The composition of CCPR would be same as SAC. For SAC-IR: In addition to the composition mentioned above, an expert from Ayurveda and Homeopathy doctors are included in the team.

8.2 Quorum:

Three members should be present to form a quorum for each Advisory committee.

8.3 Functions and Procedures

a) The current list of members with their qualifications and designation is enclosed in Appendix II.

b) The Advisory committees are required to assess the scientific soundness and technical excellence of the submitted Clinical Trial/Study/Protocol/Research Proposal. In addition the Advisory committees are also required to assess the amendments/follow-up study/sub-study/ SAEs and progress reports etc. of the approved protocol.

c) The study proposals shall be reviewed first by the Advisory committees. Its recommendations shall be documented and signed by all Advisory committee members and then forwarded to IEC Proposals are evaluated by committee as per the assessment form attached in appendix XI.

d) The meetings of Advisory committees shall be convened about 10 days prior to the meeting of IEC for that month (except for the month of May and November). SAC will therefore be generally convened on 2nd Tuesday of that month and CCPR will be convened on second Monday of the month. SAC-IR will be conducted once in two months on second Monday of the month (June, August, October, and December). The Advisory committees meeting shall be convened as per the requirement of the expedited review procedure, as and when necessary and shall precede the expedited review meeting of the IEC.

e) While considering a study proposal, the Advisory committee members may be required to take into consideration related issues such as administrative feasibility, financial considerations

and/or overall impact on the reputation and smooth working of the site (hospital as an Institution) and may bring these issues to the notice of the Medical Director, whose decision shall be final in such matters. However, it is not obligatory for them to do so. It is to be remembered that decisions related to any administrative aspect of the trial/study is the sole discretion of the research Department of the institution. The Principal Investigator (P.I.) for himself/herself or for the C.R.O. or the Sponsor shall be getting the necessary clarifications required, if any, from the Research department.

f) In turn, there shall be proper representation of members of Advisory committees in the IEC.

g) The provisions, to invite experts as Special Invitees, the role of the Principal Investigator in presentation and defense of the study etc., are the same as in SOP 1: IEC.

h) Decisions as recommendations to IEC should as far as possible be arrived at the properly called meeting of the members.

i) In an event when the members are unable to arrive at a unanimous decision in the meeting, then their views shall be recorded in writing and placed before the IEC for consideration. There is, however, no provision for voting in the Advisory committees

j) After the decision of the members of the Advisory committees has been finalized, the same shall be conveyed in writing to the IEC prior to IEC's scheduled monthly meeting.

k) Sub-committee members will be given a copy of an evaluation form. At least 2 members of Advisory committees have to evaluate the proposal & duly sign the same.

l) In exceptional circumstances if the decision is not made in a meeting or if a member is unable to be present at the said meeting, he/she shall give the opinion in writing in the given form and duly signing the same.

m) Similarly, if it is not possible to hold a meeting then each member of sub-committee will be required to give the opinion in writing.

n) The decision/s of Advisory committee shall be suitably incorporated in the agenda of the ensuing meeting of the IEC. If it is not possible to do so then the Member Secretary of the Advisory committees will be required to table the findings of the Advisory committee to IEC at the time of the meeting

o) A proposal shall not be treated eligible for consideration by the Advisory committee and will thus not be eligible to be placed before the IEC unless it is reviewed, considered, pondered upon and recommended by half the number of members of the Advisory committees Such ineligible matters may be kept for discussion in the next Advisory committee’s meeting.

p) CCPR and SACIR these will work on same rules/regulations.

q) For all CCPR and SAC-IR projects Approval letter will be issued only after receiving a copy of budget signed by PI and Finance Manager, DMHRC

9. Financial Matters for IEC and SAC

9.1 Fees:

The committee may, after discussion with the Medical Director, decide upon/ announce/ change/ amend/ alter, from time to time, announce and implement the fees for Clinical Trial / Study / Protocol / Research Proposal. The said fees are payable by the Sponsors. The fees chargeable may be classified variously under heads such as: protocol processing fees, per amendment/ follow-up study fees, and expedited review fees.

The processing fees are to be paid before approval of the protocol/amendment. An IEC approval letter will not be issued until copy of the receipt of processing fee is submitted to the Department of Research.

9.2 Fees charged for various types of documents.

Type of Documents	Fees (Rs.)
Review of a sponsor-based basic project	25000/-
Expedited review of a sponsor based project	35000/-
Sub study of a sponsor based and IEC approved project	10000/-
All amendment to a Sponsor based and IEC approved project (initiated by Sponsor)	10000/-
Expedited amendment review of a sponsor based project	35000/-
Investigator/ DMHRC initiated project at various site Collaborative projects: if project is initiated by institution other than DMHRC Collaborative projects: If project is initiated by PI	Nil 5000/- 5000/-

who is not affiliated to DMHRC	

The IEC review fees for Institutional Research Projects (CCPR / SAC-IR) or collaborative projects can be waived off at the discretion of IEC.

Every payment of protocol fees to the accounts department has to be accompanied by:

- The protocol fees form
- Copy of advice received from the Sponsor/CRO

Kindly note - All the above fees are non-negotiable and non-refundable.

- The sub-study will be considered equivalent to an amendment for purposes of levying fees, provided the same is mentioned in the original protocol approved by the IEC. Otherwise the same shall be treated as a fresh protocol proposal and the protocol processing fees in vogue will be applicable.
- Fees for Investigators initiated & collaborative projects are optional and shall be stipulated and/or waived by the IEC. Financial considerations-

- Payment of Institutional overheads as stated in the latest updated SOPs shall be mandatory for all clinical trials.
- Additionally, a certain proportion of total study budget (excluding SAE and miscellaneous cost) will be designated and charged as fees/power charges of the Site Management/ person. The exact amount (%) shall be decided by Finance Dept DMHRC depending upon nature of clinical trial.

9.3 Traveling/Conveyance Allowance:

The Medical Director is seized with the matter of payment of traveling / conveyance allowance to the members and the special Invitee/s not affiliated to the Institution, at the rate decided by Accounts Department of the Institution from time to time, and payable on the basis of every meeting attended.

9.4 Honorarium/Payments:

The Medical Director has directed the administration for the payment of honorarium to the member(s) for investing extra time and intellectual capital in decision making process.

10. Monitoring

10.1 Introduction

It is stated herein as a message of abundant precaution that a random monitoring of research projects may be conducted from time-to-time by the IEC member and/or Research associate and/or accounts department to internally evaluate/ inspect/ monitor/ audit working of the approved proposals, to assess effectiveness, efficiency and observance of the norms by the P.I. All monitoring will be conducted in accordance with the ICMR guidelines,2006. Researchers will be expected to provide all the documents as requested by the IEC member and/or designee for review. Researchers will be given one weeks' notice prior to an intended monitoring. The P.I. and his/her research team shall have to cooperate with officer designated for the same. The IEC may send a report of their findings to the investigator

10.2 Purpose

Selection of the site for monitoring and monitor the site for ensuring that -

a) The reported trial data is accurate, complete, and verifiable from source documents.
b) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

ICH GCP E6, 5.18 (Monitoring) 21 CFR Part 312.56 (Review of ongoing investigations)

10.3 Scope

This SOP applies to any visit and/or monitoring of any study sites as stated in the Institutional Ethics Committee of Deenanath Mangeshkar Hospital and Research Centre approved study protocols.

In general, on-site random monitoring will be conducted before, during, and after the trial.

a) Random Monitoring will be conducted every year during Jan to Oct during which strengths and weaknesses will be assessed and a report will be issued to the PI suggesting corrective actions. Follow up visits will be conducted during the same year to check if the PIs have taken the corrective actions.
b) Access to patient data as mentioned in ICH (Page 36 sec 7.2)
c) The IRB/IEC, and the regulatory authority(ies) of DMHRC will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.[1]

10.4 Responsibility

It is the responsibility of the designated IEC-DMHRC member(s) or designated qualified Monitor to perform on-site inspection/monitoring of selected study site(s) of relevant projects it has approved. The IEC-DMHRC members or Secretariat in consultation with the Chairperson may initiate an on site evaluation of a study site for a routine monitoring visit/Audit.

10.5 Responsibility Delegations

No.	Activity	Responsibility
1	Selection of study sites.	Research dept. / IEC
2	Selection of monitors for site Monitoring	Research dept/ Member IEC
3	Before the visit	Research dept.
4	During the visit	Research dept / Member IEC
5	After the visit	IEC / Research dept.

10.6 Detailed instructions

a. **Selection of study sites**

- Research dept/IEC-DMHRC will identify the site(s) for routine monitoring of ongoing trial site/study.
- Selection of the site/study will be on random basis. One sponsored trial and one In-house trial in alternate month should be selected randomly for IEC monitoring.
- The Research dept. will identify and designate one or more monitors and/or IEC-DMHRC member to carry out routine monitoring of the study site.
- In some cases IEC may identify a particular site for **Monitoring** that will be decided by Regulatory Dept / IEC.

This cause could include any one or more of the following:

- High number of protocol violations
- High Budget Study
- More than 5 trials/studies carried out at the study site or by the investigator.
- High and continuous number of SAE reports,
- Non compliance,
- Suspicious conduct,
- Complaints received from participants,
- Any other cause as decided by IEC.

After discussion at Research Dept. / IEC-DMHRC meeting, decision regarding conducting Monitoring will be taken.

b. **Before the visit**

Director / Assistant Director of Research Dept. will designate a monitor / IEC-DMHRC member to perform the task of monitoring.

The Monitor will inform the Principal Investigator in writing about the date/time of Monitoring visit one week before and request for confirmation from the Principal Investigator and if possible respective co-investigator and coordinators to be available for the monitoring visit.

The monitor will:

- Contact the site to notify them that they will be visiting them. At that time, the monitor and the site will coordinate the time for the site evaluation visit.
- The Research dept will review the DMHRC's project files for the study and site profile and make appropriate notes.
- The monitor will be provided with relevant reference material/ documents related to the project that may have to be referred to during the study visits and collect the Site Monitoring Visit Report Form.

- Site visit
- Medical monitoring
- Financial monitoring.

c. **During the visit**

Monitoring will be conducted in following three parts,

I) The monitor/ IEC-DMHRC member at site visit will…

- Check if the site is using latest IEC-DMHRC approved versions of the protocol, informed consent documents, Investigators broacher, diaries, advertisements, etc.
- Review the informed consent document to make sure that the site is using the most recent version.
- Observe the informed consent process, if possible.
- Review subject files to ensure that subjects are signing the correct Inform consent form.
- Review the medical aspects of the study participants such as all SAE and AE reports,

study medication accountability and treatment given.

- Review the project files of the study to ensure that documentation is filed appropriately.
- Review the source documents for their completeness.
- Collect views of the study participants, if possible.
- Fill the Site Monitoring Visit Report Form, sign and date it.

II) Medical monitoring

- For Medical monitoring Monitor will contact a physician preferably IEC member.
- Medical monitor then will monitor medical and therapeutic aspects of the trial.
- Medical monitor will select randomly source documents of subject for monitoring.

III) Financial Monitoring

- For financial monitoring, monitor will coordinate with accounts department.
- Monitor will provide financial monitoring form to Accounts Department and collect the completed form from the Accounts Department.

d) After the visit

The Monitor will submit the completed Site Monitoring Visit Report Form to the research dept for further evaluation.

The report should describe the findings of the monitoring visit. This Monitoring report is presented at the next full board IEC meeting and the concerned monitor/IEC member will provide additional details/ clarifications to members, as required. The PI may be called for the meeting to seek clarification when the monitoring report is to be discussed.

The IEC-DMHRC will discuss the findings of the monitoring process and take appropriate specific action by voting or combination of actions, some of which are listed below:

- Continuation of the project with or without changes,
- Restrictions on enrollment,
- Recommendations for additional training,
- Recruiting additional members in the study team,
- Recommendations for changes or appropriate action.
- Revising/ providing qualifications/ experience criteria for members of the study team,
- Termination of the study, Suspension of the study, etc.

- The final decision taken at the full board IEC meeting by the Chairperson is recorded in Monitoring visit follow up letter.
- The Research dept. will convey the decision to the Principal Investigator in writing within 1 week after the meeting.
- The Research dept. will place the copy of the report in the protocol file.

11. IEC Resolutions

The IEC has discussed the following issues and has evolved a certain procedure in the form of resolutions. The issues related to (1) Local ICF and (2) Transfer of Biological materials, genetic and pharmacogenomic components of the clinical trial protocols and collaborative research projects, etc. These resolutions form part of the SOPs of the IEC and it is expected that the P.I./s, CROs SMOs, Sponsor/s as a participating party observe those in the best interest of biomedical, medical and health research, involving human beings as volunteers, clients (patients), etc.

1) ***Subject: Regarding Local Informed Consent Form:***

Preamble:

It has been observed that the Informed Consent related documents as part of the protocol/s submitted for review and approval of SAC, IEC DMH&RC, are many a time inconsistent with reference to the English and vernacular translations. The inconsistencies also vary from conveying different meanings to stating issues that have no direct relevance to the consenting patients (subjects) participating in a trial at this site, namely, DMHRC.

Resolution:

The IEC, therefore, has resolved that in addition to the English and vernacular versions submitted by the sponsor as a part of protocol, the Principal Investigator should necessarily prepare appropriate English and vernacular versions (including Hindi, if needed) of Local Informed Consents and submit those along with the protocol.

It may please be noted that the protocol will be considered incomplete and will not be accepted by the dept. for review and approval of the IEC if the Local Consent Forms are not submitted together with the Protocol.

2) **Subject: Export of biological material under Clinical Trial/Protocol requires the permission**

Preamble:

If the clinical trial/protocol involves export of biological material, the Principal Investigator (P.I.) shall

be submitting the following document/s along with the submission.

- Permission letter for export of biological material from the DCGI.
- "If any biological material is being sent out for further research without any involvement of the DMHRC it should be considered as outside the scope of the IEC and this is a management decision."

OR

- Undertaking from the Principal Investigator that (s)he will not be exporting the biological material under the subject clinical trial/protocol from this centre, viz. Deenanath Mangeshkar Hospital & Research Centre, Pune.

The approved clinical trial/protocol cannot be commenced unless receipt of the above document/s by the IEC is obtained from the P.I.

Resolution:

The IEC is granting approval in good faith to the protocol under specific conditions, namely:-

- That if for any reason it turns out that the ultimate use was at a variance with the policy of Govt. of India, ICMR and the Ministry of Health in particular, you will be required to shoulder the responsibility and the sponsor will have to sort out the issues with the appropriate authorities. No onus thereof shall lie on the IEC because it had granted the approval.
- That the material will not be used for any other reason than the one mentioned in the protocol, and the sponsor shall arrange all the unused material to be sent back to the P.I. at the site where the study is to be conducted, and the sponsor shall give a written declaration to that effect without which the study shall not be closed out.

OR

- As you are aware of the decision of the IEC with reference to the related issue, if this aspect of the study is not to be carried out at this site, you are required to submit a letter to that effect from the sponsor so as to release the approval of IEC.

3) **Subject: Regarding contact information to be included in the Informed Consent Form (ICF).**

Preamble:

It has been observed that Informed Consent Form (ICF) document is incomplete as regards name and contact information of the Principal Investigator and that of the IEC designee.

Resolution:

In light of the above, a resolution is hereby passed wherein the Sponsor and/or Principal Investigator should verify if name and contact information of the Principal Investigator and an IEC designee is clearly typed-in prior to submitting the document for IEC review. Failing to have the information will result in the document being rejected by the IEC for review.

12. Site Management Service

For new trials staring from Jan 2013 DMH will provide a person power support (CRC), if requested by the concerned PI/ CRO/ SMO. The present arrangements of direct appointment by the concerned will also continue if so desired by the concerned PI/ CRO/ SMO.

Aims

1. To improve quality of clinical research
2. To support for pre study activities- feasibility to SIV
3. To encourage new PI to take up clinical trials
4. For better co ordination with all concerned-
    - *Smooth financial transactions*
    - *Reduce start up timelines*
    - *Single point of contact for all CRO and sponsors*
    - *To establish uniform structure*

CRCs appointed by DMHRC will assist the PI in-

- Carrying out day to day clinical trial related activities
- ICF documentation
- Conducting patient visits
- IP handling accountability and storage
- Source documentation
- Completing CRF/ e CRF
- Use of IWRS
- Facilitate all study specific evaluation completion
- Ensure that the lab and other relevant investigations are carried out and reports are reviewed by PI
- Maintain Trial Master File
- EC and sponsor communication
- Attend all SMV and follow up with action items
- Compliance with GCP and EC SOPs

Please note that the ultimate responsibility of the over all conduct of the trial and well being of trial participants is always that of the PI

Department of Research will supervise-

- Over all clinical trial related activities by DMHRC appointed CRCs
- Regular sponsor, PI and CRA feedback
- Arrange CRC training review meetings
- Review monitoring reports
- Feasibilities
- Provide help in start up activities
- Sponsor communication

Financial considerations-

- Payment of Institutional overheads as stated in the latest updated SOPs shall be mandatory for all clinical trials.
- Additionally, a certain proportion of total study budget (excluding SAE and miscellaneous cost) will be designated and charged as fees/power charges of the Site Management/ person. The exact amount (%) shall be decided by Finance Dept DMHRC depending upon nature of clinical trial.

APPENDICES

INSTITUTIONAL ETHICS COMMITTEE

Lata Mangeshkar Medical Foundation's

DEENANATH MANGESHKAR HOSPITAL AND RESEARCH CENTRE (DMHRC),

Erandawane, Pune 411004, INDIA.

A. APPENDIX I : ABBREVIATIONS

ANDA	:	Abbreviated New Drug Application
BA	:	Bioavailability
BARC	:	Bhabha Atomic Research Centre
BE	:	Bioequivalence
CDER	:	Centre for Drug Evaluation and Research
CDSCO	:	Central Drug Standard Control Organization India
CFR	:	Code of Federal Regulation, a Publication of US FDA
CIOMS	:	Council for International Organization of Medical Sciences
COA	:	Certificate of Analysis
COMP	:	For the Designation of "Orphan" Medicines for rare diseases (See EMEA)
CPMP	:	Term Responsible for Medicines for Human Use (See EMEA)
CRF	:	Case Record Form
CSM	:	Committee on Safety of Medicines UK
CSR	:	Clinical Study Report
CTA	:	Certificate of Authorization
CTC	:	Clinical Trial Certificate (Not in vogue due to introduction of CTA)
CTX	:	Certificate of Exemption (Not in vogue due to introduction of CTA)
CVMP	:	For Veterinary Medicines (See EMEA)
DCG	:	Drug Controller General
DCGI	:	Drug Controller General of India

DDX	:	Doctor and Dentist Exemption
DOH	:	Director of Health
DTAB	:	Drugs Technical Advisory Board
EC	:	Ethics Committee
EIR	:	Establishment (e.g. Investigator's site) Inspection Report(s). It has three categories: NAI, VAI and OAI
Eu	:	European Union
EMEA	:	The European Agency for Evaluation of Medical Products, a decentralized body of the European union (Eu) with headquarters in London. It has three committees, namely CPMP, CVMP and COMP.
FAQ	:	Frequently Asked Questions
FDA	:	U.S. Food and Drug Administration
GCP	:	Good Clinical Practice
GEAC	:	Genetic Engineering Approval Committee
GLP	:	Good Laboratory Practice
GMP	:	Good Manufacturing Practice
HHS	:	Health and Human Service
IB	:	Investigator's Brochure
ICD	:	Informed Consent Document (=ICF : Informed Consent Form)
ICH	:	International Conference on Harmonization
ICMR	:	Indian Council of Medical Research
IDE	:	Investigational Device Exemption
IEC	:	Independent Ethics Committee
IEC	:	Institutional Ethics Committee

IND	:	Investigational New Drug
IRB	:	Institutional Review Board. The FDA term for Ethics Committee.
MHRA	:	Medicines and Health Products Regulatory Agency (U.K.) (Advised by CSM)
NAI	:	No Objectionable Conditions or Practices were found during inspection. (See EIR)
NCR	:	No Carbon Required (Ref. CRF)
NDA	:	New Drug Application
NSRD	:	(= or NRD) Non significant risk Device (= Non Critical Device)
OAI	:	Regulatory and/or Administrative action recommended. (See EIR)
QA	:	Quality Assurance
QC	:	Quality Control
SD	:	Source Data / Document
SDV	:	Source Data Verification or Source Document Verification
SRD	:	Significant Risk Device (Critical Device)
VAI	:	Objectionable Conditions or Practice were found but no Regulatory Administrative action recommended. (See EIR)
WMA	:	World Medical Association
WHO	:	World Health Organization

B. APPENDIX II: LIST OF MEMBERS

List of IEC Members

(Effective from 20th February 2014)

1	Dr. Avinash Joshi	Ph.D. (Biochemistry)	Chairperson*
2	Dr. Manohar Dhadphale	M.B.B.S.,DPM,MRCP(Psych)MD,FRCP(Psych)	Vice Chairperson*
3	Dr. Dhananjay Kelkar	M.S.(Gen Surgery)	Clinician
4	Dr. Jitendra Deuskar	M.S.(Gen Surgery)	Clinician
5	Dr. B. Y. Pawar	M.D. (Medicine) IDCC	Clinician
6	Dr. Ashwini Joshi	DNB (Medicine), MNAMS	Clinician
7	Dr. Prema Shidore	M.D. (Pharmacology)	Pharmacologist (Basic Medical Scientist)*
8	Dr. Medha Kshirsagar	M.D. (Pharmacology)	Pharmacologist (Basic Medical Scientist)*
9	Ms. Meena Gokhale	M.A. In Social Work with specialization in Social Welfare Administration	Social Scientist*
10	Dr. Sujala Watve # Dr. Vanita Patwardhan	B.Sc. (Chemistry), M.A. (Psychology), Ph.D. (Psychology) M.A. (Psychology), Ph.D. (Psychology), M. Ed., Dip. in Yoga Education (Govt. recognized)	Ethicist*
11	Adv. Sheel Rege # Adv. (Dr.) Milind Salunke	B.A.,L.L.B. BHMS, DHA,MBA,L.L.B.	Legal Expert*
12	Mrs. Uma Vengurlekar # Mrs Hemlata Hirve	Diploma Commercial Art B.A (Sociology)	Lay Person*
13	Col.J.C.Pendse, VSM (Retd.)	B.A. (Hons)	Member Secretary
14	Dr. Vaijayanti Pethe	Ph.D. (Biochemistry)	Joint Member Secretary

[* Members who are not on the 'staff-list' of the hospital/site.]

[# Alternate members- these are invited only when the primary person is unable to attend the IEC meeting]

List of SAC Members

Effective from 20th December 2013

1	Dr. Dhananjay Kelkar	M	M.S. (Gen. Surgery)	Chairperson
2	Dr. Jitendra Deuskar	M	M.S. (Gen. Surgery)	Hon. Member
3	Dr. B. Y. Pawar	M	M.D., IDCC	Hon. Member
4	Dr. Ashwini Joshi	F	D.N.B. (Medicine), MNAMS	Basic Medical Scientist
5	Dr. Shailesh Shende	M	M.D. (Radiation Oncology)	Hon. Member
6	Dr. Mahesh Mandolkar	M	M.D. (Path) DNB(Path)	Hon. Member
7	Dr. Pratibha Phadke	F	M.D. (Medicine)	Hon. Member
8	Dr Anupama Nadkarni	F	M.D (Paediatrics)	Hon. Member
9.	Dr Vaijayanti Pethe	F	Ph.D. (Biochemistry)	Joint Member Secretary
10.	Col.J.C.Pendse, VSM (Retd.)	M	B.A. (Hons.)	Member Secretary

List of SAC-IR Members

Effective from 20th December 2013

1	Dr. Milind Modak	M	M.S.(Ortho), DNB, MNAMS	Chairperson
2	Dr. Ushatai Khire	F	Ph.D.	Hon. Member
3	Dr. Dhananjay Kelkar	M	M.S. (Gen. Surgery)	Hon. Member
4	Dr. Shireesh Phansalkar	M	LCEH	Hon. Member
5	Dr. Yogesh Khare	M	BHMS	Hon. Member
6	Dr. Narendra Pendse	M	BAMS, MD (AYURVED)	Hon. Member
7	Vd. Ajit Joshi	M	BAMS, MD (AYURVED)	Hon. Member
8	Dr. Jitendra Deuskar	M	M.S. (Gen. Surgery)	Hon. Member
9	Vd. Shailesh Vaidhya	M	BAMS, MA	Hon. Member
10	Dr Vaijayanti Pethe	F	Ph.D. (Biochemistry)	Joint Member Secretary
11	Col.J.C.Pendse, VSM (Retd.)	M	B.A. (Hons.)	Member Secretary

List of CCPR Members

Effective from 20th December 2013

1	Dr Vaijayanti Pethe	F	Ph.D. (Biochemistry)	Joint Member Secretary
2	Dr. Shailesh Shende	M	M.D. (Radiation Oncology)	Hon. Member
3	Dr. Jitendra Deuskar	M	M.S. (Gen. Surgery)	Hon. Member
4	Dr. Ashwini Joshi	F	D.N.B. (Medicine), MNAMS	Hon. Member
5	Dr. Mahesh Mandolkar	M	M.D. (Path), DNB (Path)	Hon. Member
6	Dr. Sampada Patwardhan	F	M.D. (MICROBIOLOGY)	Hon. Member
7	Dr. Koumudi Godbole	F	M.D. (MEDICINE)	Hon. Member
8	Mr. Ajit Shete	M	B.com. CA (Inter)	Hon. Member
9	Dr. Asawari Kanade	F	Ph.D (Biomerty and Nutrition)	Hon. Member
10	Col.J.C.Pendse,VSM (Retd.)	M	B.A. (Hons.)	Member Secretary

C. APPENDIX III: FORMAT FOR APPROVAL OF INSTITUTIONAL ETHICS COMMITTEE

(The Institutional Ethics Committee of Deenanath Mangeshkar Hospital & Research Centre works as per its Work Document and SOPs per provisions of Good Clinical Practices, ICMR Code 2000, Ethical Guidelines for Biomedical Research on Human Participants ICMR 2006, Guidelines for Clinical Trials on Pharmaceutical Products in India, CDSCO, DGHS, GCP, Govt. of India, Schedule 'Y' in particular; and ICH Good Clinical Practice Guidelines.)

In Principle Approval Format

To,

Dr. ----------

Principal Investigator

Dear Dr. ----------

Ref: your letter dated- ----------

The Institutional Ethics Committee reviewed and discussed your application to review the Protocol/ amendment/ ICF entitled**." ----------**

IEC has reviewed and **approved in principle** the above mentioned Protocol/ amendment/ ICF

The following members of the Institutional Ethics Committee were present at the meeting held on date **----**at **time** at Deenanath Mangeshkar Hospital and Research Centre.

Please note that the Principal Investigator was invited to explain the protocol. He/She and/ or other study staff members did not participate in the decision making / voting procedures.

Please note that this is "Approval in Principle "

The study can not be initiated unless final approval is issued.

The Final approval will be issued after completing all the pending items/ documents as per regulatory requirements and IEC SOPs-

Yours sincerely,

Date of Issue-

Member Secretary OR Joint Member Secretary, IEC

Deenanath Mangeshkar Hospital & research centre.

(The Institutional Ethics Committee of Deenanath Mangeshkar Hospital & Research Centre works as per its Work Document and SOPs per provisions of Good Clinical Practices, ICMR Code 2000, Ethical Guidelines for Biomedical Research on Human Participants ICMR 2006, Guidelines for Clinical Trials on Pharmaceutical Products in India, CDSCO, DGHS, GCP, Govt. of India, Schedule 'Y' in particular; and ICH Good Clinical Practice Guidelines.)

Final Approval letter Format

To,
Dr. ---------
Principal Investigator

Dear Dr ----------

Ref: In Principle approval letter dated---

The Institutional Ethics Committee reviewed and discussed your application to review the protocol/ amendment/ ICFs for the **"Protocol entitled----------."**

The following documents were reviewed:

Sr. No.	Document Name	Document Details (Version & Date)

The IEC approves the above documents in the present form. To be conducted in its presented form.
The following members of the Institutional Ethics Committee were present at the meeting held on **---------** at **-------** at Deenanath Mangeshkar Hospital and Research Centre.

Please note that the Principal Investigator was invited to explain the protocol. He/She and/ or other study staff members did not participate in the decision making / voting procedures.

The Institutional Ethics Committee expects (i) you to abide by Privacy and Confidentiality, (ii) to be informed about the progress of the study, (iii) to be informed about any SAE occurring in the course of the study, (iv) to be informed about any changes in the protocol and patient information/informed consent and (v) to be provided with a copy of the final report.

Please be informed that the approval for a clinical trial protocol starts from the date of this letter and is for duration of one year or for the stipulated duration, whichever is less, unless specified otherwise. In case of approval for any other study related document/s, approval would start from the date of this letter and is effective only till the basic protocol approval remains valid. In case the study is not completed within this time frame, an application should be made for renewing the approval for the study at least two months prior to the expiry of current validity period.

Yours sincerely,

Date of Issue-

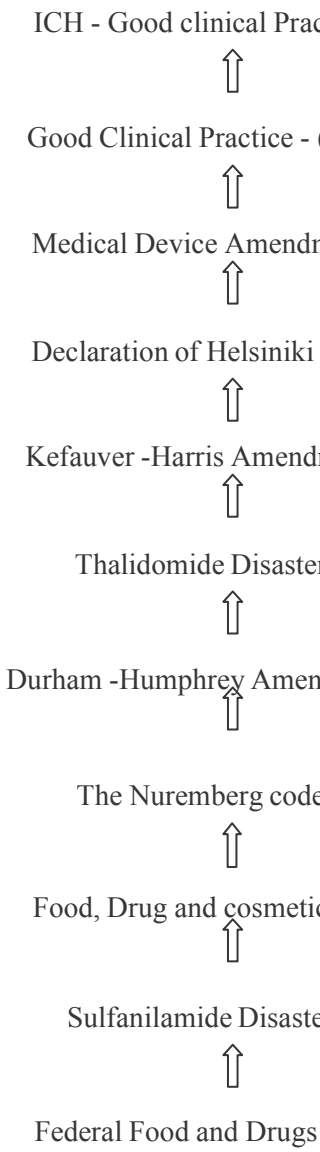
Member Secretary OR Joint Member Secretary, IEC-DMH&RC,
Deenanath Mangeshkar Hospital & research centre.

Credit / Acknowledgement : As per schedule 'Y'. The Gazette of India : Extraordinary Part II Sec. 3 (i) page 109-110

D. APPENDIX IV: HISTORY OF ICH

The historical account of the evolution and standardization of Clinical research just cannot be complete without reference to horrendous instances of the darker and deceitful side of the human mind, the saga of the participants, the pitfalls and so on. Yet it is also a shining example of the conscientious, careful, critical and collaborative organizational efforts of the caring human minds especially from European Community, the Scandinavian countries, United States of America, particularly the Food and Drug Administration (FDA) of USA, Japan, Australia and World Health Organization (WHO) that have made landmark contributions. These resulted into the development of very important documents such as the Nuremberg code, World Medical Association's (WMA) Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS), giving directives for Human experimentation. Similarly, the FDA reference books and the European GCP document are the results of these efforts. The concern for safety and dignity of human life has been the basis for all this co-operation. These efforts eventually have resulted in the development and final adoption on 17th January 1997. The acronym stands for the full form: International Conference on Harmonization of Technical Requirements for The Registration of Pharmaceuticals for Human Use (ICH) that formulated the Tripartite Guideline for Good Clinical Practice (GCP). Since then these define the one, uniform common standard that the clinical researchers, throughout the world are required to adhere to. In a way, today these guidelines are the very bible of Clinical Research. As a sequel of this worldwide adherence to GCP, the clinical research has become cost-intensive, requiring more staff and has also added considerably to the administrative burden. Yet the most important outcome of adherence to uniform GCP has been threefold.

- The data obtained in the clinical trials are correct and reproducible.
- The standard of the quality has gone up, and
- The volunteers and patients consenting to participate in clinical trials are definitely better protected.


ICH - Good clinical Practice of 1997
Good Clinical Practice - (1980- 1990)
Medical Device Amendment of 1976
Declaration of Helsiniki (1964-2000)
Kefauver -Harris Amendment of 1962
Thalidomide Disaster of 1951
Durham -Humphrey Amendment of 1951
The Nuremberg code of 1946
Food, Drug and cosmetic Act – 1939
Sulfanilamide Disaster of 1937
Federal Food and Drugs Act of 1906

E. APPENDIX V: THE PRINCIPLES OF ICH GCP

The ICH - GCP document is divided into eight chapters. The Glossary refers to the description of different terms. Chapter 2 states the principles of ICH-GCP. Chapter 3 is related to the Institutional Ethics Committee. It deals with the responsibilities, composition, functions, operations, procedures and records that are required, adopted and followed by the members of IEC. Chapter 4 & 5 deal respectively, with the responsibilities and role of Investigators and the Sponsors. In Chapter 6 the detailed information about the trial protocol and the amendments, if any, of the protocol is given. The information about the important document called Investigator's Brochure is dealt with in Chapter 7. Chapter 8 describes the essential documents for the conduct of a clinical trial

The Principles of ICH GCP

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).
2. Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.
3. The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interest of science and society.
4. The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.
5. Clinical trials should be scientifically sound, and described in a clear, detailed protocol.
6. A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB) / independent ethics committee (IEC) approval/ favorable opinion.
7. The medical care given to, and medical decision made on behalf of, subject, should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.
8. Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).
9. Freely given informed consent should be obtained from every subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows it accurate reporting, interpretation and verification.
11. The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

12. Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

F. APPENDIX VI: WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland. June 1964. and amended by the 29th WMA General Assembly, Tokyo, Japan. October 1975
35111 WMA General Assembly, Venice, ltaly. October 1983
1st WMA General Assembly, Hong Kong. September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa. October 1996 and the 52nd WMA General Assembly. Edinburgh, Scotland, October 2000
Note of clarification on Paragraph 29 added by the WMA General Assembly. Washington 2002
Note of clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words. "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human

subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles For All Medical Research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should

be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance *of* the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of ending, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent lo decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give

informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations, in publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined With Medical Care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists. See footnote.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study. See footnote.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient- physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research,

designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Note**: Note of clarification on paragraph 29 of the** WMA **Declaration of Helsinki.**

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method: or
- Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

Note: Note of clarification on paragraph 30 of the WMA Declaration of Helsinki.

The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

The Declaration of Helsinki (Document 17 C) is an official policy document of the World Medical Association, the global representative body for physicians. It was First adopted in 1964 (Helsinki, Finland) and revised in 1975 (Tokyo, Japan), 1983 (Venice, Italy), 1989 (Hong Kong), 1996 (Somerset-West, South Africa) and 2000 (Edinburgh, Scotland). Note of clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

G. APPENDIX VII: PHASES I/II/III/IV OF CLINICAL TRIALS/STUDY

Human/Clinical Pharmacology trials (Phase I)

The objective of phase I of trials is to determine the maximum tolerated dose in humans; pharmacodynamic effect, adverse drug reactions, if any, with their nature and intensity; and pharmacokinetic behavior of the drug as far as possible. These studies are often carried out in healthy adult volunteers using clinical, physiological and biochemical observations. At least 2 subjects should be used on each dose.

Phase I trials are usually carried out by investigators trained in clinical pharmacology and having the necessary facilities to closely observe and monitor the subjects. These may be carried out at one or two centers.

Exploratory trials (Phase II)

In phase II trials a limited number of patients are studied carefully to determine possible therapeutic uses, effective dose range and further evaluation of safety and pharmacokinetics. Normally 10-12 patients should be studied at each dose level. These studies are usually limited to 3-4 centers and carried out by clinicians specialized on the concerned therapeutic areas and having adequate facilities to perform the necessary investigations for efficacy and safety.

Confirmatory trials (Phase III)

The purpose of these trials is to obtain sufficient evidence about the efficacy and safety of the drug in a larger number of patients, generally in comparison with a standard drug and/or a placebo as appropriate. These trials may be carried out by clinicians in the concerned therapeutic areas, having facilities appropriate to the protocol. If the drug is already approved/marketed in other countries, phase III data should generally be obtained on at least 100 patients distributed over 3-4 centers primarily to confirm the efficacy and safety of the drug, in Indian patients when used as recommended in the product monograph for the claims made.

Data on ADRs observed during clinical use of the drug should be reported along with a report on its efficacy in the prescribed format. The selection of clinicians for such monitoring and supplyy of drug to them will need approval of the licensing authority under Rule 21 of the Act.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, assessment of therapeutic value, treatment strategies used and safety profile. Phase IV studies should use the same scientific and ethical standards as applied in pre-marketing studies. After a product has been placed on the market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.

H. APPENDIX VIII: CLINICAL TRIALS WITH SURGICAL PROCEDURE / MEDICAL DEVICES

Of late, biomedical technology has made considerable progress in the conceptualization and designating of bio-equipments. Several medical devices and critical care equipments have been developed and many more are in various stages of development. However, only through good manufacturing practices (GMP) can the end products reach the stage of utilization by society. Most of these products are only evaluated by Central Excise testing for taxation purposes, which discourages entrepreneurs to venture in this area with quality products especially when they do not come under the strict purview of the existing regulatory bodies like ISI, BSI and Drug Controller General. This is evidenced by the very low number of patents or propriety medical equipments manufactured and produced in the country. As the capacity of the country in this area is improving day by day the need for a regulatory mechanism / authority is increasingly obvious. The concept of regulations governing investigations involving biomedical devices is therefore relatively new in India. At present, except for needles and syringe these are not covered by the Drugs and Cosmetics Act, 1940. The Chief Executive of the Society of Biomedical Technology (SBMT) set up under the Defense Research Development Organisation (DRDO) has drafted proposal for the setting up of a regulatory authority, tentatively named as the Indian Medical Devices Regulatory Authority (IMDRA). Until the guidelines are formulated and implemented by this regulatory authority the clinical trials with biomedical devices should be approved on case to case basis by committees constituted for the specific purpose.

Definitions:-

Medical Devices :- A medical device is defined as an inert diagnostic of therapeutic article that does not achieve any of its principal intended purposes through chemical action, within or on the body unlike the medicated devices which contain pharmacologically active substances which are treated as drugs. Such devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intraocular lenses, orthopedic pins and other orthopedic accessories.

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 of e.g. Thermometer, B.P. apparatus.

b) **Critical devices:** An investigational device that presents a potential risk to the health safety, welfare of the subject - for example pace makers, implants, internal catheters ***Guidelines:-***

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

- A clinical trial of medical devices is different from drug trials, as former cannot be done in healthy volunteers. Hence phase I of drug trial is not necessary for trial on 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 device not used regularly have less risk potential than those used regularly, for example, contact lens Vs intraocular lenses.
- Safety procedures to introduce a medical device in the patient should also be followed as the procedure itself may cause harm to the patients.
- Informed consent procedures should be followed as in drug trials. The patient information sheet should contain information about procedure to be adopted if the patient decides to withdraw from the trial.

I. APPENDIX IX: INVESTIGATOR: NECESSARY REQUIREMENTS

- Qualifications and Agreements (MOU, CTA)
- Adequate Resources
- Medical care of Trial subjects
- Communication with IEC
- Compliance with Protocol
- Investigational Product(s)
- Informed consent of Trial subjects
- Records and Reports
- Progress Reports
- Safety Reporting
- Final Report(s)

Roles & Responsibilities of Investigator

Investigator is a person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. Sub-investigator is any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows).

FDA regulations (21 CFR 312.52), Indian GCP Guidelines (3.3.1) and ICH Guidelines (ICH 4.1) mandate that sponsors only use trained and qualified investigators. An investigator has the following chief roles and responsibilities:

1. Initiating a Clinical Trial:

a) **Contracts & Agreements:** Investigator is responsible to enter into all trial related agreement as per applicable regulatory compliance i.e. Confidentiality agreement, Protocol/Trial Acceptance, Roles & Responsibilities, Grants & Payments agreements, CVs etc.

b) **Obtaining ERB/IEC/IRB approval to conduct the trial:** It's the responsibility of investigators) to get approval from ERB(s) of the institution(s) and to ensure the patient enrolment at the institution(s) begins after such approval only.

c) **Constituting a study team** including Co-investigator(s), Sub-investigators), Clinical research coordinator (s), Study nurse/Pharmacist.

d) **Planning and ensuring resources required for the conduct of trial:** The investigator is responsible to ensure adequate number of available qualified staff and facilities at site for safe and proper conduct of trial.

e) **Attend the trial training meeting along** with **the study team:** The investigator is responsible to ensure all of his/her staff/team members who would be participating in the trial would have attended trial training meetings being organized by sponsor for the smooth conduct of trial.

2. Conduct of the Trial

a. Recruitment/Enrolment of the subjects in the study:

- The investigator is responsible for unbiased selection of suitable subjects for enrolment into study as per protocol. If required, he/she may seek the co-operation of other physicians to obtain a required number of subjects. In order to assess the probability of an adequate recruitment rate for subjects for the study it may be useful to determine prospectively or review retrospectively the availability of the subjects.

- The investigator is responsible to maintain subject's/patient's identification log as well as subject's seeing/enrolment log to documents identification and enrolment of study subjects.

b. Informed Consent Document (ICD) administration:

i. The investigator is responsible to comply with the applicable regulatory requirements), in obtaining and documenting informed consent.

ii. It's the responsibility of the investigator to ensure that ICD has been approved by IRB/IEC's and it may be revised and re-approved by ERB whenever important new information becomes available that may be relevant to the subject's consent.

iii. It's the responsibility of investigator that neither he/she, nor any of the trial staff, is coercing or unduly influencing a subject to participate or to continue to participate in a trial.

iv. It is the responsibility of investigator to provide clear oral and written information concerning the trail in a language most easily understandable by subject or his/her legal representative.

v. Investigator should ensure that before obtaining the informed consent, ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial, has been provided to the subject or the subject's legally acceptable representative.

vi. Investigator is responsible to ensure that the written informed consent form has been signed and dated by the subject or his/her subject's legally acceptable representative, and by the person who conducted the informed consent discussion/documentation and also by an impartial witness in case subject or his/her legally acceptable representative is unable to read, prior to a subject's participation in the trial.

vii. Investigator is responsible to ensure that both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects is explaining not less than, the purpose of the trial, the trial treatment(s) and the probability for random assignment to each treatment, the trial procedures to be followed (experimental / non-experimental), including all invasive procedures, the subject's responsibilities, the foreseeable risks or inconveniences and expected benefits, the alternative procedure(s) or course(s) of treatment options that may be available to the subject with their benefits and risks, the compensation and/or treatment available to the subject in the event of trial-related injury and voluntary nature of the subject's participation in the trial.

viii. Investigator is responsible to ensure that the confidentially of subject identity and their records would be maintained in/during the trial related publications/ regulatory submissions.

c. Medical care of the trial subjects: The investigator is responsible to ensure that adequate medical care is being provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial, during and following a subject's participation in a trial.

d. Compliance with protocol schedule of events:

i. The investigator/institution is responsible to comply with the protocol agreed to by the sensor for the conduct of trial. Any deviation or changes in the protocol should not implement by the investigator without agreement by the sponsor and prior review and documented approval by IRB/IEC, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s).

ii. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted to the IRB/IEC/sponsor/applicable regulatory authority (ies) for review and approval.

e. Compliance with ICH-GCP/applicable regulatory requirements: The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

a. Investigational product(s) storage, handling and accountability:

i. The investigator is responsible to get himself/herself thoroughly familiar with the appropriate use of the investigational product(s), as per protocol/investigator's Brochure/product information.

ii. The investigator is responsible for maintaining the investigational product(s) accountability at the trial site(s) including records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s).

iii. The investigator is responsible to maintain records documenting drug administration (i.e. dose/interval) to the subjects and storage conditions (i.e. temperature).

b. **Randomization procedures and unblinding!** If trial requires randomization, then the investigator is responsible to follow the trial's randomization procedures and should ensure to promptly document if any premature unbinding is done, properly explaining the reason for the same to the sponsor (e.g., accidental unbinding, unbinding due to a serious adverse event).

h. Communication with IEC: The investigator/institution is responsible to supply ongoing safety updates, progress reports (periodic) of trial status report, re-approvals (if required) to the IRB/IEC annually, or more frequently, if required by applicable authority(ies). Half yearly progress report to be submitted in the last week of every December and June. PIs are

requested to submit 3 copies of each report to IEC. One to be given back to PI, one for IEC record and one will be given to Accounts dept. See earlier comment on this. 2 copies are enough.

i. Communication with sponsor—enrolment, randomization, safety reporting etc:

i. The investigator/institution is responsible to immediately report all serious adverse events (SAEs) to the sponsor followed promptly by detailed, written reports except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting.

ii. The investigator should also comply with the applicable regulatory requirements) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

iii. All other trial related communication like patient enrolment updates, randomization done, un-blinding etc. should be done by the investigators as per the protocol.

j. Facilitate data collection and monitoring: The investigator is responsible to ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. He/she should provide support in facilitating data collection and monitoring by the sponsor.

k. Documenting errors, violations, noncompliance etc. and taking action to avoid them in future.

l. Financial tracking: The investigator is responsible to maintain records for all payments made to trial staff or to subjects if any and for other trial related expenses. The Financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

m. Ensuring confidentiality of Trial Subjects and Integrity of Trial Data throughout the course of Trial and thereafter as recommended.

n. Facilitate & co-operate in Site Audit (if any). EC should be informed about planned audits. (Sponsored / Third Party / Regulatory) at least 7 days prior and the audit report

should be submitted to EC

3. Site Closure

a. **Final Report to IEC:** Upon completion of the trial, the investigator, where applicable, should inform the institution: the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required. Acknowledgement of closeout report will not be issued unless accounts clearance is completed.

b. **Providing all data/documents required at site closure to Sponsor.**

c. **Return of equipment (if any), investigational product (unused) and grants re-conciliation.**

d. **Archival of trial data for the duration as specified in the contract:** All trial related essential documents should be retained by the investigator/institution from 5 to 15 years as per the applicable regulatory requirements or as per agreement with the sponsor.

e. **Premature Termination or Suspension of a Trial:** In case of premature suspension/ termination of a trial for any reason, it's the responsibility of the investigator to promptly inform the trial subject, and to take care for appropriate therapy and follow-up for the subjects. In case the investigator terminates or suspends a trial without prior agreement of the sponsor, he/she should inform the institution/sponsor/IRB/IEC with a detailed written explanation of the termination or suspension.

- A Clinical Investigator should
    - Follow the protocol, including:
    - Keeping records of the disposition of drug.
- Properly maintaining case histories.
- Personally conduct or supervise the study.
- Inform subjects that the study is investigational and obtain informed consent.
- Report adverse events to sponsor on time.
- Ensure that all subordinates are informed about their duties.
- Ensure that an IRB will be responsible for reviewing the study and the investigator will promptly inform the IEC of:

- All changes in the research and not implement until approved by IEC (except if to eliminate an immediate hazard).
- Properly maintaining case histories.

Investigator - Examples of Violations

- Failure to personally supervise study.
- Failure to obtain informed consent.
- Failure to follow the protocol.
- Inadequate or inaccurate record keeping - e.g.:

  i. Case histories

  Missing lab reports

  - incorrect entries
  - "penciled" entries - tests not performed (e.g., entering vital signs when not taken)
  - inconsistent entries

  ii. Drug or device accountability
- Failure to report adverse events to sponsor
- Other types:
  - Violating a clinical hold.
  - Violating import rules *etc.*

J. APPENDIX X: SOME SPECIAL TERMS BRIEFLY EXPLAINED

(Note: All terms may not necessarily be appearing in the core part of the work document. These are primarily included here for general information with reference to Clinical Trials)

Adverse Drug Reaction (ADR)

All noxious and unintended responses to a medicinal product related to any dose is considered adverse drug reaction.

Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a casual relationship with this treatment. An adverse event (AE) can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

Advertisement

When used for subject recruitment, it is a document that provides brief study outline to recruit the potential patients. It is important to ensure that recruitment measures are appropriate and not coercive.

Amendment (to the protocol)

See Protocol Amendment.

Applicable Regulatory Requirement(s)

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards)

The affirmative decision of the IEC that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IEC, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

Audit

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedure (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Audit Certificate

A declaration of confirmation by the auditor that an audit has taken place.

Audit Report

A written evaluation by the sponsor's auditor of the results of the audit.

Audit Trial

Documentation that allows reconstruction of the course of events.

Bioavailability (BA)

It is the degree of activity of amount of an administered drug (or other substance) that becomes available for activity in the target tissue. Bioavailability of a drug is the degree to which the unchanged drug reaches the systemic circulation. It is defined as the rate and extent of drug absorption to systemic circulation. such studies are conducted in healthy volunteers for documenting the rate of absorption and excretion of the active ingredients of the administered compound from the body. Such studies are conducted both at the beginning of human testing or just prior to the marketing of the product (drug) for demonstrating that the safety or efficacy as ascertained in clinical trials is equivalent to the product / drug that will be distributed for sale. Bioavailability studies are carried out on marketed products whenever the mode or method of administration is changed e.g. from an injection to oral dose form; or when the composition of the drug or concentration of the active ingredient or process of its manufacture is changed.

Bioequivalence (BE)

With reference to Pharmacology / drug, the term means that the product / drug has the same effect on the body, as another product / drug, usually one nearly identical in its chemical formulation. (e.g. a bioequivalent drug).

Two medicinal products can be termed bioequivalent if these are pharmaceutically equivalent and if their bioavailability after administration in same molar dosage are similar to such degree that their effects, with respects to both efficacy and safety, will essentially be the same.

A bioequivalence study is basically a comparative bioavailability study designed to establish equivalence between test and reference products.

Blinding / Masking

A procedure in which one or more parties to the trial are kept unaware of the treatment assignments(s). Single-blinding usually refers to the subject(s) being unaware, and double-binding usually refers to the subject(s), investigator(s), monitor and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

Case Report Form (CRF)

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Clinical Trial/Study

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and /or other pharmacodynamic effects of an investigational product(S), and /or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

Clinical Trial /Study Report

A written description of a trial/ study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report.

Co-investigator (See term: Investigator)

A person who is responsible for the conduct of a clinical trial at a trial site and leads the team in

the absence of the leader often called the Principal Investigator.

Comparator (Product)

An investigational or marketed product (i.e. active control), or placebo, used as a reference in clinical trial.

Compliance (in relation to trials)

Adherence to all the trial- related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

Confidentiality

Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Contract

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

Coordinating Committee

A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.

Coordinating Investigator

An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.

Contract Research Organization (CRO)

A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Direct Access

Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g. domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the

constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subject's identities and sponsor's proprietary information.

Documentation

All records, in any form (including, but not limited to , written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Essential Documents

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

Good Clinical Practice (GCP)

A standard for the design, conduct, performance, monitoring, auditing, recording, analyzing, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

Independent Data-Monitoring Board, Monitoring Committee, Data Monitoring Committee

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or to stop a trial.

Impartial Witness

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

Independent Ethics Committee (IEC)

An independent body (a review board or a committee, institutional, regional, national, or supranational,) constituted of medical/scientific professionals and non-scientific members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by among other things, reviewing and approving/providing favourable opinion on, the trial protocol, the suitability of the

investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in ICH-GCP guideline.

Informed Consent

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

Inspection

The act by a regulatory authority (ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority (ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority (ies).

Institution (Medical)

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

Institutional Review Board (IRB)

An independent body constituted of medical, scientific, and non- scientific members, whose responsibility is to ensure the protection of the rights, safety and well -being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

Insurance Statement

A document to indemnify the compensation to subject(s) for trial related injury/injuries.

Investigational Product

A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

Investigator

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the Principal Investigator. See also Co-investigator / Sub investigator.

Investigator / Institution

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

Investigator's Brochure

A compilation of the clinical and non clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

Laboratory Reference Range

A document containing normal values and/or ranges of the laboratory test at the individual trial site/laboratory.

Legally Acceptable Representative

An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Monitoring

The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), Good Clinical Practice, (GCP), and the applicable regulatory requirement(S).

Monitoring Report

A written report from the monitor (as the sponsor's designee) to the sponsor after each site visit and/or other trial-related communication/progress according to the sponsor's SOPs.

MOU (Memorandum of understanding)

A memorandum of understanding (MOU or MoU) is a document describing a bilateral or multilateral agreement between parties. It expresses a convergence of will between the parties, indicating an intended common line of action

Multi-centric Trial

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

Non-clinical Study

Biomedical studies not performed on human subjects.

Opinion (in relation to Independent Ethics Committee)

The judgment and or the advice provided by an Independent Ethics Committee (IEC).

Placebo

It is an inactive substance (e.g. saline, distilled water or sugar, or a less than effective dose of a harmless substance such as water soluble vitamin) prescribed as if it were an effective dose of a needed medication.

Protocol

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

Protocol Amendment

A written description of a change(s) to or formal clarification of a protocol.

Quality Assurance (QA)

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

Quality Control (QC)

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial related activities have been fulfilled.

Randomization

The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

Regulatory Authorities

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authority includes the authorities that review submitted clinical data and those that conduct inspections. These bodies are sometimes referred to as competent authorities.

Resource Bank

A nationwide database of clinical Research professionals.

Sub-study

A Sub-study is a part of the original study that –

- Either consists simply of additional testing that will be done on the subjects or specimens already included in the original study;
- Or is simply an extension of the original study for a longer period of time;
- Or can be reasonably considered an extension of the original study for the purpose of expanding what will be learned from the conduct of the original study without extending into wholly novel areas of investigation.

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,

Requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity.

Or

Is a congenital anomaly/birth defect.

Source Data

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Source Documents

Original documents, data and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial.)

Sponsor

An individual, company, institution or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

Sponsor - Investigator

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g. it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

Standard Operating Procedures (SOPs)

Detailed, written instructions to achieve uniformity of the performance of a specific function.

A well documented SOP, in fact, details the way in which a certain work will be conducted. In laboratory and clinical research the SOPs undoubtedly enhance uniformity of method and consequent responsibility of results. Therefore SOPs when they are in place are **the** documents against which the performance of the stakeholder (e.g. an investigator, IEC/IRB, site and others) will be judged as success or failure in the event of an audit. Needless to say, over a course of time while the SOP is being practiced, some new or unforeseen problems and their repeated occurrence could reveal the weakness of an SOP. It should not be considered as a major problem, but merely

an indication of the need of revision of the SOP.

Sub Investigator

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial -related decisions (e.g., associates, residents, research fellows). See also Investigator.

Subject / Trial Subject

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

Subject Identification Code

A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

Trial Site

The location(s) where trial-related activities are actually conducted (e.g. hospital, institution).

Unexpected Adverse Drug Reaction

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved investigational product or package insert/ summary of product characteristics for an approved product).

Vulnerable Subjects

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Washout

It is described as the subject enrolled into the study but has not yet received active study medication. Washout subjects receive either no medication or medication with no active ingredient (Placebo).

Usually it is a necessary requirement that study subjects be taken off their prior medication for several days to a week before treating them with the study drug, essentially or as a necessity to rule out any potential drug interaction. In recording an adverse event the starting point begins as soon as the subject signs a consent form and has been enrolled in the study. **This includes any wash-out period.**

Well - being (of the trial subjects)

The physical and mental integrity of the subject participating in a clinical trial

K. APPENDIX XI: PROTOCOL/PROPOSAL EVALUATION FORM BY ADVISORY COMMITTEE

Form to be filled by Reviewers of SAC/SAC-IR/CCPR

Serial No. of the SAC Management Office:
Proposal Title:

Principal Investigator:

Co-Investigator
1.
2.
3.

Project Status: New □ Revised □

Review: Regular □ Interim □

Date of Review:

1. Research Design (Please tick the correct option A = >75%, B = 50-75%, C = <50%)

i.	Appropriateness of study design to objectives.	A	□	B □	C	□
ii.	Relevant to contribute to further knowledge.	A	□	B □	C	□
iii.	Strategy for recruitment of research participants.	A	□	B □	C	□
iv.	Is this study important medically for the community			Yes □	No	□

2. Risks (Please tick the correct option A = >75%, B = 50-75%, C = <50%)

i.	Is there physical/ social/ psychological risk/ discomfort?	A	□	B □	C	□
ii.	Is the overall risk/benefit ratio			Acceptable? □	Unacceptable?	□

3. Benefits:

i.	Direct	Reasonable	□	Undue □	None	□
ii.	Indirect	Improvement in science/knowledge	□	Any other □		

4. Subject selection:

i.	Inclusion/ exclusion criteria addressed?	Yes	□	No	□
ii.	Vulnerable subjects (women, child, and mentally challenged, seriously or terminally ill, foetus, economically or socially backward and healthy volunteers) adequately protected?	Yes	□	No	□
iii.	Special group subjects (captives, students, nurses & dependant staff) adequately protected?	Yes	□	No	□

5. Budget: Appropriate □ Inappropriate □

6. Decision of review:

Recommended □ Recommended with suggestions □
Revision □ Rejected □

Any other remarks/suggestions:

Reviewer's name and signature:

L. APPENDIX XII: PROTOCOL/PROPOSAL EVALUATION FORM BY IEC-DMHRC

Form to be filled by Reviewers of IEC

Serial No. of the IEC Management Office:
Proposal Title:

Principal Investigator:

Co-Investigator
1.
2.
3.

Project Status New □ Revised □

Review: Regular □ Interim □
Date of Review:

1. **Privacy & confidentiality maintained?** Yes □ No □
2. **Patient Information Sheet.** Adequate □ Inadequate □
3. **Consent form components addressed adequately?** Yes □ No □
4. **Compensation (if applicable) addressed adequately?** Yes □ No □
5. **Is there a conflict of interest?** Yes □ No □
   If yes, Acceptable □ Unacceptable □
6. **Decision of review**
   Recommended □ Recommended with suggestions □
   Revision □ Rejected □

Any other remarks/suggestions:

Reviewer's name and signature:

M . APPENDIX XIII: DOCUMENTS REQUIRED FOR APPROVAL OF BASIC PROTOCOL

10 sets of the following documents should be submitted. Each binder / file is required to be submitted in the following format.

(Please separate each section by a separator.)

Separator Number	Documents to include
1.	**Cover Letter+ Status Report**
2.	**Protocol**
3.	**Blank (initially)**
4. (a)	**Patient information sheet and local version of the same**
4. (b)	**Consent form and local version of the same, patient identification card survey questionnaires, eCRF/CRF, etc. [any other patient related documents]**
5.	**Other documents DCGI letter, CTA (draft /final), Insurance (initial renewed), CV of PI , Co-PI, CRC , PI Undertaking, Photocopy of Review Fees Form with Fee Receipt and CTRI registration number**
6.	**Blank (initially) [Approval Letter for the protocol]**
7.	**Investigators Brochure**
8.	**Blank**

N. APPENDIX XIV: ON SITE SAE REVIEW FORM BY SAC/IEC

Protocol Title-

Date of Review-

SAE details as provided by PI-

Protocol No.	Initial/ Follow Up	Patient Initials	Date Of Event`	Date Of EC Reporting	Diagnosis	Is It Related To The IP? (Yes/No)

SAC/IEC remarks-

1. Diagnosis - □ Acceptable □ Not acceptable
   Comments if not acceptable-
2. Investigations and Treatment - □ Acceptable □ Not acceptable

Comments if not acceptable

3. Casual Relation-

☐ Related to IP

☐ Related to Placebo

☐ Related to trial related procedures Violation of approved protocol, scientific misconduct negligence by sponsor, it's representative, investigator

☐ Failure of IP to provide intended therapeutic effect

☐ Adverse effects of concomitant medication excluding standard care necessitated as part of approved protocol

☐ Injury to a child in utero because of participation of a parent in a clinical trial

☐ unrelated

4. Any other additional information required? □ yes □ No, if yes please mention-------
5. Estimated compensation amount-
6. After risk and benefit assessment, study can be continued? □ yes □ No

Name, Sign and date of SAC member-

Name, Sign and date of IEC Chairperson-

O. APPENDIX XV: POLICY FOR COLLABORATIVE RESEARCH-

DMHRC takes part and is actively involved with external parties in industry, other institutions and universities, public and private companies in carrying out research collaborations

Special consideration will be given for projects between DMHRC and Central/state government agencies

For any collaborative medical or non medical research projects following guidelines apply

A permanent / time bound agreement (MOU) should be in existence between DMHRC and the collaborative institute before any research project is initiated.

- Study sites-
  For all non clinical non interventional studies like observational studies surveys etc multiple sites can be acceptable however for clinical drug / device trials study site should be DMH only
- Finance-
  Financial liability should be shared by both the parties in agreeable ratio.
- Data-
  Full data from other participating centers should be made available to Research Dept, DMHRC at every six months.
- Samples-
  a. Samples must be collected as a part of routine diagnostic or therapeutic procedure and not solely for the study.
  b. All the diagnostic procedures/ evaluations that are available in DMHRC must be carried out at DMHRC.
  c. IEC approval (DMHRC) and written informed consent from the patient must be obtained before any such sample collection.
  d. When diagnostic procedures/ evaluations are carried out at multiple sites other than DMHRC, IEC approval from all those respective institutes must be obtained and a copy submitted to IEC (DMHRC)
- Resources-
  MOU should clearly mention about what resources (human and other) will each party provide (please see the clear definition of MOU as per appendix X of EC SOP)
- Publications-

1. Publication rights should be shared by both the parties in agreeable terms
2. Principle Investigator / Co Investigator should be from DMHRC
3. Names of the Principle Investigator / Co Investigator from DMHRC should be mentioned in all the publications as author not just as acknowledgment.
4. Study report after conclusion of study should be submitted to DMHRC before publication.

P. APPENDIX XVI: AUDIO VIDEO CONSENT PROCEDURE

As per the office order issues by DCGI, dated 19/11/2013 audio visual consent is mandatory for all clinical trials including global clinical trials.

As per directions given by management of DMHRC Audio Video Consent Procedure
Will be as follows-

1. A separate consent form should be designed in English and regional languages like Marathi & Hindi (to be duly approved by IEC) will be used to inform patients about AV recording of consent procedure.

2. Informing Subject and Documentation

- The Purpose and Process of Audio Video Consenting should be explained to patient in details while adhering to the principle of patient confidentiality.
- After patients agree for AV recording of consent procedure - documentation of patient's voluntary willingness to Audio Video Consenting must be conformed by getting subject's signature on "Patient Information sheet/ Informed consent Form for Audio-Visual Recording".
- Subject's photo identification must be obtained and preserved along with ICF documents

3. After patient signs the consent procedure form, actual consent process should be initiated.

4. Infrastructure Provisions:

- 'VL scopy room' in ENT Dept will be dedicated for AV consent
- The room will be well lit and noise free
- The room will have restricted access and kept locked for security purpose. Keys of the consent room will be available at main reception. A separate register will be maintained. The register/ log book will have information about name of person taking the keys, PI name, protocol number, time of taking the keys and return time
- Fixed Video camera with external mike/microphone for Audio Video Consenting will be provided by DMHRC.
- CD writer or USB access can not be provided to all (PI specific) computer/ laptops

5. Consent Process-

- During the consent process PI & his/her study team members (if applicable), patient his/her relatives, LAR (if applicable), impartial witness (if applicable) would be present in the 'Consent Room'
- Faces of all the persons involved in the consenting (PI/designee,, subject, LAR, impartial witness etc including other study team members) should be recorded in the video-Audio recording. Complete process to be recorded (from start to End of the session).
- PI & his/her study team members (if applicable),would provide all the information relevant to the study as per schedule Y appendix V.
- PI/Designee should ensure that all the questions / concerns of subject/LAR/IW are addressed.
- After the subject is satisfied with the information provided and voluntarily aggress to sign the consent, the audio video recording will be completed with both subject and PI/designee's signatures on the written ICF.

6. After the consent-

- PI /Designee should verify the quality of the entire recording of the AVC process
- After the consent process is over the recording will be saved on the 'non re writable CD.'
- CD will be numbered with protocol number, PI name, study specific patient number and date of consent For example

  AV Consent.
  Protocol No:
  PI Name:
  Patient No. :
  Date :
  Confidential, do not copy

- CDs will be protected with password and will have a restricted access
- Two copies of each CD would be made. One CD should be stored with other patient related source documents in specific study location. Second CD should be stored separately by PI at secured location as a back up.
- It is PI's responsibility to retain both CDs

- After the recording is transferred to CD it should be permanently deleted from the computer/system .

7. Financial considerations- The facilities provided by DMHRC for AV recording will be charged as per the Finance policies of DMHRC management and will be updated in EC SOPs

8.Other important considerations-

- PI & his/her study team members are requested to adhere strictly to principles of confidentiality throughout the consent procedure.
- It is the responsibility of PI to ensure that the consent procedure is carried out , documented, recorded and archived as per the applicable regulatory guidelines
- And the same should be made available to inspectors, auditors of regulatory authorities, IEC members (as and when required)
- As per the DCGI order dated 19 Nov 13, there no requirement to share a copy of the AV consenting CDs with the participating subjects, hence it is advisable to not to share the recordings with the subjects for the purpose of confidentiality. However the same can be provided if demanded legally.
- Photo Identification of the subject must be obtained before initiating AVC recording and the same should be retained along with other consent documents.
- Name of the video grapher should be mentioned in the protocol specific duty delegation log
- AV Consenting is applicable only to new subjects to be enrolled from immediate effect, and not required for re-consenting of ongoing patients or on ICF amendments etc.
- AV consenting is to be done in addition to usual consenting and does not replace paper ICF
- All study related procedures must be initiated only after ICF procedures are completed
- For all currently ongoing studies Informed consent Form (ICF) will have to be amended according to the regulatory guidelines

Q. APPENDIX XVII: RECEIPT FOR COMPENSATION

Protocol Number and Title:

PI name:

Sponsor Name:

Details of the SAE for which compensation is to be given-

Sr No	**Initial/ Follow Up** (as applicable)	**Patient Initials**	**Date Of Event`**	**Date Of EC Reporting**	**Diagnosis**

Cheque Details-

Cheque Number	
Bank Name	
Branch Name	
Amount	
Date of Issue	

Recipient Details-

Name of receiver-

Age:

Address-:

Relation with patient/ self:

Sign and Date

PI sign & Date: