GUIDANCE DOCUMENTS FOR REGULATORY SUBMISSIONS

In an effort to help stakeholders get over the regulatory complexities involved in their interactions with the Health Authorities, ministries or regulators, Indian Society for Clinical Research (ISCR) has attempted to provide a gist of the various process documents that are required for submission in the various categories of trials and what needs to be done / submitted, in a simple, easy to understand format.

DISCLAIMER

For document see below

CLINICAL TRIALS WITH MEDICAL DEVICES

According to Drugs and Cosmetics Act,1940, Chapter 1, Clause 3(b)(iv)- drug includes "such devices intended for internal or external use in the diagnosis, treatment, mitigation or prevention of disease or disorder in human beings or animals, as may be specified from time to time by the Central Government by notification in the official Gazatte, after consultation with the Board." (The Drugs Technical Advisory Board (DTAB)). Hence, all the regulations of a drug trial will apply to the notified devices and the drug devices combinations. Earlier, only needles, syringes and blood bags were covered by the Drugs and Cosmetics Act, 1940. Now sterile devices like cardiac stents, drug eluting stents, catheters, intraocular lenses, IV cannulae, bone cements, heart valves, scalp vein set, orthopedic implants, internal prosthetic replacements have been included in the list with effect from 1.3.2006.

Definitions:

Device : "An instrument, apparatus, implement, machine, contrivance, implant, in vitro agent, or other similar or related article, including a component, part or accessory, intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease in man, or intended to affect the structure or any function of the body of man, and which does not achieve any of its primary intended purposes/ uses through chemical action within or on the body of man, or by being metabolized within the body."

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

Medicated devices : These are devices that contain pharmacologically active substances which are treated as drugs.

Medical devices include diagnostic test kits, crutches, electrodes, pacemakers, arterial grafts, intra-ocular lenses, orthopaedic pins and other orthopaedic accessories. Their purpose varies from being used primarily for specific affected parts of the body to being used as adjunct to primary therapies, for eg. lithotripsy with drug therapy for kidney stone. Depending upon risks involved the devices could be classified as follows:-

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

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

All the general principles of clinical trials described for drug trials should also be considered for trials of medical devices. As for the medicated devices, safety evaluation and pre-market efficacy of devices for 1-3 years with data on adverse reactions should be obtained before pre-market certification. The duration of the trial and extent of use may be decided in case-to-case basis by the appropriate authorities. However, the following important factors that are unique to medical devices should be taken into consideration while evaluating the related research projects :

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

DOCUMENTS REQUIRED FOR CLINICAL TRIAL APPLICATION OF NOTIFIED MEDICAL DEVICES IN INDIA

(NOTE: DATA ON ITEM NUMBER 5-10 IS REQUIRED, AS APPLICABLE FOR THE PROPOSED STUDY, IF NOT AVAILABLE IN THE DEVICE MASTER FILE AND INVESTIGATOR'S BROCHURE)

1. **Delegation of responsibility**: on the sponsor's letterhead

2. **Protocol**

3. **Investigator's brochure**

4. **Device master file**

5. **Device Information:**

   - Device and/or Drug information [Generic Name, Chemical Name or International non-proprietary name (INN)]
   - Specifications of the materials used
   - Qualitative and quantitative particulars of the constituents
   - Information on sterility and stability of the product
   - Labeling details
   - Variations in shape, style or size of the device, if applicable
   - List of accessories and other devices or equipment to be used in combination with the device. Other descriptive information, including accessories packaged with the product.
   - Physician manual and promotional literature (Literature insert) in English.(if any)
   - Packaging description including pack sizes
   - Recommended storage conditions

6. **Animal Pharmacology:**

   - Summary
   - General pharmacological actions
   - Specific pharmacological actions
   - Follow-up and supplemental safety pharmacology studies
   - Pharmacokinetics: absorption, distribution, metabolism, excretion (drug specific if any)
   - Data on Biocompatibility studies

7. **Animal toxicology:**

   - Systemic toxicity studies
   - Local toxicity
   - Allergenicity/Hypersensitivity

8. Clinical studies with device

- Clinical study reports on the device

9. Global Regulatory status:

A. Clinical trial in each participating country:

- Copies of regulatory approval letters, IRB/EC approvals, recruitment figures (Protocol specific) from participating countries (if available)

a) **Regulatory status of device and/or drugs in other countries (if applicable):**

- Approved
- Marketed (if marketed a copy of package insert)
- Withdrawn, if any, with reasons
- Free sale certificate or certificate of analysis, as appropriate
- ISO Certificates and/or CE certificate (if available)

10. Study Status :

A. Status of the proposed study Worldwide:

- Number of countries participating
- Name of countries participating
- Number of study centres per country
- Anticipated recruitment in each country

B. Status of the proposed study in India:

- Number of patients
- Number of study centres

11. Investigator's Undertakings

12. Ethics committee approval letters (if available)

13. Informed consent form and patient information sheets

14. Case record form

15. Relevant published literatures

16. Suspected Unexpected Serious Adverse Reaction (SUSAR) from other participating countries if any reported and summary of any reported problems.

17. Affidavit from the sponsor that the study has not been discontinued in any country and in case of discontinuation the reasons for such a discontinuation and that the applicant would further communicate to DCG(I) about the future discontinuation and Investigator's Brochure containing the summarized information is based on the facts. **(on a plain paper duly notarized and apostilled)**

DOCUMENTS REQUIRED FOR IMPORT LICENCE APPLICATION:

1. Justification for the quantity of devices need to be imported
2. Country from where the study device will be imported
3. Packaging information

References:

1. GUIDELINES FOR IMPORT AND MANUFACTURE OF MEDICAL DEVICES

http://www.cdsco.nic.in/medical%20device%20A42.html

2. **GOOD CLINICAL PRACTICES GUIDELINES**

http://www.cdsco.nic.in/html/GCP1.html

3. ETHICAL GUIDELINES FOR BIOMEDICAL RESEARCH ON HUMAN PARTICIPANTS

http://www.icmr.nic.in/ethical.pdf