Multi centric trials in Research and the associated issues and feasibility in India.

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"Well-designed and rigorously conducted multi centric trials provide extremely useful information that can inform, if not guide, clinicalpractice."

–Lawrence A. Appel

Evidence-based practice requires clinical trials to be performed. Clinical trial is a research study to develop new tests and treatments with the aim of gauging its effects on human health. In epidemiology, bigger studies are considered more powerful and we rely on their results in clinical decision making, hence Multi centric trials (MCTs) are an important tool for research. According to Royal Decree 561/1993, a multicenter research trial is 'a trial carried out in two or more centres with the same protocol and a coordinator who is responsible for processing all the data and for analysing the results.' As per National Research Council (US) MCT is defined as'a clinical trial that follows a single protocol but conducted at more than one medical center or clinic for study of a drug, biologic or device in human subjects with the intent to discover potential beneficial effects.'By minimizing confounding factors, MCTs revolutionized our understanding of many diseases, and helpedresearchers to develop and study many new treatment regimens. Phase III trials are mostly conducted for MCTs.[1]Conducting a multicenter trial is a complex and time consuming undertaking but the results of MCTs tries to answer scientific questions and find better ways to prevent diagnose or treat a disease. The number of centers enrolled for MCT research depends upon the effects of statistical power. A rule of thumb is that the number of subjects enrolled in each center should not be less than the number of centers in a MCT. It goes without saying that there is a need for multisite studies during early-phase research. The key points for conducting a successful MCT are:

- Assuring standardization
- High quality data collection
- Uniformity of procedure
- Collaboration across sites of a MCT

In multi centric trials, activities of protocol development, development of study materials, training, communication, laboratory determinations, data processing and management, report generation, statistical analysis and manuscript development are often centralized because of the need to standardize them across all sites. The investigator(s) at different sites of MCT work as co-investigators in the planning of the study protocol/procedures and they are scientifically responsible for all the study results. The large number of subjects from different geographical locations can participate, hence the possibility of including a wider range of population groups become more. All of these increase the generalizability (external validity) of obtained results from MCTs. Moreover, the enrollment of the subject(s) in MCTs is Competitive. If the subject recruitment rate is lower than expected at one centre and higher than expected at another, planned allocation numbers should be transferred from the centre with low subject recruitment to a centre with high recruitment where subject inclusion is expected to be completed earlier than planned.[2]This is done to help ensure that subject enrollment is completed as planned.(Figure 01)

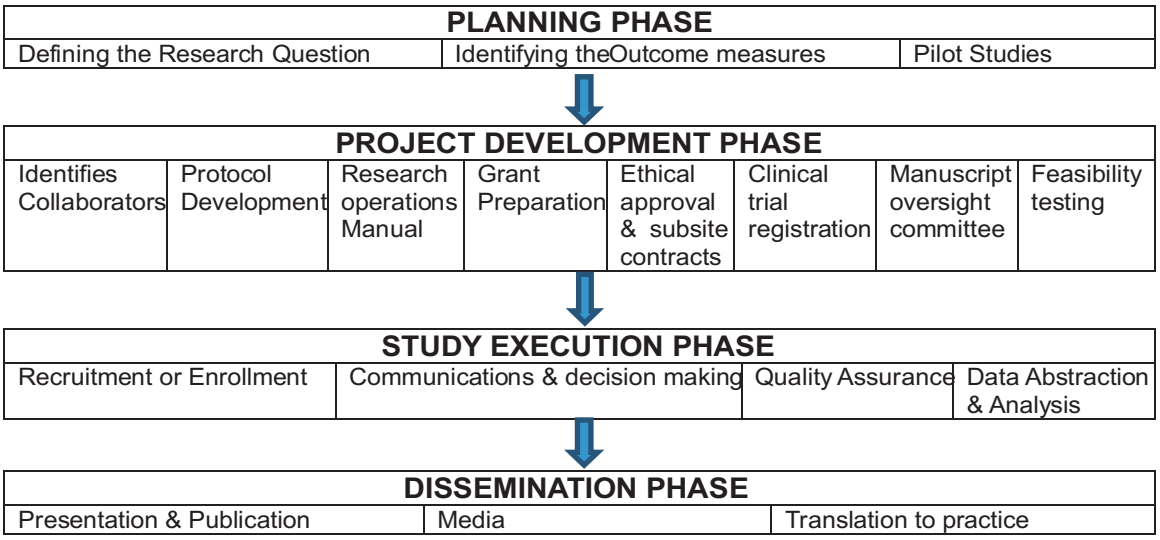

Figure 01:Phases of planning & conducting a Multicentric Trial Research

Two kinds of multicenter trials have been developed with different purposes and different organizational structures:

1. Large, simple, multicenter trial, which is designed to solve important clinical issues and has hard endpoints, limited data collection, and limited monitoring.
2. Trials which focus on patients with a precisely defined disease entity and have soft endpoints, extensive data collection, and quality assurance.

This second type of trial is most commonly performed during the pre-registration phase of a new drug (Phase III) and must comply with regulatory requirements.

The golden rules of multicenter trails are that protocol design be kept relatively simple and the same at all centers, that careful planning of the initiation, conduct, and analysis of the study is mandatory and that statisticians be involved in the process, and that communications problems be minimized through all possible techniques. The centers must be comparable in their equipment, staff, timetables and recruitment. Only examinations performed in identical conditions and providing results of similar reliability can serve as a criterion for the evaluation of a multicenter trial. The equipment used to assess the results should be standardized and easily available. The availability of staff and their training in conducting therapeutic trials should be similar for each center. The schedules for meal distribution, examinations and drug administration should not differ greatly. The recruitment of patients should be uniform in all centers.[3, 4]

There should be a common protocol for all centers in MCTs. As any difference in the interpretation of the protocol can lead to a defect in homogeneity, it should be considerably more detailed than when applied by a single center. In-depth discussions with all of the staff in each center involved in the trial are highly desirable. To increase the chances of a successful trial, the protocol should be written clearly and be as simple as possible.

A particular element known as the center factor should be taken into account when the results are analyzed by a suitable statistical method in MCTs. This factor allows inter-center variability to be deducted from residual variability, thereby improving sensitivity in the detection of differences between treatments. It is also important to check whether differences between treatments (other

than random variations) have been found in all the centers. If important differences exist, they can be revealed by a significant "treatment per center" interaction test. The cause of such discrepancies could be a difference in the initial characteristics of subjects from one center to another; an abnormal proportion of drop-outs or non-observers in one or more centers, which could be due to laxity in interpretation of the protocol or inadequate motivation of investigators in these centers; and/or a real variation in differences between treatments in one or more centers.[5]

In international MCTs there can be a diversity of languages and concepts. It is essential to use translations of protocols, but a reference version should exist in a language understood by all participants. Differences in nosology are sometimes involved. It is also necessary that the assessment tools be translated into the language of the investigator and that this translation be validated to be sure that it corresponds to the original. It is necessary that the intensity of the pathology studied is close to one country to another and does not depend on variations in cultural appreciation.[6] This is the case of studies in generalized anxiety where some countries only treat severe forms with drugs.

Key challenges and considerations [7, 8] while conducting Multi-centric trials include(s):

1. There are multiple approvals required for conducting the MCTs. In the pre-initiation stage, the sponsor will have to obtain import or manufacturing licensing for the study drug/ treatment, register the clinical trial with the CDSCO and receive an approval to commence the trial. Post the commencement of clinical trials, periodic permissions to conduct trial must be applied for at every phase to proceed to the next phase of the trial. The timeline for grant of each approval is typically 30-90 working days.
2. In case of any changes in protocol or study design of MCTs fresh clinical trials to be conducted in accordance with the CT Rules.
3. The usual sample size and power calculations in MCTs depend upon the assumption that the differences between the compared treatments in the centres are unbiased estimates of the same quantity. It is important to design a common protocol and to conduct the trial with this background in mind.
4. There are strict timelines for interim reporting obligations under the CT Rules. Interim and progress reports must be submitted periodically and annually to the CDSCO. In addition, serious adverse events must be reported within twenty-four hours of occurrence and a report detailing the occurrence and redressal must also be submitted. All forms of reporting must conform to the standard reporting formats provided under the CT Rules.
5. Informed consent from trial subjects in MCTs must be obtained in conformity with the format prescribed under the CT Rules. There are specific informed consent requirements for minors, pregnant women, foetuses & neonates and mentally impaired individuals under the ICMR Guidelines.
6. Under the CT Rules, maximum liability is imposed on the licensee for the clinical trial. This is either the sponsor or its representative. Under the CT Rules, violations may result in revocation of approvals and debarment of the sponsor from conduction of future clinical trials in India. Parallelly, a civil or criminal action may be brought against the sponsor.
7. First-in human MCTs of drugs/treatments developed outside India are not permitted. All Foreign New Chemical Entities may require trial data and approval from a foreign jurisdiction before trial initiation in India.
8. A non-uniform healthcare system, with varying standards in the government and private sectors, desperate poverty and lack of access to healthcare, illiteracy, lack of information and poor enforcement constitute a chaotic milieu which is a major challenge for conducting MCTs in India.

In general terms, trial feasibility is a process of evaluating the possibility of conducting a particular clinical program / trial in a particular geographical region with the overall objective of optimum project completion in terms of timelines, targets and cost. This process includes assessing internal and environmental capacity, alignment of the trial in terms of study design, dose of investigational product, comparator, patient type, with the local environment and assessing potential of conducting multi-centric trial in different areas of a specific country. At a global or regional level, feasibilities are often managed by the global study teams but the actual execution is done by the country offices (sponsor) or contract research organizations (CRO) as the case may be. The process of selecting a region (country) with a sufficient number of quality sites and investigators is one of the most challenging tasks in conducting multi-centric trials. Proper region selection can not only impact the financials and monitoring resources requirements but can also affect the credibility/acceptance of the data generated from the clinical trial. Conventionally, the feasibility for conducting any MCT ina country depends upon these factors:[9]

1. Shortlisting prospective regions/countries
2. Building a database of prospective investigators and sites in each region
3. Developing a list of questions to be answered (Feasibility Questionnaire)
4. Contacting investigators and sites with the preliminary information
5. Getting responses from sites on clinical trial feasibility questionnaire (FQ)
6. Compiling regulatory and procedural details, including timelines
7. Preparing a comprehensive clinical trial feasibility report

As believed by Von Claude Bernard (1813-1878), "when we meet a fact which contradicts a prevailing theory, we must accept the fact and abandon the theory, even when the theory is supported by great names and generally accepted." India has been an attractive place for MCTs for decades owing to the diverse large population and favourable regulatory landscape. In India, for the purpose of regulation, MCTs can be broadly categorized into:

- **Interventional Multicentric Clinical Studies:** Clinical studies which involve the administration of an intervention- new drug or investigational new drug for a commercial purpose, which are regulated under the clinical trial (CT) Rules.
- **Academic and Biomedical Multicentric Clinical Studies:** Academic clinical trials and biomedical and health research are regulated by the ICMR Guidelines. Biomedical and health research includes research where no investigational new drug or new drug is involved and is primarily conducted for the purpose of collecting scientific knowledge about diseases and conditions.

The Indian legal framework and regulation under which Multi centric trials (clinical and medical research) have to be carried out mainly comprises [10]of the following:

1. Drugs and Cosmetic Act, 1940 and Drugs and Cosmetics Rules, 1945
2. New drugs and Clinical Trial Rules, 2019
3. National Ethical Guidelines for Biomedical and Health Research involving Human Participants, 2017
4. Good Clinical Practice Guidelines for Clinical Research in India issued by the CDSCO
5. Good Clinical Laboratory Practices.

It is mandatory for the sponsors of the MCTs to register the clinical trials including academic clinical trials with the Clinical Trial Registry of India (CTRI). The CTRI is a central repository of clinical trials undertaken in India. Approvals are required at each

stage of the trial, from subject recruitment and approval of the clinical trial protocol, up until Phase IV studies. Applications to conduct MCTs in India are to be submitted online via the SUGAM portal (hosted and developed by CDSCO). All MCTs in Indiaare conducted, broadly under one of these categories.

1. Study on vulnerable population
2. Public health research and social and behavioural science research for health
3. Human Genetics testing and research
4. Research during humanitarian emergencies and disasters.

Few Examples of MCTs conducted in India:

1. An Indian Multi-centric Phase IV Study to Assess the Safety of Crizanlizumab in Sickle Cell Disease Patients. (2020)
2. A multi-centric cross-sectional study to characterize the scale and impact of poly-pharmacy in rural Indian communities, conducted as part of health workers training. (2019)
3. Oral health in India: A report of a Multi-centric Trial. (2020)
4. Computer and Internet in Dental education system of Kerala, South India: A Multicentric trial.

Feasibility of Mct's In India:

The extraordinary caseload in India and the reduced per capita workforce made the organisation of a combined-site start-up meeting of MCTs for all sites unfeasible. Persistent electricity outages, poor internet connectivity, and the large digital divide were some of the additional obstacles that the MCT team had to negotiate at sites. Internet quality was inconsistent, meaning that accessing study websites for randomisation and entering data into electronic case record forms was difficult. Participants were reluctant to comply with the follow-up needed in clinical trials. Moreover there is lack of participation by remote and smaller health units in India for MCTs. According to ICMR, the median (IQR) duration between submitting applications of MCTs and ethics committee approval was 60 days, but there are substantial delays introduced by infrequent meetings, adherence to the traditional format of initial scientific sub-committee review before full ethics committee review, and the mandate for legal approval for clinical trial agreements before considering the ethics application.

In the end, it is concluded that no doubt we have very fertile platform for conducting MCTs in India but researchers needs to face many challenges during the various phase(s) for successfully conducting such trails in India.

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