Issues and Developments in Clinical trials of Traditional medicines

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ABSTRACT

Traditional medicines have been used since the beginning of human life on earth. Traditional medicines form a part of the household not only in India but also in western countries. According to WHO, traditional medicines are those extracts from plants which are of medicinal value. Around 80% of the world’s population relies on traditional medicines for medicinal purposes or as nutraceuticals. There is a well-established procedure for conducting clinical trials of western medicine, but when in the case of traditional medicines, there are several obstacles in the path. Where traditional medicines are the oldest form of medicines used by human’s specific issues like lack of infrastructure, lack of sponsors and lack of skilled manpower hinders the clinical trial process for traditional medicines. The articles focus on various issues for conducting clinical trials and the steps taken by the government to address these issues. Centres like the National Center for Complementary and Alternative Medicine, All India Institute of Medical Sciences are working rigorously to research traditional medicine to establish safety and efficacious data at par with modern medicines. Standardization of the collected raw material, in-process standardization and quality control check of the final product will further help in reducing the harmful adverse effects.

INTRODUCTION

The primary aim of science is, understanding the environment and, delivering the end product to society (Ginsburg and Phillips, 2018). The science of traditional medicine is determined by empirical research, i.e. the collection of the observational facts (Semwal et al., 2015). Science is always trying to find an answer, “why”; to understand the mechanism, this answers the many questions to reveal many facts related to clinical research, especially from reverse pharmacology to networking pharmacology (Pan et al., 2013). It is observed that for more than a few decades, elaborate attempts were made in clinical research to develop standards which play an important role to understand the descriptive knowledge of an evidence-based reality (Grimshaw et al., 2012). A clinical trial in traditional medicine has its issues like the use of a substitute, controversial, and adulterated drugs may lack literary review (Ekor, 2014).
being (Telles et al., 2014).

The demographic, and socio-economic atmospheres of developing markets like Africa and India with their large market for traditional medicines, if it is strategic and product improvement assistance, along with technical manpower would help in delivering and creating an excellent platform to the universal pharma industry to address the challenges of growth and innovation in the development of the traditional medicine. The African continent has a good advantage in conducting clinical trials on traditional medicine due to its rich practice of herbal medicine, easy availability, and affordability. These medicines are desired by many patients, as well as extensively used (Rutebemberwa et al., 2013).

India, after globalization entered into the hub of conducting clinical trials (Selvarajan et al., 2013). The clinical trials mainly focus on manifestations like degenerative and autoimmune diseases like rheumatoid arthritis, sclerosis, cancer, cardiovascular diseases etc. To conduct clinical trials on genomics, generative, tissue culture, stem cell etc. requires complex infrastructure, experienced human resource specialized in scrutinizing quality, data, pharmacovigilance, regulatory affairs, approvals from ethics and monitoring committee, good clinical practice, cost commutability (Mittal, 2013).

Nowadays, people across the globe use traditional medicine as in the form of dietary supplements, nutraceuticals etc. (Das et al., 2012). The traditional medicine comprises a different system of medicines like Ayurveda, Chinese traditional medicine, Kampo etc. There is a various treatise on clinical trials like ‘Canon of Medicine’, ‘placebo remedy’, ‘Treatise on Scurvy’ etc. which mentions the earlier studies on clinical trials (Bhatt, 2010). But still, like contemporary medicine, traditional medicine has no governing or monetary mesh for controlling their medicine molecule before they are promoted. It is the right time to follow regulations and guidelines such as Good Manufacturing Practices, Good Clinical Practices, Good Laboratory Practice and Good Clinical Laboratory Practices. Clinical trials are the systemic study of new drug molecules on human subjects with their consent. This helps to validate data of pharmacodynamics and pharmacokinetics, toxicity and efficacy of the novel traditional drug molecule (Yuan et al., 2016).

At present, clinical trials on traditional medicine are gaining importance, to introduce new medicine molecule to suffering humanity. The scientific folk must design their preclinical trial accepted worldwide (Vijayananthan and Nawawi, 2008). But nowadays to conduct a clinical trial on the traditional medicine faces various issues like cost compatibility and timeline, intellectual property rights, the clinical trial sponsored agencies having their guidelines for IPR. (Bhattacharya and Saha, 2011). The main issues and concerns in the preclinical studies are

**Lack of Sample and Study design**

Proper sample size and study design play an important role in clinical research, but most of the traditional medicine clinical trials do not come out with phase III clinical trials (Di and Tang, 2013). Clinical trials play a pivotal role in the reverse pharmacology of already established drug molecule (&amp; Raut et al., 2017). A literature review will put a light on the history of traditional use, about adverse effects, etc. thus reducing the requirement for preclinical toxicological studies and requires less funding and becomes more cost-effective clinical trials (Jamshidi and Cohen, 2017). For a study design to be always straightforward, the adequate information to answer the research question must be observational, prospective randomized, retrospective etc. (Aslam et al., 2012).

The study protocol must include data about dosage modalities, dose, and risks and benefits (Shen et al., 2019). The central aspect of any kind of clinical trial is the maintenance of the subject confidentiality (Sng et al., 2016). Duration of the study, methodology, needs of the study, citations and data significantly contribute to the study (Molléri et al., 2018). The clear mentioning of the inclusion and exclusion criteria of the subjects, along with safety and efficacy procedures for monitoring and compensation, also has a significant role in clinical trials (Garg, 2016).

**Financial assistance**

It is evident that the vast amount and more number of years are required for the discovery and development of a new drug molecule (Mohs and Greig, 2017; Cleary et al., 2018). This is usually not happening in the traditional medicine sector; logically, it is very difficult to afford such a huge amount (Muhammad and Awaisu, 2008). Though, most of the pharma companies invest a huge amount in clinical trials, in countries like Africa, India, and China where the patient population is poor than those in the West has resulted in more number of trials at a lesser cost than the US (Bajpai, 2013). But in recent years due to the more rigid guidelines and regulation impediments from Indian government keeping the patient safety in view, India is losing its emerging market status to conduct the clinical trials comparing to the other countries (Alemayehu et al., 2018).

**Time management**


Time constraint is one of the hindering factors to conduct clinical trials in traditional medicine. It is mainly due to the lack of awareness of pharmacovigilance—improper utilization of Drug and Cosmetics Act, Patents Act, Intellectual property Act. Trade-Related Aspects of Intellectual Properties (TRIPS) etc. more time is being consumed (Sampat and Shadlen, 2018).

**Lack of infrastructure and lack of skilled manpower**

These issues are mainly due to the operational cost, the requirement of proficient, qualified professionals, a huge group of patients, world-class laboratories, and institutions, well-established information technology hub.

While to conduct clinical trial well educated skilled team is required. The team should comprise of traditional healers, qualified traditional practitioner, a person from quality assurance, Botanists, anthropologists, pharmacologist, Chemists clinician and Statisticians (Bodeker and Kronenberg, 2002).

**Various accreditation, as well as governing agencies**

These agencies will monitor the clinical trials of traditional medicine in various countries around the globe. Depending upon the nature of work they are, Consolidated Standards of Reporting Trials (CONSORT) (Grant et al., 2018). Uniform requirements for Manuscripts (URM), Drugs Technical Advisory Board (DTAB), Drug Consultative Committee (DCC) Central Drug Laboratory (CDL), and Drugs Technical Advisory Board (DTAB). The government of India deliver guidelines on clinical research and clearly says that all clinical trial should be registered under clinical research repository (Monera-Penduka et al., 2017).

**Slow functioning of the Institutional ethical committee**

The ethical committee must take fair decisions. In many times ethical committees will not allow conducting a clinical trial on traditional medicine in stipulated time (Chatfield et al., 2018). For instance, In India, The Indian Council of Medical Research (ICMR) issued the ethical guidelines for the clinical trials and acceptable clinical practices (Saxena and Saxena, 2014). Institutional ethical committee (IEC) initiate clinical trials on the traditional medicine only after obtaining Biochemical, Pharmaceutical, Animal trial, Safety and efficacy data and patient consent. It also clearly observes the exclusion criteria must include in the case of vulnerable subjects (Das and Sil, 2017). It must monitor major or minor changes in the clinical trials. All adverse events have to inform, Directorate General of Health Services, Sponsor, and all stakeholders within 14 days and progress in studies must be submitted in every six months and once the study concluded it has to be reported to IECs in a prescribed format (Imran et al., 2013).

**Patient-Centred Outcomes Research**

Research goal is always patient-centred as it helps people make informed health care decisions. But most of the traditional medical research does not do this. The main issue of concern is using animal models for various clinical trials to evaluate the efficacy of traditional drug molecule used for the preventive, curative and management of a complex human disease. It is most commonly observed that in clinical trials, the disease process is introduced to the animal.

These may lead to uncertainties potency of tested traditional drug molecule for the human applicability as the traditional system of medicines based on their metaphysical theories. For instance, Swarna ksheeri (Argemone mexicana) used to treat many manifestations with an extract like Spondias mombin (Malagi et al., 2013).

The growing interest of the patient in traditional medicine all over the world encourages the world to focus more on this sector. Various countries like China is working on developing infrastructure for conducting clinical research in traditional medicine. In this area, India is slow yet started to focus on documenting its treasury on drugs of traditional medicine. In this regard, the Indian government took initiatives like the formation of

1. National Center for Complementary and Alternative Medicine (NCCAM)
2. AIIMS (All India Institute of Medical Sciences).

These agencies make provisions for conducting scientifically rigorous research to provide evidence-based touch to the safe and effective traditional medicine practice.

We have to focus on standardization of the trial drug in the arena like quality, safety purity, and impurity with pesticide residues. It is observed that all the included studies, the study design or quality of the primary outcomes have been measured as low. At the same time, some publications advocate the potential effects of clinical trials in Traditional medicine. Appropriate literature reviews were sought based on the inclusion criteria and free from bias.

The mission of NCCIH (National Center for Complementary and Integrative Health) is to define,
through laborious scientific investigation, the usefulness and safety of complementary and integrative health interventions and their roles in improving health and healthcare. It is better to document the safety of excellent traditional remedies which are thoroughly accompanying with speedy and comprehensive recovery with less failure rate.

NCCIH’s vision is that scientific evidence will inform decision making by the public, by health care professionals, and by health care policymakers regarding the use and integration of complementary and integrative health approaches. Various traditional systems of medicine like Ayurveda, Siddha, (India), Kampo (Japan), have personalized treatments and lack of standardization of herbal medicines and proper publication.

CONCLUSIONS

Inadequate data are available to conclude whether clinical trials in traditional medicine fulfil the standards and are free from bias. So well-designed, larger, double-blinded trials are required to determine the potential benefit of traditional medicine. Sample size calculations should be performed before initiating these studies of clinical trials. Traditional medicine is an evidence-based treatment option for many manifestations. Further, to improve a new cost-effective Traditional Medicine, clinical trials play a significant role in estimating safety. Reverse pharmacology and networking pharmacology are viable modes for the growth and development of traditional medicine. It is an attractive and desirable method can be developed in parallel with conventional drug development, but more evidence, including deciding the dose is a crucial step. Conducting clinical trials in developing countries with condensed cost, and availability of subjects is always beneficial to pharma agencies, the traditional system of medicine and economy of the particular country. These issues can be overwhelmed by adopting recent advance practices plus guiding principle for the clinical trials. We have to use modern standardization methods like standardization during the collection of raw materials, during process and standardization of finished product at WHO or ISO certified units. Evaluation of strategic and operational planning scientific study design is one of the essential parts of the success of any kind or phase of the clinical trial. To obtain consistent results, double-blind experiments should be applied with a sufficient number of subjects.

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Conflict of Interest

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