soft power can help to overcome these issues, it also necessitates significant investment from both the public and private sectors. Emerging institutions, such as farmer producer organizations, should also play a larger part in this massive undertaking.

Strengthening APMC markets

The existing 7320 Primary Agricultural Market Committee (APMCs) market yards are the backbone for all marketing activities including exports. The simplification of procedures and strengthening infrastructure of APMCs and electronic-National Agricultural Markets is a starting point for increasing export capabilities at local level. On a war footing, infrastructure development in marketing yards, regulations for allocation of properties in marketing yards, agricultural market information system and contract farming laws must be streamlined[1].

Overall, India has a vast agricultural export potential if it prioritizes high value exports. For a long time, India has been at the bottom of the global agricultural export value chain, with the majority of its exports being low-value, raw or semi-processed, and bulk-marketed. In India, the percentage of high-value and value-added agricultural output in the agricultural export basket is less than 15%, compared to 49% in China. This can only be accomplished with significant investment and a consistent export promotion policy.

1. Reddy, A. A. and Mehjabeen, *IIM Kozhikode Soc. Manage. Rev.*, 2019, **8**(2), 143–155.

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COMMENTARY

Robust clinical trials in Ayush systems: compelling necessity

Rajeshwari Singh, Pradeep Dua and Sumya Pathak

The COVID-19 pandemic caused by the virus SARS-CoV-2 is one of the biggest challenges confronting the world in this century. It has posed a challenge to the global healthcare system. Policymakers, doctors and scientists are working round the clock to tackle this grave emergency and find solutions to minimize the adverse effects and threats to life caused by this pandemic. The emerging scourge of non-communicable diseases, including diabetes, hypertension, cancer and mental illness needs to be addressed proactively and national paradigms must be developed to meet this challenge.

We also need to be prepared for emerging and re-emerging viral diseases like dengue, chikungunya, nipah and now the ongoing COVID-19 pandemic. It is paramount to use the information generated by research activities to improve the performance of health systems at the national level. To achieve this, the output of research must balance its eventual utility. For this, the output of research must balance its eventual utility. There is ardent need for a drug regulatory framework to facilitate research and its translation into health policy from the inception stage itself, with research being a programmatic imperative and driven by operational needs.

There are collective efforts underway to limit the progression of this deadly virus. Numerous clinical trials have been taken up across the globe for breakthrough medicine, including vaccines[1]. Similarly, 203 clinical trials exploring the interventions for COVID-19 are registered in India's Clinical Trial Registry (CTRI). Interestingly, 61% was based on various AYUSH interventions and sponsored by the Government of India (GoI)[2,3].

The first incidence of COVID-19 was reported in Wuhan, China, December 2019 and the virus infiltrated India on 30 January 2020. There was a surge in COVID cases in the mid of April 2020 (ref. 4). The GoI has taken various measures like travel restrictions, community surveillance, institutional quarantine, identification of hotspots or containment zones, etc. along with strict lockdowns to flatten India's case-growth trajectory curve. The National Clinical Management Protocol for COVID-19 was released on 3 March 2020. Subsequently, the Ministry of AYUSH, GoI, also issued guidelines and advocacies based on AYUSH fundamentals. Ayurveda and Yoga interventions were integrated in the National Clinical Management protocol for COVID-19 on 2 October 2020 (ref. 5). Many controversies arise by media and health workers as well as other health associations for clinical efficacy and product registration.

In the current paradigm of clinical research and evidence-based medicine, clinical trials are essential to establish the safety and efficacy of drug interventions in any setting[6]. Unfortunately, the paucity of robust clinical trials in the AYUSH sector has led to the widespread use of unlicensed or off-label medication, as well as misunderstanding about the safety and efficacy of AYUSH products. On the other hand, meticulously conducted clinical trials adhering to international norms in terms of scientific rigour and ethical robustness, and state-of-the-art statistical analysis is perhaps the only way to counter the allegations regarding safety, effectiveness and scientific rationale for AYUSH interventions levied time and again by the so-called fly by night researchers.

India is endowed with pluralistic healthcare, i.e. modern and AYUSH systems of medicine are practised in the country[7]. Interestingly, the modern system of medicine and Ayush systems are governed by the Ministry of Health and Family Welfare and the Ministry of AYUSH, GoI respectively. Central Acts recognize these systems. Different Acts regulate education and practice, but the manufacturing, import, distribution and sale of drugs and cosmetics of these systems are regulated by the single Act, viz. Drug and Cosmetics Act, 1940 (D&C) and rules thereunder[8].

In the context of the drugs of modern medicine, Rule 2(j) in the New Drugs and Clinical Trials Rules, 2019 defines 'clinical trial' in relation to a new drug or investigational new drug means any systematic study of such new drug or investigational

new drug in human subjects to generate data for discovering or verifying its (i) clinical or; (ii) pharmacological including pharmacodynamics, pharmacokinetics or; (iii) adverse effects, with the objective of determining the safety, efficacy or tolerance of such new drug or investigational new drug'[9].

As per the extant provisions, the term 'clinical trial' per say does not exist in the statute concerning Ayurvedic, Siddha and Unani (ASU) drugs. However, as a regulatory requirement, only textual rationale, published literature and pilot studies are needed to generate evidence regarding the efficacy of ASU drugs. Further, a pilot study is required only when there is no textual rationale, published literature and textual indications based on authoritative ASU books supporting the intended ASU drug. Clinical trials for classical (Section 3a of the D&C Act, 1940) and proprietary (Section 3h(i) of the D&C Act, 1940) ASU drugs have different approaches. Classical formulations have a strong history of human usage; hence, the scope of clinical trials is deemed limited. However, in proprietary ASU drugs, clinical trials add to the scientific validation of clinical safety and efficacy, facilitating acceptance and recognition in the global market. The requirement of proof of safety and effectiveness for issuing manufacturing licenses for various categories of ASU medicines is covered under Rule 158(B); II-A of D&C Rules, 1945. There is no requirement of safety studies for any classical formulation even with variation of dosage and a new indication for issuance of licence. Eventually, under the same rule, CAT II B suggests the requirement of specific safety studies for patent and proprietary along with proof of effectiveness to be supplemented by pilot studies. Further, for an ASU drug containing any of the ingredients listed in Schedule E(1) of the D&C Act, 1940, studies are required for safety and effectiveness. Similarly, in case of Medicinal Aushadh Ghana (extract), studies for safety and efficacy are required for issuance of license for hydro-alcoholic extract (B1) but safety studies are not required for Aqueous (A1 and A2) and B) hydro-alcoholic extract (B1).

The licencing of ASU medication is currently controlled by the states. The licenses for manufacture and sale of ASU drugs are granted by the respective State Licensing Authorities. It is not uncommon for a manufacturer to be denied a licence in one state but receive one in another, allowing him to advertise his wares across the country. There is no central regulatory agency for awarding and licencing of new pharmaceuticals in ASU.

The Ministry of AYUSH, GoI, is persistently involved in validation studies of classical formulations and other interdisciplinary research in collaboration with various institutions through research councils. It has initiated clinical research in order to create substantial scientific evidence to strengthen the community's trustworthiness. However, the D&C Act is silent on the modus operandi of conducting clinical trials on ASU drugs. To facilitate scientific rigour and temperament, the Ministry of Ayush issued a notification on 21 April 2020 for conducting clinical trials on COVID-19. The main intention is to prohibit tall claims for the cure of many diseases, including COVID-19, by the stakeholders. However, the Act prohibiting such claims is the Drugs and Magic Remedies Act (Objectionable Advertisement) 1954 (DMR 1954). Even then, there is a flood of advertisements making such fallacious and tall claims. Therefore, the Ministry of AYUSH, GoI has issued a notification on 28 July 2020, which directs the regulators to verify their claims and get clearance from the Ministry[11].

It is difficult to design befitting clinical trials for AYUSH interventions. With well-known limitations in terms of variability in raw material, inadequate standardization primarily due to limitations of existing scientific techniques, regulatory gaps, lack of equipped clinical trial sites, insufficient number of trained clinical trial experts and the scarcity of reputed scientific journals which are ready to accept research papers based on innovative trial designs, it is indeed an arduous task to conceive, design, conduct, analyse and publish clinical research that adheres to the sanctity of the principles of traditional systems of medicine and is simultaneously commensurate to the benchmark laid by clinical research in conventional medicine. The Central Government directive for conducting research and law enforcement is missing in the AYUSH sector. The provision for prior regulatory approval to conduct an AYUSH clinical trial and accreditation of AYUSH Ethics Committees by the regulator can pave the way for rational clinical trials that can add science to the existing wisdom. The Indian system of medicine is still an untapped domain for its potential. This plethora of ancient wisdom and knowledge needs a new framework of regulation, wherein its utilization is limited. Keeping in view the surge in acceptability for Ayush systems, an augmented regulatory framework is poised to appropriately tap the potential of these systems to contribute in the national healthcare system. It is the right time to properly implement the new provisions and amendments in regulations to utilize AYUSH systems with administrative, infrastructural and financial support to the identified institutions for conducting interdisciplinary research.

1. Gavriatopoulou, M. *et al.*, *Clin. Exp. Med.*, 2021, **21**, 167–179.
2. Charan, J. *et al.*, *Indian J. Clin. Biochem.*, 2020, **35**, 1–5.
3. Bhapkar, V., Sawant, T. and Bhalerao, S., *J. Ayurveda Integr. Med.*, 2022, **13**, 100370.
4. Rimesh, P. and Urmila, Y., *J. Primary Care Community Health*, 2020, 11.
5. https://pib.gov.in/PressReleseDetail.aspx?PRID=1662012 (accessed on 21 August 2021).
6. Masic, I., Miokovic, M. and Muhamedagic, B., *Acta Inform. Med.*, 2008, **16**, 219–225.
7. Shankar, D. and Patwardhan, B., *J. Ayurveda Integr. Med.*, 2017, **8**, 137–139.
8. Karan, A., Negandhi, H., Nair, R., Sharma, A., Tiwari, R. and Zodpey, *BMJ Open*, 2019.
9. New Drugs and Clinical Trial Rules, 2019. Ministry of Health and Family Welfare; https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/New-Drugs_CTRules_2019.pdf (accessed on 21 August 2021).
10. Drugs and Cosmetics rules, 1945. Ministry of Health and Family Welfare; https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/acts_rules/2016-DrugsandCosmeticsAct1940Rules1945.pdf (accessed on 21 August 2021).
11. https://www.ayush.gov.in (accessed on 21 August 2021).

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