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Asian Biotechnology and Development Review
Vol. 21, No. 1&2, pp 1-3

Editorial Introduction

K. Ravi Srinivas*

Welcome to this issue of ABDR. As like other issues, we offer you a rich content which I hope will be of interest to you.

I would like to share the good news that ABDR is now listed in the UGC-CARE List Group A of UGC List of Approved Journals. Group A list consists of journals from all disciplines which are indexed in Scopus (Source List) or Web of Science. This recognition means that authors of articles published in ABDR can use this to claim that they have published in a journal approved by UGC. This listing also inspires us to maintain high standards in publishing in terms of quality and academic integrity and improve them.

In the article "Clinical Trial Research in India and China: Myths vs Realities", Swapan Kumar Patra and Mammo Muchie examine clinical trials in terms of quantity and qualitative aspects. As both countries are leaders in clinical trials and are also leading countries in innovations in health such studies are necessary to understand the effectiveness of policies on clinical trials and how off-shoring of R&D activities and clinical trials benefit these countries. Their extensive analysis tells us that in both countries, the number of clinical trials have increased and the maximum trials are in phase three. Further they point out that there is wide variation in them in terms of disease conditions investigated with Diabetes Mellitus, Type 2 leading the list in India with 275 trials and in China it is Hepatocellular Carcinoma, with 252 trials They also point out the number of trials on Neglected Tropical Diseases is much less in both countries. Another interesting finding from this study is that while in China, the major sponsors are mostly the institutions or institutes including state sponsored universities, research institutes and medical colleges while in India the main sponsors are pharmaceutical companies including MNCs and indigenous firms. Although the study does not explain or discuss this, I think this deserves further analysis and perhaps

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this also indicates that educational institutions and universities in India are less engaged in clinical trials, irrespective of the stage of the trial, than their Chinese counterparts. Does it mean that there is a division of labour among various actors in pharmaceutical R&D in India, with pharmaceutical companies preferring to engage more in clinical trials with universities and other institutions focussing predominantly on the stages prior to clinal trials. I am sure that insights from this article will result in more research questions and studies.

With CRISPR/Genome Editing getting adopted as a disruptive technology in life sciences, there is no dearth of literature on the ethical, social and legal implications of the same and it is expanding day by day. But the point is not just in the increase in literature, it is also in the diversity of views and positions advocated. The editing of human germline is controversial and inter alia, World Health Organization is also studying the implications and regulatory possibilities. One key feature is that many academies of Sciences and professional bodies are also examining the implications and have started articulating their views. The debates and controversies cannot be understood as mere continuations of earlier controversies on genetic engineering and biotechnology although there are some recurring themes like use of precautionary principle and blurring of boundaries between nature and artificial. In the article 'Application, Regulation, Ethical Concerns and Governance of Genome-Editing Technologies: An Overview', Amit Kumar summarises the key points in the debate, the regulatory initiatives and explores the relevance of the regulatory mechanism in India for governing the genome editing applications in agriculture and health sector. The article discusses the various view points that have emerged in the debates and shows that at least in case of crop genome editing the CRISPR/Genome Editing has resulted in crops with specific traits. The potential is enormous, so are the concerns and expectations. While ethical issues have become central to the debate in case of applications in health, in case of applications in agriculture the key issue in regulation is whether these crops/products should be considered as Genetically Modified Organisms are not. The article discusses that aspect also. In future issues also we will carry articles on various aspects of genome editing and technologies like CRISPR.

Do Science and Technology contribute significantly to economic growth and if so how to measure it.

It is assumed that S&T contributes to economic growth but applying this hypothesis to district level data and verifying it has been done perhaps for the first time, in the article 'Relationship between Science and Technology (S&T) and Gross District Domestic Product (GDDP) in select Indian Districts' by R K Mishra, P. S. Janaki Krishna, Usha Nori and Ch Lakshmi Kumari using a methodology, consisting of inter alia, Principal Component Analysis (PCA), showing that the correlation is positive. They have analysed data on industry, agriculture and services. They have constructed specific indices and have shows that despite variations S&T contributes to economic growth in a major way This has policy implications A similar methodology was used in a Discussion Paper published by RIS "Science, Technology, Innovation in India and Access, Inclusion and Equity: Discourses, Measurement and Emerging Challenges" by Sachin Chaturvedi, Krishna Ravi Srinivas, and Rashmi Rastogi (RIS Discussion Paper 202 December 2015, http://ris.org.in/sites/default/files/pdf/DP202-Prof_Sachin%20Chaturvedi_and_Dr_Ravi_Srinivas.pdf)

Interested readers may contact the authors of the article published in ABDR to know more.

Your comments, responses and ideas are welcomed.

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Clinical Trial research in India and China: Myths vs Realities

Swapan Kumar Patra*
Mammo Muchie**

Abstract: In the recent years two emerging economies, India and China are into the limelight because of many reasons. Among the many, it is reported from the various studies that many major global multinational firms are offshoring their Research & development (R&D) activities in these two-countries. In this context, this study is an empirical investigation of clinical trials being conducted in India and China. For this study, data has been downloaded from the ClinicalTrials.gov database maintained by the National Institute of Health (NIH), National Library of Medicine (NLM), the United States of America. The website is an excellent repository of clinical studies conducted globally. The study examines the number and the growth patterns of clinical trials. In addition, it was further investigated the different phases, disease conditions where the maximum trials are being conducted. From the sponsors' information, the collaboration network of sponsors is drawn. The study observed that there are certainly growth of trials in these two countries but not at the same rate as the global growth. The maximum number of trials are conducted in the mature phase of a drug (phase 3). There is variation in the type of sponsors or collaborators profile. In China, the Chinese institutes are the major actors (universities, government research institutes and other organizations). In India, both indigenous and foreign firms, are predominating in conducting trials. The empirical observations from this study will be useful for scholars, firms, policy and decision-makers in the governments.

Keywords: Clinical Trial, India, China, Social Network Analysis, Globalization of R&D

Introduction

Biopharmaceutical science is a highly complex, collaborative and resource-intensive process. This high technology science requires a skilled workforce, long-term investment, vision and commitment. Generally, the average time to develop a drug is about 10 and 15 years and costs about $1.2 billion. In

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the drug development process, there is very high risk of failures in different phases. R&D process to develop drugs require clinical trials in different phases.

With the increase in R&D costs across the market of developed countries many of the global Multinational Enterprises (MNEs) are offshoring their clinical trials in the emerging economies like India and China (Patra & Muchie, 2017). These two emerging countries are advantageous in terms of their large and diverse treatment-naïve population, wide variety of diseases, English-speaking healthcare professionals, reasonably well-developed health care facilities, easy access to Information Technology (IT) infrastructure, Good Clinical Practice (GCP), relatively strong bioethics guidelines, quite easy volunteer recruitment process and good quality of clinical research data. It is found that cumulative of all these factors cost about half the costs of any developed country (Gupta & Padhy 2011).

With this background, this study is an empirical investigation of clinical trials being conducted in India and China. The study will ask the following research questions; what is the growth pattern of clinical trials in these two countries in terms of the number of trials that are being conducted? How the policies in both the countries differ? Who are the major actors and how they are collaborating with each other and so on?

Literature Review

Clinical trial in India

According to World Health Organization's (WHO) estimates, India has 17 per cent of the world population and 20 per cent of global disease. However, there is only about 1.2 per cent of total global clinical trials being conducted in India (Venkatasubramanian, 2019). According to MarketLine database, in 2018, the Indian consumer health care market was US$ 4,102.9 million (Fixed 2018 ex rates, Constant 2018 Prices) and it is estimated that the market will touch about US$ 5174.2 million by the year 2023 (Figure 1).

India is a big market and an attractive destination for many big pharmaceutical firms. In recent years, India is emerging as one of the foremost global destinations for clinical trials (Varawalla & Jain 2011). Among the many reasons, the big Indian market and conducive intellectual

property regime after WTO are perhaps major attractions for seeking clinical trial sites in India (Bajpai 2013).

In 1988, Schedule Y was inserted in the Drugs and Cosmetics Act, 1940 to regulate and governs clinical trials in the country. This schedule mandated phase 3 clinical trials for the registration of a new drug and supported the growth of a predominantly generic drug based Indian Pharmaceutical industry. However, it only permitted clinical trials at a phase lower than its global status (phase 2 could be conducted in India only if phase 3 has been conducted elsewhere. The Drugs and Cosmetics (IInd Amendment) Rules, 2005 by the Ministry of Health, Government of India, extensively revised the previous Rules with the objective to bring Indian regulations at par with internationally accepted definitions and procedures. These 2005 amendments enabled global clinical trials to be conducted in India.

According to Nundy & Gulhati (2005), the change was made in response to the demands from MNEs and other interested parties. This further cut down the cost of many trials and made India a preferable destination (Nundy & Gulhati 2005). On 19th March this year, the New Drugs and Clinical Trials Rules, 2019 were passed. These Rules have superseded Part XA and Schedule Y of the Drugs and Cosmetic Rules 1945, and for the first time, regulations governing clinical trials are available in one comprehensive document.

There were reports of many deaths in ongoing trials in the last decade in India. This lead to major public uproar. It was reported that the death happened due to lapse in various safety measures in different phases. It also initiated debate questioning the robustness of the Indian regulatory system. With the pressure from different stakeholders and with the interventions of the Supreme Court of India, the Indian government proposed laws to strengthen the protection of participants' rights (Porter 2018) and compelled the government for better regulation (Chowdhury 2012). The Supreme Court of India directed the Ministry of Health, Government of India to develop systems for appropriate compensation to the participants in case of death or other injuries occurring during the trials. Indian government strengthened the regulatory framework with new and complex regulations, which made India an unattractive destination for clinical trials during that period (Barnes et al. 2018). As a result, drug trials in India were reduced significantly (*The Hindu*, April 21, 2013).

Since the past few years, the country's regulatory framework (Table 1) moved towards more positive transformation which favoured the ethical conduct of clinical trials, appropriately supporting patients' safety. The adjustments made to the existing policies are predicted to bring a 'paradigm shift' in the overall regulatory scenario (Lahiry et.al, 2018). Lately, for some specified needful indications, India has waived off local clinical trials for those new drugs that have been approved in some select other countries specified by Central Licensing Authority (CLA). Therefore, it is expected that this move will fast-track approvals and benefit patient populations in India (Venkatasubramanian 2019).

Clinical Trial in China

China is the second-largest drug market in the world after the US (Tremblay 2017). According to MarketLine database's estimate, the Chinese consumer health care market in 2018 was about US$ 40,173.5 million (Fixed 2018 ex rates, Constant 2018 Prices). It is predicted that the Chinese market will reach US$ 52,663.0 million by 2023 (Table 1). This large attractive market is one of the major reasons for many clinical trials being conducted in China. Besides the potential healthcare market, easy access to patient and cost-effectiveness are the possible reasons for the attractiveness for conducting clinical trials in China (Kong 2014). The large patient pool in China's population is a major advantage, there are many patients, that are treatment-naive and recruitment of Chinese volunteers in clinical trials is quite easy (Fan & Gagnon 2011). Moreover, China is rapidly modernizing its healthcare sector to become the world's fifth largest pharmaceutical market and an important hub for local and global clinical trials. Hence, there are significant changes in the pharmaceutical and healthcare industry in China. Chinese pharmaceutical industry emphasizes the growing trends of foreign investments by pharmaceutical companies, thus indirectly fueling the growth of the CRO market (Sahoo 2012). In this way, China is attracting more MNEs to conduct clinical trials because of the large market, fast volunteer recruitment process and relatively low cost.

According to Fan & Gagnon (2011), Clinical trials in China are assessed by the Center for Drug Evaluation (CDE) and approved by the State Food and Drug Administration (SFDA). Earlier, the regulatory review approval

period was lengthy. From 2007 onwards, the process has become quicker because of the implementation of many facilitatory new regulations (Table1). The SFDA also regulates clinical trials by insisting on the use of Good Clinical Practice (GCP) and compulsory GCP training. Under Chinese GCP, only SFDA-certified drug clinical trial institutions are eligible to conduct clinical trials in China (Fan & Gagnon 2011).

Good Clinical Practice (GCP) guidelines were introduced in China in 1998 by the Ministry of Health. The guidelines were further revised in 1999 by the SDA which is now known as State Food and Drug Administration (SFDA) / China Food & Drug Administration (CFDA). However, China has no independent Institutional Review Board (IRB). Instead, IRBs are attached to the institutes where the clinical trials are conducted (Fan & Gagnon 2011).

CFDA has been reforming its drug registration process for several years. In the reformation process, it is implemented that foreign firms could start testing drugs in China only after they had demonstrated the safety of their drugs conducted in some other countries. The major disadvantage for the foreign firms in this process was that by the time their drugs gained approval for conducting the clinical trials in China, competing versions of the same drugs manufactured by Chinese firms were often already available in the Chinese market. Recently, the Chinese government has agreed to accept data from clinical trials conducted outside China for the approval of new drugs (Tremblay 2017).

Table1: Clinical Trial Process and regulations in India and China

	India	China
Application Language	Not Specified but generally in English	Original document along with a Chinese translation
Regulatory authority	"The Central Drugs Standard Control Organization (CDSCO), which is under the Drugs Controller General of India (DCGI) act as Central Licensing Authority (CLA)"	The National Medical Products Administration (NMPA). It was previously known as the China Food and Drug Administration (CFDA)

Table 1 continued...

Table 1 continued...

Parallel regulatory and ethical review permitted	Yes	Unspecified (Proposal Under Consideration)
Ethics Committee	Decentralized process. The ethical review of clinical trial applications requires the Institutional ethics committee's (EC) approval for each trial site. There is no national level EC for approval of new drug clinical trials. ECs are based either at institutions/organizations or function independently. The process must meet all applicable regulations and guidelines. Prior to initiating and throughout the duration of a trial, every trial site must be overseen by an EC registered with the CDSCO. For biomedical and health research EC has to register with the Department of Health Research (DHR). Each of these organisations are responsible for developing policies for EC registering under them.	Decentralized process. The ethical review of clinical trial applications requires institutional ethics committee (EC) approval for each trial site. The ethical review process is implemented through a three-tiered structure - national EC, provincial ECs, and institutional ECs. The National Health Commission (NHC) of the People's Republic of China is responsible for managing ECs nationwide, establishing the National Committee of Medical Ethics Experts, and for developing policies relating to ethical review. Each institution that conducts biomedical research is required to have an EC that is responsible for reviewing clinical trial applications.
Clinical trial registration required	Yes	Yes

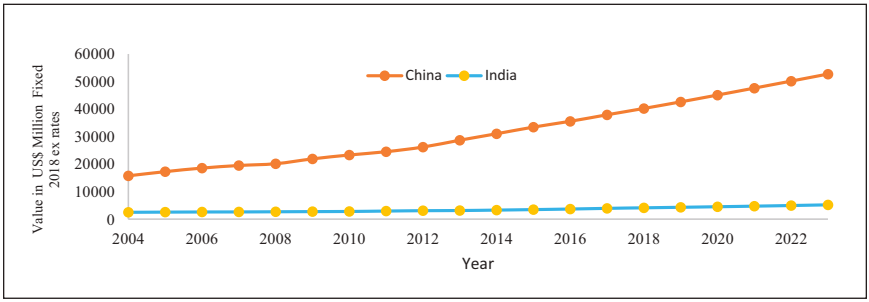
Table 1 continued...

Table 1 continued...

In-country sponsor presence/ representation required	Yes	No (Except for Application Submissions)
Age of minors	Under 18	Unspecified
Specimens export allowed	Yes	Yes

Source: https://clinregs.niaid.nih.gov/country/india/china#_top https: https://cdsco.gov.in/opencms/export/sites/CDSCO_WEB/Pdf-documents/NewDrugs_CTRules_2019.pdf

Figure 1: Value of China and India's consumer health market and prediction



Source: Market line database

Research Objectives

Having reviewed the status of the clinical trials conducted in India and China, this study is an attempt to investigate the clinical trials conducted in both these countries. In the scholarly literature as well as policy discourses, these two countries are compared because these are emerging economies and have huge potential in terms of their healthcare resources and infrastructure. Hence, the lessons learnt from these two countries will perhaps help in formulating the strategies for other developing countries.

This study will investigate the following research objectives:

- What are the growth patterns of Clinical Trials in India and China?

- In which phases are the studies being conducted?
- Who are the sponsors of these trials?
- For which disease conditions the trials are being conducted?
- How the sponsors are collaborating and are there any differences in patterns of collaborations?

Methodology

The data for this study was collected from the ClinicalTrials.gov. The website is a registry and repository of clinical trial results. It is a database of public and private sector supported clinical trials all over the globe. This database was launched in September 2008 to implement Section 801 of the Food and Drug Administration Amendments Act of 2007 (FDAAA 801). According to that act, all studies have to submit the "basic results" for clinical trials. Generally, the results are to be submitted within one year after it is completed (ClinicalTrials.gov). The database is maintained by the US National Library of Medicine. In the last week of May and early June 2019, the database listed about 3,10,344 clinical trials all around the globe. For the purpose of this study, 14,746 clinical trials from China and 3,734 clinical trials from India were downloaded for analysis to meet the above-mentioned research objectives.

Social Network Analysis

This study uses Social Network Analysis (SNA) tools to map the collaboration patterns among the different actors in collaboration of clinical trials. SNA is a multidisciplinary research field based on mathematical graph theory (Borgatti et.al. 2009). Besides this SNA is an interdisciplinary research area with contributions from various fields of knowledge (Oliveira & Gama 2012).

A social network can be constructed from the relational data of social entities, such as people, groups, organizations and so on, with some relationships or interactions between them (Borgatti et.al. 2013). In a social network, a node or vertex or actor represents the social entities and edges or links represent the existing ties or connections between them (Newman 2018). According to the level of analysis, a network can be investigated at two levels. At the first level, the small units, such as the nodes level

study, the general measures of centrality are explored (node level centrality measures are; degree, betweenness, closeness and eigenvector) to understand how the nodes are situated within the overall structure of the graph. These types of centrality measures help to identify the key players in the network. At the second level, or the whole network level, various measures provide information about the overall structure of the network (Tabassum et.al. 2018). This study is one mode network because the actors here are the different firms or institutes and it is assumed that they have equal weightage in their collaborations in conducting clinical trials.

For analysing the collaboration patterns, Social Network Analysis software Gephi (Heymann 2014), Ucinet Netdarw (Borgatti et.al., 2014) and VOSviewer (van Eck & Waltman 2009) are used. These open source softwares are freely available on the Internet for different types of network's centrality measures. The Gephi and UCINET Netdraw are used to draw the network graphs and VOSViewer is used for constructing and visualizing the association between the keywords used in different trials on different disease conditions

Results

In June 2019, the detailed records of clinical trials have been downloaded from the US National Institutes of Health website clinicaltrials.gov/ for the trend's analysis of clinical trial research in India and China. Of these 3,734 records are from India and 14,746 from China. Further studies are based on these retrieved records.

Globalisation of Clinical Trial

The concept of outsourcing of clinical research for drug development has become widely accepted in the pharmaceutical industry due to the increasing cost and the uncertainty in the process. As it is seen from the literature review, many empirical evidences substantiate that, India and China are the two countries that are the preferred location for conducting clinical trials, major reasons being the huge treatment naive population, high skilled but low-cost expertise, conducive regulatory and changing economic environment (Maiti & Raghavendra, 2007). Hence, there is an increasing trend towards outsourcing and internationalisation of clinical research by MNEs in India and China (Santiago-Rodríguez 2009).

Studies have shown that since last couple of years, the number of trials conducted outside US has doubled. At the same time, the number of trials conducted in the developed world has decreased (Glickman et.al. 2009). It is observed that, since 2002, the trials conducted outside the US has grown by 15 per cent annually (Getz 2007). These trends suggest that clinical research is undergoing a paradigm shift and at the pace with the globalization process (Glickman et.al. 2009).

Based on the available records maintained by the clinical trial website of the National Institute of Health, US National Library of Medicine, ClinicalTrials.gov, there are about 3,10,202 trials listed in the month of May / June 2019. Among these, only about 3,734 are being conducted or ongoing in India and 14,746 trials in China. Of global trials in this database, India constitutes about 2 per cent and China about 5 per cent. Most of the trials are still being conducted in North America and Europe. There are 136,280 studies in North America (about 44 per cent) and 88, 286 studies (about 29 per cent) in Europe (Table 2).

Table 2: Number of Clinical Trials Being conducted in different parts of world

Region	Number of Studies	Percentage
World	3,10,202	100.00
Africa	8,668	2.79
North America	1,36,280	43.93
Europe	88,276	28.46
Japan	5502	1.77
East Asia	34,025	10.97
China	14,746	4.75
Hong Kong	1,946	0.63
Republic of Korea	10,161	3.28
Taiwan	6,150	1.98
India	3,734	1.20

Source: ClinicalTrials.gov (accessed on May/ June 2019)

So, it is evident from the table 2 that most of the trials are still being conducted in the developed regions of the globe with a very limited number of trials conducted in the developing part of the globe including India and China. However, the findings are still inconclusive because the database is

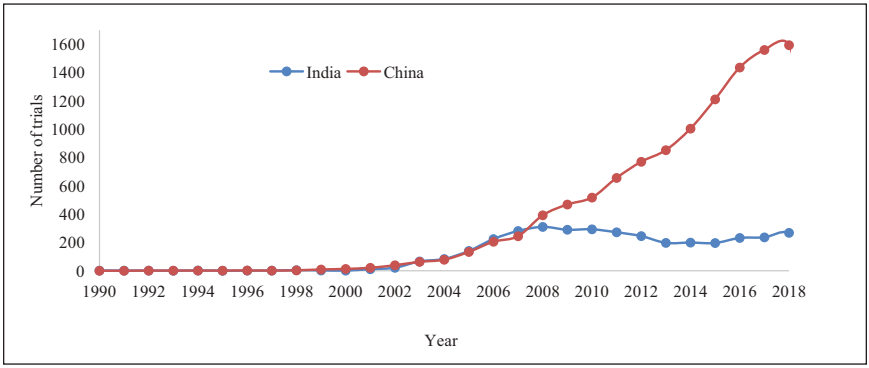
maintained by the National Institute of Health, US. The database may not adequately cover EU region or developing part of the globe and it may have an inherent country bias. The investigation of clinical trial database from the respective governments' database (i.e. India and China) will perhaps give a better, clear and holistic picture of the ground-level situation of the clinical trials in both the countries.

Growth of the Clinical Trials in India and China

In any clinical trial, the 'date of start' is the date when a participant is enrolled in a clinical trial. Based on the date of the start, it is observed that in India, the maximum number of trials started in the year 2008. There was a minor decline during the period 2013-2015. Over the years the number of clinical trials are as follows; 2013 (197 studies), 2014 (199 studies) 2015 (196 studies). The low growth of listed clinical trials in the above mentioned years was perhaps due to new rule on compensation that created concern among the pharma companies during that period. Further it may be due to the death of young girls in Andhra Pradesh and Gujarat in the year 2010 related to the HPV vaccine which was not a clinical trial but a demonstration study (Sarojini et.al., 2010).

However, it was a very minimal effect on the overall growth of trials in India. After the situation stabilized, significant growth started in the year 2016 (232 studies), which is a constant and linear growth. From the last couple of years, there are about 250 studies per year have started in India (Figure 2).

Figure 2: Growth of clinical trial in India and China



The start of trials in China was almost exponential after the year 2010. From the last couple of years, the trend suggests that more than 1,500 trials per year have been listed in China (Figure 2). According to the date of start, it appears that the number of trials both from India and China were growing in a similar fashion till the year 2007. After that, there was a clear and visible growth of clinical trials in China and it outperformed the overall growth in India.

Phases

Generally, in clinical research different types of interventions/ non-interventions are involved. It could be studies on epidemics, life-style modifications, prognostic studies, health records and so on. However, clinical research on new drugs is termed clinical trials. Moreover, new drug-related clinical trials are designed to test the efficacy, safety and technical viability of prospective new drugs or medical devices (Santiago-Rodríguez 2009).

According to the US Food and Drug Administration (FDA), there could be five phases in Clinical trials of a drug or biological product. These phases are; Early Phase 1 (earlier this phase was known as Phase 0), Phase 1, Phase 2, Phase 3, and Phase 4 and 'Not Applicable'. The phase "Not Applicable" means, those trials which do not fall in the category of USFDA-defined phases, i.e. trials on medical devices or behavioral interventions.

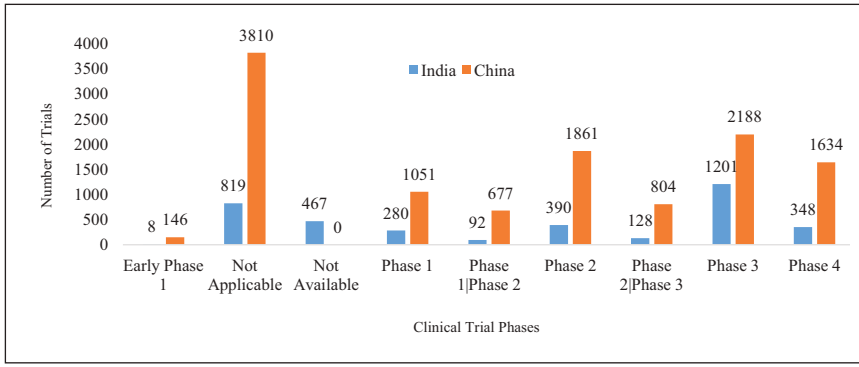
Early phase 1 or Phase 0 is conducted before phase 1 without therapeutics or diagnostic aim and administrated to a very limited number of healthy human participants.

Phase 1 constitutes the administration of new chemical entities in limited human volunteers. Mainly aims to safety and adverse effects. Phase 2 is to determine the drug's effectiveness in certain disease conditions. Placebo effects are also studied in this phase. Phase 3 tests drugs effects and side effects with different combinations of drugs in different doses among diverse population. Phase 4 consist of optimal use, safety, efficacy and post-marketing studies.

Phase 4 trials or post-marketing phase, the phase of surveillance after the medicine is made available to doctors, who start prescribing it. The effects are monitored on thousands of patients to help identify any unforeseen side effects. (Definition source: https://clinicaltrials.gov/ct2/about-studies/glossary).

Figure 3 shows the different phases of trials conducted in India and China. In Indian case information of about the phase of 467 trials are not available. In China 3,810 studies are conducted where the phase information is 'not applicable' whereas in India these are about 819 trials. It means these trials are not conducted on human participants and are related to medical related devices or other behavioral interventions. In India, the maximum number of studies are conducted in Phase 3 (1,201) studies. In China the maximum number of studies are 'Not Applicable phase' followed by Phase 3 (2,188) studies. Also, there are combinations of Phase 1 and Phase 2 (92 studies in India and 677 studies in China) and Phase 2 and Phase 3 (128 studies in India and 804 studies in China). So, from the figure 3 it is observed that most of the studies conducted in both the countries are in Phase 3 or Phase 'not Applicable'.

Figure 3 Different phases of clinical trial in India and China



Source: Own compilation, based on the data downloaded from the website https://clinicaltrials.gov/

Conditions

Based on the conditions for which trials are being conducted, this study further analysed these disease conditions. According to the definitions, *the conditions are the disease, disorder, syndrome, illness, or injury that is being studied. On ClinicalTrials.gov, conditions may also include other health-related issues, such as lifespan, quality of life, and health risks*. (https://clinicaltrials.gov/ct2/about-studies/glossary)

Based on the keywords used for disease conditions, there are 2,396 different types of disease conditions in India and 6,152 disease conditions

in China are being investigated. However, there may be overlaps because one disease may be investigated from different perspectives. **Table 3** lists the top 10 disease conditions that are being experimented upon in these two countries. It is observed from the table 3 that predominantly majority of the trials in India are conducted on diabetes and the related diseases in India and cancer and cancer related diseases in China.

Table 3: Different disease conditions being investigated in these two countries

India		China	
Conditions	Number	Conditions	Number
Diabetes Mellitus, Type 2	275	Hepatocellular Carcinoma	252
Healthy	178	Breast Cancer	229
Diabetes	122	Non-Small Cell Lung Cancer	214
Breast Cancer	57	Gastric Cancer	195
Schizophrenia	49	Healthy	134
Rheumatoid Arthritis	41	Coronary Artery Disease	127
HIV Infections	39	Nasopharyngeal Carcinoma	118
Tuberculosis	37	Colorectal Cancer	108
Asthma	35	Diabetes Mellitus, Type 2	107
Hypertension	33	Hypertension	101

Source: Own calculation based on the data downloaded from the website https://clinicaltrials.gov/

Further the conditions are being mapped using software VOS viewer (van Eck & Waltman 2009). This open source software tool is used for creating cluster maps based on network data. The software has the strong Graphical User Interface for visualizing and exploring cluster maps.

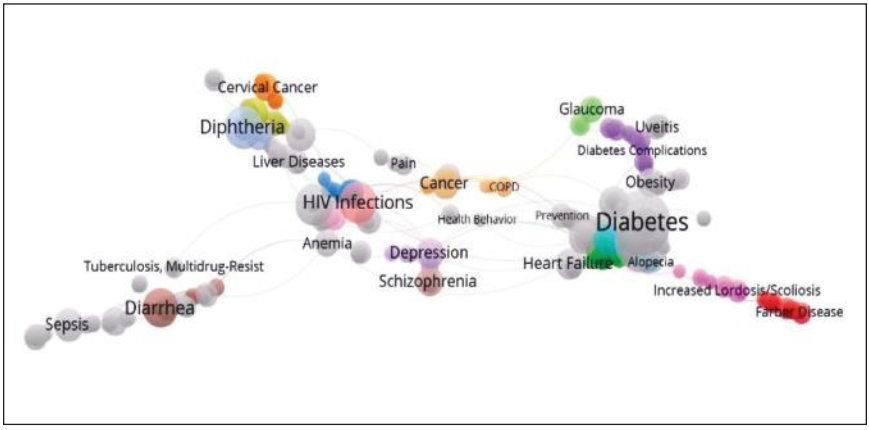
Figure 4 and Figure 5 are showing the different clusters of disease conditions. The keywords obtained from the different disease conditions formed distinct clusters. In Indian case 252 clusters are formed from similar keywords of different disease conditions. The largest cluster consists of 695 components. The major disease conditions in this component are HIV

Infections, Tuberculosis, Breast Cancer, Diarrhea, Diabetes, Cardiovascular Diseases and so on. The second largest cluster has 17 keywords and the disease conditions cluster around Acute Myeloid Leukemia.

In Chinese disease conditions there are 448 clusters. The largest cluster has 2,758 keywords. This component consists of mainly cancer related diseases. The major keywords from this cluster are, Gastric Cancer, Colorectal Cancer, Lung Cancer, Breast Cancer, Hepatocellular Carcinoma, Surgery, Esophageal Cancer and so on. The second largest components also consist of cancer related diseases. The important keyword in this group is "Recurrent Hypopharyngeal Squamous Cell Carcinoma". The third component is formed by Stage III Squamous Cell Carcinoma of the Hypopharynx and so on.

So, there is a clear distinction between the disease conditions for which the trials are being conducted in these countries. In India, there is diversity in disease conditions where as in China it is mainly on cancer related disease. Also, it is important to note that, in both the countries, the focus of clinical trials is on the universal and global diseases. The major focus is not on the most prevalent neglected diseases, predominantly occur in these countries. Hence, focussed research and attention at all levels may require for the types of diseases that are prevalent in these countries.

Figure 4: Trials on different disease conditions conducted in India

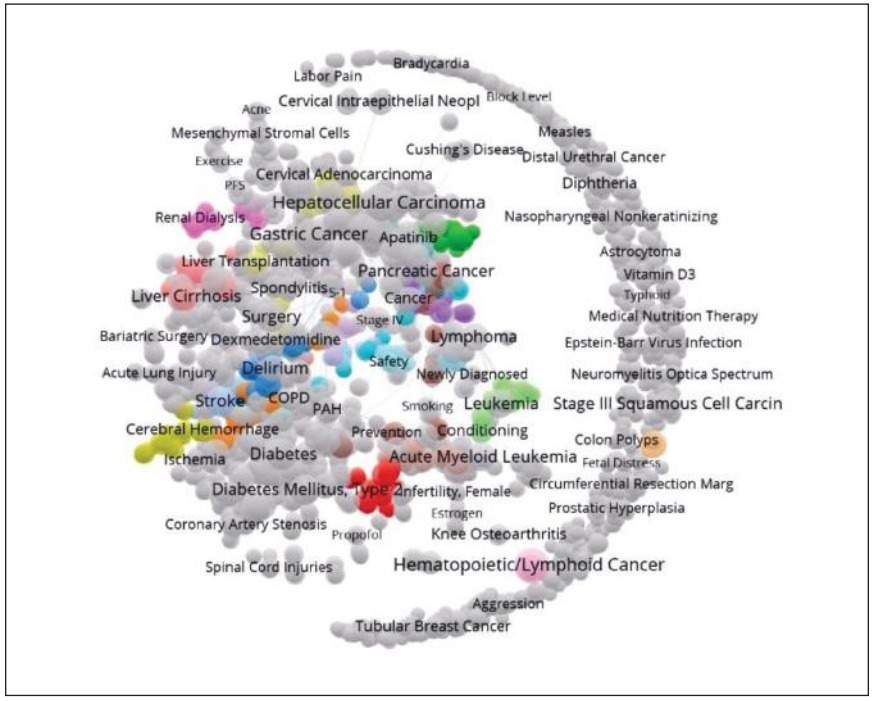


Source: Own calculation based on the data downloaded from the website https://clinicaltrials.gov/

Sponsor or Collaborator

According to USFDA Definition the sponsor or collaborator is *"the organization or person who initiates the study and who has authority and control over the study"* (ClinicalTrials.gov). They provide financial or institutional support in terms of infrastructure, expertise or other means to conduct the clinical study. The database has listed the following four types of sponsors or collaborators. These categories are *Industry* (pharmaceutical firms and device manufacturing companies), *National Institutes of Health (NIH),* and *U.S. Federal agency* (for example, the Food and Drug Administration, Centers for Disease Control and Prevention, U.S. Department of Veterans Affairs), and Others (individuals, universities, and other non US based entities and so on)

Figure 5: Trials on different disease conditions conducted in China



Source: Own drawing based on the data downloaded from the website https://clinicaltrials.gov/ using the SNA software Gephi and UCINET.

Table 4: Sponsors of different category

Different types of sponsors	India	China
Industry	2039	2922
Other	1412	8249
Industry | Other	99	423
Other | Industry	63	475
Other | NIH	58	51
NIH	28	17
Other |U.S. Fed	14	14
Industry | NIH	3	-
Other | NIH | Industry	3	3
NIH | Other	2	1
Other | NIH |U.S. Fed	2	1
Industry | Other | NIH	1	1
Industry | Other | U.S. Fed	1	-
Industry | Other |U.S. Fed | NIH	1	-
Industry | U.S. Fed	1	-
Other | Industry | NIH	1	2
Other | NIH |U.S. Fed | Industry	1	-
Other | U.S. Fed | Industry	1	1
Other | U.S. Fed| NIH	1	-
U.S. Fed	1	2
U.S. Fed | Other	1	6
NIH | U.S. Fed	-	1
U.S. Fed | Industry | Other	-	2

Source: Own calculation based on the data downloaded from the website https://clinicaltrials.gov/

Table 4 shows the different types of sponsors from different categories. It is observed that the maximum number of trials are conducted by the industries (2,049 from India and 2,922 from China) followed by the other categories (1,412 from India and 8,249 from China). The other category here is predominantly formed by universities, medical colleges, or other educational institutions. The joint or collaborative trials are listed based on the sequence of occurrence of the sponsors. The maximum number of collaborations have happened between the industry and Other category (99 and 63 from India, 423 and 475 from China respectively).

Table 5: Top sponsor / Collaborator from China and India

China		India	
Name of the Institute	Number of trials	Sponsor/Collaborators	Number of trials
Sun Yat-sen University	1142	Novartis	269
Peking University and Peking University People's Hospital	591	Pfizer (including Wyeth)	168
Fudan University	518	Postgraduate Institute of Medical Education and Research	167
Shanghai Jiao Tong University	392	All India Institute of Medical Sciences, New Delhi	139
Novartis	328	AstraZeneca	122
Chinese Academy of Medical Sciences	319	Sanofi (include Genzyme)	115
Peking Union Medical College Hospital	306	GlaxoSmithKline	110
Chinese PLA General Hospital	249	Eli Lilly and Company	109
Jiangsu HengRui Medicine Co., Ltd.	206	Dr. Reddy's Laboratories Limited	101
Nanfang Hospital of Southern Medical University	199	Institute of Liver and Biliary Sciences	97
Xijing Hospital	177	Novo Nordisk A/S	85
The University of Hong Kong	175	Tata Memorial Hospital	77
Chinese University of Hong Kong	167	Boehringer Ingelheim	69
RenJi Hospital	159	Ranbaxy	59
Hoffmann-La Roche	154	Bristol-Myers Squibb	57
Ruijin Hospital	150	Hoffmann-La Roche	51
Pfizer	150	Indian Council of Medical Research	49
Shanghai Zhongshan Hospital	145	Torrent Pharmaceuticals Limited	45
AstraZeneca	140	Bayer	45
West China Hospital	139	National Institute of Allergy and Infectious Diseases (NIAID)	40

Source: Own compilation based on the data downloaded from the website https://clinicaltrials.gov/

Table 5 shows the top 20 sponsors or collaborators from the two countries. From China the maximum number of trials are conducted by Sun Yat-sen University (1,142), while in India it is Novartis at the top with 269 trials. Apparently, in China a good number of studies are being conducted by the universities or other institutions including the medical institutions. While in India the majority of the trials are being conducted by the industries. This includes the global MNEs like Novartis, Pfizer, AstraZeneca and so on and the Indian firms like Dr. Reddy, Ranbaxy, Torrent and so on. There is a comparatively limited number of Indian universities or medical institutions that are participating in drug trials. It is also evident from the **Table 5** that in Indian case industries are predominant sponsors than the universities or institutions. However, this issue requires further investigation to come up with a valid conclusion.

Collaboration Network Analysis

The collaboration network from the sponsors is examined in this section to find the whole network and also the individual level collaboration dynamics. In these types of collaboration, it is assumed that both the collaborators have equal participation in the experiment by giving every collaborator equal weightage.

Among the total 3,734 trials from India 1,101 (about 30 per cent) are collaborative trials. From China among 12,171 trials, 4,097 (about 34 per cent) are collaborative trials. The whole network level statistics **(Table 6)** shows that in Indian collaboration network there are 1,276 actors or nodes and 3,498 edges or connections between them. The network has average degree 2.36. The collaboration network in China shows **(Table 6)** that the overall network has 3,489 nodes and 6,884 edges or connections between them. The network has average degree of 3.94.

The degree shows the number of connections of a node to the other members of the network. By definition 'The average degree is simply the mean of the degrees of all vertices in a network'. The higher degree centrality value shows the important actors or nodes in the network. Diameter is the longest geodesic distance between any two vertices (Newman, 2018). Here the diameter of Indian network is 13 and Chinese Network is 11. It may be concluded here that; Indian network is sparse. The Chinese network is comparatively dense and shorter in diameter.

Density shows the connectedness of components or actors or nodes in a network. The density value can be between 0 to 1. In a perfectly connected network, the value is 1 and it is 0 if there are no connections between the actors. The respective value of the density of the network shows the density of the Indian network is 0.002 which means that only about 0.2 per cent of possible connections are present. In case of the Chinese network, the density value is 0.001 which means only about 0.1 per cent of possible connections are present between the actors.

Components are subgraphs in a graph in which all the pairs of nodes or vertices are connected to each other by at least one path. In Indian case there are 119 connected components and in Chinese case there are 81 connected components.

Path length is the geodesic distance or the shortest path between nodes in a network. This distance shows the average distance between nodes and is useful to understand the flow of information in a network. The average path length matrix is almost similar in both the countries.

Table 6: The whole network level statistics of sponsor collaboration network

Parameters	India	China
Node	1,276	3,489
Edges	1,506	6,884
Average Degree	2.36	3.94
Diameter	13	11
Density	0.002	0.001
Connected Component	119	81
Average Path length	4.90	4.13

Source: Own compilation based on the data downloaded from the website https://clinicaltrials.gov/

Collaboration Network

Using social networking software different actor level network matrix is obtained. The micro level or actor level centrality measures are; *degree centrality*, *betweenness centrality*, *closeness centrality* and *eigenvector centrality*. Among the various network centrality measures, the degree centrality measures are perhaps quite simple and easy to understand. The *degree centrality* shows the number of connections an actor has in a network.

Table 7: Network centrality measures of actors from India

Name of the institute	Degree	Name of the institute	Betweenness	Name of the institute	Closeness	Name of the institute	Eigenvector
All India Institute of Medical Sciences, New Delhi	54	All India Institute of Medical Sciences, New Delhi	100572.781	PsiOxus Therapeutics Ltd	1625625	All India Institute of Medical Sciences, New Delhi	0.403
London School of Hygiene and Tropical Medicine	52	Johns Hopkins University	59007.004	Veeda Oncology	1625625	Indian Council of Medical Research	0.272
University of California, Los Angeles	43	Population Health Research Institute	51986.883	Dr Meru S	1625625	Johns Hopkins University	0.219
Johns Hopkins University	39	Indian Council of Medical Research	51151.234	Uttaranchal Dental & Medical Research Institute	1625625	Society for Applied Studies	0.203
International Atomic Energy Agency	39	London School of Hygiene and Tropical Medicine	49357.34	Oertli Instruments AG	1625625	Emory University	0.203
Indian Council of Medical Research	37	Emory University	42793.316	University of Geneva, Switzerland	1625625	London School of Hygiene and Tropical Medicine	0.181
NICHD Global Network for Women's and Children's Health	35	University of California, Los Angeles	40129.801	Philip Moons	1625625	NICHD Global Network for Women's and Children's Health	0.167
Texas Scottish Rite Hospital for Children	32	Bayer	32943.512	Universitaire Ziekenhuizen Leuven	1625625	Christian Medical College, Vellore, India	0.159
Emory University	31	International Atomic Energy Agency	31252.6	TotipotentRX Cell Therapy Pvt. Ltd.	1625625	Postgraduate Institute of Medical Education and Research	0.158
Population Health Research Institute	28	Tata Memorial Hospital	31033.996	TotipotentSC Scientific Product Pvt. Ltd.	1625625	Tata Memorial Hospital	0.156

Source: Own compilation based on the data downloaded from the website https://clinicaltrials.gov/

In the simplest term the higher degree centrality of an actor in a network means the actor is more powerful and can influence the network. The *betweenness centrality* measures the extent to which a vertex lies on paths between other vertices. Nodes with high betweenness centrality means the actors are situated in between many actors and have substantial influence within a network to control information flow between actors. *Closeness centrality* is the mean length of all shortest paths from one node to all other nodes in the network (Newman 2018). The higher closeness is a measure of reachability, that measures how fast a given actor can reach to everyone in the network. However, this measure only computes the nodes within the largest component (Tabassum, et.al., 2018). Another centrality measure is the *eigenvector centrality*. It gives each node a score proportional to the sum of the scores of its neighboring nodes. A node connected to a powerful node will have a higher eigenvector centrality score.

Indian Collaboration Network

Figure 6 shows the collaboration network and Table 7 shows the top 10 different actor level centrality scores. As it is discussed in the pervious section, that the different centrality measures shows the importance of actors in the network. These four centrality measures i.e. Degree, Betweenness, Closeness, Eigenvector are shown in Table 7. (Borgatti, et.al., 2009; Borgatti, et.al., 2013; Newman, 2018).

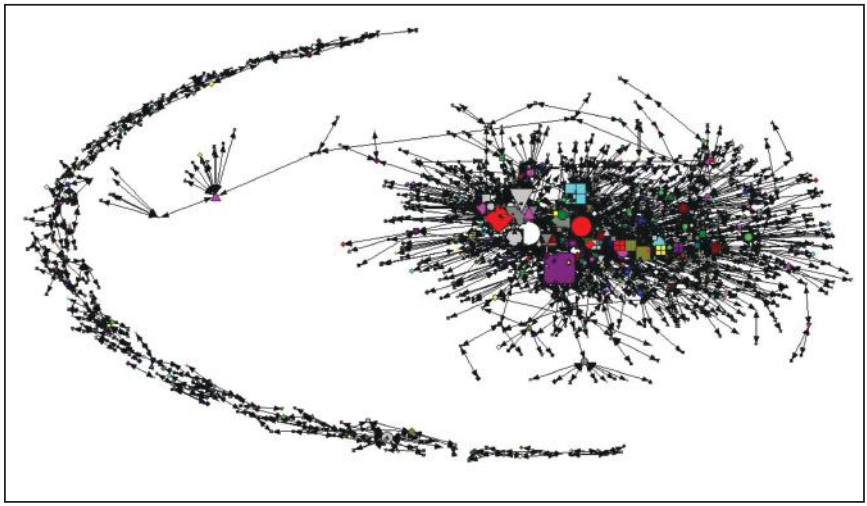
In Indian collaboration networks, All India Institute of Medical Science (AIIMS) has the highest degree centrality score (54). This institute has also higher betweenness and eigenvector centrality scores. Among the top actors, the other actors are the foreign entities. Closeness centrality is generally computed based on the largest component. All the actors in the Table 7 show a similar score because these actors are connected to a single and big component. The network has 199 components and the largest component consists of 939 institutes. There is a distinct core and periphery structure among the collaborating entity. So, it can be concluded that maximum collaboration happens among the core groups and isolated collaborations happens among the other actors situated in the periphery of the network.

Table 8: Network centrality measures of actors from China

Name of the Institute	Degree	Name of the Institute	Betweenness	Name of the Institute	Closeness	Name of the Institute	Eigenvector
Sun Yat-sen University	256	Sun Yat-sen University	795504.75	Globe Health Institute LLC	12166144	Sun Yat-sen University	0.259
Fudan University	168	Fudan University	496046.531	Globe Biomedical Co., Ltd.	12166144	Fudan University	0.207
Peking Union Medical College Hospital	132	Chinese Academy of Medical Sciences	354362.094	Adagene (Suzhou) Limited	12166144	Shanghai Zhongshan Hospital	0.192
Shanghai Zhongshan Hospital	131	Changhai Hospital	323426.094	Adagene Inc	12166144	Peking Union Medical College Hospital	0.19
Xijing Hospital	122	Peking University First Hospital	293948.594	Haining Health-Coming Biotech Co., Ltd.	12166144	Changhai Hospital	0.181
Chinese Academy of Medical Sciences	119	The University of Hong Kong	290158.531	Alphacait, LLC	12166144	Chinese Academy of Medical Sciences	0.16
Changhai Hospital	114	Peking Union Medical College Hospital	266834.563	3D Medicines (Sichuan) Co., Ltd.	12166144	Peking University People's Hospital	0.159
Shanghai Jiao Tong University School of Medicine	110	Shanghai Jiao Tong University School of Medicine	259279.641	Alphamab Co., Ltd.	12166144	Shanghai Jiao Tong University School of Medicine	0.153
Chinese PLA General Hospital	106	Xijing Hospital	255863.641	Celgene	12166144	The First Affiliated Hospital with Nanjing Medical University	0.149
Peking University First Hospital	104	Chinese PLA General Hospital	255265.656	BeiGene	12166144	Chinese PLA General Hospital	0.145

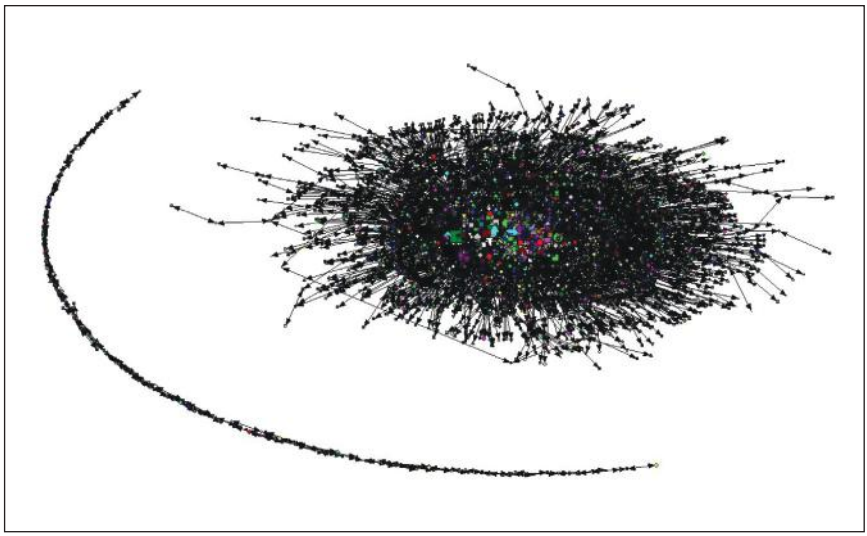
Source: Own compilation based on the data downloaded from the website https://clinicaltrials.gov/

Figure 6 Network of collaborators from India



Source: Own drawing based on the data downloaded from the website https://clinicaltrials.gov/ using the SNA software Gephi and UCINET

Figure 7 Network of collaborators from China



Source: : Own drawing based on the data downloaded from the website https://clinicaltrials.gov/ using the SNA software Gephi and UCINET.

Figure 7 shows the collaboration network structure among the different entities or institutions in China, Table 8 shows actor level centrality measure of collaborating networks. The Chinese collaboration network has 81 components and the largest components have 3,289 actors. From the Figure 6 it can be seen that like Indian case there is a distinct core and periphery structure of the network and a large core component is the predominant in the network

The four different actor level centrality (Degree, Betweenness, Closeness and Eigenvector) scores are presented in Table 8. These centrality measures shows the importants of different entities in clinical trial collaboration networks. Sun Yat-sen University (256) has the highest degree centrality score followed by Fudan University 168. It is evident from the actor level centrality measure that unlike India, most of the prominent actors are Chinese Institutes (universities, medical colleges or hospitals). The closeness centrality indicators of the actors are computed based on the largest component. Hence the closeness score of these actors is the same as for top actors. The actors with high degree centrality scores also have high eigenvector centrality scores. This shows that the actors are well connected among themselves and together formed the influential core in the whole network.

Concluding Remarks

This study is an empirical investigation of clinical trials conducted in two emerging economies i.e. India and China. The study downloaded clinical trial data from the ClinicalTrials.gov website of the US. It is observed that there is certainly an increase in the number of trials being conducted from both the countries. However, only about 4.75 per cent of global trials are conducted in China and only about 1.2 per cent of trials are being conducted in India. Therefore, the globalization of clinical trial and the uproar that many MNEs are increasing their trials in both these countries are certainly a myth. Most of the trials are still being registered in the developed part of the globe i.e., North America and Europe. However, the study is based on the database maintained by the US. So certainly, the database has an inherent country bias. The database maintained by the respective countries will perhaps yield a better picture of the situation.

The study has observed that the maximum number of trials are being conducted or ongoing in the later phase of the trial (Phase 3). In addition, a number of trials are not involving any phase trial (not applicable category). These studies are generally related to medical-related equipment or behavioral interventions and not for any disease conditions.

In India, the number of trials is conducted in Diabetes, HIV, Tuberculosis, and so on. The trials in China are mostly on cancers and related complications. These countries have many prevalent 'neglected tropical diseases'. The neglected diseases are a diverse group of diseases, very common among developing countries. Generally, the trial focus should be more on neglected diseases. Contrary to this, the trials on neglected diseases are comparatively less and require particular attention. The emphasis may be given on the diseases, which are more prevalent in the local populations.

Among the sponsor category, there is a significant difference. In China, it is mostly the government research institutes (Chinese Academy of Medical Science, Chinese Academy of Science etc.), universities, medical colleges and other institutions whereas in the case of India, they are predominantly the pharma firms; both foreign multinational as well as indigenous firms.

The network analysis shows that there is core and periphery structure. There is a big component with many prominent actors of the network and they are well connected with each other. There are many minor institutes which are comparatively less connected are at the periphery and are less important actors. Some prominent institutes form the core and quite strong links between them. In further studies, the linkage and spillover from these types of collaborations require further investigation.

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Application, Regulation, Ethical Concerns and Governance of Genome-Editing Technologies: An Overview

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Abstract: Genome-editing offers great potential applications in various sectors including healthcare, agriculture and environment. With the advent of CRISPR technology, which is easily available and inexpensive, the advancement in this domain has been rapid in the recent times. However, there have been various concerns raised around the possible unintended consequences of its application, particularly in reference to human germline modifications; and the associated ethical issues and challenges related to its regulation and governance. This paper discusses the genome-editing technology, its applications, existing regulatory paradigm (with special reference to India), emerging ethical concerns and challenges related to its governance. Finally, it concludes by suggesting a way forward.

Keywords: Genome editing, ethical concerns, governance, regulatory frameworks, India.

Introduction

Genome-editing technologies are technologies that allow editing of DNA of an organism through adding, altering or removing genetic material at target places. There are many such technologies developed over a period of time (Nuffield Council on Bioethics, 2016). Some of the prominent ones are as follows:

Recombinant DNA (rDNA) Technology: This technology allowed the cutting and splicing together of DNA molecules. Starting from bacteria and viruses, this was subsequently applied to multi-cellular organisms such as plants and animals. Using this technology, *transgenesis* emerged as a powerful biological tool in the 1970's. The major limitation in this

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technology was that it only allowed genes to be added and offered no control in its placement.

ZFNs and TALENs: In early 2000s, two new gene targeting technologies viz. Zinc Finger Nucleases (ZFNs) and Transcription Activator-like Effector Nucleases (TALENs) were discovered. ZFNs and TALENs are proteins that work in a conceptually similar manner, containing one module that can be engineered to recognise a specific DNA sequence and guide a second, attached module to cut the DNA. These technologies overcame the limitation of the rDNA technology.

CRISPR-Cas9: In early 2010s, newer technology comprising of 'Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) RNA' and 'CRISPR-associated Protein 9 (Cas-9)' was discovered, which could make all DNA molecules amenable to editing (addition, deletion, substitution). The comparatively short length of DNA coding used in this technology allowed for its delivery by viruses, better target selection and target specificity. CRISPR-Cas-9 has spread much rapidly in the recent times owing to the easy availability of the inexpensive CRSIPR-Cas-9 kits which require less technical skills (compared to ZFNs and TALENs), thereby making it an off-the-shelf/DIY technology. The comparative advantage of CRISPR-Cas9 over other genome-editing tools is summarized in the Table 1.

Table 1: Properties of Genome-editing Tools

Property	ZFNs	TALENs	CRISPR/Cas9
Number of proteins	2	2	1+1 RNA
Production	Not very easy	Easy	Very easy
Cost of production	5000 Euros	1000 Euros	10 Euros
Time needed for an experiment	Months	Weeks	Days

Source: Friedrichs *et al* (2019a, p.1030)

Besides, this technology allows for *in vitro* experiments, which are quick to design and execute, thus making its progress rapid without expensive equipment and reagents. However, since the technology is still at the nascent stage of development, there is a concern regarding the chance of 'off-target effects' taking place i.e. editing happening at sites in the genome other than those intended.

Key Benefits and Applications of Genome Editing

The wide and diverse range of possible applications of genome editing have positioned the technology as a possible means to develop novel solutions for addressing challenges on the global scale, as well as those at the national and sub-national level in various domains such as in human health, agriculture and the environment (Shukla-Jones *et al*, 2018).

The potential benefits and applications of genome–editing across various sectors are further discussed.

Applications in agriculture

Benefits and applications of the genome-editing technology in the agricultural sector as are follows:

- Yield increase and greater productivity
- Efficient control of crops genetic and vector-borne diseases
- Increases crop diversity
- Reduces acreage
- Can add traits to meet consumer preferences
- Enables development of perennial crops
- Reduces animal breeding costs

Applications in Human Health

Genome editing technologies can be used in basic research, preclinical research and clinical applications and in both human somatic cells (non-reproductive cells) and human germline cells (early embryos or in eggs).

Benefits and applications of the genome-editing technology in the human health sector are as follows:

- Develop treatment and therapies for genetic diseases
- Controls vector borne diseases
- Improves vaccines
- Enhancement

Applications in Environment

Gene-edited microbes could be used to degrade contaminants such as

oil spills. Following benefits can accrue from the use of genome-editing in the environment.

- Environmental conservation
- Bioremediation
- Control of invasive species
- De-extinction and protection of endangered species

Additionally, genome-editing can also result in improved industrial bioprocesses and biofuels, thus having potential application in the domain of energy sector.

Rao (2019) has enumerated many potential applications and benefits of genome-editing such as:

- Treatment of infectious diseases as well as cancer
- Human trait enhancement: physical traits such as mass, height, appearance as well as traits such as intelligence
- Efficient introduction of desired characteristic in plants (advanced breeding)
- Mutating multiple plant genes

He points out the beneficial traits/qualities that can be derived from the genome-editing technology in various crops/fruits such as:

- *Cisgenics/intragenics:* apple scab resistance, potato late blight resistance, drought and cold tolerant maize, fungal resistant papaya, improved forage ryegrass
- *SDN (-1/-2/-3):* improved nutritional quality maize, high yielding tomato, disease resistant wheat, improved nutritional quality canola, nematode resistance
- *ODM:* herbicide tolerant oilseed, herbicide tolerant flax.

NASEM (2017) in its report on 'Human Genome Editing' has provided many examples of potential therapeutic applications of somatic cell genome editing that are in progress around the world (Table 2).

Table 2: Potential Therapeutic Applications of Genome-Editing

Sl. No.	Disease	Strategy Used
1.	Sickle-Cell Disease	Edit to non-disease causing variant
2.	Beta Thalassemia	Induction of fetal hemoglobin
3.	Severe Combined Immino deficiency X-linked (SCID- X1)	Knock-in of full or partial complementary DNA (cDNA) to correct downstream disease-causing variants
4.	X-Linked Hyper IgM Syndrome	Knock-in of full complementary DNA (cDNA) to correct downstream disease-causing variants
5.	Hemophilia B	Express clotting factor from a strong promoter
6.	Cystic Fibrosis	Edit to non-disease causing variant
7.	HIV	Engineer resistance to HIV
8.	HIV	Engineer constitutive secretion of anti-HIV factors
9.	Cancer Immunotherapy	Engineer more potent cancer specific T-Cells
10.	Duchenne's Muscular Dystrophy (DMD)	Deletion of pathologic variant to convert DMD to milder Becker's muscular dystrophy
11.	Huntington's Disease	Delete disease-causing expanded triplet repeat
12.	Neurodegenerative Diseases	Engineer cells to secrete neuro- protective factors

Source: NASEM (2017, p. 92)

Wargelius (2019) based on the research on Atlantic salmon has described the potential application of genome editing in aquatic farm animals, thus addressing some of the pressing sustainability issues such as disease resistance and Omega-3 production. Tizard *et al* (2019) have observed that that the genome-editing holds great promise for positive contributions to the poultry farming by providing disease resilience, improved health and improved product qualities.

Ricroch (2019) has argued that the genome-editing in agriculture could significantly speed up the breeding processes. It can help develop

desired traits in crops and also allow improvements in yield and pest resistance, adaptation to climate change, as well as promote industrial and pharmaceutical applications. She illustrated a number of predictable benefits that the application of genome-editing techniques in agriculture would bring to consumers, organic farmers, farm animals and agricultural industries.

Zhang *et al* (2018) have found that many gene knockout mutants, gene insertion and replacement mutants have been produced using genome-editing technologies in a wide variety of plants and many of these mutants have been found to be useful in crop trait improvements (Table 3). They further argued that the risks involved in altering genomes through the use of genome-editing technology are significantly lower than those associated with GM crops.

Table 3: Crop Traits Improved by Genome-Editing Techniques

Crop species	Gene editor	Target trait
Maize	ZFNs	Herbicide tolerant and phytate reduced maize; Trait stacking
Rice	ZFNs	Trait stacking
Rice	TALENs	Bacterial blight resistance; Fragrant rice
Wheat	TALENs	Powdery mildew resistance
Maize	TALENs	Reduced epicuticular wax in leaves; Induction of haploid plants
Sugarcane	TALENs	Improved cell wall composition; Improved saccharification efficiency
Soybean	TALENs	High oleic acid contents; low linoleic contents
Potato	TALENs	Minimizing reducing sugars
Brassica oleracea	TALENs	Flowering earlier
Tomato	TALENs	Purple tomatoes with high anthocyanin
Rice	CRISPR/ Cas9	Tiller-spreading; Enhanced grain number, larger grain size and dense erect panicles; High amylose content; Enhanced rice blast resistance; Bacterial blight resistance; Herbicide resistance; Induction of haploid plants
Wheat	CRISPR/ Cas9	Increased grain weight and protein content; Powdery mildew resistance
Camelina sativa	CRISPR/ Cas9	Decreased polyunsaturated fatty acids

Table 3 continued...

Table 3 continued...

Maize	CRISPR/ Cas9	High amylopectin content; Thermosensitive male-sterile; Herbicide resistance; Drought stress tolerance
Potato	CRISPR/ Cas9	High amylopectin content; Herbicide resistance
Tomato	CRISPR/ Cas9	Powdery mildew resistance; Bacterial speck resistance; Earlier harvest time; Parthenocarpy; Induction of haploid plants
Grapefruit	CRISPR/ Cas9	Alleviated citrus canker; Citrus canker resistance
Orange	CRISPR/ Cas9	Citrus canker resistance
Cucumber	CRISPR/ Cas9	Virus resistance
Mushroom	CRISPR/ Cas9	Anti-browning phenotype
Soybean	CRISPR/ Cas9	Herbicide resistance
Flax	CRISPR/ Cas9	Herbicide resistance
Cassava	CRISPR/ Cas9	Herbicide resistance

Source: Zhang *et al* (2018, p.3)

As it can be seen from the Table 3, genome-editing technologies (ZFNs, TALENs and CRISPR/Cas9) have been used across both cereal as well as horticultural crops while imparting many useful and desired traits such as herbicide resistance, drought stress tolerance, virus resistance etc. This may lead to higher productivity and better quality agricultural products.

Regulatory Approaches towards Crop Genome-Editing

There are different approaches being discussed and practiced across various countries pertaining to the regulation of crop genome-editing. One of the major point of differentiation in these different approaches is to whether the interpretation is to be based on process or on product.

Friedrichs *et al* (2019b) described three main regulatory approaches to the governance of genome editing. These approaches are as follows:

1. *Existing Process-triggered GE/GM regulatory system:* In this approach, the regulatory system use the process-based criteria to regulate GE/GM

organisms. Countries which are following this approach include Australia, New Zealand, Europe and India. The existing regulations and guidelines are being examined and reviewed in order to clarify whether all forms of genome-editing fall under the existing framework in these countries.

2. *Existing Product-triggered GE/GM regulatory system*: In this approach, the regulatory system use the product-based criteria to regulate GE/GM organisms. Here, the novelty of trait in question is considered on a case-by-case basis, irrespective of the technology used to develop it. Canada and USA follow this approach.
3. *New Regulations on Genome-Editing*: Argentina became the first country to introduce a new regulatory resolution on New (Plant) Breeding Techniques (N(P)BTs) in 2015, which covers New Breeding Techniques (NBTs) including genome-editing. This new regulatory approach is based on the following components:
    - All NBTs involve recombinant DNA techniques, which leads to the presumption of GMOs.
    - If the NBT does not have a new combination of generic material (e.g. does not use a transgene/uses a transgene which is removed in the final product), a non-GM regulatory classification is applied.
    - If the NBT has a new combination of genetic material (e.g. uses a transgene which remains in the final product), the regulatory classification stipulates that the final product falls under GM classification.

Table 4 summarizes current regulatory options for genome-edited crops in different countries.

Table 4: Regulatory Paradigm for Genome-Edited Crops in Some Countries

Country	Implementing Agency	Act	Regulatory Stand on Genome-edited Crops
USA	USDA-APHIS	Plant Protection Act	*Covered under existing frameworks *May escape regulatory overview if the crop does not present pest risk or obnoxious weed properties

Table 4 continued...

Table 4 continued...

EU	EFSA	Directive 2001/18/EC	*Opined that ODM, SDN-1 and SDN-2 techniques as a form of conventional mutagenesis *In July 2018, European Court of Justice (ECJ) ruled that genome-edited plants have to be treated as GMOs *Final policy is awaited
Australia	OGTR	Gene Technology Regulation	*Has exempted chemical and radiation mutagenesis techniques for producing GMOs under Schedule 1(A) *Invited public comments on four possible options to regulate genome-edited products *Final policy is awaited.
New Zealand	EPA	HSNO Act	*Minor amendment in the existing HSNO Act *Not to regulate transgene-free organisms considering such techniques are as same as conventional chemical mutagenesis
Brazil	CNTBio	Brazilian Biosafety Law	*Has not made a clear policy statement on this matter *Although the existing policy has excluded all techniques for modification that do not involve the introduction of DNA molecules or rRNA.
Argentina	SAGyP	Resolution No. 173/15	*First country to frame specific regulation on genome-editing *Will not regulate if the GM crops have no transgene or used transiently during development and is final product and if there is no combination of genetic material

Source: Rao (2019)

Regulatory Framework in India

India has been one of the first countries to establish a Department of Biotechnology in 1986. India's 1989 "*Rules for the manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or c*ells", notified under the Environment Protection Act 1986, cover the entire spectrum of activities relating to research, development and use of Genetic Engineering and their products developed using Genetic Engineering.

The 1989 Rules defined "gene technology" as

> "*the application of genetic engineering including self-cloning and deletion as well as cell hybridisation, where 'genetic engineering' means the technique, by which heritable material, which did not usually occur naturally in the organism or cell concerned, generated outside the organism or the cell is inserted into said cell or organism. It shall also mean the formation of new combinations of genetic material by incorporation of a cell into a host cell, where they occurred naturally (self cloning), as well as modification of an organism or in a cell by deletion and removal of parts of the heritable material*."

In India, thus, there is already an existing regulatory regime that can be adapted to regulate genome-editing in the country. Over a period of many years , a series of rules, guidelines and policies were framed from time to time by the regulatory agencies to address issues related to biotechnology (Chimata and Bharti, 2019). This is the same regulatory architecture which has been in place for regulating GMOs and GM crops in the country.

These rules have also defined the competent authorities and agencies for handling various aspects of the rules (Warrier and Pande, 2016). Rules 1989 are implemented by the Ministry of Environment, Forests and Climate Change (MoEF&CC), jointly with the Department of Biotechnology, Ministry of Science and Technology and state governments (Ahuja, 2018).

Rules 1989 has notified six competent authorities and their composition that includes:

- rDNA Advisory Committee (RDAC)
- Institutional Biosafety Committee (IBSC)

- Review Committee on Genetic Manipulation (RCGM)
- Genetic Engineering Appraisal Committee (GEAC)
- State Biotechnology Coordination Committee (SBCC)
- District Level Committee (DLC)

The roles and functions of these six authorities are given in Table 5.

Table 5: Six Competent Authorities and Their Function

Statutory Committee	Role and Function	Administrating Agency
rDNA Advisory Committee (RDAC)	Advisory role; advises on biosafety of emerging biotechnologies	DBT
Institutional Biosafety Committee (IBSC)	Regulating role; regulates R&D and contained experiments	Set-up in registered research centres, universities and private companies; reports to RCGM
Review Committee on Genetic Manipulation (RCGM)	Regulating role; oversees scientific risk assessment of plants, animals, biopharma, microbes and guidelines	DBT
Genetic Engineering Appraisal Committee (GEAC)	Regulating role; Provides final approval for environmental release including confined field trials	MoEF&CC
State Biotechnology Coordination Committee (SBCC)	Monitoring role; supervision at state level	Concerned state governments
District Level Committee (DLC)	Monitoring role; supervision at local level and overseeing compliance	Concerned state governments

Source: Ahuja (2018, p.6)

In addition to the Rules 1989, there are few other acts and rules also to regulate certain specific aspect of products involving genetic-engineering

technology (particularly related to food and agriculture). Table 6 summarizes all relevant acts/rules.

Table 6: Relevant Acts/Rules Regulating GM in India

Act/Rule	Implementing Agency	Scope
Rules 1989	MoEF&CC	Covers entire spectrum of activities involving GM and products thereof including manufacture, sale, storage, export, import.
Plant Quarantine (Regulation for Import into India) Order 2003	Ministry of Agriculture and Farmers' Welfare	Covers regulation of import of germplasm/GMOs/transgenic plant material for research purposes
Biological Diversity Act 2002	National Biodiversity Authority	Regulates the use of biological resources including regulation of access and benefit sharing
Food Safety and Standards Act 2006	Food Safety and Standards Authority of India	Regulates manufacture, storage, distribution, sale and import of food which includes GM

Source: Ahuja (2018, p.8)

Ethical Concerns about Human Genome-Editing

In the wake of the revelations made by the Chinese researchers about the use of genome-editing technology (CRISPR) in human embryos to investigate inherited anemia and HIV resistance, there was a global uproar within and outside the scientific community in 2015 (COGEM-Health Council of the Netherlands, 2017). This got further inflamed and an international outcry ensued in 2018, when a Chinese scientist claimed to have helped make the birth of world's first genome-edited babies. Dr. He Jiankui, a genome-editing researcher at the Southern University of Science and Technology of China, claimed that he used the popular CRISPR–Cas9 genome-editing tool to disable a gene called *CCR5*, which encodes a protein that allows HIV to enter a cell and then impregnated a woman with this edited embryos (Cyranoski, 2015; Bosley *et al*, 2015; Baltimore *et al*, 2015; NASEM, 2015; Cyranoski and Ledford, 2018; ARRIGE, 2018; Ladikas, 2018).

The questions related to ethics and morality of this type of research which have consequences both for the individual, future generations and for society at large, were raised globally. Many researchers, scientists, social scientists, ethicists, policy makers, and civil societies expressed their concern and called for a moratorium and an international debate on how to proceed in a responsible and ethical manner. Various organizations have issued position statements on the use of gene-editing technologies for germline modification in research and in clinical applications (ISSCR, 2015; The Hinxton Group, 2015; UNESCO, 2015; SBD, 2015; ASGCT-JSGT, 2015; ASHG, 2016; NASEM, 2015; CBE, 2015; EGESNT, 2015; Danish Council on Ethics, 2016; ARRIGE, 2018).

Most of the statements/reports have made a distinction between the use of gene-editing technology in somatic cells (gene therapy), in research on *in vitro* human embryos and in clinical applications of the technology for germline modification. Gene therapy applications in somatic cells have not been considered to be problematic. However, almost all the position statements call for a moratorium on the clinical application of germline gene-editing technologies until evidence can be established about the safety and effectiveness of these techniques. They have also stressed the need for a global debate on the ethical, legal and social implications of germline genetic modification.

NASEM (2015, 2017) has highlighted the following major issues relating to the germline editing:

> *"the risks of inaccurate editing (such as off-target mutations) and incomplete editing of the cells of early-stage embryos (mosaicism); the difficulty of predicting harmful effects that genetic changes may have under the wide range of circumstances experienced by the human population, including interactions with other genetic variants and with the environment; the obligation to consider implications for both the individual and the future generations who will carry the genetic alterations; the fact that, once introduced into the human population, genetic alterations would be difficult to remove and would not remain within any single community or country; the possibility that permanent genetic 'enhancements' to subsets of the population could exacerbate social inequities or be used coercively; and the*

moral and ethical considerations in purposefully altering human evolution using this technology".

Based on these serious concerns, it argued that "*it would be irresponsible to proceed with any clinical use of germline editing unless and until (i) the relevant safety and efficacy issues have been resolved, based on appropriate understanding and balancing of risks, potential benefits, and alternatives, and (ii) there is broad societal consensus about the appropriateness of the proposed application. Moreover, any clinical use should proceed only under appropriate regulatory oversight".*

International Bioethics Committee (UNESCO, 2015) updated its reflection in light of the rapid advancements in genetics and genomics including genome-editing and deliberated upon the following four ethical principles and societal challenges:

- *Respect for autonomy and privacy*: an individual's genetic data needs to be protected to ensure the respect for autonomy and privacy;
- *Justice and solidarity* these advancements and its potential significance in healthcare should be shared with society as a whole and with the international community to uphold the principle of justice and solidarity;
- *Understanding of illness and health*: since behavioral, social, and environmental determinants play a crucial role in health, any underestimation of the complexity of factors influencing health should be avoided;
- *Responsibility towards future generations*: since genome-editing allows for the modifications of human germline genes, which can be passed on to the future generations; greater need for caution is required.

COGEM and Health Council of the Netherlands (2017) in their report on 'Editing Human DNA' observed that the "*There are also broader societal concerns about the desirability of germline modification: it could widen existing differences between people if the technology is available only to a select group. Finally, there is a debate about whether germline modification may be used for human 'enhancement' or that limits should be set on human genetic engineering*". (P.7)

NASEM (2017) has highlighted the following ethical, legal and social implications that are associated with the human genome editing.

- *Abuse of Human Rights and Human Dignity:* The potential future use of germline genome editing for 'enhancement' of human traits and capacities has triggered a debate on its impact on human dignity. The value of human should be assessed by the virtue of normal human values and not because of their enhanced capacities. This is tantamount to the abuse of human rights.
- *Issue of Eugenics:* Human genome editing may lead to the practice of Eugenics where deliberate interventions are aimed at improving the genetic quality of the human population. Another criticism is that eugenic policies eventually lead to a loss of genetic diversity, resulting in inbreeding depression due to a low genetic variation.
- *Economic and Social Justice:* Given the high cost of treatment based on human genome editing at present, it is also argued that the benefits of this technology would be accessible only to a few in society, who are wealthier or better insured. This could exacerbate the existing inequalities in the society.
- *Missing Informed Consent:* There is a fear of putting at risk the future generations of the unanticipated inheritable negative impacts in case something goes wrong with the human genome editing exercise, without having been given a chance to place their informed consent for the treatment.
- *Designer Babies and Genetic Supermarket:* With the prospects of 'enhancement' using human genome editing very much possible, there are chances that parents might incline towards this technology for perfecting prospective children with particular qualities which are deemed superior such as improved intelligence, increased positive personality traits, artistic talent, height, gender, skin/hair/eye colour etc. This would lead to newer form of consumerism and would propel the rise of 'genetic supermarkets', advertising and selling their products promising superior traits.

Nuffield Council on Bioethics (2018) has concluded that the use of heritable genome-editing interventions "*could be ethically acceptable, provided if, and only if, two principles are satisfied: first,*

that such interventions are intended to secure, and are consistent with, the welfare of a person who may be born as a consequence, and second, that any such interventions would uphold principles of social justice and solidarity –by this we mean that such interventions should not produce or exacerbate social division, or marginalise or disadvantage groups in society." (P. vii)

Lanphier *et al* (2015) argued that the key to all discussion and future research in the field of genome-editing is making a clear distinction between genome editing in somatic cells and in germ cells. A voluntary moratorium in the scientific community could be an effective way to discourage human germline modification and raise public awareness of the difference between these two techniques. However, they rightly appealed that the legitimate concerns regarding the safety and ethical impacts of germline editing must not impede the significant progress being made in the clinical development of approaches to potentially cure serious debilitating diseases using this technology.

Since, human genome does not have national boundaries, the governance of genome-editing and its implications for societies calls for an inclusive and global perspective. In order to dwell on this, WHO has recently set-up a global, multi-disciplinary expert advisory committee on 'Developing Global Standards for Governance and Oversight of Human Genome Editing' to examine the scientific, ethical, social and legal challenges associated with human genome editing (both somatic and germline). This Committee is of the view that "*it would be irresponsible at this time for anyone to proceed with clinical applications of human germline genome editing*" and there is a need for developing "*a responsible and responsive governance framework*". (WHO, 2019)

It is expected that guidelines and framework for regulation and governance will evolve from the work of the Committee. However, given the absence of an international convention or treaty, soft law or voluntary guidelines alone may not be sufficient to regulate and control Human Genome Editing.

Ethical Guidelines Related to Genome-Editing and Health in India

India has two sets of non-binding guidelines which address genome editing. First one is the ICMR-National Ethical Guidelines for Biomedical

and Health Research Involving Human Participants, and the second one is the ICMR-DBT National Guidelines for Stem Cell Research.

The National Ethical Guidelines for Biomedical and Health Research Involving Human Participants (ICMR, 2017), sets out specific principles for human genetics and genomics research, stressing that

"*Genetic manipulations have consequences for the future, some of which are unknown. Hence, greater care towards potential dangers is necessary".* (P.112)

The 2017 Ethical Guidelines acknowledged that

> *"Somatic cell genome editing has an immediate clinical translational potential and can be used in a variety of areas such as drug development, gene surgery understanding genetic variation, and it also has implications for biomaterial, fuels, food etc."(P.123)*

Therefore,

> "*Somatic cell gene therapy is permissible for the purpose of preventing or treating a serious disease when it is the only therapeutic option. It should be restricted to alleviation of life threatening or seriously disabling genetic disease in individual patients and should not be permitted to change normal human traits."* (P.123)

However, on the human germline therapy, the Guidelines has categorically stated that

> *"Germ line therapy is prohibited under the present state of knowledge."* (P.122)

Moreover, according to the Guidelines, the genetic engineering/ manipulations for carrying-out any human enhancement research and development are also strictly prohibited.

> *"Eugenic genetic engineering for changing/selecting/altering genetic characteristics and creating so called designer babies is prohibited. These should not be attempted, as we possess insufficient information at present to understand the effects of attempts to alter/ enhance the genetic machinery of humans. It would be unethical to use genetic engineering for improvement of intelligence, memory, formation of body organs, fertility, physical, mental and emotional characteristics, etc. even if specific gene/genes are identified in future". (P.122)*

The 2017 Ethical Guidelines is also wary of the challenge of upholding the principle of privacy in the wake of increasing digitization of medical records.

> *"Each individual's genome is a unique and definite identity, which in spite of anonymization of such data will always be associated with individual's identity, and this would be in conflict with the principle of privacy. With the advent of digitized medical records of such sophisticated data, additional efforts should be made to maintain confidentiality."* (P.123)

Though, the Guidelines very well acknowledges the emergence of newer technologies which have significant potential to contribute to the human healthcare, but at the same time is not oblivious of the ethical concerns that would pose in the future.

> *"New technologies like CRISPR technology have unmasked new knowledge that could find solutions to diseases or inherited disorders but could also create ethical debates due to uncertain future". (P.1*23)

On the potential risks associated with the newer technologies such as genome-editing, the 2017 Guidelines has enumerated the following serious concerns, which seems to be very valid.

- *Risk of inaccurate genome-editing:* Such risk can bring irreversible changes in germline, which can pose serious implications for future generations. It's interactions with other genetic variations and environment may have permanent long-term effects.
- *Off-target mutations:* CRISPR-Cas9 can sometimes identify a wrong target; and such off-target mutations may cause disease or alter germline or DNA of future generations of humans.
- *Possibility of human enhancement:* These technologies can be used to change certain genes (such as eye colour, memory, intelligence), leading to designer possibilities. This could lead to eugenics and may cause social disparity.
- *Damage to environment and biodiversity:* The application of this technology in plants and animals can lead to possible lateral transfer and emergence of irreversible damage to biodiversity and environment which can be a risk to not only human and animal life but also the

environment due to its long-term consequences. It can also possibly be used for bioterrorism.

- *Ensuring rightful access:* Ensuring rightful access to this technology, in light of the high possibility of its commercialization and patenting, is an important concern and needs to be discussed and deliberated upon thoroughly.

To promote public engagement and research on various issues relating to the technology, the Guidelines states that

> "*An open and transparent discussion, advocacy and public engagement should be encouraged with various stakeholders to understand, build trust and be involved in decision making. Capacity building is required not only of researchers but also regulators and policy makers to carefully consider social and ethical aspects and put systems in place to ensure safety. At the moment, there is a need for initiatives to increase knowledge base, infrastructure, funding, guidelines, inter agency communications and interactions, engagement with public and other stakeholders, and establish science communication. In addition, attempts should be made to foster research to assess the feasibility, efficacy and safety of CRISPR technology"*. (P.124)

The competent bodies regulating such research/trials are the National Bioethics Committee under Department of Biotechnology (DBT) and the local Intuitional Ethics Committee and Central Ethical Committee (CEC) of the ICMR.

The second set of relevant guidelines is the National Guidelines for Stem Cell Research (ICMR-DBT, 2017) which is also non-binding. Their preamble notes the "*there are challenges related to gene editing/ modification, human germline engineering and reproductive cloning*" (P.13).

The National Guidelines categorise research into permissible, restricted and prohibited, based on the ethical and safety concerns, necessitating additional review and monitoring. Genome-editing has been placed under "restrictive area of research", which include basic and translational research activities requiring additional oversight/monitoring due to contentious issues involved. Such activities needs close supervision and strict adherence to the guidelines.

> "*Genome modification including gene editing (for example by CRISPR-Cas9 technology) of stem cells, germ-line stem cells or gamete and human embryos is restricted only to in vitro studies. It will require thorough review by the IC-SCR, IEC and IBSC, and finally by Review Committee on Genetic Manipulation (RCGM). Research teams involved should have appropriate expertise, requisite training and infrastructure in gene editing/genome modification and characterisation". (P.25)*

Notably, research related to human germline gene therapy has been placed under the "prohibited area of research" together with the use of genome modified human embryos, germ-line stem cells or gametes for developmental propagation and research involving implantation of human embryos after in vitro manipulation into humans or primates.

The Guidelines establish two bodies for overseeing stem cell research and clinical trials, namely, the National Apex Committee for Stem Cell Research and Therapy to set out guidelines and regulate at the national level, as well as the Institutional Committee for Stem Cell Research, which approves and monitors stem cell research at the institutional level.

Conclusion

Given the rapid development of the genome-editing technologies, their potential applications, state of regulation and the ethical challenges, many scholars/organizations from across the world have called for treading the path cautiously particularly in reference to its application on human germline modification and called for ban on any such endeavour at least as long as the safety and efficacy of the procedures are not adequately proven.

Even the two leading scientists of the original CRISPR discovery team, Jennifer A. Doudna and Emmanuelle Charpentier, argued that

> *"The era of straightforward genome editing raises ethical questions that will need to be addressed by scientists and society at large. How can we use this powerful tool in such a way as to ensure maximum benefit while minimising risks? Regulatory agencies will also need to consider how best to foster responsible use of CRISPR-Cas9 technology without inhibiting appropriate research and development."*(Doudna and Charpentier, 2014)

Jasanoff and Hulbert (2018) have argued for setting-up a global observatory for gene-editing, which would serve as a clearing house, where it would consolidate and make universally accessible the global range of ethical and policy responses to genome editing and related technologies, including literature, and position statements from civil-society groups, especially from the global South. This network would also keep track on the activities and outputs of formal bioethics bodies, such as the Nuffield Council on Bioethics (UK), German Ethics Council, and intergovernmental agencies, such as the Council of Europe and the World Health Organization. Such observatory would convene periodic meetings among the various stakeholders which could help in more informed decision-making process. Burall (2018) also argued for setting-up consortiums in the similar lines to promote engagements among all the stakeholders. Ladikas (2018) argued for developing certain "global ethics" in S&T, with real-time ELSI analysis based on inter-disciplinary and inter-cultural principles. This would help in exploring and comparing value systems around the world and thus raising awareness of the different perspectives; which eventually will lead towards identifying a common understanding of morality in the various research contexts.

The setting-up of a global registry (or national registries) by funders or governments to record preclinical research that involves gene-editing in human embryos can play an important role in developing a sound regulatory and governance architecture (Nature, 2018). The 2016 Guidelines from the International Society for Stem Cell Research also recommended that the funding bodies, industry, and regulators should work to establish public repositories and databases of clinically useful lines for a particular disease therapy, which can be shared among the interested parties (ISSCR, 2016). Given the plethora of concerns associated with the development of genome-editing, the NASEM (2017) report recommended for establishing a framework for governance and regulatory oversight. It argued that in absence of any such framework, it would be very difficult to monitor and check the direction of research, particularly in the domain of human germline editing. However, it is easier said than done. Developing a global regulation and harmonization framework can pose to be a challenge because countries have different priorities and different ethical/moral approaches towards technologies (Kumar, 2017; Peschin, 2017).

In terms of dealing with the ethical and governance challenges associated with genome-editing in India, Mathur (2018) stated that issues of genome-editing are not yet addressed at policy level in India and there is a need for a detailed guidance on the germline research; while R&D in somatic cell therapy using genome-editing should be promoted, as it is less hazardous. She argued that for better understanding about the issues related to rights to technology, patenting, ownership and access of technology, protection of rights of individuals, safety issues, and protection against any discrimination; scientific community and other stakeholders must engage in a broad-based discussion to map the way forward for this technology. She further argued that it is important for India to involve in the ongoing global debate to learn, understand and devise an appropriate ethical and regulatory framework.

Genome-editing in agriculture is less controversial but there is no consensus in this. As Srinivas (2018) argued that it would be interesting to analyse whether the two major approaches (product and process) is sufficient to regulate genome-editing (with respect to crops) or do we need to explore better regulatory approaches and *sui generis* alternatives. He further expressed that from a technology governance perspective, regulating genome-editing is going to be more challenging than regulating genetic engineering.

Effective governance of genome editing is necessary so that the technology is sufficiently regulated, has trust of the public and is harnessed well. How to do this is a big challenge. It is hoped that countries will work together, so that while the worst fears about human genome editing are addressed, the technology *per se* is deployed with care and caution for common good.

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Relationship between Science and Technology (S&T) and Gross District Domestic Product (GDDP) in select Indian Districts

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Abstract: Science and Technology (S&T) are the key contributing factors in shaping the economic growth of nations. Despite the fact that S&T impacts the growth processes, the assessment of this relationship is not simple, as there are also a number of other factors that impact growth. The present paper describes the findings of the study that analyzed the relationship between 'science and technology (S&T) inputs' and economic growth as represented by 'Gross District Domestic Product (GDDP)' at the district level. This distinctive study contributed to the identification of 'S&T Indicators' in three sectors of the economy viz; agriculture, industry and services and also developed 'Index of S&T Indicators' for five Indian districts. The empirical findings of the study clearly exhibited that technological interventions in all three sectors have a great impact on the growth of the districts. The study thus sets a new pathway in its approach to constructing the relationship between technology and economic growth.

Keywords: Technology, GDDP, Relationship, Agriculture , Industry, Services, Index of Indicators

Introduction

Technology is a critical cause in inducing economic growth/development by lowering costs, improving quality, creating new products and helping reach new markets. There are several instances that demonstrate far-reaching development impacts of simple technologies. For instance, a

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simple technology adoption under green revolution had tremendously boosted agriculture production and benefitted the farmers to a large extent in irrigated areas. Technology and technological progress not only helped in boosting agricultural and industrial productivity but also embodied in production and services systems.

Technology led growth though is not a new phenomenon; there are very few studies that have actually assessed the economic impact of technology. Whatever studies thus exist are all focused on the macro level and mostly confined to the impact of R&D on new technologies, products, publications and patents.

Despite the relative infancy of technology studies in developing regions, anecdotal evidence suggests that access to technology has a beneficial economic impact (Eric Brewer et al, 2005). Wang Licheng (2011) analyzed economic growth by using science and technology inputs in China, based on the neo-classical growth models which considered technical progress as an important factor for economic growth. A similar study by Gary and Murphy (1992) compared the share of national S&T invested funds on the GDP among the OECD Member Countries. Guellec and Bruno (2001) also studied the long term implication of different R&D inputs on economic growth. In the growth theory literature neoclassical economists, classical economists and other modern theorists, though have discussed different models, all converge on the 'role of technological change' in achieving sustainable economic growth. The "Neo Classical Growth Theory" is built on the idea that a given level of natural resources requires the use of labour, capital and effectiveness of labour (technology) to spring up a production process. Neo classical economists opine that a technological change brings in increased specialization of labour and leads to discovery of new goods and methods of production in a self-perpetuating process of economic growth. No matter at what level the factors of production are employed, a change in technology results in long-run growth of an economy. It was considered that the effectiveness of labour (knowledge or technology) is the fundamental determinant of high level of sustainable economic growth (Musa Jega Ibrahim, 2012). Thus, economic theory offers a series of text book approaches to understanding economic change. One of the first such theories was initiated in 1776 by Adam Smith, who emphasized the role of the division of labour in promoting increasing output per person. Smith

in his work stressed that increasing specialisation, mediated mainly by market forces, would lead to rising efficiency in production, and therefore to rising living standards. Understandably, Smith's model of the division of labour did not draw primary attention to innovation since he was living at the time when the Industrial Revolution was just gaining force (Jeffrey Sachs and McArthur, 2003).

During the period between 1870 and 1950, most of the studies revealed that the measured growth of inputs (i.e., in capital and labour) could only account for about 15 per cent of the actual growth in the output of the economy. In a statistical sense, there was an unexplained residual of no less than 85 per cent, which means that only 15 per cent of the growth in the economy is stimulated through capital and labour and the remaining 85 per cent is attributed to technology (OECD, 2004). Even after 1950s several economists worked further on this aspect and found similar results. Solow (1956) a Nobel Prize winner in Economics, was one of those economists who discovered a very large residual, using a very different methodology and different time period and got the same result for the size of the residual – 85 per cent. It was precisely the size of this residual that persuaded most economists that technological innovations must have been a major force in the growth of output in highly industrialised economies. Hence, an exogenous rate of improvement in labour productivity was identified, which presumably is the result of technological advancement. Solow's research studies further denoted that understanding long-term economic growth requires an understanding of technological innovation. All these neo-classical approaches, both exogenous and endogenous growth models on technological change are considered as over-simplistic, ignoring a comprehensive analysis of technological characteristics. This is reflected in a number of applied economic models based on such theories. The exogenous economic growth models assume that technological change is a deterministic time trend with exponential or whatever form of exogenous factor growth. Steve Pierson (2011) further acknowledged that capital and labour accounted for less than two-thirds of growth and the remainder was attributed to technology. Thus, the importance of technological component in measuring economic growth has gained momentum since 1980s. The 1980's era was brimmed with research articles on the measurement of GDP using technology as one of the components along with labour and capital at national and international level. Realizing the contribution of technology

and its role in economic growth, several economists empirically tried to measure technological change using a standard measure i.e. Total Factor Productivity (TFP). The Similar concept of measuring growth using TFP continued even during 90s and is in vogue till date. TFP is the residual calculated by subtracting the contributions of labour and physical capital from GDP. In other words, TFP though volatile, the fluctuations average out over long periods of time. At lower frequencies or over longer periods, the trend in TFP measures the rate of technological advance. Growth and development theories have increasingly analyzed the process of technological innovation as a central feature of growth rather than as something that was simply 'brought in' from outside. Romer (1986) attributes long-term economic growth to the positive externality of cumulative knowledge, which is enhanced by Research and Development (R&D) investment with the economic system. Further, major contributions by Lucas (1988), Romer (1990), Grossman and Helpman (1991), Aghion and Howitt (1992), analyzed the impact of technology change as an 'exogenous' feature of an economy to 'technological change' as an 'endogenous' feature. Jeffery et.al, (2002) measured how this technology as one of the input helps in stimulating the growth process of an economy.

Several other studies estimated the relationship between technology and economic growth using Cobb-Douglas production function. Similar empirical work is carried out on the Romanian economic growth during 1990-2007, focusing on the role of technical progress captured in its exogenous and endogenous forms. Considering the large role played by R&D activities and related investments in creating technological progress, different variables related to research and development activities in Romania were included in the Cobb-Douglas production function model. The analysis was undertaken at both national and regional scale, using time series and cross-sectional data, respectively.

It is observed from the available literature that a similar exercise has been done by various economists in their research studies. Various empirical studies *viz.,* UNCTAD (2005), UNIDO (2002), UNDP (2001) and Porter and Stern (2003) have extensively used Principal Component Analysis (PCA) for constructing various indices relating to technology (World Bank, 2008). These studies have focused much on technology innovation and technology achievement index. In contrast, this study focused on technology inputs (causes) and their relationship with district's economic growth. Thus, an

attempt is made by authors to establish the relationship between 'technology and economic growth' at a micro level i.e; at district level. In other words, the study examined whether the existing levels of technology in the districts of Andhra Pradesh and Telangana states in India, have any significant impact on the districts' economic growth or not.

Methodology

The study identified S&T inputs that would have a bearing on economic growth, across the three sectors viz. Agriculture, Industry and Services at the district level. Districts were selected based on the preliminary study, wherein multiple scenario analysis of GDDP and its growth were carried out for all the districts in Andhra Pradesh and Telangana and accordingly districts were grouped/ranked based on average absolute GDDP, average growth rate of GDDP and average per capita GDDP. Finally, districts were segregated based on the level (absolute GDDP) and growth (average growth rate) of GDDP. Based on the analysis, the following districts were identified for the study:

- Vishakhapatnam (High level & high growth)
- East Godavari (High level & low growth)
- Guntur (High level & low growth)
- Adilabad (Low level & high growth)
- Srikakulam (Low level & high growth)

Thus, for the study purpose, four districts in Andhra Pradesh State viz; Viskhapatnam, Guntur, East Godavari and Srikakulum and one district in Telangana State in India were selected.

The study largely used secondary data on GDDP and for construction of S&T indices across the three sectors in the five districts during the period (2000-01 to 2011-12). GDDP values are based on new series (2004-05) that are extracted from the State Domestic Product of Andhra Pradesh 2004-05 to 2012-13 (first revised edition). Statistical methods such as trend method and moving averages have been used to smoothen certain data sets where there were data gaps and inconsistencies. The study team also collected primary data by interacting with officials at Directorate of Economics and Statistics (DoES), Chief Planning Officers and relevant government departments, industries and industry associations in the identified districts.

Basically, the authors carried out empirical investigations based on time series data of S&T indicators and district economic growth indicator (GDDP) for the identified five districts from 2001 till latest Indian Census Year 2011. Besides interacting with district officials, the study largely used secondary data for the construction of S&T indices across the three sectors in the five districts. The novelty of the study is to derive the 'S&T Index' which can be obtained from various methods. Mathematically an index is constructed using simple methods like Ranking, Indexing, Log transformation, Standard score and World Bank HDI methodology that takes care of maximum and minimum values of the data to arrive at index. The present study focused on the principal component analysis (PCA) mainly to reduce the large dimensionality of data which is not possible from the former methods. Data taken from various sectors with varying units of measurement and time poses difficulties to construct index unless a consistency is brought by standardizing in terms of unit of measurement and time. In this context, PCA is proved to be a more sophisticated tool that helps in developing the index by bringing consistency in the data. Hence, the study majorly employed Principal Component Analysis (PCA) to obtain S&T indices and Multiple Regression Analysis to find out the relationship between S&T inputs (technology causes) and GDDP (economic growth). As an initial effort, a correlation matrix is developed wherein the pairwise correlation values are generated between S&T indicators and GDDP, to understand the relationship between the said parameters. This has precisely formed the basis for construction of the S&T index using PCA. The study further employed the below mentioned multiple regression equation to analyze the relationship between S&T indices (technology causes) and GDDP (economic growth).

$Y_{it} = GDDP_{it}$

$GDDP_{it} = \alpha_1 + \beta_1 \text{Agri index}_{it} + \beta_2 \text{Livestock index}_{it} + \beta_3 \text{Industry index}_{it} + \beta_4 \text{Services index}_{it} + \mu_i$ …… (1)

$i = i^{th}$ district $= t^{th}$ time period.

$i = 1,2,3,\ldots 5$ $t = 12$

α_1 = Intercept for each index, β_1 = Agriculture S&T index, β_2 = Livestock S&T index, β_3 = Industry S&T index

β_4 = Services S&T index

Identification of S&T Indicators

S&T being a complex domain with multidimensional nature cannot be measured directly. Hence, indicators are used as proxies for measuring S&T inputs. Wilk (1996) defined S&T indicator as 'statistics which measure quantifiable aspects of the creation, dissemination and application of science and technology'. Thus, S&T indicators serve as analytical tools traditionally defined as 'a series of data designed to answer questions about the science and technology system (STS), its internal structure, its relation with the economy and society, and the degree to which it is meeting the goals of those who manage it, work within it, or are otherwise affected by its impacts' (OECD, 1992). S&T indicators measure activities at different scale (micro, meso, macro), deal with different aspects (allocation of resources and definition of objectives) and different contexts of decision whether scientific, operational or strategic (Barre, 2009). A good indicator should be scientifically sound, technically robust, easily understood, sensitive to the change that it is intended to represent, measurable and capable of being updated regularly.

Sirilli (1998), Archibugi and Coco (2005) and Hall and Jaffe (2012) reviewed the indicators used for measuring science, technology and innovation (STI). Currently, STI indicators used in various studies comprise of mainly five accepted dimensions namely R&D, human resources, patents, innovation and technology balance of payments (UNCTAD, 2010). Most commonly quantified and studied S&T indicators in various contexts include gross domestic expenditure on R&D (GERD), number of R&D manpower, number of S&T institutions, enrolment in higher education, outturn of scientific and technical personnel from universities, number of research publications, number of patents, royalties and licence fees receipts etc.

Thus, to examine the technology led growth, it is necessary to identify those factors or inputs that would promote growth. Since technology is a multi-dimensional phenomenon, there is a need to carefully identify inputs from each of the sectors viz; agriculture, industry and services, which have a bearing on growth.

To identify the **'Agriculture S&T Indicators'**, input variables were considered on the premise that agricultural development of any district depends on the factors viz., (i) adoption of modern technology,

(ii) availability of agricultural infrastructure and (iii) irrigation; as they invariably lead to faster agricultural development. Likewise, industrial sector constitutes the second highest in the share of India's Gross Domestic Product (GDP). The study mostly relied on the data published by Annual Survey of Industries (ASI) while identifying the 'Industry S&T Indicators'. The services sector constitutes a large fraction of the Indian economy both in terms of employment potential and its contribution to national income. This sector covers a wide range of activities from the most sophisticated in the field of Information and Communication Technology to simple services pursued by the informal sector workers, including hawkers or vegetable sellers. Accordingly 'Service S&T Indicators' were identified. Finally, the S&T indicators used in the three sectors for analysis are presented in Table 1.

Table 1: S&T Indicators used in the three Sectors of Economy

Agriculture	**Industry**	**Services**
Total Cropped Area	Number of factories	Power consumption
Fertilizer Consumption	Number of employees in factories	No. of Bank Branches
Pesticide Consumption	Fixed Capital	No. of Medical Facilities
Area under Tube wells and Dug Wells	Working capital	No. of Educational institutions
Area under Fodder Development	Fuel consumption	No. of Vehicles
No. of Artificial Inseminations	Material consumption	
No. of Castrations	No. of MSME units	
No. of Vaccinations	No. of Employees in MSME Units	
No. of Animals Treated	Investments in MSME Units	

Source: Authors own calculations.

Relationship between S&T inputs and GDDP: District Analysis

Firstly, to examine whether each of the indicators are meaningfully correlated with the GDDP or not, pair wise correlations have been carried out. Results thus obtained indicated that some S&T indicators in all the three sectors indicated a positive correlation with the GDDP. These indicators have been precisely used for further construction of the S & T Index using PCA.

In Visakhapatnam district among the agriculture S&T Indicators, agri-chemicals like fertilizers, pesticides and livestock indicators such as vaccinations and artificial insemination showed high correlation with GDDP. However, in Srikakulum district, among all the indicators, total cropped area, fertilizer consumption, animals treated, castrations, and vaccinations have shown high correlation with GDDP. Guntur district showed positive correlation with GDDP for the indicators like consumption of fertilizers and area under tube and dug wells, numbers of vaccinations and artificial inseminations. In East Godavari district, total cropped area, fertilizer consumption, area irrigated under tube and dug wells, animals treated; castrations and artificial insemination have shown positive correlation with the GDDP. Except number of animals treated and area under fodder cultivation all other indicators have shown positive correlation with GDDP in Adilabad district (Table 2).

Table 2: Correlation between Agriculture S&T indicators and GDDP across districts

Agriculture S&T Indicators	Correlation Coefficient				
	Visakhapatnam	Srikakulam	Guntur	East Godavari	Adilabad
Total cropped area	-0.54	0.74	0.41	0.75	0.79
Fertilizer consumption	0.69	0.84	0.98	0.66	0.95
Pesticide consumption	0.89	0.04	0.32	0.50	-0.73
Area irrigated under tube wells and dug wells	0.51	-0.05	0.92	0.64	0.60
No. of animals treated	0.54	0.68	-0.42	-0.58	0.04
No. of castrations performed	-0.24	-0.80	0.42	-0.69	-0.69
No. of vaccinations carried out	0.64	0.73	0.82	0.25	0.95
No. artificial insemination done	0.92	0.45	0.96	0.86	0.94
Area under fodder cultivation	-0.15	0.26	0.48	-0.36	0.20

Source: Authors own calculations.

In the industrial sector all the indicators showed positive relationship with GDDP except MSME units in Visakhapatnam district, number of factories in Srikakulum, Guntur and East Godavari districts and number of factories and employees in Adilabad district (Table 3). In the Services sector all indicators in all the five study districts showed strong positive correlation with GDDP (Table 4).

Table 3: Correlation between Industry S&T indicators and GDDP across districts

Industry S&T Indicators	Correlation Coefficient				
	Visakhapatnam	Srikakulam	Guntur	East Godavari	Adilabad
No. of factories	0.64	0.28	0.55	0.00	-0.65
No. of employees in factories	0.87	0.95	0.83	0.91	-0.61
Fixed capital	0.89	0.97	0.93	0.98	0.95
Working capital	-	0.94	0.92	-	0.97
Fuel consumption	0.96	0.98	0.90	0.97	0.95
Material consumption	0.94	0.99	0.94	0.95	0.97
No. of MSME units	-0.08	0.95	0.98	0.89	0.86
No. of employees in MSME units	0.67	0.98	0.97	0.98	0.98
Investments in MSME	0.79	0.97	0.88	0.97	0.98

Source: Authors own calculations.

Development of S&T Index

In all the three sectors, the indicators that showed positive correlation with GDDP were subjected to PCA analysis in order to derive the principal components. In Visakhapatnam district one principal component was derived from agriculture S&T indicators with 86.56 per cent of variance and is labeled as 'Agriculture S&T Index'. In industry also only one principal component explaining about 81.62 per cent of variation was extracted, which is labeled as 'Industry S&T Index'. In services all the indicators have high factor loadings on a single component that explained 92.23 per cent of variation and is labeled as the 'Services S&T Index'. In Srikakulum district the Agriculture, Industry and Services S&T Indices, showed a variance of 51.97 per cent, 95.53 per cent and 82.43 per cent respectively. Guntur district showed total variance of 98.61 per cent for 'Agriculture S&T Index', 86.73 per cent for 'Industry S&T Index' and 90.76 per cent of variance for 'Services S&T Index'. In East Godavari district, 'Agricultural S&T Index' with 63.95 per cent of variance, 'Industry S&T Index' with variance of 94.41 per cent and 'Services S&T Index' with 92.25 per cent variance was extracted. Similarly, the 'Agriculture S&T Index' with 97.17 per cent, 'Industry S&T Index' with 93.30 per cent and 'Services S&T Index' with 90.03 per cent variance were extracted in Adilabad district (Table 5).

Table 4: Correlation between Services S&T indicators and GDDP across districts

Services S&T Indicators	Correlation Coefficient				
	Visakhapatnam	Srikakulam	Guntur	East Godavari	Adilabad
Power consumption	0.94	0.92	0.93	0.93	0.87
No. of bank branches	0.84	0.85	0.86	0.89	0.82
No. of medical facilities	0.86	0.97	0.86	0.96	0.93
No. of educational institutions	0.94	0.97	0.91	0.97	0.99
No. of vehicles	0.96	0.96	0.94	0.95	0.90

Source: Authors own calculations.

Table 5: Total Variance of S&T Agriculture, Industry and Services Index

District	Comp-onent	Initial Eigen Values			Extraction Sums of Squared Loadings		
		Total	% of Variance	Cumu-lative %	Total	% of Variance	Cumul-ative %
Total Variance of S&T Agriculture Index							
Visakhapatnam	1	1.73	86.56	86.56	1.73	86.56	86.56
Srikakulam	1	1.04	51.97	51.97	1,04	51.97	51.97
Guntur	1	1.97	98.61	98.61	1.97	98.61	98.61
East Godavari	1	2.55	63.95	63.95	2.55	63.95	63.95
Adilabad	1	1.94	97.17	97.17	1.94	97.17	97.17
Total Variance of S&T Industry Index							
Visakhapatnam	1	5.71	81.62	81.62	5.71	81.62	81.62
Srikakulam	1	7.64	95.53	95.53	7.64	95.53	95.53
Guntur	1	7.81	86.73	86.73	7.81	86.73	86.73
East Godavari	1	6.60	94.41	94.41	6.60	94.41	94.41
Adilabad	1	6.53	93.30	93.30	6.53	93.30	93.30
Total Variance of S&T Services Index							
Visakhapatnam	1	4.61	92.23	92.23	4.61	92.23	92.23
Srikakulam	1	4.12	82.43	82.43	4.12	82.43	82.43
Guntur	1	4.54	90.76	90.76	4.54	90.76	90.76
East Godavari	1	4.64	92.95	92.95	4.64	92.95	92.95
Adilabad	1	4.60	90.03	90.03	4.60	90.03	90.03

Source: Authors own calculations.

Note: Extraction method: PCA

Relationship between S&T Index and GDDP

To examine the impact of S&T inputs on the district's economic growth, regression analysis is carried out in the respective sectors with the concerned index (Agriculture S&T Index, Industry S&T Index and Services S&T Index) representing the independent variables and GDDP as the dependent

variable. Model estimates of the relationship between S&T Indices and GDDP growth in the five districts and the three sectors are presented in Table 6.

Table 6: Model Estimates of the Relationship between S&T Indices and GDDP Growth

District	Beta Coefficient	Sig level	R^2	SEE
Agriculture S&T Index				
Visakhapatnam	0.97 (13.46)	.000	0.94	0.00001
Srikakulam	0.73(3.38)	.007	0.71	96200.48
Guntur	0.98(15.32)	.000	0.96	74298.06
East Godavari	0.89(6.42)	.000	0.81	0.00009
Adilabad	0.97(12.56)	.000	0.94	0.06
Industry S&T Index				
Visakhapatnam	0.92(7.52)	.000	0.85	2519.47
Srikakulam	0.99(28.7)	.000	0.98	0.026
Guntur	0.95(9.82)	.000	0.91	1125.98
East Godavari	0.97(13.32)	.000	0.94	0.045
Adilabad	0.97(14.58)	.000	0.95	0.060
Services S&T Index				
Visakhapatnam	0.94(9.47)	.000	0.90	0.102
Srikakulam	0.95(10.75)	.000	0.92	0.07
Guntur	0.95(9.44)	.000	0.89	0.08
East Godavari	0.99(22.49)	.000	0.98	0.03
Adilabad	0.97(13.05)	.000	0.94	0.05

Source: Authors own calculations.

Note: Figures in parenthesis denote t stat values

Visakhapatnam District

In Visakhapatnam district, agriculture technology inputs in the form of chemical fertilizers and modern methods of livestock breeding are contributing to the growth. The R^2 value of 0.94 explains the strong impact of Agriculture S&T inputs on GDDP. The beta coefficient of 0.97 shows high impact of Agriculture S&T Index. Thus, every one unit increase

in technology input in agriculture brings about 0.97 units increase in GDDP. Industrial technology has also influenced the economic growth of Visakhapatnam district. This could be seen through high R^2 value (0.85), which clearly indicates a strong relationship between technology and growth. The beta coefficient value (0.92) of Industry S&T Index indicates a strong influence of industrial technology inputs on the growth of the district. Thus, every one unit increase in technology input in industry brings about 0.92 units increase in GDDP. More so, S&T inputs in the services sector have significant impact on the growth of the Visakhapatnam district. R^2 value of 0.90 and the beta coefficient of 0.94 reflect that the Service S&T Index has a positive and significant impact on the GDDP. It is observed that one unit increase in technology input in services brings about 0.94 units increase in GDDP.

Srikakulum District

From the model estimates of the relationship between S&T indices and GDDP growth In Srikakulum district, the R^2 value of 0.71 supports the argument that the technology interventions in agriculture have strong and positive relationship with GDDP. The beta coefficient value of 0.73 indicates the positive impact of agricultural technologies on GDDP growth in Srikakulam district. Thus, for every one unit increase in technology input in agriculture brings about 0.73 units increase in GDDP. Industrial technology has also influenced economic growth in Srikakulam district. The value of R^2 (0.98) is quite indicative that there exists a strong relationship between S&T inputs and economic growth. The beta coefficient value of 0.99 of Industry S&T Index indicates that every one unit increase in technology input in industry is bringing about 0.99 units increase in GDDP. Services S&T index, when regressed upon GDDP, reveals a strong and positive impact as observed from high R^2 value (0.92). The beta coefficient of 0.95 corroborates the fact that every one unit increase in technology input in services in Srikakulum district brings about 0.95 units increase in GDDP growth.

Guntur District

High R^2 value (0.96) signifies that technology interventions in agriculture have significant relationship with GDDP. The beta coefficient value of 0.98

of Agriculture S&T Index indicates a highly significant positive relationship between technology inputs and economic growth of the district. In other words, one unit increase in technology inputs is giving rise to 0.98 units of growth in GDDP. The regression results in the industry sector showed that technology adoption influenced economic growth in Guntur district. The high R^2 of 0.91 clearly indicates a strong relationship between technology and economic growth. The beta coefficient (0.95) of Industry S&T Index indicates a highly significant positive relationship between technology inputs and economic growth of the district. In other words, one unit increase in industry technology inputs has given rise to 0.95 units of growth in GDDP. In the services sector, the high R^2 value (0.89) indicates that technology has a strong positive relationship with the economic growth of district. The beta coefficient of 0.95 confirms the fact that S&T inputs in service sector have greater impact on the GDDP and one unit increase in services technology inputs brings 0.95 units of growth in GDDP.

East Godavari District

S&T interventions in the agriculture sector have greater influence on the economic growth of the district, which is evident from the high R^2 value (0.81). Beta coefficient value of 0.89 also indicates significant impact of S&T Index on GDDP. It is inferred that for every one unit increase in technology input in agriculture has brought about 0.89 units increase in GDDP. S&T inputs in industry sector have also influenced the economic growth which is evident from high R^2 value of 0.94. The beta coefficient value of Industry S&T Index (0.97) indicates a strong influence of industrial technology inputs on the growth of GDDP. It is inferred that for every one unit increase in technology input in industry has brought about 0.97 units increase in GDDP. S&T inputs in services sector have significant impact on the growth of the district, which is evident from the R^2 value (0.98). The beta coefficient of 0.99 indicates that the Services S&T Index has a positive and significant impact on the GDDP. It is indicated that for every one unit increase in technology input in services has brought about 0.99 units increase in GDDP. Services sector has outpaced other two sectors in the contribution of district's economic growth. The findings also support this argument since Services S&T Index has shown highest significant relationship with GDDP when compared to agriculture and industry.

Adilabad District

The 'Agriculture S&T Index' showed a greater impact on the economic growth of Adilabad district which is evident from the high R^2 value (0.94). The significant positive impact of technology inputs in agriculture on the growth of Adilabad district is evidenced by the standardized beta coefficient (0.97) indicating the fact that one unit increase in S&T input in agriculture raises 0.97 units of growth in GDDP. The R^2 value of 0.95 is quite indicative that there is a strong relationship between industrial S&T inputs and economic growth of the district. The positive impact of technology inputs in industry on the growth of the district is evident from the beta coefficient (0.97) which means that one unit increase in S&T input in industry raises 0.97 units of growth in GDDP. S&T inputs in services sector also have significant impact on the economic growth of the district, which is evident from the high R^2 value of 0.94. Services S&T Index is also observed to have significant impact on the growth of Adilabad as evinced by the beta coefficient (0.97) indicating that one unit increase in S&T input in services gives rise to 0.97 units of growth in GDDP.

Thus, the authors while establishing the relationship of S&T Indices with GDDP came up with unique set of district wise S&T Indicators for all the sectors that contribute to economic growth. The consolidated '**Index of S&T Indicators'** is presented in Table 7.

Summary and Conclusions

The study analyzed the relationship between Science and Technology (S&T) inputs and economic growth at the district level taking a comprehensive coverage of all the three sectors viz; agriculture, industry and services that contribute to economy. The study covered five districts viz; Visakhapatnam, Srikakulum, Guntur, East Godavari and Adilabad in Andhra Pradesh and Telangana States in India. The positive influence of technology across the districts economic growth in the three sectors was empirically proved using 'Principal Component Analysis (PCA)'. From the study it was inferred that S&T unequivocally has a positive relationship with districts' economic growth. The unique contribution of the study was the development of district wise 'Index of S&T Indicators' for every sector.

Table 7: Index of S&T Indicators

Visakhapatnam District	Srikakulum District	Guntur District	East Godavari District	Adilabad District
Agriculture S&T Index • Fertilizers Consumption • Pesticides Consumption • No. of Vaccinations • No. of Artificial Inseminations	**Agriculture S&T Index** • Total cropped Area • Pesticides Consumption • Area under Tube and dug wells • No. of Castrations • No. of Vaccinations • No. of Artificial Inseminations	**Agriculture S&T Index** • Fertilizers consumption • Area under Tube and Dug wells • No. of Vaccinations • No. of Artificial Inseminations	**Agriculture S&T Index** • Total cropped Area • Fertilizers consumption • Area under Tube and Dug Wells • No. of Artificial Inseminations	**Agriculture S&T Index** • Total cropped Area • Fertilizers Consumption • Area under Tube and Dug Wells • No. of Vaccinations • No.of Artificial Inseminations
Industry S&T Index • Number of Factories • Number of Employees • Fixed Capital • Fuel Consumption • Material Consumption • Number of Employees in MSMSE Units • Investment in MSME Units	**Industry S&T Index** • Number of Employees • Fixed Capital • Working Capital • Fuel Consumption • Material Consumption • Number of Employees in MSMSE Units • Investment in MSME Units	**Industry S&T Index** • Number of Factories • Number of Employees • Fixed Capital • Working Capital • Fuel Consumption • Material consumption • Number of MSME Units • Number of employees in MSME • Investments in MSME	**Industry S&T Index** • Number of Employees • Fixed Capital • Fuel Consumption • Material consumption • Number of MSME Units • Number of employees in MSME • Investments in MSME	**Industry S&T Index** • Fixed Capital • Working Capital • Fuel Consumption • Material consumption • Number of MSME Units • Number of employees in MSME • Investments in MSME •

Table 7 continued...

Table 7 continued...

Services S&T Index	Services S&T Index	Services S&T Index	Services S&T Index	Services S&T Index
• Power Consumption in the services sector • Bank branches in the district • Hospitals and Medical Units • Educational institutions • Vehicle strength	• Power Consumption in the services sector • Bank branches in the district • Hospitals and Medical Units • Educational institutions • Vehicle strength	• Power Consumption in the services sector • Bank branches in the district • Hospitals and Medical Units • Educational institutions • Vehicle strength	• Power Consumption in the services sector • Bank branches in the district • Hospitals and Medical Units • Educational institutions • Vehicle strength	• Power Consumption in the services sector • Bank branches in the district • Hospitals and Medical Units • Educational institutions • Vehicle strength

Source: Authors own construction of S&T Index.

To sum up, in agriculture sector the results indicated that technology interventions in crop protection (pesticides); soil fertigation (fertilizers) and irrigation (tube and dug wells) played significant role in improving the economy in Visakhapatnam, Guntur and East Godavari districts. Further, it was found that the economies of the dryland and relatively backward districts like Adilabad and Srikakulam, have greater dependency on the livestock production where the inroads to technology in the form of animal protection, livestock improvement boosted the production thus adding value to the district's economy. Of the selected districts, Guntur district demonstrated that technology has revolutionized the growth of the agriculture sector.

The study findings in industry sector revealed that wherever the MSME concentration is high, the sector is adding value to industrial production. This is conspicuously seen in Guntur and East Godavari districts wherein most of the industrial clusters are operating at low levels of technology. On the other hand, Visakhapatnam has larger interest in the setting up of large and mega industrial units. This has called for huge investments and is therefore quite obvious that technology intensive units have got good share that are adding value to the district's growth. It is quite interesting to observe that

Adilabad district has recorded relatively better usage of technology. This is because the existing cotton and spinning mills that loom larger in the district have upgraded technology thus contributing more to the district GDP. Srikakulam district relatively fared better due to its locational advantage of being closer to Visakhapatnam mega city. Though some of the MSME units have shown relatively good performance, it has no major industry and it is also not sufficient unless all the other existing units are toned up and raise the overall productivity.

In Services, Guntur district has given top priority for education that had a cascading effect on the generation of skilled workforce and technical personnel. This has resulted in the establishment of commercial services with enterprising workforce thus directly contributing to the growth of district GDP**.** In East Godavari, robust infrastructure transport, communications, social and community services played a significant role in districts economic growth. In Visakhapatnam district IT & ITeS largely contributed to the service sector. Human resources also added value to the services sector in the form of technical and skilled personnel channeling through various educational institutions. Robust road connectivity and wide spread telecommunications are driving the Srikakulam district's economy forward.

To sum up, authors in this paper discussed how 'Index of Science & Technology (S&T) Indicators' for the three sectors of economy - agriculture, industry and services were developed and the relationship between these indices and economic growth. The study empirically established the relationship between S&T indices and economic growth. A positive relationship between the two was found which emphasizes the dire need for development of new technologies and their diffusion and adoption in the respective districts for furthering the economic growth.

The authors believe that this paper would serve as a useful aid in policy making that encourages developing schemes and programmes in R&D and innovations in technology to bring about inclusive and sustainable economic growth.

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