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REVIEW ARTICLE

SOCIO-ECONOMIC IMPACT OF CLINICAL RESEARCH IN VARIOUS COUNTRIES

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Abstract:

This article attempts to outline the socio-economic impact of clinical research in sample geographies from around the world. With an attempt, we could sample geographies that largely represent varied population - from developed markets to developing markets, from poor to rich countries, from countries seeing increase in clinical research to countries that are struggling to retain clinical research. In absence of any research/ survey that can map socio-economic impact at global level, this article best describes the general trends at least, if not a truly global view. Largely, there are two impacts which are quite visible across all of the sampled geographies. The first one is that the advent of clinical research in any geographies have led to a palpable increase in the standards of medical care in that geographies. This is probably driven by essential training that researchers go through and thereby learning the GCP - Good clinical practice. Another effect is a definite increase in the standards of medical infrastructure, once the clinical research started. This is a reflection of the fact that general population has benefited by investment made by sponsor companies to perform clinical research. The second impact is that the effect of Clinical research activities on economy is also uniformly positive. This results from new job creation that leads to downstream economy. But additionally, it also follows from having healthier humans (those who received medical benefits of clinical trials) who pay more taxes and who further pedals the economy by spending. All in all, the size of these benefits (as measured in various markets) is significant enough not to loose on them and many countries are actively pursuing clinical research to get these benefits.

Keywords: Clinical Research, GCP, Clinical trials, economy

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Introduction:

"Research is formalized curiosity. It is poking and prying with a purpose" -Zora Neale Hurston, An influential author of African-American literature and an Anthropologist.

As Zora Hurston put down, Research is essentially poking and prying in a very crude sense. Accidental "poking" over data of daily occurrences (and subsequently, much more intrusive efforts); and "prying" on the patterns of those occurrences - led humans to build knowledge; that ended up discovering world's oldest and most widely used group of anti-bacterial agents called Penicillins. Many such discoveries of yesteryears were accidental; but they became the foundation of scientific approaches to biopharma R&D. We are benefitting from these approach even today and keep maturing them further. The act of Drug development has since evolved significantly and has been more or less standardized, across the globe.

Current drug development pathway is largely defined by requirements or specifications that Regulatory agencies worldwide have built in their respective regulations. However, they are a reflection of innumerable scientific, cultural, economic, social and other factors (or incidences e.g. Thalidomide tragedy) that influenced the pathways design/ specifications. A case in example is changes in FDA regulations that resulted from the knowledge about potential of certain classes of drugs for QT prolongation. FDA provided a detailed guidance for Pharma industry for this element and a new business, 24/7 cardiac monitoring during clinical trials came into existence. New information/ knowledge about possible risks - affect how FDA and other regulatory authorities assess (and hence influence) drug development efforts. It is a classical chain reaction - where knowledge from today's research influence the research pathways of tomorrow's dugs and that results into further downstream effects like more expenditure, longer wait for drug, higher barriers for research, more patients in trials - before a drug is born.

Between 1928 (when Penicillin was first discovered) and 1942 (when it started being widely used to treat infections[1]) - many patients had to die, waiting for a cure that Penicillin could have offered. While the wait of 14 years was a result of an accidental journey that Penicillin had to go through - all of our newer biopharmaceuticals (NCEs and NBEs) mandatorily need to go through a similar journey called Clinical trials, before being approved for use in market conditions.

Since clinical research is arguably the phase of drug development that consumes largest amount of (a) R&D investment (b) R&D time and (c) R&D human efforts - it is bound to have the largest impact on humanity - socially and economically.

This article attempts to review such socio-economic impacts of clinical research. As with any other socio-economic analysis, we have had to put many "informed"

estimates in quantifying the impact. Additionally, we had to build this article as compilation of similar, smaller articles, separately written for various geographies, rather than a holistic worldview (which would have been interesting, enormous - but erroneous), for want of standard data-sets from all countries.

Clinical research:

Clinical research may loosely be defined as any stage of research where an un-approved research drug (to include device also) is introduced in humans. This does not include accidental or un-intentional exposure, neither has it referred to any activities that's not in alignment with ethical principles mentioned in the Declaration of Helsinki - first introduced in Jun 1964 and subsequent updates.

Because of the risks associated with such experimentation - methodology of Clinical research has been designed to be quite staggered, where each new phase of development follows (a) a careful review of the data produced in the previous experiments (b) and the fact that the latest data justifies moving ahead to the next phase of research. Essentially this leads to a "Linear" path of drug development and hence not always the most efficient way of development. However, Regulatory agencies in collaboration with biopharma industry worldwide, have come up with more efficient and scientific approaches for clinical research (e.g. Adaptive clinical trials, experimental IND etc), without increasing the risk.

The process of clinical development is broadly classified as below:

Phase 1: This phase of clinical research involves exposure of the study drug to a very small number of people (mostly healthy volunteers, but patients in some settings). The objectives associated with this phase of clinical research are largely driven by "safety needs" rather than "efficiency". However, studies in this phase may also reveal many other elements related with PK and PD behavior of the research molecule e.g. Absorption profile in humans, Interactions with food or other influences, Bioavailability of the molecules and information about metabolism and excretion. Some literature further classifies this phase in Phase 0 and then Phase 1 - which is a semantic differentiation. In these literatures, Phase 0 clinical research is defined as micro-dosing or sub-therapeutic dosing of the Investigational drug to achieve the same objectives (PK,PD& sometimes cellular level information) mentioned earlier. There are no set guidelines on number of human volunteers/ Patients that can be subjected to this phase (0 or 1) - but literature puts this number as anywhere between 20 to 100.

Phase 2: In this phase of Clinical research, the development objectives are expanded to get more information on how the Investigational drug behaves in patients (as compared to healthy volunteers in Phase 1), what's the safety profile of the drug in patients, what's the efficacy behavior of

the drug in patient (early indications), How optimum is the formulation and whether any formulation changes are needed etc. Phase 2 essentially determines whether the Investigational drug can be tested in larger number of patients or not. Depending on the variety of objectives for the research - there can be multiple Phase 2 trials running in parallel or overlap or sequence. There are no set guidelines on number of patients required in Phase 2 - but usual numbers are upto 300 patients. Phase 2 trials can also be sub-classified as Phase 2a and Phase 2b - where Phase 2a indicates a focus on safety while Phase 2b indicates focus on efficacy in patients.

Phase 3: This phase indicates the large scale exposure of the Investigational drug to patients with targeted clinical profile. By the time a drug reaches Phase 3 trials, a significant data is already available for the safety of the molecule in patients and focus is to ascertain efficacy objectives and safety profile of investigational drug in larger patient population. There can be multiple Phase 3 trials running in parallel and/or sequence, where one of them serves as "Pivotal" trial. The results from this Pivotal trial forms the basis of marketing approval from the regulatory agencies. Other trials in this case serves to provide supplementary evidences, dosage info, refined target patient population etc. This phase (phase 3) can also be further sub-classified as Phase 3a - that denotes continued focus on safety and 3b that denotes focus on efficacy objectives. There are no set guidelines for number of patients involved here too - but general size varies from 300 to 3000 patients depending on the statistical model. **At times, these trials are also used to collect other ancillary data for evaluation of economic benefits, comparison of patient experience amongst competing therapies.**

Phase 4: This phase of clinical research is a connecting link between clinical research that's done in highly regulated research setting and actual exposure of the approved product to the masses. This phase of research may be indicated as necessary by regulatory agencies while according marketing approval OR may be done by the sponsor company to gather additional information that helps in marketing message for the drug. Largely, these trials are aimed at collecting data of wider exposure of the drug, including HEOR (Health economics & Outcome research), Post-marketing obligations to submit AE data etc.

Why study impact of clinical research on humanity?

As mentioned above, out of all R&D activities - Clinical research can have the biggest impact on all of us, because these research efforts are highly intertwined with how we live (also in alignment with the objectives of clinical research i.e. exposing Investigational drugs in controlled, scientific and ethical way to human beings).

A classical example[2] of how clinical research affects the society - is probably as old as first attempt of conducting clinical research on humans.

The first recorded experiment resembling a clinical trial was not conducted by a medical, but by King Nebuchadnezzar a resourceful military leader. During his rule in Babylon, Nebuchadnezzar ordered his people to eat only meat and drink only wine, a diet he believed would keep them in sound physical condition. But several young men of royal blood, who preferred to eat vegetables, objected. The king allowed these rebels to follow a diet of legumes and water — but only for 10 days. When Nebuchadnezzar's experiment ended, the vegetarians appeared better nourished than the meat-eaters, so the king permitted the legume lovers to continue their diet. It is hard to imagine now - but classically demonstrates how human beings may be impacted by conduct of clinical research.

In current times, Clinical research is very intensely governed by regulations based on ethical principles (which obviously have very high human touch) and its impact on our life has only increased since 562 BC (the time of Nebuchadnezzar).

Having established the point that there is a materially significant impact of Clinical research activities on human society, let us explore some general phenomenon that reflect the impact of clinical research on the world:

Globalization of clinical research:

While the earlier Pundits of Clinical research & the Regulatory agencies defined the phases of Clinical research - they would not have an idea how far this research will grow. This is evident from the fact that none of the definitions of Phases i.e. Phase 1, 2, 3 or 4 - define trials in terms of geographic spread, ethnicity of the participants etc. It just speaks of the research objectives & number of volunteers/ Patients. Global spread of clinical trial is dealt with, in a case by case manner within a wide spectrum in a pivotal trial (all patients from USA to no patients from USA).

As evident from the infographic[3] below - Number of clinical trials intended for submission to the US-FDA have proliferated far, wide & thick. The 4 snapshots below captures the number of trials registered on clinicaltrials.gov in 4 decades, from 1980 to 2018. It paints a very interesting picture of how clinical trials have spread over the years.

Driven by the economics of the effort - globalization of clinical research has led to variety of effects on us, some of which we will review in country specific analysis also. However, the most important effects of globalization of clinical trials are:

- Increase in number of uniformly trained (ICH-GCP) Investigators & clinical research professionals around the world
- Access to newer medicines/ devices/ procedures - in the remotest regions of the world
- Downstream economy from activities that support clinical research in newer region

Impact of process of Clinical research on health service outcomes[4]:

While the Clinical research activities proliferated across the world - global healthcare markets did not necessarily have similar service standards. Worse, even within same countries; healthcare service levels varied significantly from each other, based on factors like Government facility v/s Private facility, Self-pay versus Payers, Rural v/s Urban and more. Clinical research got globalized on top of vastly dissimilar healthcare standards in different markets.

Did the globalization help in equalizing the healthcare standards?

While there is ample literature that shows "first translation gap" i.e. the gap between Laboratory research and Clinical research, there is hardly any literature that described "second translation gap" i.e. difference between Clinical research (conducted in dissimilar settings) & how the results from these trials are implemented in real-world. A workshop was organized in September 2009 by International Agency for Research in Cancer, at Lyon, France - that focused on dwelling upon this aspect. The participants in the workshop came out with some startling view on how the research activities affect the service standards in healthcare facilities:

- Participants strongly agreed on importance of the subject - Comparing the Healthcare service outcomes between trial participants and non-participants in similar set-up. However they also agreed that it was quite difficult to study this for variety of reasons.
- There was preliminary evidence to suggest that a Research active system improved clinical performance.
- There have been efforts all around the world, to develop comprehensive infrastructure within healthcare system to support and promote clinical research.

While the workshop could not establish evidence or direct link between clinical research and improvement of Health service outcomes, there are enough of surrogate evidences to suggest that service standards amongst erstwhile heterogeneous countries - are increasingly being "assimilated" because of Clinical research.

Social Media and Clinical Research:

Because of the ethical & confidentiality regulations around Clinical research, one might expect not to see much information/ engagement of trial subjects through social media. However, Social media having become such an inseparable part of our "being" nowadays - early signs of a huge impact (that social media can have in future) are becoming increasingly visible[5]. Some examples:

- Many of the frontrunner regulatory agencies e.g. US-FDA and EMA - have come out with guidance documents or other communications,

attempting to address the usage of social media. At this stage, the guidelines are quite general - but they are certainly a welcome sign.

- Novartis used a Twitter feed to boost awareness about a phase 2 trial involving stomatitis and breast cancer, and others have used textmessaging.

- Many regulatory agencies as well as Pharma companies, routinely monitor social media feeds to identify and process Adverse events, reported by patients in social media feeds (social media listening).

- Companies routinely build specific websites for their large clinical trial programs. Currently, the scope of most of these website stays limited to engaging investigators, CRO teams and others. However, with clearer guidelines, Social Media can become the choicest of tools, to achieve Patient centricity in clinical research.

Millennial and their influence on Clinical research:

While we are dwelling upon how Clinical research has impacted humanity, it might also be a very interesting to see how the new generation of millennial physicians is changing clinical research itself. In some ways, the active engagement of millennial generation to change/ challenge the process of clinical research itself indicate a socio-economic impact of clinical research! Few very interesting examples are given below:

- Early & intense collaboration: Matthew Howes, executive vice president, Strategy & Growth for PALIO, wrote, "We should expect this generation to tear down walls between sponsors, vendors, and sites involved in clinical programs. Drug development of the future will see research sites and investigators brought in, before protocols are developed to create a highly collaborative team environment". This prophecy statement written in 2011 - looks quite real now in 2018 - just over past 7 years.

- Technology integration: The advent of technology in clinical research has been much fast paced in recent years, compared to the first 3 decades of clinical research. This is a reflection of millennials' willingness to think beyond the legacy inefficient systems and integrating newer technologies in research activities. Online tools like RateClinicalTrials.co.UK, PatientsLikeMe and Yelp - significantly engage patients and improvise their participation. Movement of trial data from disjointed databases to integrated clouds - is making the decision process quick and efficient for Sponsors.

While we did highlight the positive side of impact of clinical research, we must also not forget about following general issues associated with clinical research:

- **Ethical issues**: The issues around problems in Informed consents, how "voluntary" the consent is etc.; are frequently referred to in global media. While these might not be 100 % substantiated, it is quite essential that all we form our regulations and practices in a way that can ensure an over-compliance to the ethical principles in Declaration of Helsinki.

- **Access to trial V/s Access to medicine**: While clinical trials give an early access to the newer medicines in a research setting, it does not guarantee the access to successful products as companies don't always launch it (soon enough) in the market that they use for trials.

We will now study country specific impact of clinical research as they are studied and reported:

Africa, Burkina Faso: Africa has generally witnessed a lot of research activities for diseases like HIV, Infectious diseases and especially Malaria. Largely these activities were sponsored by philanthropic organizations as well has world health bodies like WHO, UNICEF and many others. The research proliferation has been heterogeneous with some of the geographies having received a lot, while some have not seen any research, despite having a lot of disease burden.

Conducting clinical research in African continent is quite challenging because of infrastructural as well as geo-political issues. However a sample of how clinical research can positively benefit the general population, has been nicely documented in a case study[7] reported from Burkina Faso.

The need for conducting clinical trial in Malaria in the region, led to creation of Clinical Research Unit of Nanoro (CRUN) - which effectively led to building of an entire ecosystem to conduct International standard clinical research. Following tangible changes were achieved:

- Between 2008 and 2013, a fully functional, ICH-GCP compliant research facility was established in Burkina Faso that attracted a total of 25 research grants from Private and Government agencies to conduct more research.

- Research team grew in the same time from 10 to 254.

- A Health and Demographic Surveillance System (HDSS) was set up, that covered a total population of about 60,000 people spread in 24 villages.

- The research facility got the electricity connection from National grid, which was then extended to entire village, resulting into positive engagement of population.

- A clinical laboratory was set up (first in that region) with modern equipment, resulting into a positive outcome in overall healthcare provision scenario.

While in rural, undeveloped geography clinical research may generate negative perceptions; socially engaging efforts like the above can build a positive environment for people and en ecosystem to conduct more research. Efforts like these, can also contribute to the micro-economy of poorest of the poor regions.

Australia:

Despite its very thin population density, Australia has very proactively aligned its healthcare system to attract global Clinical research. The impact of the trial activities is very clearly evident in two separate reports [8,9] published in 2017.

The first report[8] attempted to estimate the value generated by Clinical research, by measuring Economic activity. This study considered the clinical research activities including both Industry sponsored Clinical trials as well as Investigators Initiated trials. Following infographic suggests a holistic representation of value generated by clinical research, directly as well as through downstream effects:

The findings (below) from this study are suggestive of huge impact on Australian healthcare system (and hence on population, in general):

- A total of 1360 trials started in 2015 and there were 6,900 trained professionals were available to support these trials.
- Total direct expenditure for ongoing trials in 2015 - was estimated at $1.1 billion (for a comparison, entire Australia's expenditure on Health and Medical R&D was about $4.3 billion in 2008).
- The above expenditure leads to downstream (flow-on) benefits to the participating patients as well as to the sector. This led to a multiplier impact, by having more spending by those earning from these activities, as well as more healthy individuals who paid taxes to the economy.

The anticipated economic benefits from R&D investment are perceived so "Assured/ Guaranteed" that Australian government has created a designated fund - MRFF for the same. MRFF will receive any savings from Health and Hospitals fund (HHF) and it has already grown to the tune of $4.6 billion in 2016. This MRFF will fund Investigators Initiated Trials as well as initiatives that can grow Australia as a world class Clinical trial destination.

Another study[9] from Australia attempted to evaluate the economic impact of Investigator Initiated Trials (subset of all trials), on a sample set of 25 trials and extrapolated the results from that detailed assessment to derive the below conclusions:

- Gross benefit for the 2014 year was estimated at $ 2 billion resulting from better health outcomes and reduced healthcare service costs.
- Reduction in healthcare service cost (on account of clinical trial activities)

was about 30 % of the gross benefit $ 580 million and it was larger than the total cost of three Trial Networks from 2004 to 2014.

- The overall consolidated benefit-to-cost ratio for the networks is 5.8:1, or a return of $5.80 for every $1 invested.
- The results of the 25 trials only needed to be implemented in 11% of the eligible patient populations for benefits to exceed costs.
- For every $1 awarded in National Health and Medical Research Council (NHMRC) grants to the 25 trials, a return of $51.10 was achieved.
- Just 9% of the $2 billion gross benefit from the trials in this study, was equivalent to all NHMRC funding received by all Australian networks between 2004 and 2014.

However startling the above numbers may look like, they surely point to a conclusion that Clinical research conducted in a country, results in a positive pay-back to the healthcare system and Australian government is proactively leading to gain these benefits.

Belgium:

Belgium historically holds a leadership position in participating in Clinical trials with a per-capita participation in trials holding as high as 9%. Belgium is also one of the world's leading countries in terms of site density i.e. number of sites per a million population. Belgium's position is only second to the USA.

However the landscape of Clinical research is changing and Belgium is fast losing its position as a preferred destination for clinical trials, to emerging countries.

Stakeholders from Belgium's pharma industry, regulatory bodies and healthcare network engaged reputed consultants PwC to research the current position of Belgium (in 2012) as well as to prescribe initiatives that can increase the clinical research activities and hence benefit from them[10]. Following data from the report - highlight the impact of Clinical trial activities on Belgian population:

- Clinical trial generate employment and contribute significantly to the local economy and also help translate the knowledge in better ways to treat diseases and improve healthcare.
- Although Belgium represents only 2.7 % of European GDP, its pharmaceutical industry represents a higher share of employment at 4.9% as well as higher R&D investment (6.6%) within Europe. This is reflected in the fact that percentage of people employed in R&D (4,600) out of total number of people employed by Belgian pharmaceutical industry (i.e. 32,200) is high at 12 %.
- Clinical trials constitute a significant share of these higher employment and investment. As surveyed in select

hospitals, 13 % of their annual budget was coming from income generated from Industry sponsored clinical trials.

Brazil[11]:

Brazil also has been having its fair share of clinical trials over past 20 years. Average relative rate of growth of trials (listed on clinicaltrials.gov) in Brazil is at 16 % versus the general growth experience outside Americas at 15%. However there is a significant need & capacity to conduct more clinical trials.

This is because Brazil enacted in 1990 a Unified Health System, which decentralized the provision of healthcare at Municipalities level. This healthcare is provided free of cost to the patients in need and who are not having any means. However the recession and local political situation has led to a decrease in the budget availability for the Universal Health System by $ 1.1 billion. So while the burden of diseases like Cancer is rapidly increasing in Brazil, available budget for the same is decreasing.

Brazil is consciously putting efforts in place that will facilitate more clinical research in Brazil and thereby (a) help Brazil's healthcare system in attaining global standards and (b) reduce the economic burden by having more patients receiving medical care by clinical trials. Below are some recent initiatives:

- A new law is under approval mechanism to expedite the regulatory approvals (which currently takes nearly 1 year). Even before it is enacted, the agencies have started reviewing the trial applications in 6 months time and hence this is already being achieved.
- On lines of similar efforts in other LatAm countries, Brazil is also coming up with Cooperative groups for Cancers. This will have a huge impetus on bringing patient awareness, getting better epidemiological data recorded and hence making it more transparent for sponsor companies.

Canada:

Canada has embarked on a mass collaboration to help her regain the human, social, and economic benefits of clinical trials[12]. There is a clear understanding and vision amongst all stakeholder groups about the economic and healthcare benefits that the country can gain by conducting Clinical research. Unfortunately, Canada is losing clinical trial opportunities that allow patients access to leading-edge drugs/devices, keep researchers at the forefront of clinical innovation, and generate economic benefits. While Canada offers great science, comparator countries who are more nimble at initiating trials are becoming preferred partners for industry investments.

To rebuild Canada's advantage, industry, academic healthcare, government and others have agreed on an action plan; secured resources and political will; and

begun initial work. To expedite progress, a Canadian Clinical Trials Coordinating Centre (CCTCC) is set up and being funded by Canada's Research Based Pharmaceutical Companies (R&D), the Canadian Institutes of Health Research (CIHR), and the Association of Canadian Academic Healthcare Organizations (ACAHO). Also, all stakeholders got together and built a nine point consensus plan, to attract more clinical trials in Canada. Following actions are being planned:

- Building of a National Advisory Panel - one single body to lead and coordinate measures to increase clinical research activities in Canada.
- Under the leadership of CCTCC, following trust building measures would be included in the action plan:
- Shared goals for all stakeholders and commitment for shared actions too
- Capacity (training of resources, building of coordinating centres, awareness amongst the patient population) building efforts, ultimately leading to more trials in Canada and more participating patients

As is evident from the above directional goals/ action items - will have an immense socio-economic impact on population.

Denmark:

Denmark has a population of about 5.3 million and had a GDP of USD 306 billion in 2017. For a relatively smaller country and economy like Denmark, it has significantly accurate estimates of socio-economic impact of clinical trials in the country. Below statistics is derived from an executive summary of "The value of Clinical trials in Denmark" that was published by Copenhagen Economics in July 2017. It lists some interesting facts as below:

- Each clinical trial initiated by the industry improved Danish GDP by an average of 902,000 kroner & boosted public finances by an average of 1,169,000 kroner.
- For every 1 krone spent by private companies on clinical trials in Denmark, a 64 øre increase in GDP is generated. This return is in far excess compared to the money invested by the pharma companies and indicates that placement of trial in the country is important.
- In 2015, Pharmaceutical companies spent 248 million kroner in clinical trials, thereby improving the quality and capacity of the public health sector. In practice, this expenditure occurred by paying for the time of doctors and nurses, as well as by sponsoring medicine and medical equipment employed at hospitals.
- On an average, 1 clinical trial initiated by the industry generates 5.3 FTEs employment, consisting of 3.1 FTEs in the private sector and 2.2 FTEs in the public sector.

- For every 1 million kroner a pharmaceutical companies invested in clinical trials, employment of 1.3 FTEs is generated, consisting of 0.5 FTEs in the public sector and 0.8 FTEs in the private sector.

Hungary:

Statistics reported[14] for Hungary also establishes a significant socio-economic correlation on account of Clinical research in the country.

- Clinical trials increased the revenue of Hungarian health care providers by US $165.6 million.
- The value of IMPs (Investigational products) was US $67.0 million - meaning that the patients benefited to the tune of this amount, by participating in clinical trials.
- Clinical trial operation and management activities generated 900 jobs and US $166.9 million in revenue among CROs and pharmaceutical companies.
- The contribution of clinical trials to the Hungarian GDP in 2010 amounted to 0.2%.

Ireland:

The socio-economic benefits of clinical trials observed in Ireland - are largely on the same line as observed globally i.e. (a) Early access to newer medicine for patients (b) reduction in cost for patients and for payers (c) expedited entry of newer medicines in the geography that also has a downstream positive impact on societies and government in terms of better healthcare scenario (d) Economic benefits, direct, indirect and induced.

A sample of these benefits are outlined in a study[15] that was commissioned by Cancer trials Ireland and was reported by DKM Economic consultants in 2016. Highlight of the socio-economic impact outlined in the reports are as below:

- Cancer Trials Ireland projected an income of Euro 7.5 million in 2016 - nearly half (Euro 3.06 million) was contributed by the Exchequer.
- For some hospitals, 1 Euro received in grant funding, resulted in attracting an income of Euro 3 from Industry for trials. This made the hospital institutions financially stronger and hence more able to support patient care.
- Drugs savings directly to HSE (Ireland's Health services) from alone cancer clinical trials was to the tune of Euro 6.5 millions. Additional saving was in form of cost of experimental drugs, cost of avoided treatments, improved health and longer lives for patients and downstream benefits in terms of less health burden for future.
- Clinical trial activities added a total of Euro 16.5 million to Ireland's GDP and a revenue to the exchequer of Euro 5.8 million per annum.

Italy:

While there have not been an extensive research conducted in Italy to study the Socio-economic impacts/ benefits of clinical research, Ipolitti et al[16] conducted a retrospective cost analysis on all patients with MPM (Malignant Pleural Mesothelioma) who were admitted between 2014 and 2015.

Result suggested a significant decrease in cost of treating first line patients, where cost of chemotherapy is relevant. Results suggested that the expected reimbursed fee to care for a patient with MPM was approximately Euro 18,214.99. This amount was reduced to Euro 320.18 only.

It might be very interesting to review the impact on a much wider scale in Italy, considering the size of the country and pharmaceutical market.

Thailand:

Clinical research industry represents a significant source of innovation and economic prosperity for Thailand. A study[17] commissioned by Pharmaceutical Research and Manufacturer Association (PReMA) and conducted by Deloitte brought out some interesting details on how the Clinical research is having an impact on Thailand.

- In 2015, a total of USD 320 million were spent on Clinical trials in Thailand. Of these, about USD 120 million were spent by Industry.
- About 111,000 Thai people participated in clinical trials in 2015.
- Every dollar spent on Clinical research in 2015, yielded a return of dollars 2.9.
- About 8,905 people were employed in conducting clinical research. This resulted in an economy of USD 150 million towards remuneration of these staff.
- Additionally, another 6,604 employees indirectly contributed to the clinical research activities.
- Trials contributed to Thailand's GDP to the tune of USD 270 million (representing about 0.05% of GDP).
- For trials conducted in 2015, expected net economic return from medicines produced was estimated at USD 13.4 million.

The above study also came out with clear recommendation on the policies to be adopted to get more clinical research in Thailand.

United Kingdom:

UK represents the developed market for Pharmaceutical Research, Manufacturing and Consumption. Though there are no studies conducted to represent entire UK market, KPMG published a report[18] in 2016 that selectively estimated the economic impact created by Clinical Research Network of National Institute of Health Research (CRN-NIHR).

It is important to note that the impact shown below is only for clinical research activities conducted by NIHR-CRN. The overall impact would be larger - if we consider all other research activities being conducted in the UK.

- The report estimates that in 2014/15, CRN supported clinical research activities generated GBP 2.4 billion of GVA -Gross value added and about 39,500 jobs in the UK.
- Additionally, CRN got an additional revenue & cost saving of GBP 192 million.

While the above study was initiated with an objective of taking a stock of the current situation, it also has resulted into an action plan that intends to proactively measure all aspect of economic activities at CRN level, NHS level, Hospital and site level, to better estimate the same.

With a large market size and mature eco-system for conducting Research, impact of these size are bound to have downstream impact on society and government and entire healthcare chain.

USA:

Being the largest market for Pharmaceuticals and at the forefront of cutting edge research, the stakes involved are quite high for USA. This naturally will have a direct impact on the healthcare providers, payers & patients. PhRMA commissioned a study with Battelle Technology Partnership practice in March 2015 - to understand and estimate the economic impact of clinical trials on state economies. The report "Biopharmaceutica Industry-sponsored Clinical trials: Impact on state economies"[19] highlights following points:

- In 2013 the biopharmaceutical industry sponsored 6,199 clinical trials of medicines in the U.S., involving a total of 1.1 million participants.
- The biopharmaceutical industry spent nearly $10 billion directly in the conduct of clinical trials at the site level across the U.S. in 2013. These amounts are in addition to the significant resources invested in clinical trial-related activities occurring outside the individual trial sites, either within biopharmaceutical company facilities or by their contractors and vendors.
- When considering the overall impact of site-specific clinical trial activity across states, i.e., the ripple effect of expenditures by clinical trial vendors and contractors and spending by industry and vendor employees, biopharmaceutical industry sponsored clinical trials generated a total of $25 billion in economic activity in communities throughout the U.S.
- The five states with the highest number of active clinical trial sites were California (3,111), Texas (2,799), Florida (2,571), New York (2,476), and Pennsylvania (1,972).

The report provided granular details of how respective state economies were positively benefitted from the clinical research.

India:

India's journey on Clinical research has been turbulent - to best describe the phenomenon. It started in late 1990s when a few multinational Pharma companies and CROs came forward to start conducting clinical trials as per ICH-GCP standards. Ironically, most of the medicines which were not available in India - got their Marketing approvals in India without any trials in Indian population (based on global data).

As the field of Clinical trials kept growing in India, the regulatory framework kept maturing better and better (which may also be considered a very positive impact of clinical trial on Indian population). This applied not only to the regulations pertaining the clinical trials, but on all aspects of Drugs control in India.

Between late 1990s and early 2000s, Clinical trial activities grew very well because of a positive regulatory mechanism for approval. However, the monitoring of clinical trials did not reciprocate the ease of getting approval and hence the activities came under a lot of criticism.

Late 2000s and early 2010s - the sector struggled a lot with credibility issues both with the industry fraternity that was conducting clinical trials, but also the regulatory agencies which were monitoring and approving the same. A significantly negative perception was built up against clinical trial activities, as a result of unfounded activism and catchy media highlights.

Between the conducive decade of 1990s and 2000s - the industry grew a reasonable capacity for conducting clinical trials. Below are some approximations (personal view of the author):

- About 20,000 employees directly associated with the conduct of clinical trials
- Another 15,000 employees working to support activities related with Clinical trials.

When the industry came under a lot of challenges and regulatory restrictions, business for many companies suffered and some of them ended up winding/scaling down their business. This resulted into downstream negative impact on the economy, by way of reduced spending by employees. Unfortunately, it is very difficult (if not impossible) to quantify this impact as it was not having any proactive support from the Government, neither it itself had developed meaningful industry bodies that accurately measured & tracked the economic activities.

Last 5 years for the industry are seeing a measured, steady turn-around for the industry and little growth is seen. However, the momentum built in the previous decade (and the expertise matured over time) was lost.

When the Industry faced local regulatory challenges (incidentally, this came immediately after the global recession of 2008), many companies started re-aligning their operations and cross-utilizing India based resources for global off-shored activities. This helped the industry in multiple ways (a) it avoided a huge job loss when the sector was scaling down(b) it avoided a significant economic loss that would have ensued while the trained professionals had to change their field of specialization and re-align their service offering and (c) it started the phase of KPO activities in Pharma R&D, clinical trial trained resources started doing activities like global DM, Medical writing, Pharmacovigilance, back-office ops for Clinical etc.

What next:

The benefits outlined for most of the countries fall into two classical area (a) Benefits to the healthcare sector, early access to medicine, faster clinical development, better care and upgradation of healthcare service standards, many more...(b) Economic benefits - direct, indirect, induced.

In whatever way that we try to comprehend the socio-economic impacts of clinical research, it does point to the need to facilitate these activities and strengthening the sectors. Many countries worldwide are already doing this and others are following suit.

For India, we are clearly sitting at a junction, where any further delay (to attract more clinical research) will push the country behind, in terms of attaining the benefits on clinical research already done so far. While not immediately visible, any delay in strengthening the sector will delay the launch of newer medicines in long term and this will have serious social and economic impact on future generations.

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