Pakistan Clinical Research Landscape Report 2022

A COLLABORATIVE PROJECT OF

APPNA MERIT AND **BMY HEALTH**

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Foreword

Clinical research is one of the most important activities that a medical professional learns for the development of scientific knowledge, guiding interventions, and clinical practice guidelines, and improving patient care over the course of time. Besides informing decision making and policy, they can be a good source of foreign exchange earnings. With one COVID-19 clinical trial, Pakistan received USD 8-10 million foreign investment. India generates as much as US$ 4-5 Billion annually with clinical trials. The scope of this market is now increasing globally, and a shift is being observed in the target locations of these investments. Recently as many as 53% of trials are shifting to South Asia. Global pharma companies are expressing serious interest now in conducting their Pharma and Vaccine CTs in Pakistan also. Though, Pakistan's contribution in the clinical research space has remained insignificant in the past, but the recent shift to South Asia brings hope for us. The need of the hour is that Pakistan realizes its potential and compete to get its due share, with the right policies and mechanisms in place. The government and sponsors need to be made aware of our huge untapped potential for expanding this market. There is a high disease burden, treatment naive population, relax regulatory policies and a growing interest in research and development of clinical trial sites recently.

For engaging stakeholders, a detailed analysis of the current trends of clinical research and a situational analysis of clinical research ecosystem in Pakistan has been presented in this report. Analysis of all main factors forming ecosystem has been done including regulation, clinical research infrastructure, trials affordability, human resource availability, and data availability. The information required to analyze was based on literature review and transcripts from a series of webinars arranged by APPNA MERIT, which is an association of Pakistani physicians of North America, chaired by Dr. Babar Rao, Professor at Rutgers Center for Dermatology, USA in 2022. These webinars were held weekly, facilitated by Dr. Syed Uzair, Dr. Umar Hayat, and Dr. Sarfaraz A. Hasni, where they invited industry leaders and academia from Pakistan, those engaged in clinical research, to speak about their organization's strengths and challenges for upscaling clinical research activities. These webinars proved to be a wonderful source of sensitizing Pakistani medical community and government about the significance of clinical research, which mobilized them to revamp the system to make it further conducive for global trials. For the first time, myths regarding Pakistani clinical research potential were removed by inspiring industry leaders. The performance of our sites is now visible to the world, giving us hope that we get our due share in clinical trials in future.

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Abbreviations

CT	Clinical Trials
CTU	Clinical Trials Unit
BA/BE studies	Bioequivalence/ Bioavailability studies
CRO	Clinical Research Organization
DRAP	Drug Regulatory Authority of Pakistan
CSC	Clinical Study Committee of DRAP
NBC	National Bioethics Committee Pakistan
CTA	Clinical Trial Application
IMPs	Investigational Medical Products
R&D	Research and Development
JCI	Joint Commission International
ICH-GCP	International Conference on Harmonization- Good Clinical Practice
HEC	Higher Education Commission Pakistan
PHRC	Pakistan Health Research Council
HRI	Health Research Institute
NIH	National Institutes of Health
FDA	Food and Drug Administration US
NCDs	Non Communicable Diseases
HTN	Hypertension
CVDs	Cardiovascular Diseases
CAD	Coronary Artery Disease
LBW	Low Birth Weight
HIV	Human Immunodeficiency Virus
TB	Tuberculosis
LMICs	Low Middle Income Countries
MNC	Multinational Companies

Introduction

Clinical trials (CTs) are the integral means of evaluating preventive, diagnostic, and therapeutic interventions. These evaluations are required for regulatory approvals of new drugs, and clinical practice guidelines.[i] Globally, the trend of Clinical Trials is rising, as can be seen from the figure below. Trend is discussed with regards to time, coverage of populations and diseases.

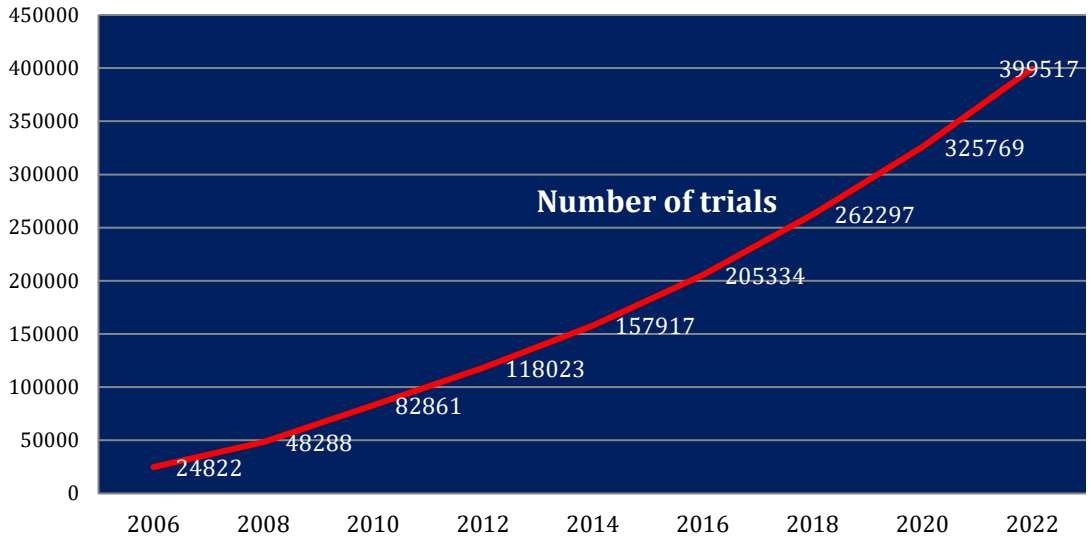


Figure 1: Number of registered studies over time
(The table shows the total number of studies posted on ClinicalTrials.gov since 2006, based on the First Posted date.[ii])

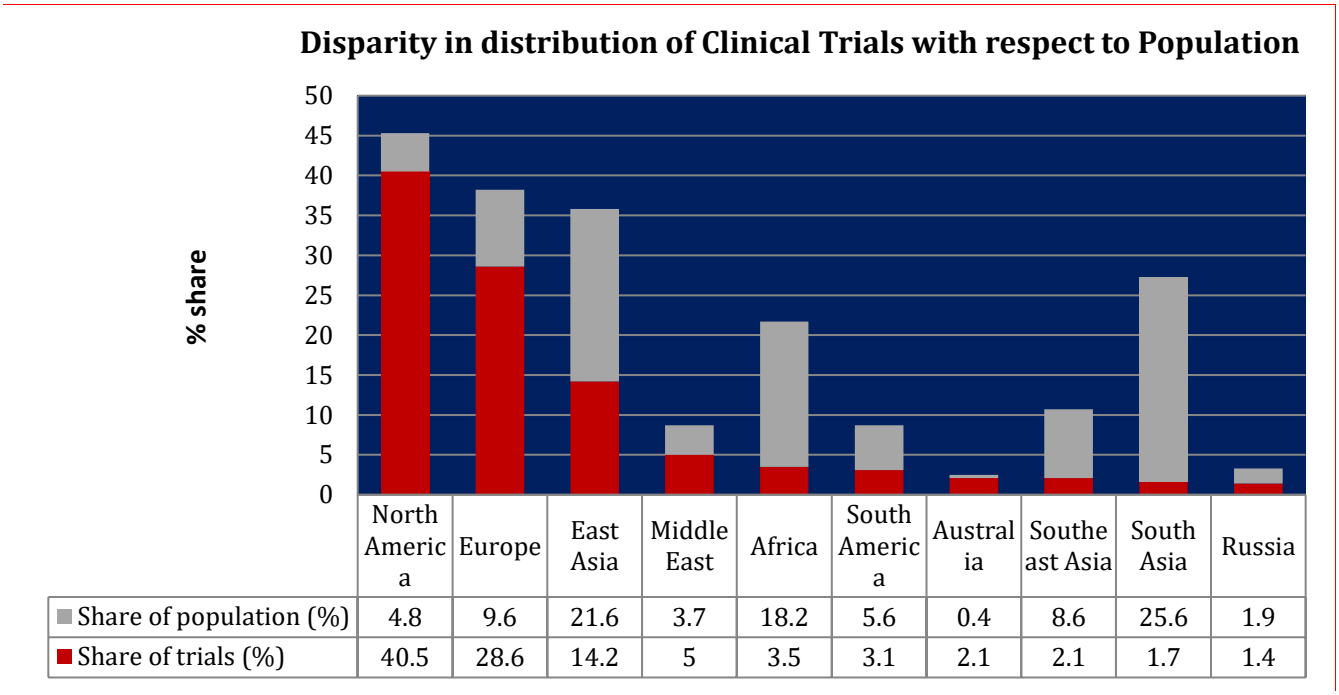
The rise in this industry is significant since COVID19. The aggregate number of Clinical Trials (CT) subjects exceeded 2 million for the first time in 2021, half of them for COVID-19.
"**Pakistan can comfortably be contributing over USD150 million in clinical research globally, if all the key stakeholders support the ecosystem in a compliant and efficient manner."** [iii]
The industry of Clinical Research Organizations (CRO), which support these CTs execution in partnership with academia, clinical setups and other research centers are a big source of revenue. In 2010, this market generated revenue of around $24 billion globally, followed by a 50% growth due to rise in CTs market up till 2015. In Pakistan, there are only few CROs and they promote their business with international funding. Multinational pharma companies (MNC) also contribute to CTs funding in Pakistan, however this contribution is lesser as compared to their funding for our neighboring countries, despite the higher disease burden in Pakistan as compared to other regions of South Asia.[iv] Though recently output of research is on the rise and two big phase 3 trials have been carried out in COVID19 successfully in Pakistan, still we are far behind in global CTs distribution.

Trends in Coverage of Regions

Global trends show most research publications have been coming from North America, Western Europe, and China making an impression that research output is maximal in big countries with big funds. This may seem

untrue looking at countries in the Middle East with low output despite big funds, Iran publishing twice as much as Pakistan with a population as less as one third of Pakistan, Israel running >8000 trials[v] in a small country with support from Diaspora and Pakistan despite being a highly populated country has run <2000 trials until 2020.

We retrieved data regarding population and number of trials in different regions of world and analyzed for equity in distribution of trials according to size of population. An overview of trials distribution in different regions of world is given below.



	North America	Europe	East Asia	Middle East	Africa	South America	Australia	Southeast Asia	South Asia	Russia
Share of population (%)	4.8	9.6	21.6	3.7	18.2	5.6	0.4	8.6	25.6	1.9
Share of trials (%)	40.5	28.6	14.2	5	3.5	3.1	2.1	2.1	1.7	1.4

Figure 2: Clinical Trials coverage of world's population[vi] [vii]

In contrast to the CTs distribution, disease distribution shows the opposite trends. Trends for some DALYs rates have been shown below.

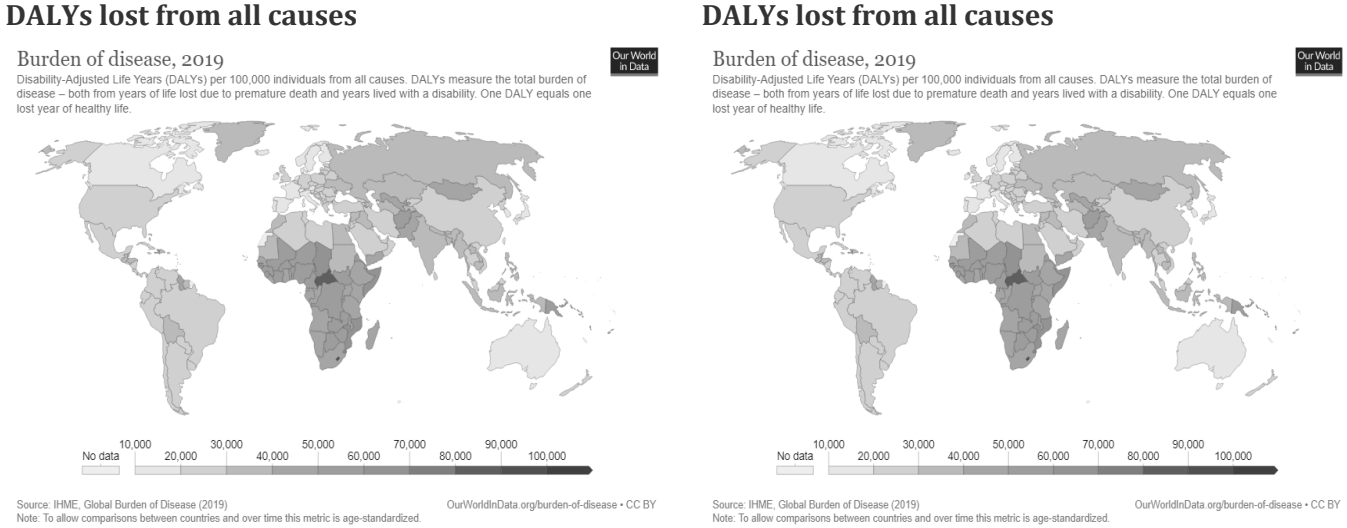


Figure 3: World map of DALYs distribution[viii]

As evident above, in developing countries despite higher disease burden, there is gross under-representation in global CTs.

"Diseases which are more common among deprived communities are being studied in healthier populations. This matters because findings from healthier populations may not hold true in communities which face greater challenges to health and well-being. It is also unjust as publicly funded research should be accessible to all." [ix]

The reasons of low representation of developing countries are lack of commercial viability and research capacity, regulatory and operational barriers, and lack of funding.[x] There a big gap in coverage of studies in terms of covering regions, ethnic groups, and covering communities according to their susceptibility to the disease under study.

Trends in Coverage of Diseases

Global demand for CTs is more in the therapeutic areas of Oncology, Infectious Disease, Rare Diseases, Gastroenterology (Hepatology), Diabetes, and Cardiology.[xi]

Oncology remains the main focus, comprising 37% of products, followed by Neurology (10%). The therapy area with the highest growth rate is eye and ear conditions (17.3%), followed by Vaccines including COVID vaccines (15.3%), oncology (14.4%) and gastrointestinal products (14.2%), with advances in cell and gene therapies and mostly focused on rare diseases. Endocrinology is one field which saw a decline in products development over the last decade. [xii]

Clinical Research Trends in Pakistan

The academia in Pakistan has been actively involved in CTs in the country. First trial dated back to 1992, 508 clinical trials were recorded in ClinicalTrials.gov until February2019, rising to 1846 after pandemic. Lead sponsors were either industry (23%), NIH (National Institutes of Health) of USA 1%, multiple sponsors, or others. 71.5% of observational trials) have been conducted in the last decade between 2010 and 2019.[1] In 2002, ICH-GCP (International Conference on Harmonization- Good Clinical Practice) guidelines were introduced and a committee was formed to oversee the implementation of Good Clinical Practice (GCP). Later, Drug Regulatory Authority Pakistan (DRAP) was given the mandate to deal with the sites and study approvals and drug import licenses for individual clinical trials. Clinical trial activities have been underway since late 90's with a surge in 2005.[xiii]

History of CTs in Pakistan

– 2005: There were more Phase IV trials. Pakistan Association of Pharmaceutical Physicians (PAPP) was active with mostly Multinationals companies and only few national companies. Trial registration was not mandatory and local trial data was not captured entirely.

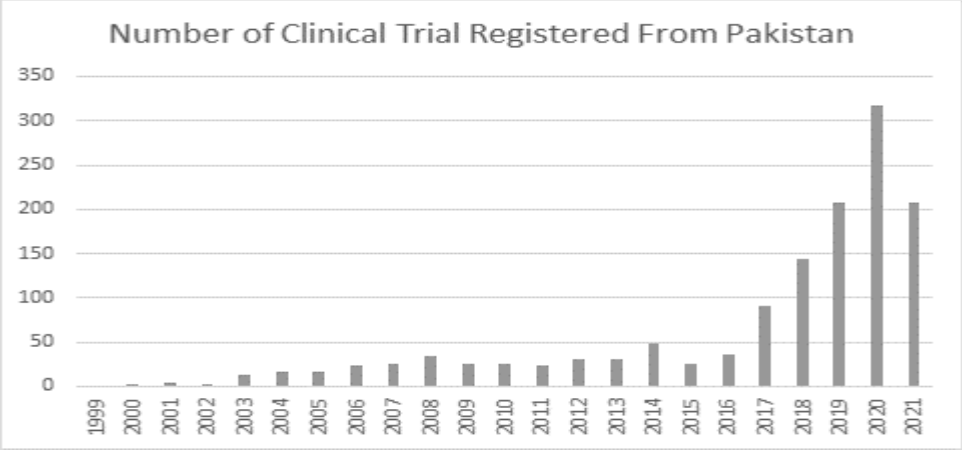


Figure 4: Trial trends in Pakistan (www.clinical trials.gov)

– 2005 onwards: Research Cooperative groups were formed. First Contract Research Organizations (CROs) started in 2005 (Dimension Research) and now there are 7-8 active local CROs in Pakistan. Partnerships with International CROs were started to promote business. Trade and Development Authority Pakistan (TDAP) realized the potential of clinical research industry in Pakistan and highlighted in a conference in 2008, inviting international sponsors.[xiv]

– COVID Era: During COVID-19, collaborations were easy and open with virtual environment. International community was more open with Pakistan for having high recruiting sites. Shifa reported that COVID19 boosted patient enrolment and randomization from 1500 in 2019 to 7000 till 2022. Fast Track Approvals were started for Vaccines, and Ventilators. Pakistan takes minimum 6-7 years in drug trials, starting from preclinical trials to 4 phases of clinical trials phases. In COVID19, phases 1 and 2 were carried out together and then phase 3 and 4 together so time compressed from 6 years to 18 months for Emergency Use Authorization as people were dying. (Dr. Javed Akram)

Analysis of Pakistan Clinical Research Market

A SWOT analysis is being presented here for clinical research market in Pakistan. Criteria presented by **Dr. Tharmaratnam** will be used in the analysis. This criteria provides insight into the selection criteria on the basis of which a country can attract clinical research business. Country attractiveness (for clinical trials) index, presented by Dr. Tharmaratnam comprises of 5 factors.

1. The most significant factor is the size and availability of **suitable patient pool**, which carries 30% weight.
2. **Cost efficiency**, which includes cost of labor and cost of facilities and travel, is weighted at 20%.
3. **Regulatory conditions** (country's regulatory laws, strength of intellectual property protection, and perspective of FDA) also carry 20% weight.
4. **Relevant expertise**, carrying weight of 15%, includes number of CROs, number of clinical trials, and size and availability of labor force with relevant skills.
5. The last factor **infrastructure and environment**, carrying weight of 15%, includes protection of IP, level of healthcare infrastructure, level of country infrastructure, country risk factors. (WTO Cell, TDAP, 2008)

A situational analysis will be done of all these factors one by one.

1. Access to Pool of Patients

Strengths

- We have a huge population with a huge burden of diseases, which can serve as the potential data to be studied. Trial sponsors can be attracted to invest in setting up mechanisms for data capture in our sites. They can be convinced with the following details.
- **Large Population**- We are the 5th most populous country, with high population growth rate. (Worldometer)[xv]
- **Literacy**- 62.3% of our population is literate and hence eligible to be considered for trials.[xvi]
- **Consent for trial**- Our patients get convinced with little monetary incentive due to poverty. This may increase after the recent flood and unemployment.

Burden of Diseases

- Pakistan has a double burden of diseases with communicable and non-communicable diseases. It is endemic for Hepatitis B and C, has fifth highest rate of TB in the world, high risk for malaria, HIV, vaccine preventable disease. We are the last country left with indigenous poliovirus transmission and are left behind for achieving targets of COVID-19 vaccination. High rates of smoking, hypertension, cardiopulmonary diseases, cancers including breast, lip and oral cavity, cervix uteri, colorectum, lymphomas leukemias and bladder cancer, and multiple factors including poverty, low literacy, gender discrimination, treatment gap, population growth exceeding more than the resources, and health access disparities between regions present as a risk to mental health. Pakistanis are still dying

with preventable diseases, neonatal diarrheas, respiratory infections, TB, XDR TB, COPD, diabetes, chronic liver disease due to hepatitis B, C and fatty liver disease, to name a few. 50% childbearing females are anemic, while 50% of school age children are obese/ overweight according to our studies. Obesity has been underestimated by WHO to be 9%. World population is aging, and Pakistan is the youngest nation in world with 32.8 million children <5 years, 50 million child bearing women, and have highest fertility rate in the world >750 children born every hour. Worldwide 15% babies have LBW, in South Asia it is 26.4%, while in Rawalpindi Pakistan it was estimated to be 27.4%, which is a risk factor for NCDs in future. Hence, we are facing a huge mammoth of NCDs. According to 2016 study, every second Pakistani is hypertensive, whether they are knowing or not. However, we are controlling <7% of HTN only, which is lowest in the world.[xvii] The recent disaster by flood has pushed us further back in the spectrum of diseases, with high rates of infections, vector borne diseases, poverty leading to further complicating diseases and mental health issues.

- Incidence of cancer in Pakistan is 730,956/annum. The population of Pakistan has been reported to have the highest rate of breast cancer of any Asian population (excluding Jews in Israel) and one of the highest rates of ovarian cancer worldwide. Recessively inherited genes may contribute to breast and ovarian cancer risk in Pakistan.[xviii]

Table 1: Burden of selected diseases in Pakistan in comparison with neighboring regions[xix,xx]

Country	Diabetes prevalence as of 2000 given as prevalence (cases)	Hypertension (urban, rural)	% under5s affected due to ARIs in last 2 weeks	% under5s affected due to diarrhea in last 2 weeks	Mortality per 1000 live births	HIV prevalence in adults 15-49 years (%)	No of new smear positive cases/ 100000 population	Estimated % of new cases with multidrug resistance
Bangladesh	2.2 (1 564)	-	18	6	47	0.02	105	1.4
Bhutan	2.1 (19)	-	-	-	-	<0.10	-	-
India	4.0 (22 878)	20%, 40%	19	19	48	0.8	79	3.4
Maldives	2.5 (3.2)	-	70	8	-	<0.10	-	-
Nepal	2.2 (263)	-	34	27	47	0.5	90	-
Pakistan	**7.1 (5 310)**	**23%, 18%**	**24**	**26**	**42**	**0.10**	**77**	**9.6**
Sri Lanka	2.6 (318)	17%, 8%	-	5	10	<0.10	26	-

Genetic differences in Pakistani population

The guidelines which we import to apply in Pakistan are not studied on our population, leading to a generalizability crisis. Some of the genetic differences are mentioned below.

- We are diabetogenic country with >50million diabetics, about 25% of our population is either prediabetic or diabetic. There is a huge genetic predisposition to insulin resistance in Pakistani population right from birth, translating into diabetes, dyslipidemia, hypertension, and obesity later.

- In Pakistan, our fat cells are not producing enough adiponectin and even that is resistant and not functioning well for satiety signaling.
- Unlike Caucasians who have general obesity, our obesity is central with organ obesity, affecting liver. Nonalcoholic fatty liver disease is rampant which in 2055 may be the biggest reason of transplants due to hepatitis B and C.
- We have diffuse atherogenesis, as compared to Caucasians and Blacks who have localized vascular diseases.
- We have a higher risk of CVDs, our HDL particles are smaller and less protective for CAD.
- Dose for some drugs such as thrombopoietin analogue for Southeast Asians is less, as they metabolize it slow.
- A recent epidemiological study of TLL showed only one female in a cohort of 40 patients which is surprising.
- Genetic diseases are prevalent in Pakistan due to high rate of Consanguineous marriages (>50%). consanguineous unions increase the expression of autosomal recessive trait, leading to the infant being at a higher risk of contracting them. It is estimated, in Pakistan 50% mortality in infancy is from genetic diseases.
- Rare diseases (potential for BIOMARKER STUDIES) in Pakistan include Morquio Disease, Wilson Disease, Mannosidosis Disease, Glycogen Storage Disease Type I to VIII, Cystinosis Disease, Colon- and Pancreas-carcinoma, Hurler Disease, Sly Disease, Sanfilippo Disease Type A,B,C,D, Gangliosidosis, Metachromatic Leukodystrophy, Maroteaux-Lamy Disease, Pompe Disease, Niemann-Pick Diseases, Niemann Pick Type C, Alport Disease, Cystic Fibrosis, Gaucher Disease, Hunter Disease (DRK Research, Ayaz Mir, Javed Akram)

Treatment trends in Population:

- We have treatment naïve population. This can be realized from the fact that in Punjab, which is supposed to be having the best performing healthcare system, majority of our females were not coming for first visit, only one third were coming for second visit, and 2/3rd deliveries were not attended by skilled birth attendants.
- Moreover, there is a lack of access to treatment. Taking the example of dialysis, we see there is a huge burden of renal failure due to diabetes and HTN, for which we need 600,000 dialysis machines, however we only have 29000 machines and mostly people die without getting this facility. Insulin use should have been the highest in the world according to the disease statistics, however insulin utilization of whole Pakistan is less than mere London.

Weaknesses

- Patient education and awareness lacking for clinical trials.
- Patients sign consent and still not understanding its real context, and not knowing rights to withdraw.

Opportunities

- Many international sponsors are now convinced with reducing the research gap in LMICs due to high disease burden in these countries and their attention can be gained to improve awareness regarding clinical trials in our population also.

Threats

- Because of low education and cultural differences with trial sponsors, there is an issue of spreading myths and conspiracy theories related to any new vaccines sometimes leading to difficulty in subjects' recruitment in trials.
- Poor health seeking behavior of our population sometimes lead to difficulty in enrolling some patients in trials.

Table 2: Recommendations for Access to patients

• Taking Education sector on board as a stakeholder in clinical research initiatives and improving literacy of population. • Conduct action research to improve patient awareness regarding trials and informed consent.

2.Cost Efficiency and Affordability of Trials

Strengths

- Low operational cost makes research up to 90% economical than in US because of cheaper rates in Pakistan rupees, low demand of investigators, and clinical researchers, cheap laboratory investigations, and other procedures required in trials.
- NBC charges 20,000 for multicenter study, 50,000 for reviewing private industry funded proposal, 200,000 to DRAP and 100,000 for site approval.
- Relaxed duties and taxes on import of test articles and supplies
- There are fund disbursing sources like NIH, HEC, Pakistan Health Research Council (PHRC), Pakistan Science Foundation, Science and technology, Global fund, Islamic development bank, Asian Development bank, Pakistan Society of Internal Medicine, international donors like Fogarty, and Bill and Melinda Gates. Universities also provide some funds to their researchers. For grants <20 million, Pakistan Science Foundation is followed, which is easier to work with and if budget required is higher than that, HEC can be contacted. Some trials are also funded by the national pharma industry. MNCs do not fund investigator-initiated research while local pharma industry funds them, where mostly in Pakistan our research is investigator led. (Dr. Javed Akram)

Weaknesses

- The little funding that is available is not utilized effectively according to research priorities, and this is combined with misuse of funds.
- There is insufficient contribution of the pharma industry in investment. They do not invest in trials as there is little return on investment due to drug pricing control by the government.

- Most research funding comes from researchers themselves. PhD and MPhil scholars start research from their pocket. Universities have some budget that remains underutilized. PHRC hardly gives any funding and issues mostly small grants up to 5000$. Science and technology has budgets, but difficult to disburse. Funding by Global fund, Islamic development bank, Asian Development is terribly slow. HEC budget expects cuts due to recession meltdown. (Dr. Javed Akram) Research funding had increased in 2017, but later cut down. According to an analysis, trial sponsors in Pakistan have been mostly (66.5%) non-governmental, non-industry category. [1]
- Funding from international sponsors is attracted by smooth regulations, timely approvals, and data integrity. They are ready to pay more money for quick reviews as delaying trials means delaying their drug sales, which is a big concern for them. But recently, due to regulatory barriers, Pakistan lost a big trial.
- Budgeting situation in Pakistan for clinical sites is not good. The international trials coming to Pakistan are offering exceptionally low rates (a tenth of the budgets for US clinical sites for example).
- The money that comes is further subject to tax which discourages CROs. (Mr. Khurram, DR)
- Sites often get discouraged with the condition of indemnity insurance with US demanding 2 million dollars for upfront insurance to be maintained by clinical site, which is beyond our limits and is under negotiation. (Dr. Ayaz Mir)

Opportunities

- Budget for clinical research is rising globally due to growth of pharmaceutical industry.
- Pakistan also has a large pharma industry, and its potential can be used. We are ranked as the 10th largest pharmaceutical industry in Asia Pacific with over 30 multinational and over 400 local companies and annual revenue of US$1.64billion.[xxi]
- Now international pharma companies are also realizing they cannot ignore Indo-Asian population and recently, 53% trials are shifting to South Asia and Pakistan can hope to get opportunities and boost its economy. (Dr. Syed Uzair)
- Contribution from PHRC can be expected in future. In the past, it has been in terms of evidence generation in addition to offering tiny research grants to organizations. Now it has been made as part of NIH and renamed as Health Research Institute. Their new role is to fund research only instead of doing research; and funds need to be given by scoring research based on priorities and incentivizing accordingly. (Dr. Amer Akram)

Threats

- Economic instability
- Some donors such as Bill and Melinda Gates, Welcome Trust, and Fogarty are interested in funding, but we need basic research expertise to secure their funds. Only a few centers of excellence do well to attract these grants while many others fail to grab the opportunity. Also, research priorities of donors might not be in line with our research needs, failing to develop interest of our researchers and not utilizing the opportunity well. (Dr. Farah Asif, SKMH)

Table 3: Recommendations for cost-efficiency of trials

- Address issues of pharma industry to bring them into position of trial sponsors. Similarly promote biological products industry.
- Tax breaks for R&D, and duty-free import of biologicals the way government of India has allowed duty exemption on import of Investigational Products and on Research Services.
- Negotiation with sponsors for relaxation in conditions of indemnity for developing countries that are already receiving lesser budgets than developed countries.

3. Regulatory Conditions (Approvals and Restrictions)

Strengths

Clinical Trials Approval

- DRAP (Drug Regulatory Authority Pakistan) and NBC (National Bioethics Committee) provides regulatory approval for trials. Proposal first goes to National Bioethics Committee, or Provincial Bioethics committee if it is limited to one province, then goes to DRAP where investigator defends protocol, DRAP sees budget, labs, and sites. Clinical trials approvals and oversight activities in DRAP are conducted by Clinical Studies Committee (CSC), which falls under the Pharmacy Services Division of DRAP. They provide oversight for registration and approval of Clinical Trial Sites, and CROs as per the regulations of Drug Regulatory Authority of Pakistan Act 2012, and Bio-study Rules, 2017. No person may conduct any clinical trial in Pakistan, for any therapeutic good without a certificate / license issued by the DRAP. A detailed process is given in annexure A.
- CSC approved the following agencies for reliance & consideration of relevant clinical trial decisions, reports or other information as provided under Rule 13 (8) of the Bio-Study Rules: The United States Food and Drug Administration (U.S. FDA), The Medicines and Healthcare Products Regulatory Agency, UK (MHRA), The European Medicines Agency (EMA), Health Canada, The Therapeutic Goods Administration (TGA), Australia, and Pharmaceutical & Medical Devices Agency-PMDA, Japan.
- National Bio Ethics Committee (NBC), NBC-PHRC is responsible for ethical approval of all Clinical Trials to be conducted in Pakistan, prior approval from NBC-PHRC, is mandatory for CTA to DRAP, as per Rule 9(1) of the Bio-Study Rules 2017. National Bioethics Committees provides timely approval for clinical trials in 2-3 weeks.

- Timelines for approval are:
  IRB: 02 – 04 weeks
  NBC: 02 – 03 weeks
  DRAP: 8-10 weeks
  For Covid-19 related trials the timelines are significantly faster than the above-mentioned.

IMPs import approval:

- No additional export license or permission is required for shipping the biological samples outside Pakistan from regulatory authorities.
- The drug import approval timeline varies between 12-20 weeks depending on phase of study, nature of product, patient population and time taken by the referred reviewers to give their comments. Details of import approval process is given in Annexure A.

Weaknesses

- Some regulatory barriers with clinical trials are there, mostly due to red tapism of DRAP and absence of clinical study committee in the last one year. With delays in approval by DRAP, sponsors withdraw their trials as they must work by deadlines. This is how top performing countries such as North America, Europe and Australia have become ideal destination for clinical trials by following smooth timelines of 4-6 weeks of regulatory approvals. India also attracts sponsors by its smooth regulatory processes. In Pakistan, regulatory hurdles have been the cause of decline in trials activity. In 2020, 19 clinical trials were registered in Pakistan, and 14 in 2021, while only 1 in 2022, due to absence of CSC of DRAP.
- Currently, there is a huge back log of protocols for CSC approvals as this committee has been absent since end of last year.
- Pakistan also has some extra regulatory restriction including mandatory Licensing of CROs by DRAP, and Licensing of sites by DRAP required to start trials. These restrictions are placed nowhere else in the world.
- Also initiating phase 4 trials in Pakistan has to be approved by DRAP, whereas in most parts of the world, phase 4 trials are exempt from CTA (Clinical Trial Application) filing and require only IRB approval and GCP compliance.
- The concept of satellite sites is not accepted by DRAP, as there is no mention of it in Biosafety study rules.
- For vaccine products, DRAP fails to perform its mandated facilitatory and guiding role due to the limited capacity of DRAP officials and other factors. Vaccines regulation, which should be managed by a team of vaccine specialists, Physicians, Public Health specialists, Virologists, and Immunologist is managed in DRAP by Pharmacists, and Microbiologists with insufficient concept of vaccine issues. Many technical posts have been lying vacant for a long time.
- There are hurdles in conducting BE/ BA studies because of the requirement of COPP and GMC certification from patent holders. Recently Dow University reported they have received 26 applications for BE/BA studies but cannot conduct due to this legal lacuna.[xxii]
- In Import of CTM and export of biological specimens, involvement of customs department is not streamlined. (Mr. Khurram, DR)

Opportunities

- A CSC committee has recently been nominated and the first meeting has been held. With support and supervision, it should remove the backlog of last year's applications soon.

- Supreme Court also sometimes provides facilitation in case of delays by DRAP. Dr. Javed Akram expressed that whenever they got stuck with DRAP, or bureaucratic or political hurdles, they would write to Chief Justice, Supreme Court, they put up that case within 2, 3 days and all issues got cleared up, providing a great safety valve for regulatory hurdles.
- For research regulations in Pakistan, Supreme Court and Implementation Justice helped in facilitating Biostudy Rules in 2018 and Stem-cell rules after reports of misuse of stem cell therapy and issues with commercialization. (Dr. Javed Akram)

Threats

- DRAP has become a very controversial organization due to numerous cases in the NAB and FIA. As a result, even simple decision making is avoided by officials while bold and innovative steps are required, especially in emergency situations such as recent pandemic.
- DRAP role is supposed to be registering the sites, however they unnecessarily co-opted for reviewing studies, which should have been removed from their mandate, being an irrelevant role. There was a small hook at policy level that allowed DRAP to oversee clinical trials. The policy needs to be changed which is difficult as it has to be sent back to cabinet for endorsement. Regulatory amendments required are looming due to the uncertainty that exists at government level. (Dr. Faisal Sultan)
- Government of Pakistan is not actively engaged and committed to promote clinical research activity as research is not priority agenda for government.

Table 4: Recommendations for improving Regulatory Conditions

- Health Ministry must supervise DRAP more efficiently to perform its regulatory role and speed up approvals. DRAP should be reformed for timely approvals of studies. Ideally, trial registration should come under Health Research Institute of NIH and monitoring can rest with DRAP as it is a conflict of interest that a regulatory body is endorsing for trials. Prof. Amer Akram

  To speed up our approvals and reviews process, reviewers can be paid more money, but compliance with timelines should be demanded as any delay means loss for pharmaceutical company due to delay in drug sales. (Dr. Umar)
- Improve technical capacity of DRAP by including vaccine specialists, Physicians, Public Health specialists, Virologists, Immunologists etc. The capacity of DRAP in the Vaccine technology as well as basic sciences must be enhanced, and its expertise should not be merely pharmacy focused. (Dr. Hassan)
- Biosafety study rules 2017 need revision and more clearly made in line with internationally relevant practices in clinical trials. Some suggestions include the concept of satellite sites.
- Make rules for DRAP to guide which study they can approve such as studies on new molecules.
- Govt. should provide oversight and support for large trials; the way UAE government was fully behind the SinoPharm trial and even involved in Volunteers registration which ensured success and credibility of the trial.
- Streamline customs department for import/ export of research products including biologicals.

- Data Integrity and Copy right (IP recognition) must be protected. "Companies invest in countries where IPR protection is adequate. Jordan is one example where improvement and enforcement of IPR laws, resulted in substantial increase in the size of pharma market and exports. increased, exports have grown from about US $ 49 million to more than US $ 280 million. Before IP reforms no international drug innovative company conducted clinical R&D in Jordan. Currently eight American and European Companies are carrying on clinical R&D in Jordan." (WTO Cell, TDAP, 2008)

4. Relevant expertise (Human Resource, CROs, Trials experience)

Strengths

Trials Experience

- Currently 2027 trials from Pakistan are registered in clinicaltrials.gov. An analysis of Pakistan trials conducted in showed that between 1992-2019, mostly we have gained experience in drug interventions (41.4%), mostly with focus on treatment (46.7%), and behavioral studies (13.3%). Most studies have taken place in Sindh (53.1%), second most in Punjab (24.8%) and 13.4% of the trials were conducted at multiple locations in Pakistan. The majority of the trials were randomized (66.5%). [1] Many of our sites and CROs have gained experience with preclinical and clinical studies of all phases 1,2, 3 and 4. Our sites have experience working with multinational CROs also.

Human Resource

- Pakistan has a potential pool of PIs, foreign trained, and good English-speaking professionals. Pakistanis are considered an intelligent nation, with capacity of hard work.
- There are multiple training resources in clinical research in the country. Since 2005, support from private sector, academia and CRO industry has been increasing for training of human resources. Research Cooperative groups were formed including Pakistan Society of Clinical Oncology - Cancer Research Group, Medical Research Society Pakistan, Neurology Awareness & Research Foundation, Pakistan Society of Cardiovascular and Thoracic Surgeons, which have included clinical research in their programs. Masters in Clinical Research, and GCP Training was started. Shifa International and Maroof International also provide training for clinical trials. Dimension Research provides training in collaboration with Brookfield university, UK and academia in Pakistan.
- NIH Field epidemiology & disease surveillance Training Program (FELTP) is regarded as one of the top programs internationally, now converted into a Masters degree with UHS, which is internationally accredited.
- Institutions have linkages with Pakistani doctors, who are motivated and resourceful to support country. APPNA MERIT is playing their role in projecting Pakistan potential through weekly sessions and attracting sponsors from North America. They work with government of Pakistan to resolve regulatory hurdles and facilitate skill transfer to Pakistan.

Contract Research Organizations (CROs):

- We have around 12 CROs in Pakistan.
- Dimension Research is one of the largest CRO of Pakistan. It has a nation-wide team with >70 employees, and a strong network with academic & Research Institutes. DR has capabilities to manage Phase II, III and IV clinical studies throughout Pakistan. DR provides support to sites in obtaining NBC approval, Regulatory approval (Pakistan and CIS countries), Database development and data management, Registry designing and implementation, Site Assessment and up gradation, Training for Protocol, ICH-GCP in collaboration with UK, CT management, and assisting CTM import. External audit & assessments are facilitated by Abbott, USA, Bayer Healthcare, Pakistan (Approved CRO), PharmaNet/i3 Research, USA (approved for monitoring and regulatory approval for Phase II study), Pharma Regulatory Services Inc., USA (representative for Pakistan, Bangladesh and Kazakhstan), Sentisi Research, Italy (for Phase I/ PK. Phase II monitoring and regulatory service), Kantar Health, USA (External audit for site of a Phase IV Oncology Study of a MNC), ClinServ, Lebanon, Covance , USA (for monitoring and site management services), ICON, UK (for LCPPV services) and Tigermed, China. (Mr. Khurram, DR)
- Other CROs include Pioneer Research Solutions, DRK Pharma Solutions, DRK Pharma Solutions, Metrics Research, Center for Bioequivalence Studies and Clinical Research (CBSCR) at International Center for Chemical and Biological Sciences (ICCBS), IQVIA Solutions, Cyntax Health Projects, Institute of Biological, Biochemical and Pharmaceutical Sciences (IBBPS), and Global Scientific R&D and a new CRO, Orcitrial is in process of registration.
- MNCs and big NGOs all are present in Pakistan. Some Multinational CROs that worked in Pakistan include Parexel USA, Kendle USA, PRA USA , Covance USA, and Quintiles USA.

Opportunities

- As CRO industry is small in Pakistan and still many hospitals have not established their CT sites, there is immense potential in investing and development of sites, with less competition at sites.
- There is good collaboration and cooperation among CROs, they are supportive of each other to promote the CRO industry.
- Besides APPNA MERIT, we have many more Pakistani doctors in different countries who can be mobilized to share their skills with homeland. Weekly sessions by APPNA MERIT are a major source for connecting with such professionals and exploring opportunities.

Weaknesses

CROs

- Few CROs can be considered more active and functional. Others have to struggle due to investment required to expand and get business.
- Internationally there are alliances for clinical trials for multiple centers which are approached by CRO or sponsors to help enroll patients in multiple centers. There is no such alliance in Pakistan.
- CROs and trial sites report a shortage of clinical research specialists, especially registered nurses trained for research. There is no training of clinical research during medical education, and they have to learn from scratch later.

Human Resource

- Physician investigators are demotivated due to lack of training, lack of funding, a lot of paper work, requirement of multiple approvals, humiliating oath required for clinical trial, regulatory complexities, contract negotiations, no financial incentives or recognition of efforts, disconnect between evidence generation and use, nepotism, misuse of funds, lack of trained support staff and insufficient support from institutions.
- Clinical research training for sites is currently offered only by a couple of CROs who are interested in contracting with them for clinical trial and regulatory requirements. No national clinical trials participation course exists, and DRAP does not conduct workshops for regulatory approval guidance to sites. There is no central repository of clinical trials resources. Due to lack of trained personnel, we face issues of incomplete data, protocol deviations/violations, ADR late reporting, delays in query resolution and complaints against the monitors. (Mr. Khurram, DR)
- There is a lack of MD-PhD programs to generate clinician scientists who are experts in the field.
- Also, there is a lack of awareness on research facilities, funding priorities and opportunities. Some funding was approved for dose-reduction studies in 2012 by DRAP but nobody followed it due to lack of awareness. There is no central platform connecting researchers with such opportunities and information. (Dr. Uzair, Dr. Ayaz)
- The focus of expats is still considered not as much as we see with our neighboring countries like India.
- There is poor compliance with ethics and research integrity. One reason is time constraints for physicians due to their clinical workload, and without support and supervision they may not be complying with ethics principles. They do research for their promotions and are expected to manage research with clinical duties, which puts them under pressure, and they may resort to fake data collection.
- Another reason is lack of supervision/ regulation. In the case of absence of guidelines or regulations, there is risk of malpractice. Recently as there was no guidance for Stem cell therapy, misuse was rampant, beauticians and rheumatologists were doing it, orthopedic surgeons were just centrifuging the fat taken from the tummy and injecting it (with or without Chondrocytes) and calling it Stem-cell therapy. Then UHS took Supreme Court on Board and developed Biosafety guidelines and Stem-cell rules for compliance with rules. (Dr. Javed Akram)

Issues in Trials Experience

- An analysis of Pakistan revealed that majority of trials conducted in Pakistan had less number of participants as compared to US, mean number 58, ranging between 101-1000 (47.2%) with 34% having no blinding in study design, single blinding in 17.3%, double in 9.8%, triple in 6.5%, and quadruple blinding in 9.1% trials. 23.2% CTs had missing data. Very few focused on diagnostic intervention (0.8%), basic sciences, education & counselling while none (0%) focused on genetics. (x) Our CTs performance can be glimpsed from the clinical trials list of OIC members, where Pakistan lies in the center, showing that our potential has yet to be fully utilized.
- In the latest CanSino BIO trial, management issues have been reported at sites due to absence of site managers, poor practices, lack of professionalism and poor local PI leadership. Local CRO staff failed to detect that some protocols were incomplete or culturally inappropriate. NBC and DRAP approvals

were secured before final protocols and there were changes later. The PIs were responsible for both technical and routine daily managerial functions. Electronic data system was shared late by CanSino BÍO and sites got used to manual filing and did not clear the backlog by entries in the electronic system. In some sites, poor practices, lack of professionalism and poor local PI leadership affected the quality of data. Country PI did not develop CT report, or documentation of operational experience. Logical or statistical outcomes not documented / shared by the participating team. The Third Party IDMC Report has remained confidential due to unknown reasons on the insistence of CanSino BÍO although it is a positive Report. There was lack of proper planning, and experience of the core partners.[xxiii]

Threats

- No government policies for CRO promotion exist, while huge investment (time and money) is required for CRO business. DRAP resources are short for catering to the needs of CROs/ sites as claimed by CROs. There are delays from DRAP for site approval or CRO approval due to file work, discouraging this industry.
- Investors without clinical research background entering the market.
- Brain drain.

Table 5: Recommendations for Relevant Expertise

CROs support

- Govt. should provide support to CRO industry.
- CROs need training to carefully plan, and execute trials, make checklists and complying with them.
- CRO should run ongoing internal site quality audits in place to avoid issues during real audit.
- Train CROs to avoid "Could do all" approach while asking for business. We need to be specific and develop niches/specialized areas. There should be more collaborative working between current CROs as this business grows with sharing.
- Train CROs to select ethically sound international projects as we might fall into the pit hole of unethical studies due to business pressure and lose trust of community.
- Train Site or floor managers.

HR Skill building

- Invest in capacity building of clinical researchers. Online courses that are available need to be adapted for local challenges in actual conduct of trial.
- Promote collaborations by imparting collaboration skills.
- Strengthen institutions research infrastructure through regulations. PMC standards for accreditation of medical colleges should include staffing requirements for research cells also. Because there is no such requirement, colleges don't hire any staff exclusively for guiding research of faculty, and students. These standards should be amended so that research staff is hired by every college. Their role should be to strengthen ORIC offices. This step will be an

incentive for doctors interested in making a career in medical research and will further promote research training and programs in the country.

- To improve motivation and quality of research, faculty should be given time off for research work. They should be sent on rotations for a research project, relaxing them from clinical activities. They would need breathing space for learning and developing thinking for clinical research.
- The concept of research integration and commercialization (ORIC concept of HEC) should be clearly imparted to every institution.
- Impart skills training in biostatistics, epidemiology, genetics, immunology, virology, synthetic biology, medical economics, programming (R, python) as part of medical curriculum.
- Engaging Diaspora more is required. APPNA MERIT should be taken on board for expanding trials activities, capacity building, guest lectures, research grants/ fellowships, and subscriptions/ open access publication. APPNA MERIT should invite collaborations for research on some database, publishing a list of projects calling students in Pakistan to be their workforce, as there are many volunteers available here.

Compliance with ethics and data integrity

- Considering having unannounced audits for checking compliance with ICH-GCP principles, and greater liability on the sponsor and the CROs, the way India managed to revive its lost reputation after violation of ethics principles in trials.[xxiv]
- To avoid misuse of funds, every person in the team from PI to nurse, technician, receptionist should receive a portion of money. (Dr. Umer)
- Budget release to the sites should be linked to precise deliverables and not to registrations without proper electronic entries.
- Strengthen role of national, provincial, independent, and institutional ethics committees and data safety monitoring boards. There should be a licensing system for all IRBs in country. They should be supported to seek accreditation by AHRPP which is the internationally accepted accredited body and sponsors prefer reviewing projects by accredited IRBs.

Approach to Trials

- Expand scope of trials by covering areas that are under-researched such as herbal medicine, biosimilars, proteomics, genomics, BA/BE studies, biomarkers of unique diseases or epidemic prone diseases, pharmacogenomics, and dose reduction studies. Focus more on phase 2, and 3 trials. In Pakistan, lots of research is being done at T0 level of translational research, i.e. basic sciences research, but is not translated well into T1, T2 research, where the pharmaceutical industry should be engaged.
- Trials should be approached with better management, and partnerships. Sites should be linked with outsourcing services like volunteer recruitment.
- Besides commercial research projects, we should also go for investigator-initiated trials, designing the protocol ourselves and not every time waiting for commercial project to be offered. Our local pharma industry can be helped this way if we design at least phase 3 and 4 trials for their products. (Dr. Ammad Faheem, Dr. Umar)

5. Infrastructure and Environment

Strengths

Infrastructure

- We have JCI/ ISO / DRAP approved and GCP compliant, well established health care centers serving as CT sites. There are more than 80 DRAP approved CT sites, 3 known Bio-Analytical Laboratories, and around 8 Bioequivalence and Bioavailability (BE/BA) Studies Centers. Most of the tertiary care hospitals have their own ICH/GCP compliant Ethics Committees. Details of some sites that presented in APPNA MERIT webinars is given in Annexure B.
- Good Information technology capabilities, Internet available everywhere
- All major courier services are operational in Pakistan, we can send samples to central lab anywhere in the world. Biological specimens can be shipped outside Pakistan in Liquid Nitrogen, Dry Ice, with Ice Pack or at ambient temperature depending on the requirement of specific specimens. Specimens can reach a destination in US from Pakistan within 48 hours. International safety guidelines are followed during transportation of biological specimens. (Dr. Amanullah, IQVIA)
- Availability of certified/ accredited central laboratories (Dr. Amer Akram)
- There are CTUs with Control Access, Temperature Control, 3rd Party Temperature Alarm Tab, 80 and -20 Access control Freezer, Refrigerated Centrifuge, dedicated space for Study Samples, Blood Collection Area, Dedicated space for blood draw, Certified and trained Staff, Computerize Lab reporting system, Bio-Hazard Control environment. (Dr. Amanullah, IQVIA)
- DRK has used E-Systems of global CROs and Pharmaceutical companies including Inform (PHASE FORWARD), Impact Harmony, Rave EDC, eTrack, RAMOS (Registration And Medication Ordering System), Xpress (Clinical trial medication tracking system), Axial (eCRF), CTMS, eTMF, and Medidata.
- Mechanisms for data capture are developed in some well-established clinical trial sites. Patient data is directly connected with Clinical Research Associates (CRA), whose activities & parameters are monitored by Lead CRA/ Monitors. The performance of Monitors is connected to Quality Control mechanisms and their reports are reviewed by the Quality Assurance (QA) team. CRA performance and compliance are present in Matrix for Senior Managers.[xxv]
- IT set up for Pharmacovigilance (PV) has been developed by Dimension Research, which enables data collection through web based www.phvnet.com.[xxvi]
- Institutional Databases: Some institutions have developed their registries for prevalent diseases. With availability of some institutional databases, and successful collaborations for multicenter studies, Pakistan has contributed to some impactful research, even without big funds. These addressed local problems, many of which are rare in other parts of the world. Some examples are 'Genetic inheritance of thalassemia in Pakistani families', 'Epidemiology of Aplastic anemia in Pakistan' (which is a rare disease in US) studied with 1324 cases, making a base for guidelines of this disease by European Society of Blood and Marrow Transplant with help of Pakistani team, later progressing to new protocol written by same team, 'Epidemiology of Multiple Myeloma' studied with >400 patients in Pakistan (rarely seen in young population in US), 'Diagnosis and Management of

Diffuse Large B-Cell Lymphoma' in low resource settings, 'Randomized Trial of Amoxicillin for Pneumonia in Pakistan', and 'Community Based Intervention of Hypertension'.[xxvii]

- Genetic research facilities include through-put whole genome sequencers, primer synthesizers, 300 GeneXpert's machines, and biosafety labs in National Institute of Health, Islamabad. Facilities of genetic research are available at University of Health Sciences, Lahore, Lahore University of Management Sciences, and International Center for Chemical and Biological Sciences, University of Karachi also. Details are given in Annexure B.

Weaknesses

Infrastructure

- Although there are many sites, they are still not considered enough. CROs express a need of developing more sites. Collaborations between are not strong enough. There are communication barriers between sites and lack of trust, discouraging collaborations.
- ICH-GCP compliance lacking in many sites.
- Only four hospitals are JCI accredited in Pakistan; Agha Khan University Hospital Karachi, Shifa International Hospitals Ltd. Islamabad, Shaukat Khanum Memorial Cancer Hospital and Research Centre Lahore and Shaukat Khanum Memorial Cancer Hospital and Research Centre Peshawar.[xxviii]
- Many sites need support to handle Phase II, III studies.
- In CanSino Bio trial, there were issues as sites were not ideally prepared for large Phase III CTs and there was no outsourcing mechanisms established for recruiting large number of volunteers.
- Internet connectivity and electricity fluctuations in Pakistan
- Electronic Medical Record (EMR) is not established in most hospitals, whereas every trial needs electronic source document verification. Due to lack of such systems, there is some mistrust by sponsors, who refrain from investing in trials with us.

Environment

- Pakistan health sector is a fragmented and mixed health system, with low spending on health <3% of GDP, leading to underperformance, poor governance, and regulation of health sector. Government spending in Pakistan is minimum, as compared to neighboring countries. <3% of GDP is spent and that too is issue based, like dengue epidemic, and not progressive spending to improve system. >80% spending is for tertiary hospitals and public health and prevention and research is being ignored. Research is not a priority for the government. In Pakistan, overall if we look at research output trends within the last few years, there has been a sharp rise in output since 2018. The number of PubMed reports, and number of medical schools are increasing. Budget of PMRC has also increased a little. A country comparison by Clarivate Analytics highlighted Pakistan for having the highest growth in evidence generation up to 21% in 2018 among 40 countries. This growth could be attributed to international collaborations and funding. Though, in terms of clinical research output, Pakistan remains underrepresented. The rise in publications also raises questions about the quality and impact of these research. Unfortunately, the literature shows that in Pakistan, evidence is rarely used for decision making and national policy and planning. Mostly research is under-powered, single site,

inconsistently designed, duplicative, unnecessary, and redundant. Such studies are a burden and waste of resources.[xxix]

- In a country of >220 million people, and 270 journals, we have only 3 impact factor journals. The highest impact factor is 2.4 for PJMS. Most of the research output is by a few centers of excellence, publishing up to 100 papers in a year, while others may publish up to 10 papers a year. The centers of excellence work in silos and do not share their capacity. There is a poor trend for research collaborations. Research consortium and active disease specific groups are not visible. For the little collaboration that is happening, MoUs and paperwork is felt exhausting. There is lack of will, stewardship, and underinvestment by government for capacity building and research funding. Government led research platforms for lobbing research or scientific community do not exist. Absence of national level collaborations and consortia lowers our prospects of being viewed internationally as potential research hubs for promoting collaborations. National Health Vision 2016 summarizes all issues in a statement "Research is often conducted in silos, seldom relevant to local issues, is often of poor quality because of limited capacity and resources. Compounding this, is the disconnect between researchers, implementers and policy makers." (Dr. Farah, SKMH)
- Unfortunately, there is no trial registration authority in Pakistan and many local researchers get their trials registered with international registries before publishing their research in international journals of repute. Due to non-availability of national trial registry, Pakistani journals are experiencing problems in accepting articles without UTNs.[xxx]
- Pharmaceutical industry has not flourished enough in Pakistan. We have no FDA approved pharmaceutical company. Pakistan holds annual pharmaceutical sales of 3.1 billion US-$, however, 95% of the active ingredients are being imported from abroad. We have 647 actively operating drug manufacturing licenses, and 6440 medicines were registered in the year of 2018, still the research on these drugs is meager. Only one company is GMP certified. Reasons for this industry not flourishing are at the end of DRAP, which is delaying licensing of pharmaceutical companies, licensing of drugs after manufacture, not even accepting approval of FDA, lack of entrepreneurship and appreciation of ideas. DRAP issues are due to red tape culture and not looking into the interests of the community.
- There are little prospects of commercializing biosimilar products discovered through research. There is no industry to commercialize research because of conflict of interest, little understanding of Office of Research Integration and Commercialization (ORICs), and nonexistence of any biotechnology plant in Pakistan. Also, there is no smooth regulatory pathway for commercialization. We import drugs with >40 billion rupees. Our pharma is happy refilling compounds by importing and distributing and import mafia supports this and tries to stop commercialization of locally designed biosimilars. Dr. Javed Akram reported that they tried to commercialize Pakderm and were stopped. Supreme court rescued him and issued Suo moto notice, which is still going on. (Dr. Javed Akram)

Opportunities

- Some CROs such as Dimension Research support hospitals that have the potential to develop as sites as an investment.
- A Genetic reference lab and research center is planned to be setup at Health Services Academy in collaboration with China.

- NIH has allocated Land for technology hub, IHITC hospital, Tibb Council, warehouse getting established, R&D lab at NIH in planning, center for genomics and biobank also being established.
- Growing Pharma market can also bring new technology.
- Our National Institute of Health (NIH) has gained new leadership, motivated to revamp research ecosystem. With their efforts, Pakistan became the third country to complete the Joint External Evaluation report on time and is now in its Steering Committee. Now more sites are building partnership with NIH with hopes for future.

Threats

- There are no large scale or national Clinical trial site development efforts. The process seems to be linked with an available international trial that a CRO has 'brought' to Pakistan and needed sites are then searched for related to that trial. At present there is no support from the Government for investing in sites. CROs guide for site staff, resources, space and materials, budgeting, documentation etc. for new clinical sites, however, they also offer this service to them at some cost (taking that piece of the budget from the sponsor). However, this could lead to weak clinical sites in future and CRO once 'packs and leave', the site may not be able to continue with further clinical research.
- Rising inflation, corruption and recent flood disaster may hamper technological advancement initiatives due to less availability of funds.
- There is perceived instability in government, politics, disasters in the country and foreign sponsors are reluctant to invest in trials in the country.

Table 6: Recommendations for Infrastructure and Environment

- Develop more sites, improve quality of existing ones. The government should invest in development of more sites.
- International accreditation of sites by Alliance for Clinical Research and Safety (ACRS), of US. (Dr. Amer Akram)
- Reduce barriers between sites and build trust through communication as trials cannot be done without collaborations between sites. HEC has KPIs which universities follow; they can add one KPI for the number of research projects conducted in collaboration with other organizations/visiting researchers. Secondly, HEC should be convinced to accept the flexibility in assigning a greater number of first authors, as accepted internationally to prevent conflicts on authorship in collaborative research.
- Electronic Medical Record systems should be developed in all hospitals and data collected through these systems should be linked with national health information systems (NHIS), with some policies on data access and use.
- IT regulatory framework must be an integral part of any pharmaceutical regulations and the government inspectors should be equally knowledgeable about not only the clinical trials but also the role of IT in this business. (WTO Cell, TDAP, 2008)
- A National Clinical Trial Registry and a website should be devoted to Clinical trials in Pakistan, with portals for Sponsors, CROs, Clinical sites etc. can be developed. The website can have links

to resource material for clinical researchers, CROs and sponsors. It can also contain the database of health sector variables and studies. (WTO Cell –TDAP, 2008)

- Disease registries should be developed for Cancer and Genetic Diseases, with the goal to have a database of patients with known and suspected genetic diseases and family cohorts.
- New technology should be learned and transferred through network of diaspora.
- The use of Redcap should be promoted and introduced to all. It is a free HIPAA compliant database where institutions in the US share data; some Pakistani institutions can also share data there with regulations, to be used for research.
- Govt. should support pharma industry and address their issues including drug pricing, and facilitating timely licensing of pharmaceutical companies, licensing of drugs after manufacture by DRAP, GMP certifications, FDA approvals, and encouraging entrepreneurship in this field. India pharmaceutical industry got positioned in the global market by violating patents with the protection from their courts, making other pharma industries insecure which resorted to getting their products licensed to Indian companies to maintain their patency, and they got facilitation of marketing, GTO and other arrangements also. India now has >200 FDA approved pharma companies and one third of drugs are exported to the US. Bangladesh also has 3 FDA approved pharma companies and exports to the US also. Pakistan should also encourage FDA approvals of its pharmaceutical industry, make new drugs by producing raw materials also locally, test drugs through all phases of trials and export these drugs. For this, support would be required from all sectors, govt. and linking with international community.
- To promote biosimilar patents development and research, entrepreneurs and investors should be invited to develop biotechnology plant in Pakistan and promote this industry.
- For vaccines production, Biological Products Division of NIH should be granted financial and administrative autonomy by implementing the NIH Ordinance in true letter and spirit. Public Private Partnership must be encouraged to promote the vaccine production and R&D. The private sector should be encouraged to invest in the biological productions particularly the vaccine technology sector. (Dr. Hassan)
- National Core-Group for Clinical Research: To take bold steps for harnessing potential of clinical research industry, there should be some national level leadership for clinical research. The stakeholders of the Clinical Research Business should be engaged in dialogues and their interests should be sought (including CROs, Hospitals, Healthcare practitioners/Physicians, IT people related to the field of clinical research, Pharmaceutical Industry, Patients/Subjects in particular and People of the country in general, Government of Pakistan comprising Ministry of National Health Services Regulation and Coordination, Ministry of Commerce, Ministry of Finance, Planning & Development Division/Planning Commission, TDAP, and Pakistan Medical Research Council. Interests of all should be protected in decisions on clinical research. (WTO Cell, TDAP, 2008)
- Research priorities should be defined and conveyed to all research institutions, and not to be affected by political fragility. Stakeholders must initiate a dialogue and develop collaborative mechanism for high quality research on national research priorities.
- Leaders should identify gaps in research sites of a country and cover them. A network should be established to link research cells, and bring academia, industry, community, and policy makers on one page, facilitate their interaction, reduce duplication or wastage of efforts.

- Collaborations between sites should be promoted as it is a necessary element for multi-center clinical trials (esp. phase 2, and 3). Collaboration is required across sites to ensure the same study team supervises work. All sites must be accessible to this team. Standardization and Uniformity of Procedure requires the same inclusion criteria, same line of treatment, same investigation all over the sites, and use of a centralized lab procedure. Every organization should nominate and convey their official collaborator, with some training on skills and ethics in collaboration. HEC can also add one KPI for collaborative research projects with other sites. HEC should be convinced of granting more flexibility in authorship credits or allowing multiple first authors as accepted internationally. Reducing conflict authorship this way can improve collaboration trends between organizations for large scale multicenter studies.
- APPNA MERIT can play a role in facilitating research leadership, lobbying with government, attracting sponsors, and transferring technology to their homeland. Pakistan should learn lessons from India and Israel, how they developed their country with help from Diaspora. India got its hands on CAR-T therapy for ALL also, with help from their Diaspora, convincing a company in Spain for technology transfer. By the time their phase 2 trial is over, this therapy will be available at one-tenth the cost for Indian population.

Implementation of these recommendations requires commitment from government and leaders in the medical community. We are a low resource country, and **we don't have oil, but we have human resource for development**, which if skilled and motivated can take clinical research to the next level. We will have to facilitate quick approvals like America and Australia, tax breaks and legal protection like India, easy enrolment processes like Europe, and going overboard like Chinese at every step for data integrity and achieving standards to best compete in clinical research market.

Table 7: A comparison of Clinical Research Market of South Asia

Country	Population (worldometer 2022)	No of clinical research studies (all types; as in US registry)	Strengths	Challenges
Afghanistan	38,928,346	26 0.00067 studies/ 1000 population	Disease burden, a diverse range of health problems and socio-cultural issues In the post-Taliban era, efforts are being made by the Government of Afghanistan to rebuild the healthcare system, with the help of foreign aid. [xxxi]	War-affected country, facing serious economic, socio-political issues that affected health system. Working on basic amenities and infrastructure are absent [xxxii]
Bangladesh	164,689,383	502 0.003/ 1000 population	Disease burden, interest of international sponsors in investing in trials in Bangladesh, strong local pharmaceutical market.	Bangladesh local pharmaceuticals were relying on CROs of India, Singapore, and Jordan in the past and now trying to expand CRO market. GCP guidelines also made few years back in 2015. Government is now taking interest and expanding clinical research market [xxxiii]
India	1,393,409,000	4,941 0.0035 studies/1000 population	Regulatory approvals possible in 6 to 8 weeks in India, duty exemption on import of Investigational Products and on Research Services. Local cost of trials 50-79% of cost in Europe. English speaking professionals, 750+ sites, with good facilities. India has considered some measures to ensure safety in trials such as unannounced audits, collation of Significant Adverse Events and their compensation forms,	Investigator shortage, high annual turnover of staff (28-35%), variability in ethical practices, quality of global trials and medical practices, drug/ sample storage, formal training for clinical research, issues of confidentiality, cultural differences, violation of patient rights [xxxv, xxxvi]

			stringent review of informed consent drafts, and greater liability on the sponsor and the CROs.[xxxiv]	
Bhutan	771,608	3 0.0039/ 1000 population	Efficient health system with access to basic public health services for citizens, rapidly expanding services	Shortage of specialist doctors, first and only University of Medical Sciences in the country was inaugurated only few years ago in 2014, limited clinical research, skills and motivation, clinical workload, limited or no funding and collaborations [xxxvii]
Sri Lanka	21,413,249	98 0.0046/ 1000 population	Favorable national policies, growing economy, and rapid digitalization, 92.5% literacy rate, free standard of care, non-communicable disease burden equals to western countries, qualified medical practitioners, and a core of competent and committed clinical researchers combined with its population's proficiency in English make it ideal. A robust regulatory framework and ethical reviewing process have minimized legal loopholes ensuring the rights, safety, and well-being of trial participants that are protected.[xxxviii]	Infectious diseases burden lesser than in Pakistan, India
Nepal	29,136,808	229 0.0078/ 1000 population	Diseases burden, Motivated young researchers, getting more trials to reduce research gap, experienced with WHO in Vi-DT typhoid conjugate vaccine last big phase 3 trial	Issues of training, weak planning and execution in sites, IRBs capacity building required, low resource settings[xxxix]

Pakistan	220,892,340	2027 **0.0092**/ 1000 population	Mainly high disease burden, English speaking professionals, Well-equipped CTUs, Relax regulations as compared to many other countries, Rest all mentioned in this document.	Mainly political instability, Uncertain time approvals, EMR lacking in some potential sites, Rest all mentioned in this document.
Iran	83,992,949	1192 **0.014**/1000 population	Large pharmaceutical market, fast-growing population, government's strategy to achieve self-sufficiency in pharmaceutical industry, FIPPA protection to foreign investors, Improved regulatory conditions to attract investors, modernization of the health care industry	Uncertainty of changes in laws and regulations, and protection of patent (Simone Colonnello, 2016)[xl]

Annexure A: Regulatory Process

Clinical Trial Approval

For approval by DRAP, required documents by PIs or Co-PIs include: Investigator Brochure (English) and summary (English), Final Approved Protocol (English) and Summary (English), Informed Consent Form (English, Urdu), Challan Fee 100,000 PKR/- for regulatory approval and import license, Central Ethics Committee Approval (fee 50,000 PKR/- for routine approvals), List of participating countries, Phase of the trial, Quantity of the drug that need to be imported during the study on Form 4 of MOH Pakistan Import and & Export Rules 1976, Details of the sites were trial is going to be conducted, CVs of the PI, Ethics Committee Approval with list of EC members, GMP certificate along with CPP / free sale certificate of country of origin (only if drug is being marketed there), Pre-clinical data/Safety studies, Adverse Event reporting form (English), Number of patients to be enrolled, Name of monitors/ CRA and CRO, Evidence of registration letter in the country of origin (if applicable), Copy of registration letter if drug is registered in Pakistan, Sample of label of the study drug, Authorization letter from the Pharmaceutical Company to import the drug in Pakistan for clinical research purposes. Ideally shelf life of the study drug should be ≥75% left when imported however short expiry could also be imported depending on the study and other enrolment specs. Documents should be submitted to: Chairman CSC / Director, Division of Pharmacy Services, Drug Regulatory Authority of Pakistan 3rd Floor, T.F Complex, 7 – Mauve Area, G-9/4, Islamabad OR Secretary CSC / Additional Director, Division of Pharmacy Services, DRAP.

Application for Clinical Trial Site shall be made on prescribed Form I of the Bio-Study Rules 2017. Application for authorization of the conduct of a Clinical Trial shall be made on prescribed Form II of the Bio-Study Rules 2017. Application for Renewal of License of the Clinical Trial Site, shall be made on prescribed Form III of the Bio-Study Rules 2017. All Application forms are available at the DRAP Head Office or on the DRAP website (www.dra.gov.pk) at the Division of Pharmacy Services section. Fee challan can be generated online using following link https://fee.dra.gov.pk/login. Fee challan need to be paid in the nearest Allied Bank of Pakistan, in the bank account of DRAP within due date of expiry of the challan.

Public or Private Health Institution's IRC/IRB: As per Rule 9(1) & (3) of the Bio-Study Rules 2017. IRB / IRC of the Public or Private Health Institutions shall be responsible for ethical clearance & periodic review of the clinical trial, being carried out in the institution, and submission of their reports to the CSC.

Application to IRBs and NBC can be submitted in parallel.

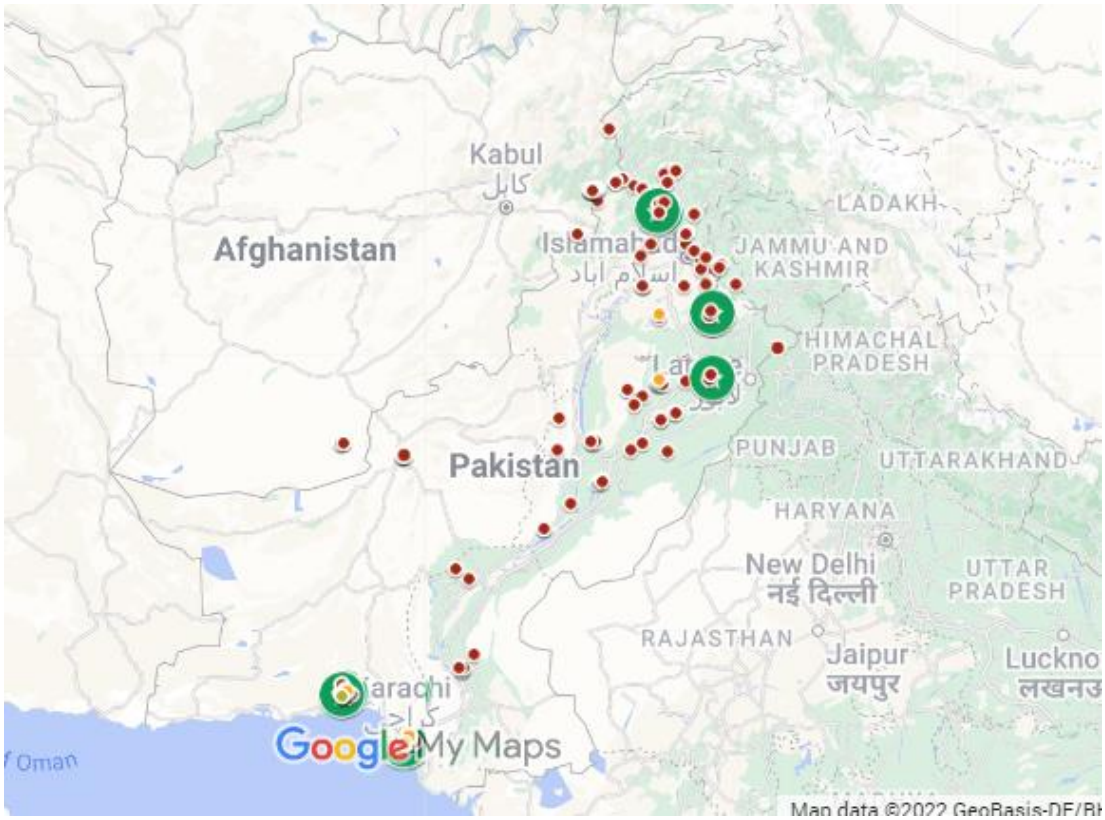
IMPs Import Approval

Approved Clinical Trial may apply for an import license (for same quantities as mentioned in the Clinical trial application) on Form-4 of the Drugs (Import & Export) Rules 1976 if importation of IMPs (Investigational Medicinal Products) is required for the trial. Form-4 along with all required documents & prescribed fee may be submitted to respective field offices of the DRAP. The Approval for importation of IMPs will be dealt / approved by Quality Assurance and Lab Testing (QA & LT) Division of DRAP, after approval of the conduct of clinical studies under the Bio-Study Rules 2017. After fulfilment of all codal formalities of Form-4 of the Drugs (Import & Export) Rules 1976, import license on Form-6 of the Drugs (Import & Export) Rules 1976 will be issued with a 2 year validity.

If a trial duration is more than 2 years, then applicant may renew import license by submitting Form-4 under the Drugs (Import & Export) Rules 1976, to respective field offices of the DRAP. The clinical research wing of the ministry of health takes care of the regulatory approval process.

It is not required to get a separate approval for the export of biological materials from Pakistan.

Annexure B: Sites in Pakistan



This Map can be opened to show clinical research sites of Pakistan registered in US clinicaltrials.gov. The map was developed with monetary and team support from BMY Health.

Below are details of some of the sites that got a chance to present in APPNA webinars in 2022.

Aga Khan University Hospital, Karachi

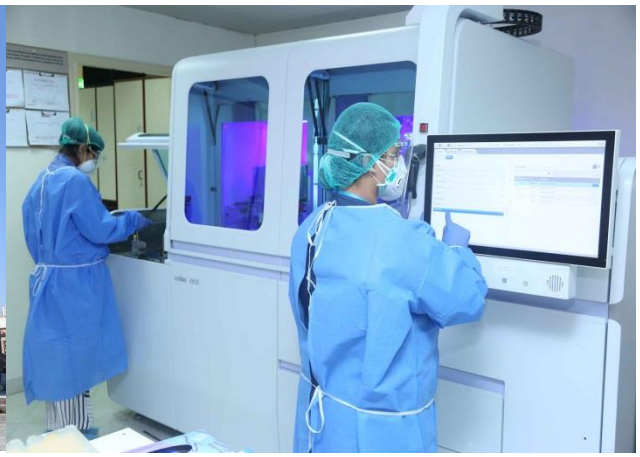
AKUK has a 650 bedded, internationally recognized hospital. It is ranked among top 100 universities for clinical medicine. They have presence in multiple countries, and in Pakistan their community and research network is spread all across country. AKU is well-equipped for clinical research, with BSL-2 and 3 facilities, 36 bench spaces, center for regenerative medicine, grants management infrastructure, animal lab, intramural research funding and CTU. They are pioneers in setting SOPs for ethical review committees in Pakistan, which they shared with others. They made research groups for faculty working on one theme that are open to collaborate with other researchers in any part of the world. Primary funding is from USA and extramural research. In last two years, they produced >135 publications and 14 extramural grants in 2021. They had 5 times increase in new grants, touching 50 million USD, last year and averaging 80 publications/ month from 500+ faculty in 2021. Their IRBs are registered with all approval bodies of US. Over the last 5 years they reduced average study approval time from 113 to 37 days by increasing the number of IRBs by 4 and introducing software to track applications, resulting in an increase in number of applications in last two

years. AKU CTU is well-equipped for phase 1-4 phase trials, with gene Xpert machine, -80 fridge and -20 freezers, registered with DRAP, and JCI accredited. They have CAP (College of American Pathologists) accredited lab which serves as reference lab for many programs like TB, and HIV in Pakistan. They facilitate training in ICH GCP, JCIA standards for human subjects' research, clinical trial management training, lab and technical protocols (IATA, biosafety). They have large number of international collaborations and got on BMGF list of trial ready global sites for vaccines. GHNR site mentions AKU as ready site for large scale vaccine trial. They were one of the sites for CANSINO trial and contributed 2900 subjects in 3 months. Other COVID trials by AKU include COPCOV trial, livzon trial, solidarity, ACT, and Meplazumab trial.[xli]

Aga Khan University Hospital CTU, Karachi, Sindh 74800, Pakistan
https://hospitals.aku.edu/Pages/default.aspx

Shaukat Khanum Cancer Hospital & Research Center, Lahore

It is a well-established 195 bedded Hospital. They have a DRAP approved and JCIA accredited clinical trial center, capacity for phase 1 to 4 trials, qualified physician investigators, research staff, scientists and statisticians, research lab, state of the art radiology and pathology services, -80C freezer specifically for research samples, 2-8 °C refrigerator for storage of investigational products in pharmacy, and pharmacy team well oriented in drug management. The Hospital cancer registry and electronic Hospital Information System further complement their research capacity.

Shaukat Khanum Memorial Cancer Hospital & Research Centre
Block R3 Block R 3 M.A Johar Town, Lahore, Punjab, Pakistan https://shaukatkhanum.org.pk/

Quaid-I-Azam University

It has strong research profile in Biochemistry, with BS, MPhil and PhD programs, different research projects going on by students and faculty in area of Signal Transduction, Cancer Genetics, Plant Molecular Biology, Cell Biology, Human Genetics, Natural Product Research, and Stem Cell. Human related research projects include development of animal models for Cell signaling therapeutic interventions, role of ncRNAs and miRNAs in human diseases, mitochondrial calcium homeostasis, and identifying genes for autosomal recessive disorders in consanguineous families (cohort of 4000 families) through genome wide genotyping, and next generation sequencing etc. They have successfully identified many genes for hearing loss, hypotrichosis, microcephaly, intellectual disability, retinal dystrophies, polydactyly and skeletal disorders in recent years. They are ranked 1st in pharmacy institutes in Pakistan, have 75 PhD scholars, with 3 faculty members having h-index>30. There are facilities for preclinical studies including rotary evaporator, HPLC, microtome, fluorescence, and centrifuge etc. Having much national and international collaboration, they are working on clinical trials, product commercialization, drug dosage development, and pharmaceutical nanotechnology with facilities of Zetasizer, Rheometer, Probe Sonicator, Franz Diffusion Cell Apparatus, Centrifuge, and HPLC etc. The Natural Product Research group came up with two patent products QULAC and QUSAFE. They worked on antimicrobial resistance and found drastic difference in genetic sequence of E Coli in Pakistan. [xlii]

Quaid-i-Azam University Islamabad, 45320, Pakistan
https://qau.edu.pk/
chairpharmacy@qau.edu.pk

Dow University Hospital, Dow University of Health Sciences (DUHS)

DUHS has facilities of: 1000 beds capacity, a CRO, Institute Of Biological, Biochemical & Pharmaceutical Science (IBBPS), National Institute of Liver & GI diseases, Urology and renal transplant, chest diseases, Laboratory Animal Sciences, Dow Institute of Life Sciences (DILS) is DRAP approved for anti-snake venom serum trial. IBBPS is certified by ISO and ICH GCP, LGC standard of UK. Dow was the first organization to be approved for phase 1 to 4 trials. Bio-Analytical lab is in process of approval by WHO. IBBPS of DUSH is one of the unique and innovative Bioequivalence Centre in Pakistan, situated along with a tertiary care hospital with state of an art ISO 17025 PNAC certified Bioanalytical Lab facility with HPLC, LCMS, and other facilities for performing the Pharmacokinetic analysis, and estimation of the drug levels in biological matrices, the ISO 15189 Certified Diagnostic Lab, Radiology, ICU, Institute of Behavioural Sciences, Institute of Life Sciences, Animal House, renal, liver & bone marrow transplantation, Oncology department, and many more facilities available under the umbrella of Dow University of Health Sciences. IBBPS is offering innovative services including BA/BE Studies, Pharmacokinetic Study, Bioavailability Study, Clinical Study phases (I-IV), CDP, Bio Waiver, Development and Validation of Biological test Methods, Quality Control Drug Testing, In Vitro Drug Profile & Pharmaceutical Equivalence, for the fulfillment of desire need of pharmaceutical requirements. Dow has conducted multiple preclinical studies, Molecular and biochemical research, toxicology studies, produced hyperimmune plasma, snake antisera, venom, now producing antirabies vaccine, which is in phase 1, developed model for adjuvant induced arthritis, atherosclerosclosis, wound healing, venom testing against influenza virus. During COVID-19 era, DILS published high impact research, studied epitope variations, developed hypothetical NTD and RBD, multivariant construct of mRNA, immune response for this protein predicted was better than Pfizer vaccine.[xliii]

Dow University of Health Sciences, New Labour Colony Nanakwara, Karachi, Karachi City, Sindh 74200, Pakistan
https://www.duhs.edu.pk/new/

The Indus Hospital Health Network

It is a network of 15 hospitals across the country. They are providing free services with donations, and being run with public private partnerships. They have a strong commitment towards building research capacity. In the last couple of years, they have got registered clinical research units, got IRB approved by OHRP of US, introduced REDCap and got Electronic Medical Record systems. Indus Health Research center is now transformed into ORIC, with capacity building activities for faculty and postgraduate researchers. Their facilities for researchers include Epidemiology unit, IRB, Programs & Grants unit, for guiding legal documentation (contracts, grants, collaboration, non-disclosure agreement, sub-award), and various aspects of grant management. They have 2 IRBs, one for social and behavioral research projects, and the second for biomedical and clinical research projects. This IRB provides consultation to partners also. CITI certification is mandatory for all consultants and trainees. In the last few years, they conducted 21 clinical trials. Since inception of CTU, there was exponential growth of clinical trial enrollment >5000 subjects in different trials. With a handsome data of >8 million patients, they are coming up with diseases registries related to pediatric oncology, clinical care and radiology, and machine learning and AI products. They are now working with many national and international partners and government.[xliv]

Indus Hospital, Darussalam Society Sector 39 Korangi, Karachi, Karachi City, Sindh, Pakistan
https://indushospital.org.pk/

Shifa Clinical Research Center (SCRC), Shifa International Hospital

This is a **550 bedded Hospital** and is a well-established site for trials with EMR. Shifa has 200 U.S, E.U, internationally & nationally trained and qualified Physicians and Surgeon. Shifa has been offering multi-specialty organ transplant services such as Liver, Kidney, Bone Marrow and Cornea. It has a JCI accredited and DRAP approved clinical trial unit, capacity for phase 1 to 4 trials, pharmacy with -20 and -80 freezer, a good team of young researchers, and great motivation in leaders to upscale CTs activity. They are collaborating with WHO, London School of Hygiene and Tropical Medicine, Roche pharma, Beijing Institute of Biotechnology and PHRI Canada for different clinical trials. Shifa International has a good clinical registry, getting 2000 patients every month and data mining can be offered with collaborations. Shifa also conducts training of GCP, IPPCR, tumor registry and clinical trial enrolment.[xlv]

Shifa Clinical Research Center, Block A-0 Shifa International Hospitals Ltd., Pitras Bukhari Road H-8/4, Islamabad – Pakistan https://www.shifa.com.pk/scrc/

Maroof International Hospital

It is a community based private hospital with 90 beds, busy ER, CCU, ICU and more than 40 consulting clinics in various health specialties with USA, UK and Pakistani trained physicians. During COVID, they trained 800+ healthcare professionals and set up their research department and CTU. Now they are running a trial with McMaster University Canada. Maroof has also partnered with Indus hospital network for inviting each other for patient enrolment wherever suitable and achieve the sponsors' targets of patient enrolment within deadlines. Maroof International facilitates training for clinical trials also and during last two years they have trained 800+ healthcare professionals, offered onsite courses also and extended their training with help of COMSTECH to other Islamic countries.[xlvi]

Maroof International Hospital, F-11 Markaz, Islamabad
https://www.maroof.com.pk/

The National Institutes of Health (NIH)

NIH is the national reference laboratory center (WHO qualified), a regional polio center with 60 collection points for polio surveillance in the environment (sewage samples) and 20 in Afghanistan. NIH has replicated and made public health labs in all provinces, which have COVID-19 PCR testing. It has a Biological production Division (working to up-scale sera, vaccines, toxoids production), Drug Control division (narcotics regulation, research on indigenous, traditional medicines), Allergy center (Islamabad and Quetta) providing allergy immunodiagnostic and immunotherapeutic services, College medical lab technology (trainings), and a Nutrition division Advise Federal Government in developing food standards and policies in collaboration with the international agencies like WHO/FAO. They have collaborations with academia, military organizations, HEC, NARC, PHRC, COMSTECH, WHO, CDC US, PHE/FF/DAI, NIH/NASEM, EU, USAID and many others. NIH is promoting the concept of High reliability organization. They are working on policies for biosafety, code of conduct for life scientist, GCP, National Lab policy, National Infection control guidelines. They have established a Center for Disease Control, Center for Occupational and Patient Safety (COPS), and

a Clinical trial Unit registered with DRAP for trials. They managed first phase 3 vaccine trial for Covid19 which was successful and has opened way for more trials.

National Institutes of Health (NIH) Park Road, Chak Shahzad, Islamabad, Pakistan
https://www.nih.org.pk/
omera_shuaib@hotmail.com

University of Health Sciences, Lahore

UHS has good labs with small and large animals, facilities for genetic testing and are establishing their CTU (Silk Road Clinical Trial Center). Outsiders are also allowed to use our lab for experimentation. They have conducted many trials in affiliated medical colleges. They have together made more than 200 publications, 90 in impact factor journals and studied Diabetes, vitamin D, NCDs, genetics in cancer, heart disease, growth hormones studies, sewerage studies for viruses, drug delivery systems, pharma proteins, genetically modified diseases, and epigenetics. Their Forensic department is working on biosatefy, biosecurity, indigenous solutions, and is now one of the main players in crime scene investigation. They investigate all airplane crashes, burn incidents and identify dead bodies through forensic Odontology. They are working on dengue serotyping, dengue vaccines, salmonella, and XDR TB and studied outbreaks, alerts, mutants, hotspots of all diseases. They studied biological control of dengue mosquito with Gambusia fish and have genetically modified Aedes Agypti and now commercializing this. They are no 1 group on deafness blindness and mental retardation of genetic origin in world and started neonatal screening for PKU, genetic defects. They are only university in Pakistan and second in the world to do gene editing for thalassemia. They are working with 1500 consanguineous families in Balochistan, where mobile labs collect samples, in collaboration with John Hopkins and Maryland university, who changed their panel of genetic testing and included 20 other genes testing after UHS study. They have gained CT experience with PROTECT trial (Pakistan randomized observational trial to evaluate covid19 T/M), and Cansino bio study (with 5000 volunteers recruited), and later ZF 2001 trial. They have 27 patents from US FDA including interferons, CSF, Insulin, Erythropoeitin, Growth Hormones, Pakderm, and some plant compounds. Pakderm was made for burns treatment by UHS, by trials on our population as burns are most common in Pakistan. Where Euroderm costs around 7-8 million Rs. for a 60kg man with 60% burns, and 5% survival chance in burn center. If we use biological skin, the chances of survival increase from 5% to 60%, in a price of only half a million Rs. (Pakderm cost).[xlvii]


University of Health Sciences, Khayaban-e-Jamia Punjab, Block D Muslim Town, Lahore, Punjab 54600, Pakistan
https://www.uhs.edu.pk/index4.php

International Center for Chemical And Biological Sciences, University Of Karachi

It is a research center run by the government, with advanced technology and facilities available. It is the only OIC Center of Excellence in Chemical Sciences, WHO Center for Pesticide Analysis, Islamic Development Bank Prize for Best Science Institution (2004 and 2010), TWAS Center of Excellence for training of scholars from Africa, Sindh Forensic DNA and Serology Laboratory, with facilities for Genome Research, Food Testing Laboratory of Sindh. It is the Drug Testing Laboratory of Sindh, has Halal Products Research and Testing Facility, COVID-19 Lab Diagnostic Testing, Nanotechnology Center, National Institute of Virology, National Facility For Laboratory Animal Research (Computer Generated Model), Center For Bioequivalence Studies And Clinical Research (120 Bed facility for clinical trials and bioequivalence studies). [xlviii]

Center for Bioequivalence Studies and Clinical Research (CBSCR)
International Center for Chemical and Biological Sciences, University of Karachi, Karachi, Pakistan
https://iccs.edu/page-cbscr
raza.shah@iccs.edu

Liaquat University of Medical & Health Sciences (LUMHS)

LUMHS has a well-established research centre in Jamhsoro. As part of the clinical research division of the Medical Research Center, the clinical trial unit was developed, which not only supports the smooth conduct of clinical studies but also aids in pre-clinical trials. The faculty and personnel at CTU-LUMHS are ICH-GCP qualified, and the Diagnostic and Research laboratory facilities are ISO accredited. The Medical Research Center collaborates closely with clinical and basic sciences faculty and assists them in conducting a variety of studies, such as genetic studies, clinical trials, in vitro studies, Molecular studies, Pharmacokinetic studies, bioavailability studies, and various basic, applied, and translational research. LUMHS has a vast network of diagnostic and research facilities, with its principal core laboratories located in Hyderabad and Karachi, to serve the university's enormous research portfolio. These labs also offer genotyping, sequencing, and karyotyping services.

Liaquat University of Medical and Health Sciences, C7PC+337, Jamshoro, Sindh, Pakistan

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[xliii] Dr. Izhar Hussain, Ms. Maria Rizvi, Dr. Sadia Asim, Dr. Mushtaq Hussain. DUHS. APPNA MERIT series of webinars
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[xlv] Dr. Muhammad Ayaz Mir. Shifa International Hospital. APPNA MERIT series of webinars
[xlvi] Dr. Waqar Hafeez, Ammad Faheem. Maroof International Hospital. APPNA MERIT series of webinars
[xlvii] Dr. Javed Akram. APPNA MERIT series of webinars
[xlviii] Dr. Raza Shah. CBSCR. APPNA MERIT series of webinars