

ORIGINAL ARTICLE

COMPREHENSIVE ANALYSIS OF CLINICAL TRIALS IN PAKISTAN
FROM SEPTEMBER 1992 TO FEBRUARY 2019Amna Siddiqui¹, Amara Zafar², Tooba Irfan²¹Loyola Medicine Hospital-United States²Dow University of Health Sciences, Civil Hospital Karachi-Pakistan

Background: Clinical trials are conducted to evaluate interventions (drugs, medical devices, surgical methods and radiation treatment) for treating diseases or conditions. They may also be done to prevent the development or prevent recurrence or determining risk factors. We wanted to review the current status of clinical trials in Pakistan. **Methods:** On searching ClinicalTrials.gov, registered clinical trials conducted in Pakistan from September 1992 to February 2019 were reviewed. The analysis evaluated the characteristics of the clinical studies including the type of intervention, geographic distribution of studies, anticipated enrolment and number of participants, blinding, allocation status, lead sponsors, age group, study type, recruitment status, gender, study results, study phase, primary purpose and subject distribution. The results were tabulated with frequencies and percentages provided by category. **Results:** There were 508 registered clinical trials conducted in Pakistan from September 1992 to February 2019. Interventional clinical trials were conducted more often than observational trials (77.2% and 22.8% respectively), with drugs (41.4%) as the most common intervention. The majority of registered trials had participants ranging between 101-1000 (47.2%) with most having no blinding in their methodology (34.1%). Most of the trials conducted were randomized (66.5%) while few (5.3%) were non-randomized. Among the sponsor categories, 66.5% of the trials belong to the 'Other' (non-governmental, non-industry) category. Although 59.6% of the registered trials have been completed, most of them (91.3%) did not report their results. Treatment intervention trials in Internal Medicine were the most common primary purpose. An increasing trend in the frequency of clinical trials was also evident. **Conclusion:** The number of clinical trials in Pakistan showed an increasing trend over the time period studied, which may reflect on the general outlook of clinical research in the country. Most clinical trials were sponsored by universities, hospitals and non-profit organizations but less than 10% of studies reported results.

Keywords: Clinical trials; Medical device; Radiation treatment

Citation: Siddiqui A, Zafar A, Irfan T. Comprehensive analysis of clinical trials in Pakistan from September 1992 to February 2019. J Ayub Med Coll Abbottabad 2022;34(3):468-73.

DOI: 10.55519/JAMC-03-8793

INTRODUCTION

Clinical trials may be conducted with several objectives: to evaluate interventions with drugs, surgery, radiation, diagnosing diseases or conditions, develop methods to prevent diseases (vaccines, drugs, behaviour modification), identify methods for determining risk factors, and finding ways to improve conditions of individuals with chronic conditions.¹ Well conducted clinical trials are regarded as the best sources of evidence on the efficacy and safety of medical interventions. They are accepted as the central means by which preventive, diagnostic, and therapeutic strategies are evaluated.^{3,4} Additionally, data gathered by means of clinical trials inform regulatory approvals of novel drugs, key clinical practice decisions, and guidelines, fuelling the progress of translational medicine.^{2,5} In order to serve their purpose, however, studies must be of high quality and transparent, as well as easily discoverable for evaluation and utilization.⁶

Randomized clinical trials rank among the highest forms of evidence in the evidence pyramid hierarchy. It is essential in the practice of evidence-based medicine, defined by Sackett as "the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."² This method of clinical practice has gained momentum globally, becoming an invaluable tool by which consistency in quality patient-care can lead to better clinical outcomes.

The academic community in Pakistan has been actively involved in clinical trials in the country. With the first trial dating back to 1992, 508 clinical trials are currently recorded in ClinicalTrials.gov - a registry that started in 2000 and quickly became the largest clinical trials registry in the world.^{7,8} In this paper we report the features of clinical trials in Pakistan, between 1992 and 2019, registered in ClinicalTrials.gov.

MATERIAL AND METHODS

ClinicalTrials.gov was searched using “Pakistan” as the location of studies. Data was downloaded on February 13, 2019 which then included clinical studies from Pakistan from 1992 to February 13, 2019. Any prior clinical trials were not included in this study.

All the clinical trials were grouped into three temporal subsets: 1992-1999, 2000-2009 and 2010-2019. Other assessments included clinical trial characteristics namely, the type of intervention, geographic distribution of studies, anticipated enrolment and number of participants, blinding, allocation status, lead sponsors, age group, study type, recruitment status, gender, study results, study phase, primary purpose and subject distribution.

The intervention types were categorized into drugs, procedural, biological, behavioural, device, radiation, dietary supplement, genetic, diagnostic and others. Studies were grouped according to the province of origin into seven categories; Sindh, Punjab, Baluchistan, Khyber Pakhtunkhwa, Federal, Azad Jammu and Kashmir (AJK) and other multiple locations in Pakistan. Anticipated enrolment/number of participants were categorized as 1-100, 101-1000, >1000. Blinding included: no blinding, single, double, triple and quadruple blinding. Allocation status was either randomized or nonrandomized. Lead sponsors were either industry, NIH (National Institutes of Health), multiple sponsors or others. Age grouping included: all age groups, birth-17 years and 18 years and above. Study type was either interventional or observational. Recruitment status was either not yet recruiting, recruiting, enrolling by invitation, active and not recruiting, suspended, terminated, completed, withdrawn or unknown status. Gender grouping included all participants, male and females. Study with and without results were grouped separately under the heading of study results. Study phases were categorized into early phase 1, phase 1, phase 1/phase 2, phase 2, phase 2/phase 3, phase 3, phase 4 and not applicable. Primary purpose of the study was categorized into treatment, prevention, diagnosis, supportive care, educational/counselling/training, health services research, basic science and others. The study subjects were broadly classified as dental medicine, internal medicine, obstetrics-gynaecology, paediatrics, psychiatry and surgery.

Intervention type, provincial distribution, anticipated enrolment/number of participants, blinding, allocation status, lead sponsors and age groups were all assessed based on 3 temporal subsets: 1992-1999, 2000-2009 and 2010-2019. Recruitment

status, gender, study results, study phase and the primary purpose of the studies were assessed overall. A yearly distribution of clinical trials over the years from 1992 to 13th February 2019 was tabulated. Frequencies and percentages are provided for categorical characteristics.

RESULTS

Interventional clinical trials have been conducted more commonly in Pakistan than Observational trials (77.2% and 22.8%, respectively). The majority of both the trials (65.5% of interventional and 71.5% of observational trials) have been conducted in the last decade between 2010 and 2019.

The most common clinical trials in Pakistan during the study period 1992-2019 were drug interventions (41.4%) with the majority (50.9%) of them conducted in 2010-2019. Behavioural studies have been the second-most in number (13.3%), with intervention type labelled as ‘Other’ in the registered data. 13.1% trials could not be analyzed in terms of intervention type due to missing data. Only 4 studies (0.8%) focused on diagnostic intervention, while none (0%) focused on genetics.

Majority of the registered trials have had a number of participants ranging between 101-1000 (47.2%). Studies with 1-100 numbers of participants accounted for 29.4% and only 23.0% had more than 1000 participants while 2 studies (0.4%) registered as having no participants at all.

The majority of trials had no blinding as a part of their methodology (34.1%). 17.3% studies had single, 9.8% had double, 6.5% had triple, and 9.1% had quadruple blinding. 23.2% of the trials had missing data.

Majority of the trials conducted were randomized (66.5%) while 5.3% were non-randomized. In 143 trials (28.2%) data was missing to classify allocation.

In the study sponsor category, other category accounted for 66.5% while 23.8% of the trials were sponsored by Industry, while the NIH sponsored only 1% of the trials. About 8.7% of the trials had multiple sponsors. Out of 121 trials sponsored by Industry, the majority (54.5%) were conducted in 2000-2009, while among the trials sponsored by the NIH (n=5), two were conducted in the time period 1992-1999 and 2000-2009, while only one was conducted recently in 2010-2019.

Majority of the studies included all genders (82.1%), however, 15.9% included only female participants and only 2% included only male participants. Currently, most trials are without results (91.3%) while only 8.7% have reported results. Majority of the studies have their focus on treatment (46.7%) while prevention was

the second most common primary purpose of trials in Pakistan. Basic sciences and education/counselling/training are the two least common areas of study (0.8% and 0.2% respectively). 24.2% of the trials had missing data. In 2018, 66 clinical trials (12.9%) were conducted in Pakistan, which stands out as the most trials conducted in a single year. The number of trials appears to be increasing with time, as shown in Figure-1. Moreover, as demonstrated in Table 1, the majority of the total registered trials (66.9%) were conducted from 2010 to 2019, while 32.1% were conducted in 2000-2009 and only 1% of the trials were conducted in 1992-1999. Analysis of geographic data revealed that most studies have taken place in Sindh (53.1%), while Punjab has been the site for 24.8% of these studies. 13.4% of the trials were carried out at multiple locations in Pakistan. The majority of the trials were conducted in medical areas: Internal Medicine (44%) followed by Surgery (19%) and Paediatrics (16%). Obstetrics-Gynecology 10%, Psychiatry 8%, and 3% in Dental Medicine accounted for the rest of the studies.

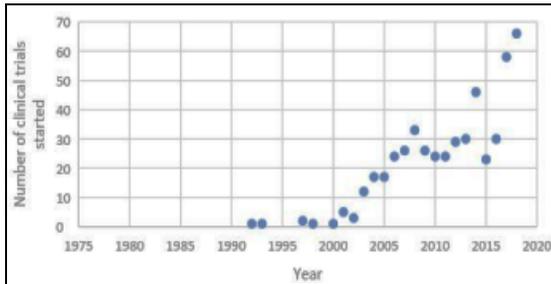


Figure-1: Yearly distribution of studies registered in clinicaltrials.gov from Pakistan, Sep 1992 till Feb. 2019

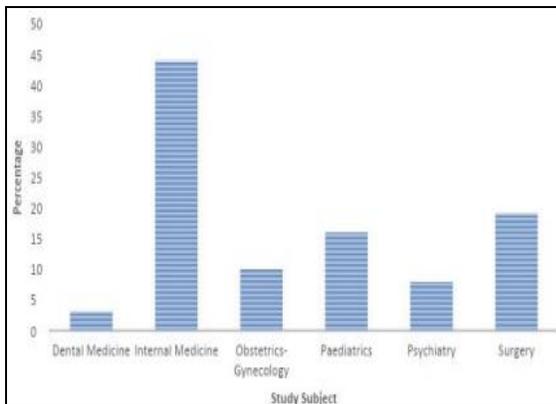


Figure-2: Subject distribution of studies registered in clinicaltrial.gov from Pakistan. Sep 1992–Feb. 2019

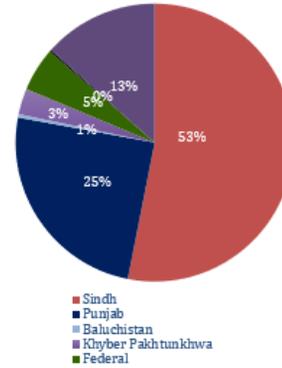


Figure-3: Provincial Distribution of Studies Registered in ClinicalTrials.gov from Pakistan, From September 1992 to February 1, 2019

Table-1: Characteristics for All Studies Registered in ClinicalTrials.gov from Pakistan, From September 1992 till 1st February 2019.

Characteristics	n	%
Gender		
All	417	82.1
Male	10	2.0
Female	81	15.9
Study Results		
With Results	44	8.7
Without Results	464	91.3
Primary Purpose		
Treatment	237	46.7
Prevention	92	18.1
Diagnosis	6	1.2
Supportive care	11	2.2
Educational/ counselling/ training	1	0.2
Health services research	22	4.3
Basic Science	4	0.8
Other	12	2.4
Missing	123	24.2

Table-2: Frequencies and percentages of clinical trials

Year of the clinical trial	Frequency	Percentage
1992	1	0.2
1993	1	0.2
1997	2	0.4
1998	1	0.2
2000	1	0.2
2001	5	1.0
2002	3	0.6
2003	12	2.4
2004	17	3.3
2005	17	3.3
2006	24	4.7
2007	26	5.1
2008	33	6.5
2009	26	5.1
2010	24	4.7
2011	24	4.7
2012	29	5.7
2013	30	5.9
2014	46	9.1
2015	23	4.5
2016	30	5.9
2017	58	11.4
2018	66	13.0
Jan- 1 st Feb 2019	9	1.8

DISCUSSION

Pakistan is a lower-middle income country where 24.3% of the population live below the poverty line.^{12,13} The healthcare sector in Pakistan accounts for less than 3% of the national budget.¹⁴ According to the WHO, the distribution of doctors and nurses and midwives per 10,000 populations is 8.1 and 10.6 respectively, which is much lower than the regional average.¹⁵

In spite of lack of resources and an effective framework, academic institutions all over the country have been actively promoting and producing clinical research. Since the early 1990s, clinical trials have been growing at a steady rate. Several hospitals and universities have state-of-the-art clinical trial units, with various educational programs and courses being offered to enhance the production of quality research from Pakistan.¹⁶

The first clinical trial in Pakistan was conducted in September 1992. Since then, there has been a steady rise in the number of trials with each passing year, particularly in the last decade. Randomization, blinding, adequate power, and a clinically relevant patient population are among the hallmarks of high-quality trials.¹⁷ In terms of number of participants, the majority of the registered trials in Pakistan have participants ranging between 101-1000 (47.2%) while 29.4% of the studies had 1-100 number of participants and only 23.0% had participants more than 1000 in number, comparable to trials in the USA. An analysis conducted on all trials reported on clinicaltrials.gov from 2007 to 2010 by Califf et al. showed that the majority of the clinical trials were small in terms of number of participants.¹⁸ Overall, 96% of these trials had an anticipated enrolment of 1000 or fewer participants and 62% had 100 or fewer participants. The median number of participants per trial was 58 (IQR, 27-161) for completed trials and 70 (IQR, 35-190) for trials that have been registered but not completed.¹⁸

Although small trials may be appropriate in many cases (e.g., earlier-phase drug evaluations, or investigations of biological or behavioural mechanisms, rather than clinical outcomes), especially in oncology, where it is believed that small trials based on genetics or biomarkers can yield definitive results, trials conducted with a small sample of participants are unlikely to provide impactful evidence in most settings.¹⁹ This principle can be applied particularly to studies focusing on efficacy of treatment with modest effects and comparison of treatment modalities to guide better clinical practice.²⁰⁻²²

Randomization and blinding are two other aspects that determine the validity of a trial.

According to our analysis, the majority of the Pakistani trials registered had no blinding as a part of their methodology (34.1%) while 17.3% studies had single, 9.8% had double, 6.5% had triple, and 9.1% had quadruple blinding. Inadequate proportion of blinding was also found in analysis conducted by Califf *et al.*, in which the majority of 72,475 interventional trials (55.9%) had no blinding, while 9.7% had single and 34.4% double blinding.¹⁸ In terms of allocation status, the majority of the Pakistani trials registered were randomized (66.5%). Similarly, Califf *et al.*, reports 70% of all interventional trials to be randomized in their study.¹⁸

We also focused on the lead sponsors of trials conducted in Pakistan. The major sponsors of clinical research in the country include the pharmaceutical industry, the NIH and organizations specified as 'other' in clinicaltrials.gov which refers to academic institutions, non-profit organizations, universities, hospitals etc. It was around 2005 when Pakistan started gaining international recognition as a potential market for research. Contract Research Organizations (CROs) also originated in the same era, which promoted global partnerships and business opportunities.¹³ In 2006, GlaxoSmithKline funded 25 oncology trials in Pakistan, and has been an active player in the field since.²⁴ This study showed that the majority of the trials (66.5%) in Pakistan were funded by "other" sponsors, while 23.8% of the trials have been sponsored by Industry. The NIH sponsored only 1% of all trials. According to an analysis of 45 620 drug trials registered on ClinicalTrials.gov and PubMed results conducted by Zwierzyna *et al.*, the proportion of studies funded by organizations other than industry or NIH has increased (mainly universities, hospitals, and other academic and non-profit agencies).²⁴ Overall, these institutions funded 36% (43,431/119,840) of all registered pharmaceutical trials, followed by big pharma with 31% (36,912/119,840), and small pharma with 21% (25,216/119,840) of studies. NIH funded 11% (13,426/119,840) of registered pharmaceutical trials. Additionally, this study found that among the 10 main study funders ranked by the overall number of trials, two belonged to the NIH category (National Cancer Institute leading with 7219 trials) and eight to the big pharma category (GlaxoSmithKline at the top with 3171 trials). Moreover, it was found that Industry was more likely than non-profit funders to fund large, international, and randomized controlled trials, although methodological differences have been decreasing with time. It was also noteworthy that Industry was more likely than non-profit trial funders to disseminate trial results, and large drug companies had higher disclosure rates than small ones.²⁵

Challenges faced by the researchers in

Pakistan are many, especially insufficient funding and resources, which may explain their research output lagging behind other developing nations in the region. Several efforts have been made since the first clinical trial in the country to counter these obstacles. In 2002, ICH-GCP (International Conference on Harmonisation- Good Clinical Practice) guidelines were identified by authorities in healthcare as the gold-standard in conducting clinical trials. Furthermore, a committee was formed to oversee the implementation of Good Clinical Practice (GCP). The establishment of Drug Regulatory Authority Pakistan (DRAP) that dealt with the approval and drug import licenses for individual clinical trials. In spite of these steps, an inadequate pool of funding for studies remains a problem.^[16] Additionally, there is no local standard trial registry in Pakistan, so trials have to be registered with ClinicalTrials.gov. This issue has been raised by multiple researchers and was addressed recently by the editor of Journal of Pakistan Medical Association Fatema Javed^{26,27}, who acknowledges the role of DRAP as the official clinical trial registry of the country and highlights the peculiarity of the lack of awareness of this registry even among major institutions and researchers of the county²³.

Another aspect to review is the ethical standard of clinical trials in Pakistan. The country is lagging behind in literacy (calculated as percentage of the population age 15 and above who can, with understanding, read and write a short, simple statement on their everyday life). The current literacy rate is estimated to be 58%, with female literacy rate even low at 48%. These statistics lead to concerns of informed consent and its role in a clinical trial. Irumnaz *et al.* also raised the issue of a predominantly patriarchal society and its role in healthcare decisions.^[16] Moreover, an absence of a regulatory body to supervise and monitor also raises concerns.

Studies have also been conducted in Pakistan to assess the attitude of junior doctors and physicians-in-training regarding clinical research. These surveys showed that trainees with prior background and education in research were more likely to be involved in conducting studies. Limited time, a poor research infrastructure and inadequate research funding opportunities were identified as major hurdles. Although funds are provided by organizations, such as, the Higher Education Commission (HEC), the Pakistan Medical and Research Council, and the Pakistan Science Foundation, Irumnaz *et al.* notes that these resources fund mainly basic research studies and are insufficient for large-scale clinical trials.¹⁶

CONCLUSION

Pakistan is a developing country with a talented pool of researchers and academic institutes keen to produce high quality clinical studies. Analysis of the characteristics of clinical trials registered in ClinicalTrials.gov showed that although output is rising, the quality may be there yet. A large portion of the registry consists of small-scale studies and the majority of the trials are drug interventions. A large majority has not reported results. Most trials have been conducted in the province of Sindh, where Karachi, a city of 14.9M is located. Non-industrial agencies, such as universities, hospitals and non-profit organizations are the major sponsors of all trials. Steps to counter obstacles such as a lack of educational infrastructure, regulatory policies, insufficient funds and inadequate training, need to be undertaken to improve the quality of research and trials in Pakistan.

AUTHORS' CONTRIBUTION

AA: Conceptualization of study design. AZ, TI: Data collection, data analysis, interpretation, write-up....

REFERENCES

1. Learn About Clinical Studies - ClinicalTrials.gov [Internet]. [cited 2019 April 15]. Available from: <https://clinicaltrials.gov/ct2/about-studies/learn>
2. Sackett DL, Rosenberg WM, Gray JA, Haynes RB, Richardson WS. Evidence based medicine: what it is and what it isn't. *BMJ* 1996;312(7023):71-2.
3. Sibbald B, Roland M. Understanding controlled trials. Why are randomised controlled trials important? *BMJ* 1998;316(7126):201.
4. The James Lind Library - Illustrating the development of fair tests of treatments in health care [Internet]. The James Lind Library. [cited 2019 April 15]. Available from: <https://www.jameslindlibrary.org/>
5. Woolf SH. The meaning of translational research and why it matters. *JAMA* 2008;299(2):211-3.
6. Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J* 2003;20(2):164-8. Ref no 6&17 are same
7. McCray AT, Ide NC. Design and implementation of a national clinical trials registry. *J Am Med Inform Assoc* 2000;7(3):313-23.
8. National Institutes of Health Launches ClinicalTrials.gov Results Database. [Internet]. [cited 2019 April 15]. Available from: http://www.nlm.nih.gov/news/expanded_clinicaltrials.html
9. Gillen JE, Tse T, Ide NC, McCray AT. Design, implementation and management of a web-based data entry system for ClinicalTrials.gov. *Stud Health Technol Inform* 2004;107(Pt 2):1466-70.
10. Zarin DA, Tse T, Ide NC. Trial registration at ClinicalTrials.gov between May and October 2005. *N Engl J Med* 2005;353(26):2779-87.
11. Zarin DA, Ide NC, Tse T, Harlan WR, West JC, Lindberg DA. Issues in the registration of clinical trials. *JAMA* 2007;297(19):2112-20.
12. The World Bank, Pakistan Data. [Internet]. [cited 2019 April 15]. Available from: <https://data.worldbank.org/country/pakistan>

13. Pakistan Population (2021) - Worldometer [Internet]. [cited 2019 April 15]. Available from: <https://www.worldometers.info/world-population/pakistan-population/>
14. Current health expenditure (% of GDP) - Pakistan | Data [Internet]. [cited 2019 April 15]. Available from: <https://data.worldbank.org/indicator/SH.XPD.CHEX.GD.ZS?locations=PK&name%20desc=false>
15. Global Health Observatory. 2013. Pakistan: Country Profile. Geneva, Switzerland: World Health Organization. [Internet]. [cited 2019 April 15]. Available from: <http://www.who.int/gho/countries/pak/en/>
16. Irumnaz A, C Nair S. Clinical trials in Pakistan: Opportunities and challenges. *Appl Clin Res Clin Trials Regul Aff* 2014;1(1):23–7.
17. Kendall JM. Designing a research project: randomised controlled trials and their principles. *Emerg Med J* 2003;20(2):164–8. Ref no 6&17 are same
18. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in Clinical Trials. gov, 2007–2010. *JAMA* 2012;307(17):1838–47.
19. Kris MG, Meropol NJ, Winer EP. Accelerating progress against cancer: ASCO’s blueprint for transforming clinical and translational cancer research. [Internet]. American Society of Clinical Oncology. [cited 2012 Feb 5]. Available from: <http://www.asco.org/ascov2/department%20content/cancer%20policy%20and%20clinical%20affairs/downl>oads/blueprint.pdf
20. Yusuf S, Collins R, Peto R. Why do we need some large, simple randomized trials? *Stat Med* 1984;3(4):409–22.
21. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of trials. *J Clin Epidemiol* 1995;48(1):23–40.
22. Califf RM, DeMets DL. Principles from clinical trials relevant to clinical practice: part I. *Circulation* 2002;106(8):1015–21.
23. Jawad F. Clinical trial registry in Pakistan. [Internet]. [cited 2019 April 15]. Available from: <https://jpma.org.pk/article-details/8802>
24. Research and Development at GSK Pakistan - GlaxoSmithKlinec2001-2010. [Internet]. [cited 2013 Nov 21] Available from: <http://www.gsk.com.pk/Research-and-Development/73/Researchand-Development-at-GSK-Pakistan.aspx>
25. Zwierzyna M, Davies M, Hingorani AD, Hunter J. Clinical trial design and dissemination: comprehensive analysis of clinical trials. gov and PubMed data since 2005. *BMJ* 2018;361:k2130.
26. Osama M, Malik RJ, Azim ME. Clinical Trial Registry: An essential requirement for physical therapy and health researchers in Pakistan. *J Pak Med Assoc* 2018;68(7):1079–83.
27. Sherin A. Clinical trial registration: Can we establish a national clinical trial registry of Pakistan? *Khyber Med J Univ J* 2012;4(2):37–8.

Submitted: October 14, 2020

Revised: February 14, 2021

Accepted: March 5, 2021

Address for Correspondence:

Tooba Irfan, Dow University of Health Sciences, Civil Hospital Karachi-Pakistan

Email: toobairfan.94@gmail.com