

Dynamics of Clinical Trial Studies

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Abstract: *Clinical trial studies are essential for safety, efficacy and reliability. These studies are conducted for new chemical entities, new dosage forms, new routes of administration, for generic versions. Bioavailability and bioequivalence studies are a part of clinical trials. Out of 194 WHO member states, 170 states have clinical trial registrations. India stands 14th among the member states in clinical trial registrations. At WHO, among the 115 health topics, clinical trial registrations for cancer are the highest. The article is emphasized on statistical status of clinical trial registrations in Indian and WHO registry.*

Introduction

Established in the year 2007, Clinical Trial Registry of India (CTRI) is hosted by National Institute of Medical Statistics, under the supervision of World Health Organisation (WHO), Indian Council of Medical Research (ICMR) and Department of Science and Technology (DST). The registry helps in ensuring transparency, accountability and accessibility of clinical trials to meet the objective of improving therapeutic regime, evidence based advancements in medical treatment. In 2009, Drugs Controller General of India (DCGI) made mandatory of registration of clinical trials conducted in India.

Researchers who wish to conduct a trial involving human participants, of any intervention such as drugs, surgical procedures, preventive measures, lifestyle modification, devices, educational or behavioral treatment, rehabilitation strategies as well as trials being conducted in the Department of AYUSH are expected to register the trial before enrollment of the first participant.

Trial registration involves public declaration and identification of trial investigators, sponsors, interventions, patient population etc before the enrollment of the first patient. Submission of Ethics approval and DCGI approval (if applicable) is essential for trial registration in the CTRI. Multi-country trials, where India is a participating country, which have been registered in an international registry, are also expected to be registered in the CTRI. In the CTRI, details of Indian investigators, trial sites, Indian target sample size and date of enrollment are captured. After a trial is registered, trialists are expected to regularly update the trial status or other aspects as the case may be. After a trial is registered, all updates and changes will be recorded and available for public display.

Being a Primary Register of the International Clinical Trials Registry Platform (ICTRP) (<http://www.who.int/ictpr/search/en/>),

registered trials are freely searchable both from the WHO's search portal, the ICTRP as well as from the CTRI (www.ctri.nic.in). Foreign countries where a primary registry facility is not available, Indian registry accepts registration of trials even though the facility is for local purpose.

Indian registry also accepts registration of trials conducted in other countries where such primary registry is not available in the specific country.

Clinical trial registry of India secretariat is constituted by a chairman, administrator, advisor, coordinator, technical working group, scientists and is publicly owned and managed not for profit organisation located at New Delhi.

The objective of the current article is to bring awareness of the clinical trial statistics conducted at national and international levels.

Methodology

Statistics available at clinical trial registries of India and World Health Organisation were taken into consideration for the analysis. It is necessary to understand that the statistics (Indian) are with respect to traced out information at the registry since inception. Several trials abandoned, cases that does not exist, with negative result may not be reflected in the data.

WHO Clinical Trial Registry

Ministerial summit on health research in 2004 at Mexico led to development of International Clinical Trial Registry Platform (ICTRP) for registration of clinical trials at World Health Organisation (WHO). WHO provides a registry network for exchange of information and for working together. The network is composed of primary registries (Australian and New Zealand, Brazil, China, Republic of Korea, India, Cuba, EU, Germany, Iran, Japan, Thailand, The Netherlands, Pan Africa, Sri Lanka), partner registries (Freiburg, German, Hong Kong University) and registries

working with the ICTRP towards becoming primary registries. The primary registries have met the criteria of standards set by WHO such as contents, quality and validity, accessibility, unambiguous identification, technical capacity, administration and governance.

Statistics of WHO Clinical Trial Registrations-Region Wise

Out of 194 member states, 173 states are listed in the registry and are categorized into jurisdiction of six WHO regional offices. Research, Table 1, indicates that a total of 2,69,471 trials were registered of which 1,01, 218 are registered at American region contributing the highest of 37.5 %, while 4,615 registrations at the African region contributing the lowest of 1.7%.

S. No	Name of Region	No. of Trials	%age Contribution
1	AMRO (American Region)	101218	37.56
2	EURO (European Region)	91507	33.96
3	WPRO (Western Pacific Region)	51100	18.96
4	EMRO (Eastern Mediterranean Region)	10744	3.99
5	SEARO (South East Asian Region)	10287	3.82
6	AFRO (African Region)	4615	1.71
	Total	269471	100

Table 1: Number of Clinical Trials Registered at WHO registry-Region wise (as on 9th Mar, 2015)

Statistics of WHO Clinical Trial Registrations-Health Topic wise -Top 20:

At WHO a provision of 115 health topics is provided for clinical trial registrations. A total of 1,19,801 clinical trial registrations were made with respect to health topic wise. Table 2, illustrates top 20 health topics with corresponding number of clinical trials registered at WHO. Among the top 20 topics registered, health topic 'Cancer' stands first with 41,943 and health topic 'Surveillance' stand lowest with 993 clinical trial registrations. Health topic titled with 'pharmaceutical products' is found with nil registrations at WHO clinical trial registry.

Statistics of WHO Clinical Trial Registrations-Country wise-Top 20:

When the number of clinical trial registrations was observed country wise, a total of 3,89,286 registrations of 173 countries are observed. Among the country's entries of clinical trial registration, United States of America stands highest with 87050 registrations,

S. No	Name of Health Topic	No. of Trials	%age Contribution
1	Cancer	41943	35.01
2	Diabetes mellitus	11538	9.63
3	AIDS	6231	5.2
4	Obesity	5343	4.46
5	Transplantation	5026	4.2
6	Education & training	4983	4.16
7	Poliomyelitis	4648	3.88
8	Suicide	3480	2.9
9	Hepatitis	3396	2.83
10	Cardiovascular diseases	3322	2.77
11	Influenza	2050	1.71
12	Smoking	1800	1.5
13	Nutrition	1683	1.4
14	Cost and cost analysis	1201	1
15	Vaccines	1144	0.95
16	Mental health	1134	0.95
17	Epilepsy	1094	0.91
18	Malaria	1062	0.89
19	Mental disorders	1011	0.84
20	Surveillance	993	0.83
	Total (Top 20 topics)	103082	86.02
	Total (115 topics)	119801	100

Table 2: Number of Clinical Trials Registered at WHO registry-Health Topic wise- (as on 9th March, 2015)

where as Dominica, Lybia and Saint Vincent and the Grenadines stands with nil registrations. If Dominica, Lybia and Saint Vincent and the Grenadines are not considered, Syrian Arab Republic, Antigua and Barbuda, Eritrea, Grenada, Nauru, Saint Kitts and Nevis and Saint Lucia have the lowest of one registration each. Figure 1, Table 3, illustrates the top 20 country's clinical trial registrations of which India stands 14th with 7,725 registrations and Austria stands 20th with 5430 registrations. When total number of trials registered country wise is compared with total of region wise, the numbers does not tally and it can be assumed that the same trials being conducted in several countries. The contribution of top 20 countries in clinical trial registration is about 77%.

Indian Clinical Trial Registry

Statistics of Indian Clinical Trial Registrations-As a whole

Research indicates that a total of 5,612 clinical trials are registered at the Indian registry since 2007. Several trials registered were conducted in several places across India and abroad and the

un-cleaned data results to 24,118 trials. It has been observed that either clinical trial being registered or being conducted by almost every state and union territory of India. In addition to this, several trials conducted at Bangladesh, Chile, Egypt, Ivory Coast, Democratic Republic of Congo, Senegal, Mali, Malawi, Rwanda, Vietnam and Argentina are being registered at Indian clinical trial registry. Research, Table 4, indicates that maximum trials of 5,355 were registered at Maharashtra, where as Uttara Khand being registered with minimum trials of 1 based on uncleaned data. However, several trials registered were observed with indication of hospital name only and no mention of place and state within India.

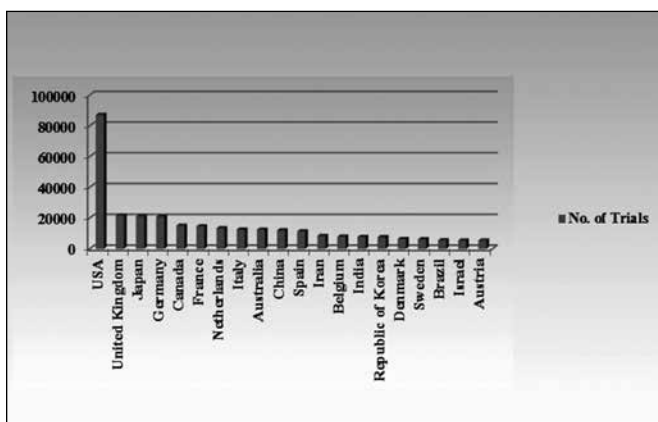


Figure 1: Clinical Trials Registered in India-Company Name wise (as on 18th March, 2015)

Statistics of Indian Clinical Trial Registrations-Type of Trial Wise

At Indian clinical trial registry, trials are categorized into four types i.e., BA/BE, interventional, observational and post market surveillance studies. Out of a total of 5612 studies, Table 5, it has been observed that interventional studies stands the highest with 4079 (72%) and least with BA/BE studies of 151 (2.7%).

Statistics of Indian Clinical Trial Registrations-Status Wise:

Statuses of clinical trials registered at Indian registry are categorized into seven categories based on recruitment status (i.e., closed to recruitment, completed, not applicable, not yet recruiting, open to recruitment, other (terminated), and suspended). It has been observed, Figure 2, that recruitment for 2,713 trials completed.

Type of Trial	BA/BE	Interventional	Not Available (Blanks)	Observational	PMS	Grand Total
No. of Trials	151	4079	622	600	160	5612
%	2.7	72.7	11.1	10.7	2.9	100

Table 5: Number of Indian Clinical Trial Registrations-Type of Trial wise (as on 9th March, 2015)

S. No	Name of Country	No. of Trials	% Contribution
1	United States of America	87050	22.4
2	United Kingdom	21725	5.6
3	Japan	21070	5.4
4	Germany	20810	5.3
5	Canada	14983	3.8
6	France	14621	3.8
7	Netherlands	13416	3.4
8	Italy	12508	3.2
9	Australia	12441	3.2
10	China	11995	3.1
11	Spain	11374	2.9
12	Iran (Islamic Republic of)	8329	2.1
13	Belgium	7876	2.0
14	India	7725	2.0
15	Republic of Korea	7575	1.9
16	Denmark	6496	1.7
17	Sweden	6186	1.6
18	Brazil	5571	1.4
19	Israel	5440	1.4
20	Austria	5430	1.4
Total (Top 20)		302621	77.7
Total 170 countries		389286	100.0

Table 3: Number of Clinical Trials Registered at WHO-Country wise-Top 20 (as on 9th March, 2015)

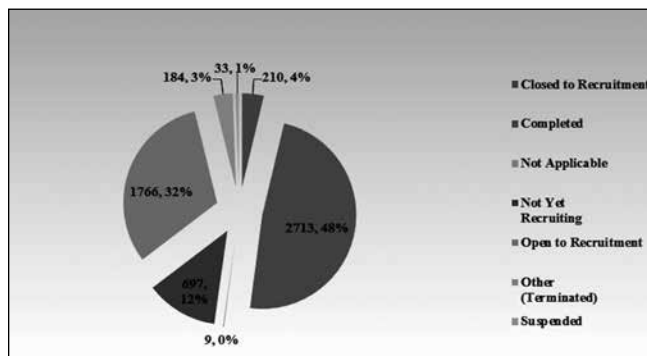


Figure 2: Statistics of Indian Clinical Trial Registrations-Status wise (as on 9th March, 2015)

S. No		Name of State/Country	No. of Trials Registered	S. No		Name of State/Country	No. of Trials Registered
1	Indian State/Union Territory	Maharashtra	5355	26	Indian State/Union Territory	Sikkim	8
2		Karnataka	3199	27		Meghalaya	6
3		Gujarat	2181	28		Andaman & Nicobar Islands	5
4		Andhra Pradesh	2130	29		Manipur	5
5		Tamilnadu	2041	30		Mizoram	3
6		Delhi	1906	31		Arunachal Pradesh	2
7		West Bengal	953	32		Chhattisgarh	2
8		Uttar Pradesh	943	33		Uttarakhand	1
9		Rajasthan	879			Not Available (No indication)	1673
10		Kerala	600	S. No		Total (Indian)	24103
11		Madhya Pradesh	374	1	Other Countries	Bangladesh	2
12		Chandigarh	349	2		Ivory Coast	2
13		Haryana	323	3		Argentina	1
14		Punjab	288	4		Chile	1
15		Bihar	217	5		Democratic Republic of Congo	1
16		Orissa	166	6		Egypt	1
17		Pondicherry	166	7		Malawi	1
18		Assam	77	8		Mali	1
19		Goa	57	9		Nepal	1
20		Himachal Pradesh	56	10		Rwanda	1
21		Jammu & Kashmir	49	11		Senegal	1
22		Jharkhand	33	12		Sri Lanka	1
23		Uttaranchal	26	13		Vietnam	1
24		Chhattisgarh	21			Total (Other Countries)	15
25		Tripura	9			Grand Total	24118

Table 4: Number of Registrations at Indian Clinical Trial Registry-Indian states, other countries-as on 9th March, 2015

Statistics of Indian Clinical Trial Registrations-Trial Phase Wise

In general clinical trials are categorized into phase 1 (Pharmacodynamic, pharmacokinetic studies in healthy volunteers), phase 2 (controlled clinical study on patients for establishing effectiveness, identify short term risks and side effects), phase 3 (controlled and uncontrolled clinical study on larger subjects for establishing over all benefit/risk ratio and for establishing labeling requirements), phase 4 (studies performed after drug is marketed and is related to the approved indication), PMS (post marketing surveillance after marketing approval). When a research is conducted on the total number of clinical

trial registrations registered at Indian clinical trial registry since 2007 to 2015, Table 6, indicates that out of 5,612 clinical trials registered, a cumulative total of 1,418 trials are in phase 3 and 693 trials are in phase 4. It has been observed 2,049 trials are indicated by N/A (not applicable-for a non-drug trial, BA/BE trial). A total of 159 studies are in stage of Post Marketing Surveillance (PMS).

Statistics of Indian Clinical Trial Registrations-Study Design Wise

At Indian clinical trial registry, clinical trials are categorized into twelve study designs. Research indicates, Table 7, during 2007 to 2015, among a total of 5,612 registrations, “Randomized

Year/Phase	Phase 1	Phase 1 & Phase 2	Phase 2	Phase 2 and Phase 3	Phase 3	Phase 3 and Phase 4	Phase 4	PMS	N/A	Grand Total
2007	0	0	13	2	11	1	3	0	1	31
2008	4	5	31	11	56	2	20	1	24	154
2009	46	16	102	27	299	13	78	3	57	641
2010	47	10	101	24	309	17	87	10	140	745
2011	21	19	96	32	194	16	120	14	230	742
2012	40	18	128	25	224	13	117	38	357	960
2013	9	16	95	23	134	22	123	39	531	992
2014	21	20	96	25	154	27	122	42	570	1077
2015	1	4	29	13	37	12	23	12	139	270
Grand Total	189	108	691	182	1418	123	693	159	2049	5612

Table 6: Number of Clinical trials registered at Indian Registry-Phase wise (2007-2015)-as on 9th March, 2015

parallel group active controlled” study design has maximum of 1,233 trials whereas “Non-Randomized, Placebo controlled” study design has minimum of 22 trials being registered.

S. No	Name of Study Design Trial	No. of Trials
1	Randomized, Parallel Group, Active Controlled	1233
2	Randomized, Parallel Group, Placebo Controlled	983
3	Single Arm Trial	900
4	Other	888
5	Randomized, Parallel Group	762
6	Randomized, Parallel Group, Multiple Arm	313
7	Randomized, Crossover	241
8	Non-Randomized, Active Controlled	125
9	Non-Randomized, Multiple Arm	84
10	Cluster, Randomized	34
11	Randomized Factorial	27
12	Non-Randomized, Placebo Controlled	22
	Grand Total	5612

Table 7: Number of Indian Clinical Trial Registrations-Study Design Wise (as on 9th Mar, 2015)

S. No	Company Name (String Name)	S. No	Company Name (String Name)
1	Novartis	19	IPCA
2	Glaxo	20	Torrent
3	Glenmark	21	Laila
4	Sun Pharma	22	Sami Labs
5	Ajanta	23	Shantha Biotech
6	Cipla	24	Micro
7	Troikaa	25	NATCO
8	Ranbaxy	26	Mylan
9	Biocon	27	Alkem
10	Reliance	28	Alembic
11	Emcure	29	Aurobindo
12	Piramal	30	Strides
13	Bharat Biotech	31	Unique
14	Dr Reddys	32	FDC
15	Lupin	33	Green Chem
16	Wockhardt	34	Macleods
17	Zydus	35	Orchid
18	Hetero		

Table 9: Clinical Trials Registered in India-Company Name wise (as on 18th March, 2015)

S. No	Year/Study Design Wise	2007	2008	2009	2010	2011	2012	2013	2014	2015	Grand Total
1	Randomized, Parallel Group, Active Controlled	11	50	205	255	166	147	172	182	45	1233
2	Randomized, Parallel Group, Placebo Controlled	11	49	180	148	151	177	121	121	25	983
3	Single Arm Trial	1	16	81	116	107	181	151	193	54	900
4	Other	1	18	57	81	98	165	223	198	47	888
5	Randomized, Parallel Group	3	0	11	17	107	165	189	205	65	762
6	Randomized, Parallel Group, Multiple Arm	3	13	50	57	48	52	31	48	11	313
7	Randomized, Crossover	0	5	29	31	29	31	45	63	8	241
8	Non-Randomized, Active Controlled	0	0	11	21	10	13	29	35	6	125
9	Non-Randomized, Multiple Arm	0	1	8	10	17	14	14	14	6	84
10	Cluster, Randomized	0	1	3	2	4	8	7	7	2	34
11	Randomized Factorial	1	0	4	5	3	5	3	5	1	27
12	Non-Randomized, Placebo Controlled	0	1	2	2	2	2	7	6	0	22
	Grand Total	31	154	641	745	742	960	992	1077	270	5612

Table 8: Number Indian Clinical Trial Registrations-Year vs. Study Design Wise (as on 9th Mar, 2015)

Statistics of Indian Clinical Trial Registrations-Year vs. Study Design Wise:

At Indian clinical trial registry, when an analysis was made with respect to year versus study design, Table 8, indicates that during 2007 to 2014, maximum trials in the year 2014 (1077 trials), where as minimum trials in the year 2007 (31 trials) were observed.

Statistics of Indian Clinical Trial Registrations-Company wise:

When research is conducted based on company wise to analyze the number of clinical trials registered (2007 to 2015) respectively, Table 9, indicates some of the companies as sponsors.

Conclusion

Statistics clearly indicates that Indian pharmaceutical industry is not only questing for generic versions but also for new chemical entities as drugs. Clinical trials registered by the companies for the new chemical entities being studied may be expected for patent protection in the Indian Territory.

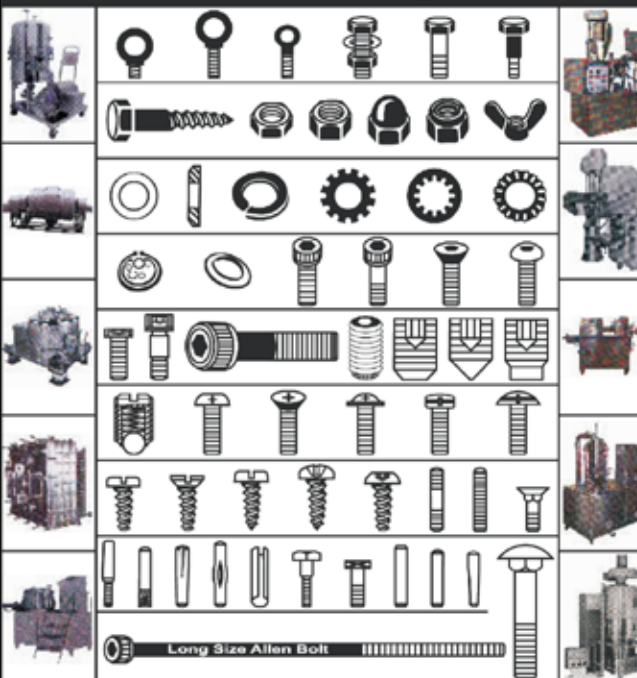
References

1. <http://ctri.nic.in/>
2. <http://apps.who.int/trialsearch/>

Disclaimer

1. All the information furnished is to the interpretation of the authors.
2. The legal status of the trials may be obtained from appropriate authority.

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