研究成果の刊行に関する一覧表

1. Kobayashi E, Matsuyama M, Suzuki K, Murakami T, Narukawa M. Characteristics of industry-sponsored drug clinical trials registered in Japan Pharmaceutical Information Center Clinical Trials Information 2010-2018. Therapeutic Innovation & Regulatory Science 2021; 55(2): 378-387.

Therapeutic Innovation & Regulatory Science (2021) 55:378–387
https://doi.org/10.1007/s43441-020-00223-2

DIA

ORIGINAL RESEARCH

Characteristics of Industry-Sponsored Drug Clinical Trials Registered in Japan Pharmaceutical Information Center Clinical Trials Information 2010–2018

Eriko Kobayashi[1] · Midori Matsuyama[2] · Katsue Suzuki[2] · Takahisa Murakami[2] · Mamoru Narukawa[3]

Received: 21 May 2020 / Accepted: 19 September 2020 / Published online: 6 October 2020

Abstract

Purpose To examine the trends and characteristics of industry-sponsored drug clinical trials registered in the JapicCTI (Japan Pharmaceutical Information Center Clinical Trials Information) in 2010–2018.

Methods A data set of 3116 clinical trials registered from Jan. 2010 to Dec. 2018 were analyzed. Fundamental characteristics of the clinical trials were analyzed by 3-year time periods. The analysis was also focused on 3 therapeutic areas: cardiovascular, mental health, and oncology.

Results Of all the trials (2010–2018), 74.7% were conducted in Japan only; the rate decreased from 82.8 to 65.3% over the 3 time periods. Most trials were phase 3 trials, which comprised 44.1% of the trials. Small trials (anticipated number of 1000 or fewer participants) made up 94.0% of the trials. Oncology trials (29.5%) were the most common type and involved more phase 1 trials than mental health and cardiovascular trials (33.6% vs 14.5% and 11.5%, respectively). Oncology trials composed the smallest proportion of trials conducted in "Japan only" at 57.3% vs 81.0% and 83.1% for mental health and cardiovascular trials, respectively ($p < 0.001$). The median of the anticipated number of participants in mental health trials were larger than those in cardiovascular and oncology trials ($p = 0.001$). Mental health trials were more likely to permit children under age 15 (10.9% vs 4.9% for cardiovascular and 1.2% for oncology). Oncology trials were more likely not to set an upper age limit (89.8% vs 51.4% for cardiovascular and 41.7% for mental health). Cardiovascular and mental health trials were more likely to be conducted as "double blind" (42.4% and 47.1%, respectively vs 16.7% for oncology).

Conclusion During this time, the majority of industry-sponsored trials in Japan were phase 3 trials, Japan only and small trials. There were differences in clinical trials among the 3 therapeutic areas: size of the trial, globalization, phase, age of participants, blinding.

Keywords Clinical trial registry · Japan Clinical trials · Industry-sponsored clinical trials · Clinical research design · Therapeutic areas studied

Abbreviations

JPRN	The Japan Primary Registries Network
JapicCTI	Japan Pharmaceutical Information Center Clinical Trials Information
JMACCT	Japan Medical Association Center for Clinical Trials
UMIN-CTR	The University Hospital Medical Information Network Clinical Trials Registry
jRCT	Japan Registry of Clinical Trials

✉ Eriko Kobayashi
erikokob@faculty.chiba-u.jp

1 Department of Social Pharmacy, Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8675, Japan

2 Japan Pharmaceutical Information Center, 2-12-15 Shibuya, Shibuya-ku, Tokyo 150-0002, Japan

3 Department of Clinical Medicine, Graduate School of Pharmaceutical Sciences, Kitasato University, 5-9-1 Shirokane, Minato-ku, Tokyo 108-8641, Japan

Introduction

A clinical trial is one of the critical elements for innovative drug development, and therefore ensuring its transparency and accessibility is important. Globally, the International Committee of Medical Journal Editors (ICMJE) has introduced a policy requiring prospective registration of phase II-IV trials for publication of research articles in its member

journals, to prevent selective publication and selective reporting of research outcomes [1, 2]. Further, the World Health Organization (WHO) established the International Clinical Trials Registry Platform (ICTRP) in 2005 [3]. The International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) published a position paper entitled, "Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases" in 2005 with the Japan Pharmaceutical Manufacturers Association (JPMA), European Federation of Pharmaceutical Industries and Associations (EFPIA) and Pharmaceutical Research and Manufacturers of America (PhRMA) [4], committing to the transparency of clinical trials sponsored by their member companies and to registering all the clinical trials with patients. In response to these global movements of clinical trial registration, the Japan Primary Registries Network (JPRN) has become a data provider of the ICTRP Search Portal [5]. The JPRN is hosted by the National Institute of Public Health, Japan and is composed of three registries: Japan Pharmaceutical Information Center Clinical Trials Information (JapicCTI) [6], Japan Medical Association Center for Clinical Trials (JMACCT) [7] and the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) [8]. In addition to these three registries, Japan Registry of Clinical Trials (jRCT) joined the JPRN in 2019 [9]. The contents of all the registries are publicly available and cross-searchable through the portal site of JPRN.

Clinical trials conducted in Japan can be divided into two major categories: (1) clinical trials for new drug application, which are sponsored by the industry, conducted in conformity with the Japanese Pharmaceuticals and Medical Devices Act, and (2) academic clinical trials for which industry is not a major sponsor. The former clinical trials for new drug application sponsored by the industry have been registered in JapicCTI in Japan, aligned with the efforts of promoting clinical trials registration of IFPMA [4] and Japanese Ministry of Health, Labour and Welfare [9].

Previous studies have examined the trends and the characteristics of the clinical trials registered in national clinical trials registries, the ClinicalTrials.gov in the USA [10–14], the Australian-New Zealand Clinical Trials Registry (ANZCTR) in Australia/New Zealand [15], the clinical projects in Finland [16], and academic trials of JMACCT in Japan [17, 18]. As over 10 years have passed since the establishment of the national clinical trial registry—JPRN in Japan, the characteristics of the industry-sponsored clinical trials have not yet been well examined.

The aim of the study was to examine the trends and characteristics of industry-sponsored drug clinical trials which were registered in the JapicCTI in 2010–2018. We also analyzed the data focusing on the clinical trials in three major therapeutic areas (cardiovascular, mental health, and oncology) contained in the registry.

Materials and Methods

JapicCTI Dataset

The JapicCTI [5] is the clinical trial registry maintained by the Japan Pharmaceutical Information Center. Sponsor companies can enter data through a web-based data entry system. The clinical trials registered with the JapicCTI meet specific criteria for content, quality and validity, accessibility, unique identification, etc. of the WHO criteria [19] and also meet ICMJE requirements.

A data set of 3534 clinical trials registered from Jan. 1, 2010 to Dec. 31, 2018 in the JapicCTI were collected via the website of the JapicCTI. Since our analysis focuses on drug clinical trials sponsored by the pharmaceutical industry, we used a data set of 3116 clinical trials after excluding the clinical trials without target drugs.

Analysis

The fundamental 8 characteristics of the clinical trials were analyzed by 3-year time periods (2010–2012, 2013–2015, 2016–2018): Primary purpose (treatment, diagnostics, prevention, other), Region (Japan only, Japan plus Asia, Europe, North America, Oceania, South America, Africa, Other), Anticipated number of participants, Study phase (1, 1/2, 2, 2/3, 3, 4, other), Study design (Interventional, non-interventional), Allocation status (Non-randomized, Randomized), Blinding (Open, Single blind, Double blind), Sponsor company (Japanese oriented company, Multinational company). Additional analyses included clinical trial characteristics according to the 3 therapeutic areas, cardiovascular, mental health, and oncology, that encompass the largest number of disability-adjusted life-years lost in Japan [20]: Primary purpose, Region, Anticipated number of participants, Study phase, Study design, Allocation status, Blinding, Gender group (male, female, both), Age group (< 15, 15–65, > 65). Further cross analysis was performed between trials phase vs region. Differences were compared with χ^2 test and Mann–Whitney U test. Time series analysis was performed with regression analysis. All analysis were performed by SPSS ver 26.0 (IBM Japan).

Results

The number of drug clinical trials registered each year in the JapicCTI from 2010 to 2018 is shown in Fig. 1. From 2010, no trend was observed ($p = 0.788$) and about 350 clinical trials have been registered in the JapicCTI every year; the

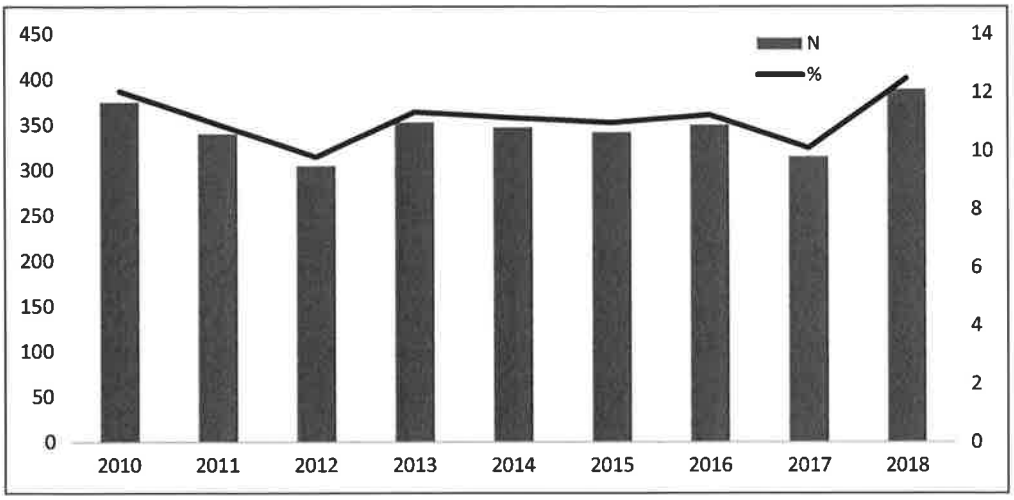

Fig. 1 Number of Clinical Trials Registered in the JapicCTI from 2010 to 2018. *N*, Number of clinical trials registered in the JapicCTI. % reflects the percentage of the numbers of the clinical trials registered in the year by all the trials registered from 2010 to 2018.

highest number, 389 clinical trials, was registered in 2018. The mean number of registered clinical trials per year is 346.2.

Fundamental characteristics of all the industry-sponsored drug clinical trials registered in the JapicCTI from Jan. 1, 2010 to Dec. 31, 2018 ($N=3116$), and the three trial subsets, as divided by 3-year time periods, are shown in Table 1. The number of the trials registered in each of the 3-year time periods was 1020, 1042, 1054, respectively, showing a slight increase over time. A decrease over time in the number of missing data elements occurred in the following characteristics among the 3 time periods: not reporting the target number of participants from 33.4 to 15.7%, not reporting the primary purpose of the study from 97.5 to 59.6%.

The majority of the trials were conducted only in Japan; they were small in terms of anticipated number of patients, and many were phase 3 trials. As a total, 74.7% of the trials were conducted only in Japan, but the rate of the trials conducted only in Japan decreased from 82.8 to 65.3% over the 3 time periods. Whereas, the trials conducted in Japan and other regions increased: from 11.6 to 20.8% in Asia, from 8.1 to 28.0% in Europe, from 7.1 to 25.9% in North America. Excluding the missing data, 94.0% of the trials had a target number of 1000 or fewer participants and 47.7% had 100 or fewer participants. 44.1% of the trials were phase 3 trials, which was the most in the trials. The rates of trials of each type of phase have not differed in these time periods.

Of all the trials, oncology trials made up the most ($N=920$, 29.5%), followed by trials for mental health ($N=331$, 10.6%) and for cardiovascular diseases ($N=243$, 7.8%). These were the therapeutic areas most frequently studied in the registered trials. Figure 2 shows the percentages of the numbers of clinical trials registered in the JapicCTI from 2010 to 2018 for these 3 therapeutic areas: oncology, mental health and cardiovascular diseases. The numbers of oncology clinical trials have been increasing from 2010 to 2018 ($p<0.002$), whereas, those of mental health and cardiovascular have been gradually decreasing ($p<0.013$, $p<0.048$, respectively).

Table 2 shows selected characteristics for trials in oncology, mental health and cardiovascular diseases. Oncology trials composed the smallest proportion of trials conducted in "Japan only" at 57.3% vs 81.0% and 83.1% for mental health and cardiovascular trials, respectively ($p<0.001$). Much more oncology trials were conducted in regions such as Asia, Europe, North America, Oceania, and South America compared to Mental Health and Cardiovascular trials. There were also differences in age distribution of participants among the 3 therapeutic areas ($p<0.001$). Mental health trials were more likely to include children under age 15 years (10.9% vs 4.9% for cardiovascular and 1.2% for oncology). On the other hand, trials in oncology areas were more likely not to set an upper age limit (89.8% for oncology vs 51.4% for cardiovascular and 41.7% for mental health).

Significant differences in trial phase and the anticipated numbers of participants were also evident in the 3 therapeutic areas ($p<0.001$, $p=0.001$, respectively). Oncology trials were more likely to involve phase 1 trials than mental health and cardiovascular trials (33.6% for oncology vs 14.5% for mental health and 11.5% for cardiovascular), whereas almost half of the mental health and cardiovascular trials were for phase 3 trials (49.2% and 49.8%, respectively). The median of the anticipated number of participants in mental health trials were larger than those in cardiovascular and oncology trials ($p=0.001$). Almost half (43.2%) of the mental health trials involved 101–1000 participants per trial, but many

Table 1 Characteristics of all the Clinical Trials Registered in the JapicCTI from 2010 to 2018.

	All the studies (*N* = 3116)		2010–2012 (*N* = 1020)		2013–2015 (*N* = 1042)		2016–2018 (*N* = 1054)	
	N	%	*N*	%	*N*	%	*N*	%
Primary purpose								
Treatment	529	17.0	23	2.3	125	12.0	381	36.1
Diagnostics	3	0.1	0	0.0	0	0.0	3	0.3
Prevention	25	0.8	3	0.3	7	0.7	15	1.4
Other	28	0.9	0	0.0	1	0.1	27	2.6
Missing	2531	81.2	994	97.5	909	87.2	628	59.6
Region[a]								
Japan only	2327	74.7	845	82.8	794		688	65.3
Asia[b]	495	15.9	118	11.6	158	15.2	219	20.8
Europe[b]	562	18.0	83	8.1	184	17.7	295	28.0
North America[b]	486	15.6	72	7.1	141	13.5	273	25.9
Oceania[b]	257	8.2	36	3.5	80	7.7	141	13.4
South America[b]	212	6.8	28	2.7	70	6.7	114	10.8
Africa[b]	42	1.3	5	0.5	14	1.3	23	2.2
Other[bc]	105	3.4	39	3.8	37	3.6	29	2.8
Anticipated no. of participants								
1–100	1119	35.9	334	32.7	343	32.9	442	41.9
101–1000	1087	34.9	313	30.7	371	35.6	403	38.2
> 1000	141	4.5	32	3.1%	65	6.2	44	4.2
Missing	769	24.7	341	33.4	263	25.2	165	15.7
Phase								
Phase 1	542	17.4	167	16.4	176	16.9	199	18.9
Phase 1/2	99	3.2	27	2.6	38	3.6	34	3.2
Phase 2	676	21.7	251	24.6	210	20.2	215	20.4
Phase 2/3	89	2.9	30	2.9	30	2.9	29	2.8
Phase 3	1374	44.1	466	45.7	440	42.2	468	44.4
Phase 4	99	3.2	27	2.6	39	3.7	33	3.1
Other	237	7.6	52	5.1	109	10.5	76	7.2
Study design								
Interventional	2978	95.6	1009	98.9	966	92.7	1003	95.2
Non-interventional	138	4.4	11	1.1	76	7.3	51	4.8
Allocation status								
Non-randomized	1713	55.0	565	55.4	620	59.5	528	50.1
Randomized	1403	45.0	455	44.6	422	40.5	526	49.9
Blinding								
Open	1336	42.9	422	41.4	446	42.8	468	44.4
Single blind	55	1.8	20	2.0	15	1.4	20	1.9
Double blind	1005	32.3	359	35.2	325	31.2	321	30.5
Missing	720	23.1	219	21.5	256	24.6	245	23.2
Sponsor company[b]								
Japanese oriented company	1738	55.8	531	52.1	627	60.2	580	55.0
Multinational company	1567	50.3	562	55.1	473	45.4	532	50.5

[a]All the registered trials were conducted in Japan. The region "Asia" means the clinical trials conducted in Japan plus Asia, other regions as well

[b]Percentages may not total 100 as categories are not mutually exclusive

[c]Includes multi-regional trials with unidentified regions

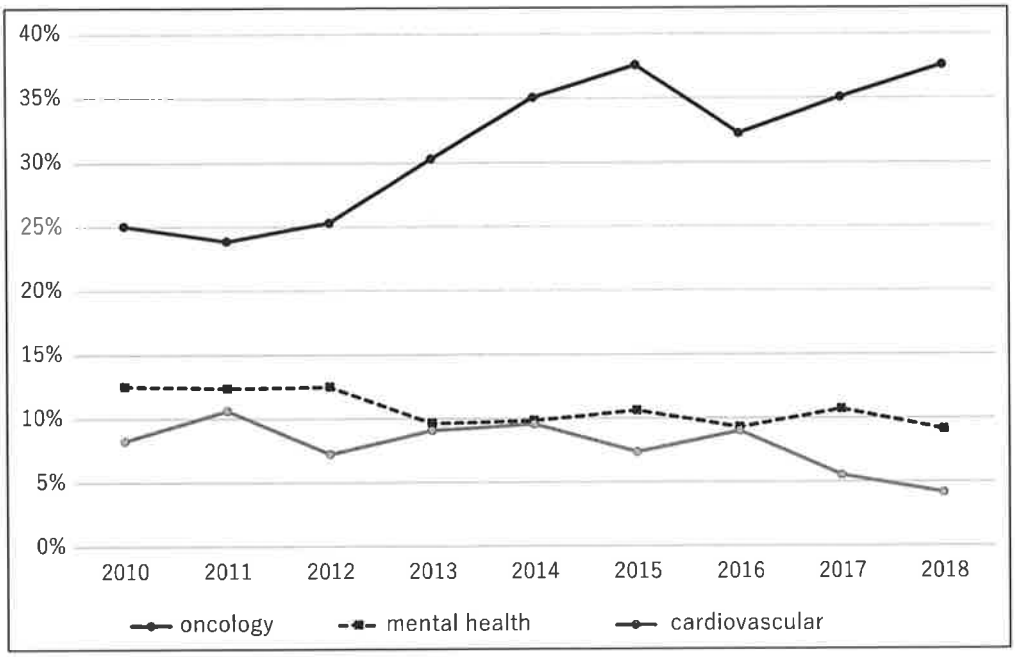

Fig. 2 Percentages of the Numbers of Clinical Trials in 3 Therapeutic Areas (Mental Health, Cardiovascular Diseases and Oncology).

oncology and cardiovascular trials involved 100 or fewer participants (42.4% and 42.8%, respectively).

There was also a difference in the blinding status of the trials among the 3 therapeutic areas ($p < 0.001$). Oncology trials were more likely to involve open trials (61.5% vs 39.9% for cardiovascular and 39.6% for mental health). Cardiovascular and mental health trials were more likely to be conducted as "double blind" (42.4% and 47.1% respectively vs 16.7% for oncology) compared to oncology trials. No significant differences were observed in study design and allocation status among the 3 therapeutic areas; almost half of the trials were conducted as "non-randomized".

Table 3 shows clinical trial phases and regions for all the trials registered in the JapicCTI from 2010 to 2018 ($N = 3116$). The difference existed in phases between Japan only trials and multi-regional trials ($p < 0.001$) More Japan only trials were conducted as phase 1 trials (20.5%), and more multi-regional trials were conducted as phase 3 trials (56.7%). More than half of the trials involving other regions were conducted as phase 3 trials (57.4% in Asia, 58.7% in Europe, 58.0% in North America)).

Discussion

We conducted a fundamental analysis of industry-sponsored drug clinical trials registered in the JapicCTI database. The majority of the drug clinical trials registered in the JapicCTI database were Japan only, small, and phase 3 trials. Oncology, mental health and cardiovascular diseases, the areas that we focused on in this study, were the therapeutic areas most frequently studied in the registered trials. This reflects the fact that pharmaceutical companies' investment has been focused on these therapeutic areas, given market pressures favoring profitable products with social needs [12, 21]. We also found systematic differences in regions, age limit of the participants, study phase, target number of the participants, study designs and blinding states among the 3 major therapeutic areas.

The annual registration numbers in the JapicCTI were relatively stable from 2010 to 2018, with only a slight increase in 2018. Though it was revealed that the rate of missing data was high in the items of "primary purpose" and "anticipated number of participants", the rate of missing data decreased gradually over the years until recently. After the JapicCTI has become one of the data providers of the ICTRP Search Portal in 2008, the Japanese Ministry of Health and Labor Welfare (MHLW) announced "Japan 5 Years Clinical Research and Trial Activation Plan 2012" in 2012, its third action plan to stimulate clinical research and trials in Japan[22]. As one of the measures to stimulate clinical trials, MHLW has been informing patients and consumers of JPRN, Japan Primary Registries Network to improve patients' access to clinical trials. That suggests that sponsors of clinical trials have made efforts to improve the handling of clinical trial data.

The study showed globalization of clinical trials. Although the rate of trials conducted in Japan only is still

Table 2 Characteristics of Clinical Trials in Three Therapeutic Areas.

	Oncology ($N=920$)		Mental health ($N=331$)		Cardiovascular ($N=243$)		
	N	%	*N*	%	*N*	%	*p* value
Primary purpose							< 0.001*
Treatment	244	26.5	47	14.2	30	12.3	
Diagnostics	0	0.0	0	0.0	0	0.0	
Prevention	0	0.0	1	0.3	3	1.2	
Other	9	1.0	1	0.3	4	1.6	
Missing	667	72.5	282	85.2	206	84.8	
Region[a]							
Japan only	527	57.3	268	81.0	202	83.1	< 0.001*
Multi-regional	393	42.7	63	19.0	41	16.9	
Asia[b]	254	27.6	49	14.8	31	12.8	
Europe[b]	286	31.1	36	10.9	29	11.9	
North America[b]	250	27.2	28	8.5	28	11.5	
Oceania[b]	143	15.5	20	6.0	9	3.7	
South America[b]	99	10.8	13	3.9	16	6.6	
Africa[b]	14	1.5	1	0.3	5	2.1	
Other[bc]	63	6.8	5	1.5	1	0.4	
Anticipated no. of participants							
Median	99.2	–	160.6	–	97.0	–	0.001*
1–100	390	42.4	102	30.8	104	42.8	
101–1000	319	34.7	143	43.2	79	32.5	
> 1000	38	4.1	11	3.3	12	4.9	
Missing	173	18.8	75	22.7	48	19.8	
Phase							
Phase 1	309	33.6	48	14.5	28	11.5	< 0.001*
Phase 1/2	65	7.1	1	0.3	1	0.4	
Phase 2	182	19.8	75	22.7	56	23.0	
Phase 2/3	9	1.0	18	5.4	8	3.3	
Phase 3	301	32.7	163	49.2	121	49.8	
Phase 4	42	4.6	10	3.0	9	3.7	
Other	12	1.3	16	4.8	20	8.2	
Study design							
Interventional	895	97.3	318	96.1	233	95.9	0.386
Non-interventional	25	2.7	13	3.9	10	4.1	
Allocation status							
Non-randomized	526	57.2	176	53.2	130	53.5	0.342
Randomized	394	42.8	155	46.8	113	46.5	
Blinding							
Open	566	61.5	131	39.6	97	39.9	< 0.001*
Single blind	2	0.2	4	1.2	1	0.4	
Double blind	154	16.7	156	47.1	103	42.4	
Missing	198	21.5	40	12.1	42	17.3	
Gender							
Male	30	3.3	18	5.4	22	9.1	< 0.001*
Female	67	7.3	1	0.3	0	0.0	
Both	823	89.5	312	94.3	221	90.9	
Age upper limit							
– 14	0	0.0	4	1.2	7	2.9	< 0.001*
15–64	13	1.4	78	23.6	28	11.5	
65–	81	8.8	111	33.5	83	34.2	

Table 2 (continued)

	Oncology ($N=920$)		Mental health ($N=331$)		Cardiovascular ($N=243$)		
	N	%	*N*	%	*N*	%	*p* value
No limit	826	89.8	138	41.7	125	51.4	
Age lower limit							
–14	11	1.2	36	10.9	12	4.9	< 0.001*
15–64	857	93.2	260	78.5	204	84.0	
65–	3	0.3	3	0.9	1	0.4	
No limit	49	5.3	32	9.7	26	10.7	

*$p < 0.05$ by χ^2 test or Mann–Whitney *U* test

[a]All the registered trials were conducted in Japan. Multi-regional trials were subdivided into regions. The region "Asia" means the clinical trials conducted in Japan plus Asia, other regions as well

[b]Percentages may not total 100, as categories are not mutually exclusive

[c]Includes multi-regional trials with unidentified regions

Table 3 Clinical Trials: Phase and Region.

	Phase 1		Phase 1/2		Phase 2		Phase 2/3		Phase 3		Phase 4		Other			
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*p* value	
Japan only[a] ($N=2327$)	477	20.5	69	3.0	480	20.6	63	2.7	927	39.8	82	3.5	229	9.8	< 0.001*	2327
Multi-regional[a] ($N=789$)	65	8.2	30	3.8	196	24.8	26	3.3	447	56.7	17	2.2	8	1.0		789
Asia[b] ($N=495$)	45	9.1	21	4.2	110	22.2	17	3.4	284	57.4	14	2.8	4	0.8		495
Europe[b] ($N=562$)	31	5.5	18	3.2	147	26.2	17	3.0	330	58.7	11	2.0	8	1.4		562
North America[b] ($N=486$)	34	7.0	19	3.9	116	23.9	18	3.7	282	58.0	11	2.3	6	1.2		486
Oceania[b] ($N=257$)	8	3.1	6	2.3	42	16.3	11	4.3	184	71.6	3	1.2	3	1.2		257
South America[b] ($N=212$)	3	1.4	3	1.4	33	15.6	10	4.7	152	71.7	7	3.3	4	1.9		212
Africa[b] ($N=42$)	0	0.0	0	0.0	3	7.1	3	7.1	32	76.2	2	4.8	2	4.8		42
Other[bc] ($N=105$)	9	8.6	4	3.8	16	15.2	2	1.9	72	68.6	1	1.0	1	1.0		105

*$p < 0.05$ by χ^2 test compared between Japan only trials and multi-regional trials

[a]All the registered trials were conducted in Japan. Multi-regional trials were subdivided into regions. The region "Asia" means the clinical trials conducted in Japan plus Asia, other regions as well

[b]Percentages may not total 100, as categories are not mutually exclusive

[c]Includes multi-regional trials with unidentified regions

high, over 60%, it was gradually decreasing until recently, and the rate of the clinical trials conducted in Japan including other regions of Asia, Europe, North America have been increasing. Differences between Japan only trials and multi-regional trials were also revealed. The rate of early phase "phase 1" trials was higher in the Japan only clinical trials (20.5%) than in the multi-regional trials (8.2%), whereas the rate of "phase 3" trials was higher in the multi-regional trials (56.7%) than in the Japan only clinical trials (39.8%). These results suggest that, in global clinical development, more early phase "phase 1" trials were conducted outside Japan and more later phase trials were conducted in Japan. Our findings were corroborated by the previous study [12] that showed that though phase 3 trials were more prevalent in many representative countries of their respective regions, there were a smaller number of phase 1 trials in these countries than India. As the authors [12] commented, a very low operation cost and a large number of healthy volunteers in the countries outside Japan might be the main reason for the sponsoring pharmaceutical companies to choose the country of phase 1 trials. The trend of early phase trials being conducted outside Japan might be accelerated by the globalization of clinical trials.

A majority of clinical trials registered in the JapicCTI were small in terms of target number of participants; around a half of the clinical trials had 100 or fewer number of participants and over 90% had 1000 or fewer participants. This finding corresponds to the finding of clinical trials registered in the ClinicalTrials.gov [10] where almost 60% of clinical trials enrolled 100 or fewer participants and almost 90% enrolled 1000 or fewer participants.

A variety of differences become evident among the trials in the 3 therapeutic areas. The rate of the trials conducted in Japan only was higher in the cardiovascular trials and the mental health trials than in oncology trials (cardiovascular 83.1%, mental health 81.0% vs oncology 57.3%). Though the number of multi-regional trials which included Japan was smaller than that including European countries in the ClinicalTrials.gov as indicated by the previous study [23], our studies revealed that oncology trials conducted in Japan have become more globalized than cardiovascular and mental health trials.

Differences in age category for subjects among the 3 therapeutic areas also existed. Clinical trials in mental health allowed children under age 15 years old much more often than those in oncology and cardiovascular (mental health 10.9% vs oncology 1.2%, cardiovascular 4.9%). As pointed out in previous studies [24–26], due to a lack of financial incentives to develop and market drugs for children, fewer trials have been registered for children than adults. This finding corresponds to the situation in clinical trials registered in clinicaltrials.gov in that pediatric trials were registered 10 times fewer than adult trials in clinicaltrilas.gov [27]. Among pediatric clinical trials registered in the ClinicalTrials.gov, mental health was the second largest category following infectious disease/vaccine [27]. These findings collaboratively suggested that the pharmaceutical industry has made efforts to address the great need in drug development for children in mental health.

Oncology trials were more oriented toward earlier phase trials (phase 1), while cardiovascular and mental health trials displayed a higher proportion of later phase trials (phase 3). Phase 1 trials usually recruit healthy volunteers, not patients, and pharmaceutical industry committed [5] to disclose trial information on clinical trials "in patients" in their joint position on the disclosure of clinical trials. Thus, information on phase 1 trials with healthy volunteers might be under registered. Phase 1 trials in oncology, on the contrary, are subject to be registered because phase 1 trials in oncology do recruit patients, not healthy volunteers, which might lead to the difference in phase of the trials registered among oncology and cardiovascular/mental health trials. This finding also corresponds to the finding in clinical trials registered in the ClinicalTrials.gov [10] where 21.0% of oncology trials were phase 1 trials but the rate of phase 1 trials was low in cardiovascular and mental health trials (6.1%, 10.6%, respectively).

Regarding the trial design, though homogeneity existed in the randomization status among the 3 therapeutic areas, a difference in blinding was evident. The majority of oncology trials were conducted as "open," whereas only less than 40% of the trials in cardiovascular and mental health were conducted as "open". The rate of "Double blind" was the highest in mental health trials. This trend was also corroborated by the previous finding in the ClinicalTrials.gov [10], where the rate of "open" trial was the highest, 87.6%, in oncology trials and the rate of "double blind" trial was the highest, 45.2%, in mental health trials.

The analysis of clinical trials registered in the National Clinical Trials Registry gives us ideas of characteristics of clinical trials as well as the current trends of drug development. This study revealed that clinical trials in the 3 therapeutic areas with high social needs were most studied in Japan and the differences of characteristics in these clinical trials did exist. Industry and government can obtain the information of drug development with unmet social needs as well as trends of drug development through the registration. Further detailed analysis depending on each therapeutic area including those with fewer clinical trials will be needed to obtain more substantial information on drug development. Government initiative is also necessary to promote drug development of rare diseases in the therapeutic areas where industry sponsored clinical trials are least conducted. Industry and Japanese government should expand multi-regional trials in mental health and cardiovascular trials, as well as oncology trial, since joining multi-regional trials is a gateway to earlier access to new innovative drugs in the world. In order to capture more real pictures of the trials conducted in Japan by reducing missing information and make sure of patients' access, a legal framework or a guidance for mandatory clinical trial registration should be developed.

Limitations

Several limitations of our study should be noted. First, the JapicCTI does not include all the drug clinical trials conducted in Japan. In Japan, as previously noted, there are 3 clinical trial registries at the time of 2018. Since the new 4th registry, Japan Registry of Clinical Trials (jRCT) participated in the JPRN in April of 2019 [8], future research is needed to explore the characteristics of clinical trials registered in jRCT as well as in JapicCTI. Second, the data we analyzed in this study were the data in almost the first 10 years from the establishment of JPRN. There might have been changes in the data collected, the definition used, and the trend of missing data since the establishment of JPRN. Future analysis on the data of the next 10 years of sustainable decade will give us more information on the characteristics of clinical trials in the registry.

Conclusion

Our study revealed the overall characteristics of the clinical trials registered in the JapicCTI. The majority of clinical trials registered in the JapicCTI were small trials, conducted in Japan only, and phase 3 trials. Clinical trials conducted in Japan have gradually become globalized; the difference of trial phase did exist between Japan only trials and global

trials. Our analysis also revealed that the 3 therapeutic areas, oncology, mental health and cardiovascular diseases, as focused in this study, were the therapeutic areas most frequently studied in the registered trials. There was significant heterogeneity in the following characteristics among the trials in these 3 therapeutic areas: size of the trial, globalization, phase, age of participants, blinding.

Author contributions

All authors contributed to the discussions and data interpretation contained in this paper and provided input on the manuscript and approved its final version. EK: Conceptualization, data analysis, original draft manuscript preparation. MM: Data curation. KS: Data curation. TM: Manuscript reviewing and editing, coordination. MN; Conceptualization, methodology, manuscript writing, reviewing and editing, and supervision.

Funding

This study was funded by Health Labour Science Research Grant from the Ministry of Health, Labour and Welfare (19IA2020).

Compliance with ethical standards

Conflict of interest

The authors declare no conflict of interest.

References

1. The International Committee of Medical Journal Editors. FAQs. *Clinical Trials Registration*. http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/. Accessed 10 Apr 2020.
2. The International Committee of Medical Journal Editors. *Editorial Issues-Clinical Trials Registration*. http://www.icmje.org/recommendations/browse/publishing-and-editorial-issues/clinical-trial-registration.html. Accessed 10 Apr 2020.
3. The World Health Organization. *International Clinical Trials Registry Platform*. https://www.who.int/ictrp/en/. Accessed 10 Apr 2020.
4. The International Federation of Pharmaceutical Manufacturers and Associations. *Joint Position on the Disclosure of Clinical Trial Information via Clinical Trial Registries and Databases 1*. Nov 18, 2008 (revised Nov 10, 2009). https://www.ifpma.org/wp-content/uploads/2010/11/Joint-Position-on-Disclosure-of-CT-Info-via-CT-Registries-Revised-Jan2018-vFINAL.pdf. Accessed 10 Apr 2020.
5. The Ministry of Health, Labour and Welfare, Japan. *Japan Primary Registries Network has Become a Data Provider of the ICTRP Search Portal Oct 17, 2008*. https://www.mhlw.go.jp/topics/2008/10/tp1017-1.html. Accessed 10 Apr 2020.
6. Japic Clinical Trials Information (JapicCTI). https://clinicaltrials.jp/cti-user/common/Top.jsp. Accessed 10 Apr 2020.
7. The Japan Medical Association Center for Clinical Trials. https://dbcentre3.jmacct.med.or.jp/jmactr/. Accessed 10 Apr 2020.
8. UMIN Clinical Trials Registry. https://www.umin.ac.jp/ctr/index.htm. Accessed 10 Apr 2020.
9. Ministry of Health, Labour and Welfare, Japan. "Clinical Trials Registration" Notification Yakuseiyakushin-hatsu No.0326-3 of the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare. May 13 2013, revised on March 26, 2018.
10. Califf RM, Zarin DA, Kramer JM, Sherman RE, Aberle LH, Tasneem A. Characteristics of clinical trials registered in ClinicalTrials.gov, 2007-2010. *JAMA*. 2012;307(17):71838–47. https://doi.org/10.1001/jama.2012.3424.
11. Roumiantseva D, Carini S, Sim I, Wagner TH. Sponsorship and design characteristics of trials registered in ClinicalTrials.gov. *Contemp Clin Trials*. 2013;34(2):348–55. https://doi.org/10.1016/j.cct.2013.01.004.
12. Jeong S, Sohn M, Kim JH, Ko M, Seo HW, Song YK, Choi B, Han N, Na HS, Lee JG, Kim IW, Oh JM, Lee E. Current globalization of drug interventional clinical trials: characteristics and associated factors, 2011-2013. *Trials*. 2017;18(1):288. https://doi.org/10.1186/s13063-017-2025-1.
13. Murthy S, Mandl KD, Bourgeois FT. Industry-sponsored clinical research outside high-income countries: an empirical analysis of registered clinical trials from 2006 to 2013. *Health Res Policy Syst*. 2015;13:28. https://doi.org/10.1186/s12961-015-0019-6.
14. Bourgeois FT, Murthy S, Mandl KD. Outcome reporting among drug trials registered in ClinicalTrials.gov. *Ann Intern Med*. 2010;153(3):158–66. https://doi.org/10.7326/0003-4819-153-3-201008030-00006.
15. Seidler AL, Hunter KE, Chartres N, Askie LM. Associations between industry involvement and study characteristics at the time of trial registration in biomedical research. *PLoS ONE*. 2019;14(9):e0222117. https://doi.org/10.1371/journal.pone.0222117.
16. Hemminki E, Virtanen J, Veerus P, Regushevskaya E. Clinical research in Finland in 2002 and 2007: quantity and type. *Health Res Policy Syst*. 2013;11:11–7. https://doi.org/10.1186/1478-4505-11-17.
17. Ito T. Differences in Investigator-Initiated Trials between Japan and other countries: analyses of Clinical Trials Sponsored by Academia and Government in the ClinicalTrials.gov Registry and in the three Japanese registries. *PLoS ONE*. 2016;11(2):e0148455. https://doi.org/10.1371/journal.pone.0148455.
18. Tang W, Fukuzawa M, Ishikawa H, Tsutani K, Kiuchi T. Review of the registration of clinical trials in UMIN-CTR from 2 June 2005 to 1 June 2010 - focus on Japan domestic, academic clinical trials. Trials. 2013;14:333. https://doi.org/10.1186/1745-6215-14-333.
19. The World Health Organization. *International Clinical Trials Registry Platform. (ICTRP). Japan primary registries network, registry profile (JPRN)*. https://www.who.int/ictrp/network/jprn2/en/. Accessed 12 Apr 2020.
20. *WHO Disease and Injury Country Estimates, Death and DALY Estimates for 2004 by Cause for WHO Member States*. https://www.who.int/healthinfo/global_burden_disease/estimates_country/en/. Accessed 10 Apr 2020.
21. Lexchin JR. Implications of pharmaceutical industry funding on clinical research. *Ann Pharmacother*. 2005;39(1):194–7.
22. The Ministry of Health, Labour and Welfare, Japan. *Japan 5-years clinical research and trial activation plan 2012. March 30, 2012*. https://www.mhlw.go.jp/topics/bukyoku/isei/chiken/dl/120403_3.pdf. Accessed 20 July 2020.
23. Kondo H, Shimada Y, Ozawa T. Promotion of Japan's participation in global clinical trials. *Drug Discov Today*. 2019;24(4):939–42.

24. Jenks S. Improving children's access to cancer clinical trials. *J Natl Cancer Inst*. 2017;109(2):djx021. https://doi.org/10.1093/jnci/djx021.
25. Caldwell PHY, Murphy SB, Butow PN, Craig JC. Clinical trials in children. *The Lancet*. 2004;364:803–11.
26. Joseph PD, Craig JC, Caldwell PH. Clinical trials in children. *Br J Clin Pharmacol*. 2015;79(3):357–69.
27. Pasquali SK, Lam WK, Chiswell K, Kemper AR, Li JS. Status of the pediatric clinical trials enterprise: an analysis of the US ClinicalTrials.gov registry. *Pediatrics*. 2012;130(5):e1269–77.