Note

Trends in Investigator-Initiated Clinical Studies at a University Hospital after Enforcement of the 2018 Clinical Trials Act in Japan

Yasutaka Sato,[a] Satoshi Sakaguchi,[a] Kenshi Takechi,[a,†] Masayuki Chuma,[a,‡] Kenta Yagi,[a] Chikako Kane,[a] Mitsuhiro Goda,[a] Hirofumi Hamano,[a] Yuki Aoe,[a] Hiroshi Nokihara,[a,§] Yoshiaki Kubo,[b] Ichiro Hashimoto,[c] and Hiroaki Yanagawa*[,a]

[a] *Clinical Research Center for Developmental Therapeutics, Tokushima University Hospital; 2–50–1 Kuramoto-cho, Tokushima 770–8503, Japan:* [b] *Ethics Committee of Tokushima University Hospital, Tokushima University Hospital; 2–50–1 Kuramoto-cho, Tokushima 770–8503, Japan: and* [c] *Certified Review Board of Tokushima University, Tokushima University; 2–50–1 Kuramoto-cho, Tokushima 770–8503, Japan.*
Received August 31, 2021; accepted December 21, 2021

In April 2018, the Clinical Trials Act pertaining to investigator-initiated clinical trials was passed in Japan. The purpose of this study was to investigate activity in investigator-initiated clinical studies before and after enforcement of the new Clinical Trials Act. This was done by analysing the records of the Ethics Committee of Tokushima University Hospital, which reviews studies based on the Japanese government's Ethical Guidelines for Medical and Health Research Involving Human Subjects prior to the Clinical Trials Act, and records of the Certified Review Board established at Tokushima University under the Clinical Trials Act in 2018. The number of new applications to these two review boards during fiscal years 2015–2017 (pre-Act) and fiscal years 2018 and 2019 (post-Act) were used as an indicator of activity in investigator-initiated clinical studies. The number of new applications to the Ethics Committee was 303, 261, 316, 303, and 249 in 2015, 2016, 2017, 2018, and 2019, respectively. The data show that the total number of new interventional studies decreased from 50.3 in average in 2015–2017 (pre-Act) to 42 in 2018 and 40 in 2019 (post-Act), respectively. These results suggest that fewer interventional studies were started following enforcement of the new Clinical Trials Act. To confirm this trend and identify contributing factors, further studies are required. In addition, possible way, such as broader contribution of clinical research coordinators, to promote clinical studies in the new Clinical Trials Act era should be examined.

Key words Clinical Trials Act; clinical research; investigator; trend; Japan

INTRODUCTION

Government regulations on clinical studies in Japan have long applied to only clinical trials required for the governmental approval of products, such as pharmaceuticals, medical devices, and regenerative medicine products (designated as registration trials). Clinical studies conducted for other purposes have been considered 'investigator-initiated clinical studies,' and in principle, the studies were conducted following the Japanese government's ethical guidelines.[1–3)]

However, in 2013, a scandal involving several clinical trials for the antihypertensive drug valsartan made headlines in Japan and around the world.[4)] Several academia-initiated clinical trials funded by industry showed secondary benefits of valsartan. Nevertheless, they were subsequently proven to be fraudulent and were retracted. Inappropriate relationships were found between investigators and industry in conflict-of-interest management.

Mainly reflected the problems in conflict-of-interest management observed in the 2013 scandal, the new Clinical Trials Act pertaining to investigator-initiated clinical trials, which came into effect on 1 April 2018.[5)] In the Act, studies conducted to examine the efficacy or safety of products, such as pharmaceuticals are considered 'clinical trials.' 'Clinical trials' funded by research funds from the product-related industry and/or those conducted to investigate the efficacy or safety of off-label use of products are considered 'specified clinical trials.' Specified clinical trials must be conducted under the new Act. The difference between the new Act and the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices that is applied to registration trials should be emphasized. The data obtained from clinical studies conducted under the new Act cannot be used to obtain government approval of products. Yet, the practical processes require increased bureaucratic procedures and costs outside of the scope of the Good Clinical Practice international standard, such as review fees, notification of trial plans to the Ministry of Health, Labour and Welfare, and preparation of detailed documents and reports, including plans for conflict-of-interest management.

Although the introduction of the new Act including bureaucratic procedures may affect Japanese clinical studies, there is still little information in such impact. This study sought to observe activity in investigator-initiated clinical studies in terms

† Present address: *Division of Pharmaceutical Information Science, College of Pharmaceutical Sciences, Matsuyama University; 4–2 Bunkyo-cho, Matsuyama, Ehime 790–8578, Japan.*

‡ Present address: *Department of Hospital Pharmacy & Pharmacology, Asahikawa Medical University & University Hospital; 1–1–1 Midorigaoka-higashinijo, Asahikawa, Hokkaido 078–8510, Japan.*

§ Present address: *Department of Respiratory Medicine and Rheumatology, Graduate School of Biomedical Sciences, Tokushima University; 3–18–15 Kuramoto-cho, Tokushima 770–8503, Japan.*

* To whom correspondence should be addressed. e-mail: niseko@tokushima-u.ac.jp

of the number of new applications received by the review boards at Tokushima University.

MATERIALS AND METHODS

Examination of Review Board Applications This study retrospectively examined the records of two review boards at Tokushima University from fiscal years 2015 (April 2015 to March 2016), 2016 and 2017 before the Clinical Trials Act went into effect (pre-Act) and fiscal years 2018 and 2019 afterward (post-Act). The year 2015 was chosen because the previous governmental ethical guidelines were discontinued and new ethical guidelines (the Ethical Guidelines for Medical and Health Research Involving Human Subjects) came into effect in 2015. One review board was the Ethics Committee of Tokushima University Hospital, which was established in accordance with the Japanese government's ethical guidelines. This committee is the successor of the first committee established in Japan to review biomedical studies in 1982.[3] Another review board was the Certified Review Board of Tokushima University, which was established according to the Clinical Trials Act in 2018.

Because the Ethical Guidelines for Medical and Health Research Involving Human Subjects of the Japanese Government[6] are not applicable to this study, ethics approval was not sought.

Ethics Committee of Tokushima University Hospital The records of the Ethics Committee of Tokushima University Hospital included the presence of intervention, invasiveness, funding sources, and other study-related information, such as types (single or multi-institutional) of clinical studies. Intervention and invasiveness were defined according to the Ethical Guidelines for Medical and Health Research Involving Human Subjects.[6] As described by Sawata and Tsutani, funding sources for studies were categorised as private organisations, including pharmaceutical companies; public agencies; foundations; and self-funded.[7]

Certified Review Board of Tokushima University Records of the Certified Review Board of Tokushima University were also analysed in this study. In pre-Act era, all investigator-initiated clinical studies with intervention were reviewed by the Ethics Committee of Tokushima University Hospital. In post-Act era, specified clinical trials among interventional studies should be reviewed by certified review boards. Some of them are reviewed by the Certified Review Board of Tokushima University. Others are reviewed by certified review boards of other institutions and are not reviewed by the Certified Review Board of Tokushima University.

Among clinical trials ongoing in pre-Act era, those categorised as 'specified clinical trials' in the new Act should be reviewed by certified review boards in 2018. Number of these switchover studies are excluded from the analysis in the present study, since they cannot be considered as an indicator of activity in investigator-initiated clinical studies.

RESULTS

Annual Number of Applications for Clinical Studies Submitted to the Ethics Committee The number of new applications submitted to the Ethics Committee from 2015 to 2019, according to presence of intervention and invasiveness, is shown in Table 1. The number of interventional studies decreased over these 5 years (Table 1a), and the number of studies with invasiveness also decreased (Table 1b).

The types (single or multi institutional) of submitted studies has also been analysed. As shown in Table 2, more multi-institutional studies were submitted in 2015 and 2016 than in 2017, 2018 and 2019.

Annual Number of Specified Clinical Trials and Trends of Interventional Studies at Tokushima University As shown in Table 3, the number of new applications to the Certified Review Board of Tokushima University increased from 0

Table 1. Annual Number of Clinical Studies Reviewed by the Ethics Committee of Tokushima University Hospital

a. Clinical studies by presence of intervention

	Annual number (%)		
	Interventional	Non-interventional	Total
2015	55 (18%)	248 (82%)	303
2016	41 (16%)	220 (84%)	261
2017	55 (17%)	261 (83%)	316
2018	35 (12%)	268 (88%)	303
2019	20 (8%)	229 (92%)	249

b. Clinical studies according to invasiveness

	Annual numbers (%)		
	Invasive	Non-invasive	Total
2015	67 (27%)	236 (78%)	303
2016	40 (15%)	221 (85%)	261
2017	77 (24%)	239 (76%)	316
2018	44 (15%)	259 (85%)	303
2019	21 (8%)	218 (88%)	249

Table 2. Types (Single or Multi Institutional) of Clinical Studies Reviewed by the Ethics Committee of Tokushima University Hospital

	Annual number (%)		
	Single-institutional	Multi-institutional	Total
2015	102 (34%)	201 (66%)	303
2016	103 (39%)	158 (61%)	261
2017	156 (49%)	160 (51%)	316
2018	166 (55%)	137 (45%)	303
2019	125 (50%)	124 (50%)	249

Table 3. Annual Total Number of New Interventional Studies at Tokushima University

	Annual number			
	Ethics Committee of Tokushima University Hospital	CRB of Tokushima University	CRB of other institutions	Total
2015	55	(no CRB)	(no CRB)	55
2016	41	(no CRB)	(no CRB)	41
2017	55	(no CRB)	(no CRB)	55
2018	35	0	7	42
2019	20	5	15	40

CRB, certified review board.

in 2018 to 5 in 2019. Among these five trials, two were single (Tokushima University only) and three were multi-institutional including Tokushima University. The number of new studies reviewed by certified review boards of other institutions increased from 7 in 2018 to 15 in 2019 and all these 22 studies were multi-institutional including Tokushima University.

To show trends in all new interventional studies at Tokushima University, Table 3 presents the number of new applications for interventional studies to the Ethics Committee and Certified Review Board of Tokushima University and to the certified review boards of other institutions. Since the average number of interventional studies in pre-Act era was 50.3, the total number of interventional studies tended to decrease in post-Act than in pre-Act.

Funding Source of Interventional Studies in Tokushima University Table 4 shows the funding sources of all interventional studies conducted at Tokushima University during 2015–2019. Funding for specified clinical trials and interventional studies reviewed by the Ethics Committee are included in the total for all interventional studies. As shown in the table, considerable percentage of interventional studies were funded by private organisations in post-Act era.

DISCUSSION

We previously reported that since 2012, approximately 300 investigator-initiated clinical studies were reviewed each year at Tokushima University.[3] This study found that the annual number of applications for interventional studies submitted to the Ethics Committee of Tokushima University Hospital decreased from 2015 to 2019 (Table 1). Given that specified clinical trials are handled separately from clinical studies and must be reviewed by a certified review board, the observed decrease cannot be considered substantial. However, as shown in Table 3, the more important observation was that the total number of interventional studies decreased.

Overall, in the minutes of the Clinical Research Committee, Health Sciences Council, Ministry of Health, Labour and Welfare (31 August, 2017), the annual number of the Japanese new specified clinical trials was estimated as 500–1000 and around 50 committees were expected to deal with 10–20 these trials, respectively.[8] In contrast, Ozaki *et al.*[9] reported certified review boards had reviewed 349 new specified clinical trials from April 2018 to October 2019. In an analysis at the National Cancer Central Hospital, Japan, Nakamura *et al.*[10] reported a decreasing trend in interventional studies following enforcement of the Clinical Trials Act. At that hospital, 205 interventional studies other than registration trials were ongoing in April 2018 (pre-Act), whereas 94 clinical trials were ongoing under the Act and 74 clinical trials were ongoing under the ethical guidelines in April 2019 (post-Act). These data are about ongoing interventional studies and cannot be directly compared to our results. Nevertheless, the decreasing trend seems to be in accordance with our results in new interventional studies. Meanwhile, results of questionnaire surveys at Tokushima University[11] showed that investigators had less interest in interventional studies after enforcement of the Clinical Trials Act than before it. Moreover, investigators' needs for 'support for preparing documents when conducting specified clinical trials' was significantly higher in investigators who were interested in conducting specified clinical trials than in those who were not interested.

Although non-interventional studies, such as those with clinical big data,[12] are as important as interventional studies to establish clinical evidence, promotion of interventional studies must be considered in the post-Act era. Various bureaucratic procedures are now required and investigators might not be familiar with these new regulations. Increased bureaucracy may be at least one reason contributing to the decreased activity seen in investigator-initiated interventional studies. Reforming the bureaucratic procedures and providing practical support to investigators are current needs. Streamlining of notification and change procedures, online submission of notifications and streamlining of conflict of interest reporting procedures should be considered. Japanese clinical research coordinators have been engaged primarily in operational roles in industry-initiated clinical trials for drug approvals (registration trials). However, broadening their contribution to cover other types of clinical research, such as specified clinical trials, may lead to an improvement in quality.[13]

The enactment of the Clinical Trials Act stemmed from inappropriate academia-industry relationships that were revealed from the valsartan scandal in 2013. Although the new law does not preclude the existence of the academia-industry relationships, it emphasises the importance of managing financial conflicts of interests. Academia-industry cooperation in the medical field[14] must be supported to promote activity in clinical trials in the current environment. Under the Clinical Trials Act, the sponsors responsible for specified clinical trials should be the principal investigators (physicians or dentists). In practice, the sponsor and funder are members of industry in some clinical trials with a purpose other than obtaining governmental approval. For example, in the post-marketing stage of pharmaceutics, the industry has interests in efficacy testing in a larger number of cases, scientific issues and data on market dominance. Ohshima *et al.*[15] reported difficulties in managing clinical trials conducted based on the interests of industry from the results of an internal survey conducted in October 2018 by the task force team of the Clinical Evaluation Expert Committee of the Japan Pharmaceutical Manufacturers

Table 4. Funding Sources of New Interventional Studies at Tokushima University

	Annual number (%)				
	Private organisations	Public agencies	Foundations	Self-funded	Total
2015	12 (22%)	22 (40%)	2 (4%)	19 (34%)	55
2016	5 (12%)	10 (24%)	4 (10%)	22 (54%)	41
2017	13 (24%)	16 (29%)	7 (13%)	19 (34%)	55
2018	7 (17%)	12 (24%)	6 (14%)	17 (40%)	42
2019	10 (25%)	10 (25%)	4 (10%)	16 (40%)	40

Association. One reason for these difficulties was that even in clinical trials conducted based on the interests of industry, physicians conducting specified clinical trials must act as the sponsor-investigator under the Clinical Trials Act. The interests of investigators and industry sometimes differ. Physicians may be reluctant to be principal investigators with various legal responsibility in clinical trials conducted based on the interests of industry if they have little medical and/or investigational interests in these trials. The position of clinical trials conducted based on the interests of industry in the era of the new Clinical Trials Act is still ambiguous.

This study has several limitations. First, it was conducted at a single university and thus the reviews might not fully reflect clinical studies nationwide in Japan. Second, the precise relationship between the decrease in interventional studies and enforcement of the new Clinical Trials Act is not clear at present. Although analysis over a longer period considering various possible factors contributing to the decrease could be conducted, the coronavirus disease 2019 (COVID-19) pandemic will no doubt have a major impact on the circumstances of clinical studies after 2020 whereas the present study reflects the circumstances of the pre-COVID-19 era.

CONCLUSION

The results of this study revealed that interventional studies at a university hospital have decreased after enforcement of the Clinical Trials Act. To confirm this trend and identify factors contributing to it, further studies are needed. Furthermore, a support infrastructure for clinical studies and the promotion of appropriate academia-industry relationships should be considered for encouraging activity in clinical trials. Accordingly, practical national strategies, such as streamlining of notification and change procedures, online submission of notifications and streamlining of conflict of interest reporting procedures should be considered and the evaluation of such strategies warrant further study.

Conflict of Interest The authors declare no conflict of interest. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

REFERENCES

1) Yanagawa H. Current regulatory systems for clinical trials in Japan: still room for improvement. *Clin. Res. Regul. Aff.*, **31**, 25–28 (2014).
2) Urushihara H, Kawakami K. Academic clinical trials and drug regulations in japan: impacts of introducing the investigational new drug system. *Ther. Innov. Regul. Sci.*, **48**, 463–472 (2014).
3) Yanagawa H, Katashima R, Takeda N. Research ethics committees in Japan: a perspective from thirty years of experience at Tokushima University. *J. Med. Invest.*, **62**, 114–118 (2015).
4) Normile D. Tampered data cast shadow on drug trial. *Science*, **341**, 223 (2013).
5) Ministry of Health. Labour and Welfare. "Ethical guidelines for medical and health research involving human subjects.": ‹https://www.mhlw.go.jp/content/10600000/000757206.pdf›, accessed 29 November, 2021.
6) Ministry of Health. Labour and Welfare. "Clinical Trials Act (Act No. 16 of 14 April 2017).": ‹https://www.mhlw.go.jp/file/06-Seisakujouhou-10800000-Iseikyoku/0000163413.pdf›, accessed 29 November, 2021.
7) Sawata H, Tsutani K. Funding and infrastructure among large-scale clinical trials examining cardiovascular diseases in Japan: evidence from a questionnaire survey. *BMC Med. Res. Methodol.*, **11**, 148 (2011).
8) Ministry of Health, Labour and Welfare. "The minutes of the Clinical Research Committee, Health Sciences Council, Ministry of Health, Labour and Welfare (31 August, 2017).": ‹https://www.mhlw.go.jp/stf/shingi2/0000179030.html›, accessed 29 November, 2021.
9) Ozaki M, Harada Y, Toya W, Yamashita N, Fuse N, Sato A, Tsuboi M. A Survey of certified review boards under the Clinical Trials Act. *Jpn. J. Clin. Pharmacol. Ther.*, **51**, 255–265 (2020).
10) Nakamura K, Shibata T. Regulatory changes after the enforcement of the new Clinical Trials Act in Japan. *Jpn. J. Clin. Oncol.*, **50**, 399–404 (2020).
11) Chuma M, Takechi K, Yagi K, Sakaguchi S, Nokihara H, Kane C, Sato Y, Niimura T, Goda M, Zamami Y, Ishizawa K, Yanagawa H. Academic investigators' interest in promoting specified clinical trials: questionnaire survey before and after implementation of the Clinical Trial Act. *J. Med. Invest.*, **68**, 71–75 (2021).
12) Kaneko S, Nagashima T. Drug repositioning and target finding based on clinical evidence. *Biol. Pharm. Bull.*, **43**, 362–365 (2020).
13) Yanagawa H, Nokihara H, Yokoi H, Houchi H, Nagai M, Yamashita R, Suganuma N, Hyodo M. Present status and perspectives on future roles of Japanese clinical research coordinators. *J. Clin. Med. Res.*, **10**, 877–882 (2018).
14) Tsuruya N, Kawashima T, Shiozuka M, Nakanishi Y, Sugiyama D. Academia-industry cooperation in the medical field: matching opportunities in Japan. *Clin. Ther.*, **40**, 1807–1812 (2018).
15) Ohshima H, Aoyagi M, Tajima M, Nishimura S, Nomura T, Kato Y, Koike R, Suzuki Y, Yamashita S, Ikeda T, Aoki H, Kondo M. Considering the future of clinical research at the turning point of implementation of the new legislation in Japan—impact of the Clinical Trials Act on pharmaceutical industries; based on the results from the internal survey in JPMA. *Clin. Eval.*, **47**, 115–125 (2019).