




BMJ Open Impact of the Clinical Trials Act 2018 on clinical trial activity in Japan from 2018 to 2020: a retrospective database study using new and conventional Japanese registries

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ABSTRACT

Objective To clarify the impact of Japan's Clinical Trials Act (CTA), which was enacted in April 2018, on subsequent clinical trial activity through an analysis of Japanese registry data.

Design Retrospective database study.

Setting We extracted information on clinical intervention studies registered between 1 April 2018 and 30 September 2020 in the conventional University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) and the new Japan Registry of Clinical Trials (jRCT). We collected and analysed information on registration dates, intervention types, funding, secondary sponsors and use of designated staff in multidisciplinary roles (research planning support, research administration, data management, statistical analysis, monitoring and auditing). The temporal trends in clinical trial activity after CTA enactment were examined.

Results A total of 577 CTA-compliant specified clinical trials (ie, studies funded by pharmaceutical companies or studies evaluating the efficacy and safety of off-label drugs or devices in humans) were registered in the jRCT. During the same period, 5068 clinical trials were registered in the UMIN-CTR. The number of specific clinical trials increased immediately after the implementation of the CTA and stabilised in late 2019, whereas the number of clinical trials registered in the UMIN-CTR generally declined over time. Specified clinical trials that received industry funding and public grants were more likely to use designated staff in multidisciplinary roles.

Conclusions The implementation of the CTA has not reduced the number of specified clinical trials, but has reduced the total number of intervention trials. The use of designated staff in multidisciplinary roles is associated with funding, secondary sponsors and multicentre studies. It was inferred that funding was needed to establish research infrastructure systems that support high-quality research.

INTRODUCTION

Clinical studies are generally regulated under country-specific legislation and guidelines. In the USA, the Common Rule is a set of

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study is a comprehensive database study of clinical trials in Japan.
- ⇒ The number of trials registered in the two databases could not be summed up or compared directly.
- ⇒ Database input was performed by the investigators, which resulted in inaccuracies.
- ⇒ The publicly available items in the Japan Registry of Clinical Trials (jRCT) did not distinguish between food and medicine.
- ⇒ Regenerative medicine products were not included due to the timing of the jRCT publication.

regulations applicable to federally funded research and these have been adopted by all relevant departments, agencies and institutions.¹ In addition, clinical research on human subjects is governed under the National Research Act, which focuses on the protection of all participants.² In the European Union, the Clinical Trials Regulation (No. 536/2014) was adopted in April 2014 and the Medical Devices Directive (2017/745) was adopted and issued in May 2017, and all clinical trials (CTs) thereafter are conducted in compliance with its requirements.³

In Japan, observational studies and CTs not intended for marketing authorisation were previously regulated under the Ethical Guidelines for Medical Research Involving Human Subjects or the Ethical Guidelines for Human Genome/Gene Analysis Research. In 2021, these two guidelines were merged into the Ethical Guidelines for Life Sciences and Medical Sciences Involving Human Subjects.⁴ CTs aimed at marketing authorisation are regulated under the Act on Securing Quality, Efficacy and Safety of Products Including

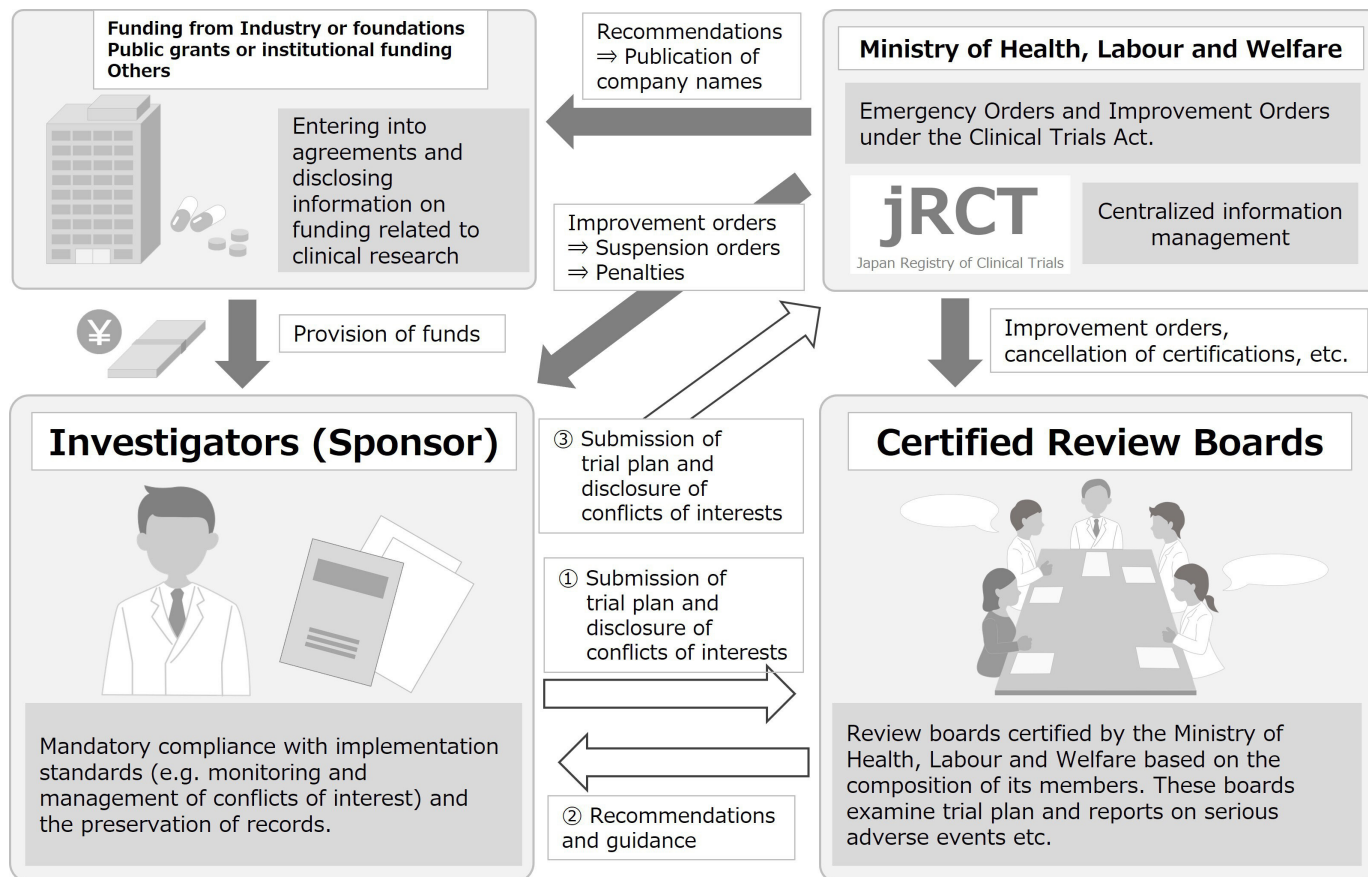


Figure 1 Overview of the Clinical Trials Act. Roles and procedures of various entities under Japan's Clinical Trials Act enacted in April 2018.

Pharmaceuticals and Medical Devices and the Japanese Good Clinical Practice Guidelines.^{5,6}

Since the beginning of the 2010s, several cases of scientific misconduct have emerged in Japan. The most prominent example is the fabrication and falsification of clinical data for the antihypertensive drug valsartan, in which a pharmaceutical industry employee was found to have participated in the research team without disclosing his affiliation,⁷ leading to withdrawal of the corresponding paper. This led to the enactment of the Clinical Trials Act (CTA) on 1 April 2018. The CTA requires the clarification of the relationship between investigators and industries/manufacturers.⁸ The following types of CTs, designated 'specified CTs' (SCT), must comply with the CTA: (1) CTs funded by a manufacturer with marketing approval for pharmaceuticals or a specially related person, and (2) CTs evaluating the efficacy and safety of unapproved or off-label drugs or medical devices in humans.⁹ Under the CTA, study plans must be submitted to the Ministry of Health, Labour and Welfare (MHLW) before implementation and must also be registered in a designated CT registry. Furthermore, the CTA requires annual conflict of interest (COI) declarations by all participating researchers, reviews by certified review boards (CRBs), written informed consent from study participants, serious adverse event reports, periodic progress reports and disclosure of the final results (figure 1).

CTs in Japan generally publish their study designs, progress and results to the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), which conforms to WHO standards.¹⁰ In addition, SCTs and other CTA-compliant CTs are required to disclose their study designs, progress and results to the newer Japan Registry of Clinical Trials (jRCT) operated by the MHLW (table 1). The jRCT functions as an international registry platform as well as a notification system for the MHLW. CT-related information is published on the jRCT website after approval by a CRB, which signifies that the MHLW has given authorisation to begin a trial (figure 1).

The annual number of registered CTs in Japan had increased until the early 2010s.¹¹ However, Japanese oncologists recently reported that the number of cancer-related CTs—especially investigator-initiated CTs without funding from pharmaceutical companies—declined after CTA enactment.¹² In addition, we have also previously reported a fall in the overall number of CTs immediately after the CTA was introduced.¹³ We postulate that this reduction was due in part to the substantial increase in administrative work requiring detailed knowledge of the CTA and scientific methodology for CTs. Therefore, it has become considerably more difficult for researchers to conduct CTs without specialised staff, departments and systems in their institutions.

Table 1 Study types and regulations according to clinical trial registry

| Registry | Japan Registry of Clinical Trials | University Hospital Medical Information Network Clinical Trials Registry |
|-------------|--|---|
| Study types | Specified clinical trials <ul style="list-style-type: none"> ▶ Funded by pharmaceutical companies. ▶ Evaluating the efficacy or safety of unapproved/off-label drugs or medical devices in humans. | <ul style="list-style-type: none"> ▶ Intervention trials or observational studies involving humans. |
| Regulation | <ul style="list-style-type: none"> ▶ Clinical Trials Act. | <ul style="list-style-type: none"> ▶ Ethical Guidelines for Life Sciences and Medical Sciences Involving Human Subjects. |

In this study, we analysed CTs registered in the jRCT and UMIN-CTR to shed light on the trends in CT activity from 2018 to 2020 following CTA enactment. We also explored the characteristics of SCTs involving multidisciplinary teams and discuss measures that may promote the revitalisation of CTs in Japan and other countries.

METHODS

Acquisition of CT information

The target SCTs and CTs were identified using the jRCT database and UMIN-CTR database, respectively (table 2). All databases were publicly available on the registries' websites. The inclusion criteria for SCTs in the jRCT database were (1) studies involving interventions for drugs, foods or medical devices; (2) studies registered between 1 April 2018 (the date of CTA enactment) and 30 September 2020; and (3) studies initiated after 1 April 2018. The inclusion criteria for CTs in the UMIN-CTR database were (1) studies involving interventions; (2) studies registered between 1 April 2018 and 30 September 2020; and (3) studies initiated after 1 April 2018. We excluded the following studies from both registries: (1) studies for marketing authorisation and (2) studies on regenerative medicine.

Table 2 presents the items and classification categories extracted from the jRCT and UMIN-CTR databases. The Japan Pharmaceutical Information Center and Japan Medical Association Center for Clinical Trials databases are mainly used to register trials that aim to obtain market approval. UMIN has the largest number of registrations among the three databases. Considering the main purpose of this study, UMIN-CTR was the most appropriate.

The outcomes

The outcomes of this work were the number of trials and the availability of staff in multidisciplinary roles of SCT.

Table 2 Items and classification categories in the jRCT and UMIN-CTR databases

| jRCT database | Classification categories |
|---|--|
| Study type | ▶ Intervention study. |
| Intervention type | ▶ Medical devices. ▶ Drugs or foods. |
| Target disease | ▶ Cancer. ▶ Non-cancer. |
| Study phase | ▶ I, I/II or II. ▶ II/III, III, IV or others. |
| Control arm | ▶ Present. ▶ Absent. |
| Number of centres | ▶ Single-centre. ▶ Multicentre. |
| Financial resources | ▶ Funding from industry or foundations. ▶ Public grants or institutional funding. ▶ Others. ▶ None. |
| Secondary sponsor* | ▶ Present. ▶ Absent. |
| Provision of products | ▶ Yes. ▶ No. |
| International study | ▶ Yes. ▶ No. |
| Staff assigned to: | |
| Research planning support | ▶ Yes. ▶ No. |
| Research administration | ▶ Yes. ▶ No. |
| Data management | ▶ Yes. ▶ No. |
| Statistical analysis | ▶ Y/N. |
| Monitoring | ▶ Yes. ▶ No. |
| Auditing | ▶ Yes. ▶ No. |
| UMIN-CTR database | Classification categories |
| Study type | ▶ Intervention study. |
| Intervention type | ▶ Medical devices. ▶ Drugs, vaccines, gene therapy or foods. ▶ Surgeries. ▶ Behaviour, education or others. |
| *Secondary sponsor is defined here as the person who shares responsibility for conducting and financing the clinical trial with the primary sponsor (investigator). jRCT, Japan Registry of Clinical Trials; UMIN-CTR, University Hospital Medical Information Network Clinical Trials Registry. | |

Statistical analysis

The characteristics of SCTs and CTs were summarised using frequencies and proportions for categorical variables. To examine the impact of the CTA on subsequent CT activity and the impact of COVID-19, we first tabulated the number of studies at the semiannual (6 months) and

Table 3 Characteristics of specified clinical trials registered in the jRCT between 1 April 2018 and 31 March 2020

| | Studies (n) | % |
|--|-------------|-------|
| Intervention studies | 577 | 100.0 |
| Intervention type | | |
| Medical devices | 184 | 31.9 |
| Drugs or foods | 393 | 68.1 |
| Target disease | | |
| Cancer | 171 | 29.6 |
| Non-cancer | 406 | 70.4 |
| Study phase | | |
| I, I/II or II | 285 | 61.4 |
| II/III, III, IV or others | 106 | 38.6 |
| Control arm | | |
| Present | 237 | 41.1 |
| Absent | 340 | 58.9 |
| Number of centres | | |
| Single-centre | 237 | 41.1 |
| Multicentre | 340 | 58.9 |
| Financial resources | | |
| Industry funding | 279 | 48.4 |
| Public grants or institutional funding | 95 | 16.5 |
| None | 203 | 35.2 |
| Secondary sponsor | | |
| Present | 43 | 7.5 |
| Absent | 547 | 92.5 |
| International study | 6 | 1.0 |

jRCT, Japan Registry of Clinical Trials.

monthly levels. Next, we explored the characteristics of SCTs that involved multidisciplinary staff. The proportions of SCTs that included designated staff in multidisciplinary roles (research planning support, research administration, data management, statistical analysis, monitoring and auditing) were compared according to the SCT characteristics. Fisher's exact test and the Cochran-Armitage trend test were used for statistical comparisons as appropriate. All analyses were performed using SAS V.9.4.

Patient and public involvement

Patients or the public were not involved in this study.

RESULTS

Trends in the number of CTs and observational studies

A total of 577 new SCTs were registered in the jRCT database between 1 April 2018 and 31 March 2020 and their characteristics are summarised in [table 3](#). SCTs that evaluated the efficacy and safety of drugs and foods accounted for 68.1% of the total and those that evaluated medical devices accounted for 31.9%. There were 171 cancer-related SCTs (29.6%). The majority of SCTs were early

Table 4 Characteristics of clinical trials registered in the UMIN-CTR between 1 April 2018 and 31 March 2020

| | Studies (n) | % |
|--|-------------|-------|
| Intervention studies | 5068 | 100.0 |
| Intervention type | | |
| Medical devices | 937 | 18.5 |
| Drugs, vaccines, gene therapy or foods | 2023 | 39.9 |
| Surgeries | 651 | 12.8 |
| Behaviour, education or others | 1457 | 28.7 |
| Target disease | | |
| Cancer | 725 | 14.3 |
| Non-cancer | 4343 | 85.7 |
| Study phase | | |
| I, I/II, II, II/III or III | 339 | 6.7 |
| IV or others | 4729 | 93.3 |
| Financial resources | | |
| For-profit organisation | 1177 | 23.2 |
| Non-profit foundation | 161 | 3.2 |
| Government, including public grants | 884 | 17.5 |
| Others | 1479 | 29.3 |
| None | 1365 | 26.9 |
| Unknown | 2 | |

UMIN-CTR, University Hospital Medical Information Network Clinical Trials Registry.

phase (phase I–II; 61.4%), single-arm (41.1%) and multi-centre (58.9%). The proportions of SCTs with industry funding and public grant/institutional funding were 48.4% and 16.5%, respectively. Next, a total of 5068 new CTs were registered in the UMIN-CTR database between 1 April 2018 and 31 March 2020 and their characteristics are summarised in [table 4](#). The proportion of CTs funded by for-profit organisations was 23.2%, which was approximately half that of industry-funded SCTs.

[Figure 2](#) shows the semiannual trends in the number of SCTs and CTs from 1 April 2018 to 30 September 2020. There were only 22 SCTs registered in the first 6 months after CTA enactment in April 2018, but this number increased thereafter. In contrast, the number of CTs gradually decreased after CTA enactment. [Figure 3](#) shows the monthly trends in the number of SCTs and CTs from 1 September 2019 to 30 September 2020. In May 2020, concurrent with the declaration of a national state of emergency for COVID-19, there was a decrease in the number of CTs registered in the UMIN-CTR; however, the number of SCTs was not significantly affected.

Characteristics of SCTs involving multidisciplinary teams

We calculated the proportions of studies that included designated staff in the various multidisciplinary roles (research planning support, research administration, data management, statistical analysis, monitoring and auditing) and compared these among the SCT

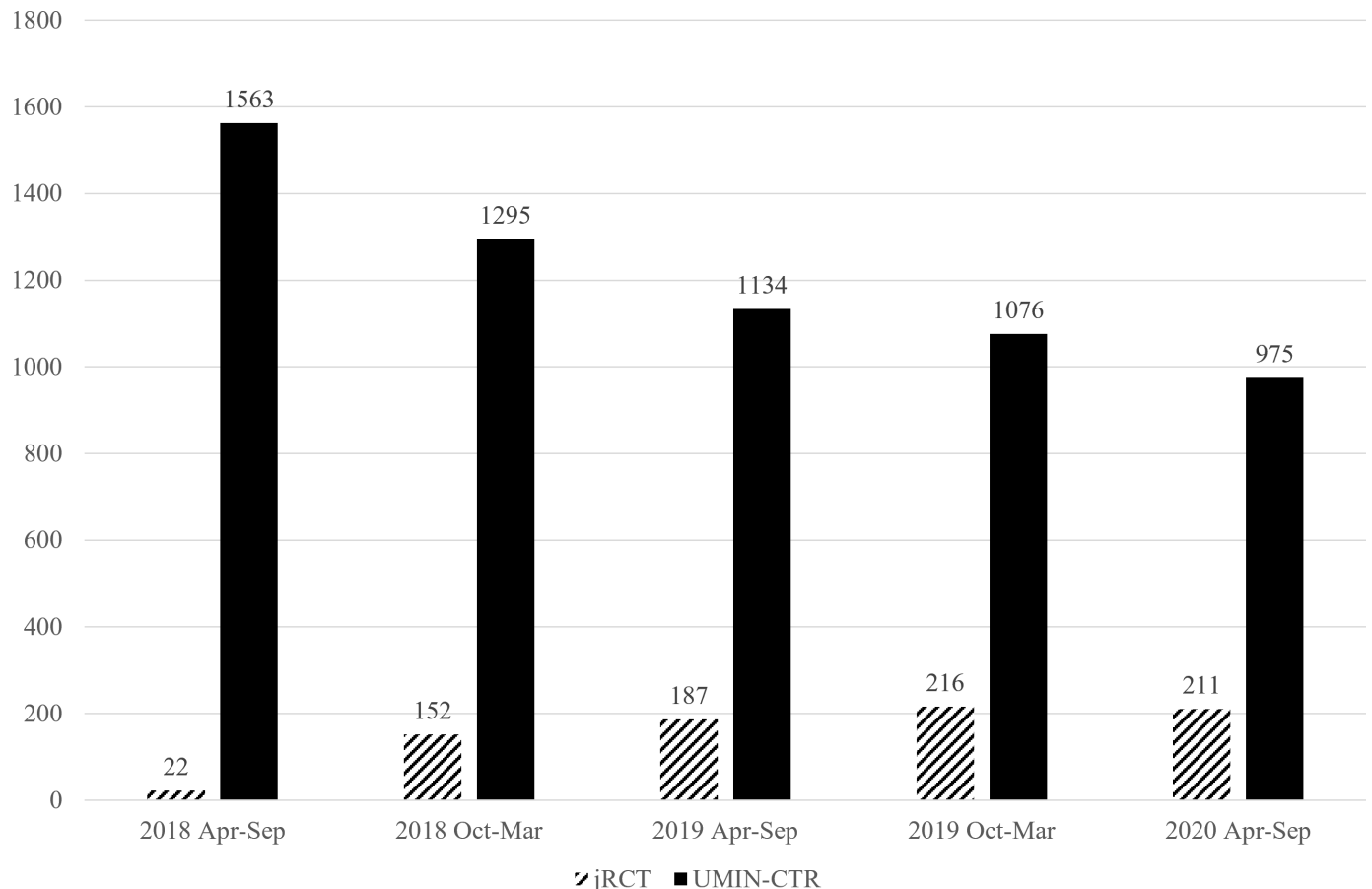


Figure 2 Semiannual trends in the number of registered clinical trials from April 2018 to September 2020. The clinical trials are categorised according to their registration dates from 1 April 2018 to 30 September 2020. jRCT, Japan Registry of Clinical Trials; UMIN-CTR, University Hospital Medical Information Network Clinical Trials Registry.

characteristics (figure 4, table 5). Almost all studies designated a person in charge of monitoring (figure 4A). There were lower proportions of studies with designated staff for research planning support, research administration and auditing than for data management and statistical analysis. Furthermore, a survey of jRCT entries revealed that in some cases the same person was responsible for both research planning support and research administration.

Funding was found to be associated with use of designated staff in multidisciplinary roles (figure 4A). In particular, industry-funded SCTs had the highest proportion of research planning support (40.9%), followed by SCTs with public grants or institutional funding (34.7%) and SCTs without funding (29.6%) (trend test $p=0.010$) (table 4). In addition, industry-funded SCTs had the highest proportions of designated staff for research administration, data management, statistical analysis and auditing; these were followed by SCTs with public grants or institutional funding and SCTs without funding. Multi-centre SCTs showed higher proportions of designated staff in multidisciplinary roles than single-centre SCTs (figure 4B). The proportions of SCTs with designated staff for research planning support and auditing among SCTs with secondary sponsors were 55.8% and 67.4%, respectively (table 5, figure 4C); these proportions were

higher than those of SCTs without secondary sponsors. The proportions of SCTs with designated staff for research planning support and auditing were higher among SCTs targeting cancer (45.0% and 48.0%, respectively) than SCTs targeting other diseases (32.0% and 33.5%, respectively) (table 5). Whether the principal investigator's appointment was at a university or not was not associated with the proportions, except for research planning support, for which the proportion was lower in the university group.

DISCUSSION

Principal findings

Between April 2018 and March 2020, there were 577 SCTs and 5068 CTs registered in the jRCT and UMIN-CTR, respectively. The number of SCTs is still much smaller than that of CTs registered in the UMIN-CTR, which is unexpectedly low. According to the CTA definition, it is likely that more intervention trials would have been classified in SCT. A previous article by Kunito *et al*¹² showed that 87% of researchers felt the CTA procedure was burdensome and 76% said that they felt it was difficult to conduct CTs because of the CTA. The results of the authors' previous study show that the complexity of the

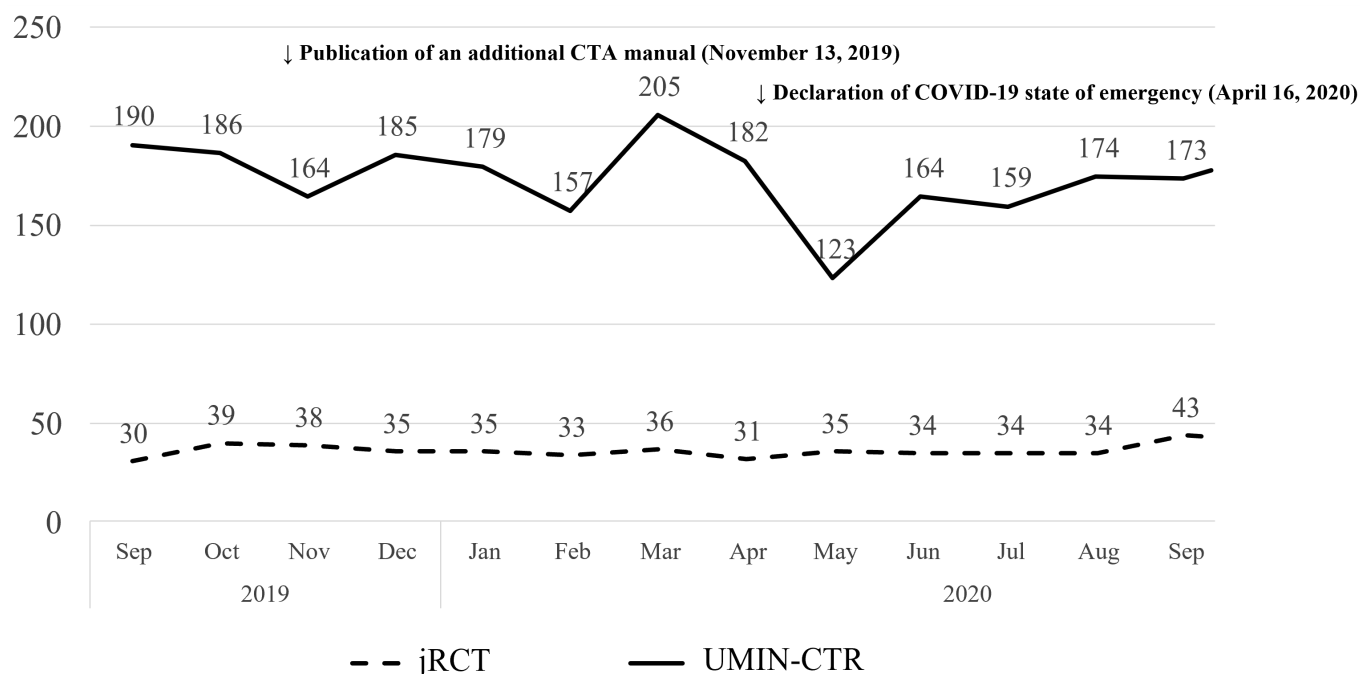


Figure 3 Monthly trends in the number of registered clinical trials from September 2019 to September 2020. The clinical trials are categorised according to their registration dates from 1 September 2019 to 30 September 2020. The additional CTA manual published on 13 November 2019 by the Ministry of Health, Labour and Welfare included answers to frequently asked questions by researchers. A nationwide state of emergency for COVID-19 was declared on 16 April 2020. CTA, Clinical Trials Act; jRCT, Japan Registry of Clinical Trials; UMIN-CTR, University Hospital Medical Information Network Clinical Trials Registry.

CTA procedure affected the overall number of CTs, as well as SCTs, resulting in fewer intervention trials and a reduction in the size of the trial.¹³ Revision of the CTA is currently under consideration. To further promote CTs in the future, streamlining the procedure and other factors of CTA needed to be considered. Some researchers have conducted observational studies to avoid the burdensome procedure of CTA. However, this would degrade the level of evidence and have a negative impact on patients in the future. It needs to be verified whether the CTA in Japan is moving towards the 'goal' of CTs, which is to provide real benefit to patients, high-quality trial and a shortened trial period'.

The proportions of SCTs in the jRCT database that evaluated medical devices and cancer treatments were approximately twice those of CTs in the UMIN-CTR database. While the SCTs focused on interventions involving medical devices, drugs and food, the CTs in the UMIN-CTR database also evaluated the efficacy and safety of other interventions, such as surgeries, behaviour and education. The number of registered SCTs had increased during 2018 and stabilised in late 2019, whereas the number of registered CTs had consistently decreased over the study period.

This suggests that investigators, companies and organisations (including hospitals and CRBs) involved in SCTs became accustomed to the CTA, although CTs decreased partly due to COVID-19. Next, we also observed that fewer SCTs had designated staff for research planning support, research administration and auditing. This may

be indicative of difficulties in budget allocation for these tasks and the lack of qualified personnel in Japan.

Finally, our analysis also showed that SCTs with funding, secondary sponsors and multiple sites have a higher percentage of staff in interdisciplinary roles. This suggests that hiring staff to perform ancillary duties can reduce the burden on researchers. The secondary sponsor described here shared responsibilities for conducting and financing the trial with the primary sponsor (principal investigator). Per the Japanese CTA, the industry/manufacture cannot be the primary sponsor and may be called the secondary sponsor.

Simplifying CTA and having a multidisciplinary team within a facility that can support CT-related tasks would ease the difficulties of conducting CTs, improve the quality of research and facilitate the conduct of CTs, which is generally expected to increase the number of CTs conducted in Japan in the long term. It would also be effective to integrate research-implementing institutions and form academic research organisations that support the planning and implementation of clinical research.¹⁴

Study strengths and limitations

This study is the first to investigate and report the numbers and characteristics of SCTs after the implementation of the CTA in Japan. Although previous studies have similarly reported on the numbers and characteristics of CTs,¹² our study also explores their

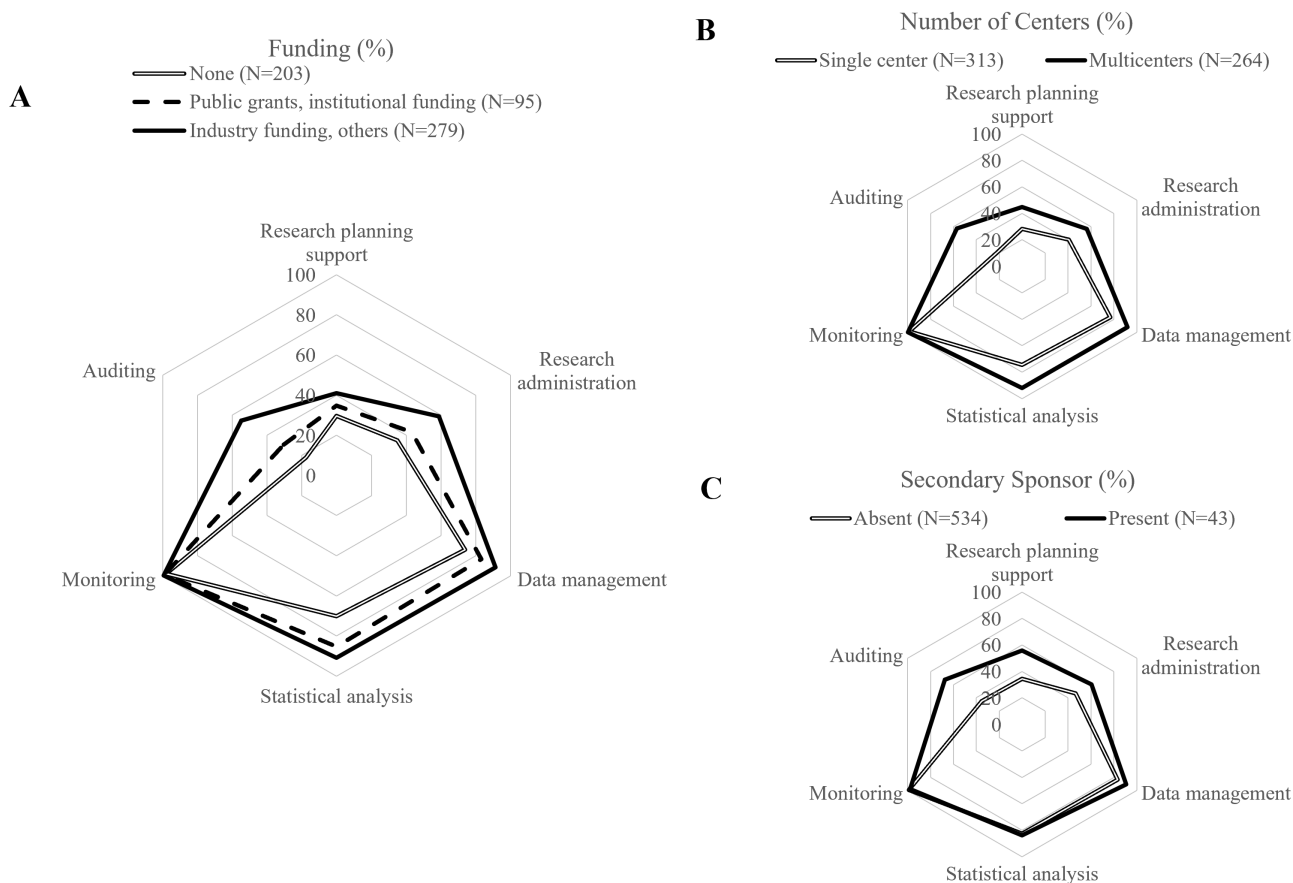


Figure 4 Relationship between (A) funding, (B) number of centres and (C) secondary sponsors in SCTs and use of designated staff in multidisciplinary roles. Each axis represents the proportion of studies that had designated staff to a multidisciplinary role. SCT, specified clinical trial.

relationships to funding and use of multidisciplinary teams. Another strength of this study is the comprehensive coverage of all SCTs conducted in Japan due to their CTA-mandated inclusion in the jRCT database. In addition, the accuracy of the registered information was also scrutinised by referring to other sources where possible.

The limitations of this study are as follows: First, the number of studies in the jRCT and UMIN-CTR databases cannot be simply summed or directly compared due to inherent differences in the types of registered studies and recorded information. Second, a few investigators appeared to have misunderstood the definitions and criteria for each multidisciplinary role, resulting in ambiguous or inaccurate descriptions when registering their trials. This may be attributed to insufficient training or explanations for new investigators. To address this problem, the jRCT should provide clear explanations, input support and educational services on clinical research methods. Third, this study did not distinguish the trials for foods or supplements from those for medicine; therefore, the conclusions may be ambiguous. Finally, trials of regenerative medicine products were not included in this study because the CTA changed during the study period (April 2019).

Comparisons with other studies

The observed reduction in the number of CTs after CTA enactment is consistent with the findings of a previous study.¹² Furthermore, the initial decrease and gradual increase were similar to the trends observed in Western Europe following the European Clinical Trials Directive in 2004.¹⁵

Research and clinical implications

In this study, we demonstrated the impact of the CTA on CT activity in Japan and clarified the importance of funding in creating a favourable research environment. To ensure transparency and social understanding regarding the acceptance and use of funding from companies, all financial COIs must be appropriately managed and disclosed. In Japan, however, COI management procedures are complex and underdeveloped and the methods vary among medical institutions. This makes it difficult for medical institutions to receive funding from companies.

Our analysis found that research funding increased the likelihood of using multidisciplinary teams and that the use of such teams was associated with multicentre studies. In modern clinical research, it is virtually impossible for a single investigator to simultaneously fulfil multiple roles.

Table 5 Relationship between SCT characteristics and use of designated staff in multidisciplinary roles

| | Research planning support | Research administration | Data management | Statistical analysis | Monitoring | Auditing |
|--|---------------------------|-------------------------|-----------------|----------------------|------------|------------|
| Intervention type | | | | | | |
| Drugs or foods (n=393), n (%) | 147 (37.4) | 198 (50.4) | 335 (85.2) | 331 (84.2) | 390 (99.2) | 168 (42.7) |
| Medical devices (n=184), n (%) | 60 (32.6) | 78 (42.4) | 149 (81) | 145 (78.8) | 181 (98.4) | 50 (27.2) |
| Fisher's exact test p value | 0.306 | 0.075 | 0.224 | 0.126 | 0.389 | <0.001 |
| Target disease | | | | | | |
| Cancer (n=171), n (%) | 77 (45) | 97 (56.7) | 149 (87.1) | 145 (84.8) | 169 (98.8) | 82 (48) |
| Non-cancer (n=406), n (%) | 130 (32) | 179 (44.1) | 335 (82.5) | 331 (81.5) | 402 (99) | 136 (33.5) |
| Fisher's exact test p value | 0.003 | 0.006 | 0.175 | 0.401 | 1.000 | 0.001 |
| Study phase | | | | | | |
| Early phase (I-II) (n=285), n (%) | 102 (35.8) | 144 (50.5) | 244 (85.6) | 227 (79.6) | 282 (98.9) | 96 (33.7) |
| Late phase (III-IV) (n=106), n (%) | 45 (42.5) | 57 (53.8) | 96 (90.6) | 98 (92.5) | 105 (99.1) | 48 (45.3) |
| Fisher's exact test p value | 0.242 | 0.572 | 0.238 | 0.002 | 1.000 | 0.045 |
| Control arm | | | | | | |
| Present (n=237), n (%) | 85 (35.9) | 113 (47.7) | 200 (84.4) | 201 (84.8) | 234 (98.7) | 91 (38.4) |
| Absent (n=340), n (%) | 122 (35.9) | 163 (47.9) | 284 (83.5) | 275 (80.9) | 337 (99.1) | 127 (37.4) |
| Fisher's exact test p value | 1.000 | 1.000 | 0.819 | 0.266 | 0.694 | 0.862 |
| Number of centres | | | | | | |
| Single-centre (n=313), n (%) | 89 (28.4) | 127 (40.6) | 241 (77) | 233 (74.4) | 308 (98.4) | 67 (21.4) |
| Multicentre (n=264), n (%) | 118 (44.7) | 149 (56.4) | 243 (92) | 243 (92) | 263 (99.6) | 151 (57.2) |
| Fisher's exact test p value | <0.0001 | <0.001 | <0.0001 | <0.0001 | 0.227 | <0.0001 |
| Financial resources | | | | | | |
| Industry funding (n=279), n (%) | 114 (40.9) | 164 (58.8) | 255 (91.4) | 253 (90.7) | 278 (99.6) | 153 (54.8) |
| Public grants or institutional funding (n=95), n (%) | 33 (34.7) | 41 (43.2) | 79 (83.2) | 81 (85.3) | 94 (98.9) | 29 (30.5) |
| None (n=203), n (%) | 60 (29.6) | 71 (35) | 150 (73.9) | 142 (70) | 199 (98) | 36 (17.7) |
| Trend test p value | 0.010 | <0.0001 | <0.0001 | <0.0001 | 0.086 | <0.0001 |
| Secondary sponsor | | | | | | |
| Present (n=43), n (%) | 24 (55.8) | 26 (60.5) | 39 (90.7) | 36 (83.7) | 42 (97.7) | 29 (67.4) |
| Absent (n=534), n (%) | 183 (34.3) | 250 (46.8) | 445 (83.3) | 440 (82.4) | 529 (99.1) | 189 (35.4) |
| Fisher's exact test p value | 0.008 | 0.112 | 0.281 | 1.000 | 0.373 | <0.0001 |
| International study | | | | | | |
| Domestic (n=571), n (%) | 204 (35.7) | 271 (47.5) | 478 (83.7) | 470 (82.3) | 565 (98.9) | 215 (37.7) |
| International (n=6), n (%) | 3 (50) | 5 (83.3) | 6 (100) | 6 (100) | 6 (100) | 3 (50) |
| Fisher's exact test p value | 0.672 | 0.109 | 0.596 | 0.597 | 1.000 | 0.678 |
| Appointment of primary investigator | | | | | | |
| Others (n=124), n (%) | 57 (46.0) | 65 (52.4) | 105 (84.7) | 101 (81.5) | 123 (99.2) | 52 (41.9) |
| University (n=453), n (%) | 150 (33.1) | 211 (46.6) | 379 (83.7) | 375 (82.8) | 448 (98.9) | 166 (36.6) |
| Fisher's exact test p value | 0.008 | 0.249 | 0.786 | 0.730 | 0.773 | 0.282 |
| SCT, specified clinical trial. | | | | | | |

Therefore, the lack of financial support may preclude the conduct of multicentre trials, which makes it more difficult to obtain sufficient data that can benefit patients. In order to make CTs easier to conduct and improve the quality of research, there is a need for government/regulatory agencies, related industries and researchers to hold

further discussions on the importance of funding and ensuring COI transparency.

Although Japan ranks third in the world in terms of research funding (cited from a government-issued report), the amount spent on SCTs is low; using industry-published data based on transparency guidelines, the

authors calculated that SCTs received approximately \$13 000 per site per year. In addition, based on the authors' experience to date, funds are needed for monitoring, data management costs and inspection costs for the study, although these vary depending on the type of trial. The use of tax incentives, educational initiatives to demonstrate the social contributions of research support and the establishment of fundraising organisations by the government and related industry groups may help to increase funding for CTs.

From a researcher's perspective, it is important to fully consider how to effectively allocate and use any received funds.¹⁶ This may be achieved through training and employment of qualified clinical research professionals, which can contribute to further improvements in research quality. However, it remains unclear if funding and use of multidisciplinary teams can directly increase the quality of CTs or the number of high-impact journal publications. These issues should therefore be explored when the jRCT database matures in a few years.

CONCLUSIONS

During the 2.5 years after CTA enactment, the number of SCTs had increased and stabilised, whereas the general number of CTs had decreased. Funding and the presence of secondary sponsors were associated with the use of multidisciplinary teams in SCTs. It was inferred that funding is an essential factor for establishing an optimal research infrastructure system that can facilitate high-quality research.

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