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# Studies registered in non-ClinicalTrials.gov accounted for an increasing proportion of protocol registrations in medical research

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## Abstract

**Objective:** To compare the recent trends and characteristics of studies registered as non-ClinicalTrials.gov in the International Clinical Trials Registry Platform (ICTRP).

**Study Design and Setting:** We included all studies on the ICTRP from January 1, 2014, to December 31, 2018. We described the characteristics of included studies and examined whether the proportion of studies registered in non-ClinicalTrials.gov on ICTRP increased by interventional design or noninterventional design. We further compared the characteristics of studies registered in non-ClinicalTrials.gov to those registered in ClinicalTrials.gov.

**Results:** We identified 235,830 studies (182,771 studies having interventional design and 53,059 studies having noninterventional design). The proportion of studies registered in non-ClinicalTrials.gov among studies registered on ICTRP increased from 2014 to 2018 (38.3% to 53.3% overall, 39.3% to 53.0% for interventional design, and 34.1% to 54.2% for noninterventional design). Studies registered in non-ClinicalTrials.gov were more often retrospectively registered as interventional design and lacked sufficient information about target sample sizes than studies registered in ClinicalTrials.gov irrespective of study design.

**Conclusion:** Studies registered in non-ClinicalTrials.gov increasingly accounted for the proportion of protocol registration among the ICTRP irrespective of study designs since 2014. Systematic reviewers should search ICTRP in addition to ClinicalTrials.gov. © 2019 Elsevier Inc. All rights reserved.

*Keywords:* Protocol registration; International Clinical Trials Registry Platform; Clinical trials registry; ClinicalTrials.gov; Meta-Research

## 1. Background

Searching a range of sources comprehensively, objectively, and reproducibly to find as many relevant studies as possible plays a pivotal role in systematic reviews (SRs) [1]. Systematic reviewers search clinical trial registries such as the World Health Organization's (WHO) International Clinical Trials Registry Platform

Protocol and Registration: We applied a prespecified protocol to perform this study (Banno M et al., 2019, URL: https://doi.org/10.7287/peerj.preprints.27298v2). The study was enrolled in the Universal Hospital Medical Information Network (UMIN) registry (ID: JPRN-UMIN000034401).

Conflict of interest: Masahiro Banno received travel fees from Yoshitomi Pharmaceutical Industries Ltd. The other authors have no competing interests to declare.

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**What is new?**

**Key findings**

- Studies registered in registries other than ClinicalTrials.gov (NC-studies) among the studies registered on the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) accounted for an increasing proportion of protocol registration irrespective of study design in the most recent 5 years.
- NC-studies were more often retrospectively registered for interventional design and lacked sufficient information about target sample sizes than studies registered in ClinicalTrials.gov irrespective of study design.

**What this study adds to what was known?**

- Proportion of NC-studies with interventional design increased through 2013 and has continued to increase since 2014.
- The ranking of countries in order of registrations was different from that of biomedical research *publications* in a previous study.

**What is the implication and what should change now?**

- This study supports the need for systematic reviewers to search ICTRP in addition to ClinicalTrials.gov when searching for clinical trials registries irrespective of study design.

(ICTRP) and ClinicalTrials.gov to find unpublished and ongoing studies in clinical trials registries and check publication bias [1]. Moreover, systematic reviewers obtain the protocol information of published studies from clinical trials registries [1].

ICTRP has evolved as a search portal of clinical trials registration and aggregated data of studies in national and regional registries all over the world since 2005 [2,3]. ClinicalTrials.gov was the largest of the 17 registries that sent data to the ICTRP as of 2013 [4] and owned 119,840 records of drug studies before 2015 [5]. The primary registries included have submitted the WHO Trial Registration Data Sets for all records on their registry to the international registry [6].

The proportion of studies registered in registries other than ClinicalTrials.gov (NC-studies) among ICTRP-registered studies dramatically expanded from 30% to 50% between 2005 and 2013 [4]. A possible explanation for this is that the non-US share of global medical research funding increased from 43% to 56% between 2004 and 2012 [7]. However, the current proportion of NC-studies among ICTRP-registered studies remains unclear.

The primary purpose of this study was to inspect the proportion of worldwide NC-studies among ICTRP-registered studies from 2014 to 2018. The secondary objectives were to a) compare the characteristics of registered studies on ClinicalTrials.gov (C-studies) and NC-studies from 2014 to 2018 and b) illuminate the distribution of studies in each registry by registered countries ordered by the number registered on the ICTRP.

## 2. Materials and methods

### 2.1. Types of studies to be included

All studies registered in the ICTRP from January 1, 2014, to December 31, 2018, were included irrespective of the study design. ICTRP provides all data sets to researchers [8]. We subscribed to the ICTRP technical updates mailing list (listserv@who.int). The project manager (Mr. Ghassan Karam) informed us of the upload of the latest ICTRP data set and the link to the file via the mailing list on March 11, 2019. We downloaded the full ICTRP data set available on the server of the ICTRP on March 12, 2019.

We included only the record with the earliest registration date [9]. As the data provided by the ICTRP project manager contained duplicates that were deleted in the ICTRP search portal, we excluded duplicates by deleting the records, which are input as ‘‘Child’’ in the data item ‘‘Bridged_type’’ of the data set [9].

### 2.2. Data extraction

We extracted the following variables: countries, study phase, target sample size (1–9, 10–99, 100–999, 1000 or more, not specified), recruitment status (ongoing, completed, terminated, unknown, enrollment by invitation), retrospective registration (Yes, No), and study design (interventional or noninterventional design). We categorized the study design as interventional design and noninterventional design. We designated as interventional design studies that included the word ‘‘intervention’’ or ‘‘interventional’’ in ‘‘study type’’ of the ICTRP registration and ‘‘noninterventional design’’ as studies other than interventional study, such as cohort, case-control, and cross-sectional studies [10]. Retrospective registration means registration after involvement of the first participant [11]. We extracted the countries in which the original registration was based (the country of the registry) and counted a record with multiple countries using the article count procedure used in the Nature Index [12], whereby a count of one is assigned to a country if one or more authors of the article are from that country, regardless of how many co-authors there are from outside that country.

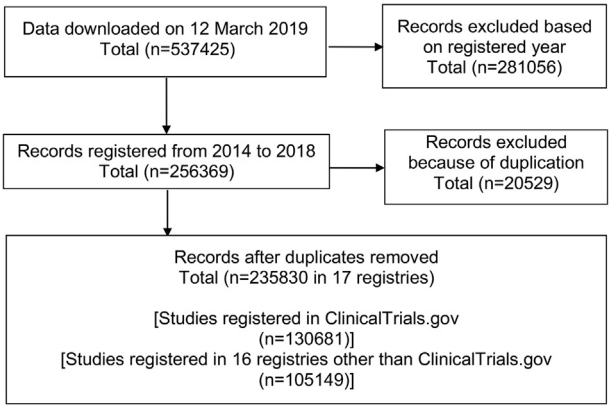


**Fig. 1.** Flowchart of the selection of records in the International Clinical Trials Registry Platform (ICTRP), 2019.

### 2.3. Data analysis

We described the proportion of NC-studies among all studies registered in ICTRP and the distribution of studies from the top five countries in each registry by number of registrations on the ICTRP. We examined the trends by calendar years using the Cochran-Armitage test and described the characteristics of the included studies by registration (those with ClinicalTrials.gov and non-ClinicalTrials.gov). We considered the study design (interventional or noninterventional) to determine important subgroups for the assessment of the difference between C-studies and NC-studies and reported them separately because noninterventional design has attracted great attention recently [10,13]. For post hoc analysis, we looked at the proportion of NC-studies with randomized design among studies with randomized design registered on ICTRP. We restricted interventional studies to those using ''randomization'' or ''randomisation'' or ''randomized'' or ''randomised'' in the ''study design'' section of the registration records. We compared the characteristics of C-studies and NC-studies using a $\chi^2$-test and the target sample sizes in C-studies and NC-studies using the Mann-Whitney U Test.

We performed all statistical analyses with Stata V.15.1 (StataCorp LLC, College Station, Texas, USA) [14].

### 2.4. Differences between the protocol and the manuscript

The study was enrolled in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (Trial registration number: JPRN-UMIN000034401).

**Table 1.** Interventional studies registered on ClinicalTrials.gov vs. 16 other registries (Non-ClinicalTrials.gov) from 2014 to 2018

| Year | 2014 (*n* = 29,806) | 2015 (*n* = 32,374) | 2016 (*n* = 36,292) | 2017 (*n* = 39,650) | 2018 (*n* = 44,649) |
|---|---|---|---|---|---|
| ClinicalTrials.gov | 18,097 (60.7) | 18,952 (58.5) | 21,163 (58.3) | 21,770 (54.9) | 21,006 (47.1) |
| Non-ClinicalTrials.gov[a] | 11,709 (39.3) | 13,422 (41.5) | 15,129 (41.7) | 17,880 (45.1) | 23,643 (52.9) |
| ANZCTR | 1197 (4.0) | 1278 (4.0) | 1554 (4.3) | 1485 (3.8) | 1838 (4.1) |
| ChiCTR | 1010 (3.4) | 1080 (3.3) | 1470 (4.1) | 2073 (5.2) | 2889 (6.5) |
| CRiS | 0 (0) | 0 (0) | 0 (0) | 2 (0) | 16 (0) |
| CTRI | 830 (2.8) | 851 (2.6) | 865 (2.4) | 2487 (6.3) | 4021 (9.0) |
| DRKS | 553 (1.9) | 696 (2.2) | 659 (1.8) | 622 (1.6) | 638 (1.4) |
| EU-CTR | 1662 (5.6) | 1820 (5.6) | 1653 (4.6) | 1510 (3.8) | 1466 (3.3) |
| IRCT | 2001 (6.7) | 2321 (7.2) | 2816 (7.8) | 3183 (8.0) | 3709 (8.3) |
| ISRCTN | 769 (2.6) | 887 (2.7) | 875 (2.4) | 932 (2.4) | 897 (2.0) |
| JPRN | 2541 (8.5) | 3058 (9.5) | 3512 (9.7) | 3535 (8.9) | 5546 (12.4) |
| NTR | 412 (1.4) | 412 (1.3) | 394 (1.1) | 469 (1.2) | 410 (0.9) |
| PACTR | 187 (0.6) | 272 (0.8) | 328 (0.9) | 478 (1.2) | 480 (1.1) |
| ReBEC | 88 (0.3) | 295 (0.9) | 469 (1.3) | 441 (1.1) | 927 (2.1) |
| REPEC | 243 (0.8) | 183 (0.6) | 140 (0.4) | 119 (0,3) | 77 (0.2) |
| RPCEC | 15 (0.1) | 17 (0.1) | 20 (0.1) | 35 (0.1) | 30 (0.1) |
| SLCTR | 37 (0.1) | 31 (0.1) | 28 (0.1) | 41 (0.1) | 43 (0.1) |
| TCTR | 164 (0.6) | 221 (0.7) | 346 (1.0) | 468 (1.2) | 656 (1.5) |

Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; ReBEC, Brazilian Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Registry; CRiS, Clinical Research Information Service Republic of Korea; CTRI, Clinical Trials Registry—India; RPCEC, Cuban Public Registry of Clinical Trials; EU-CTR, EU Clinical Trials Register; DRKS, German Clinical Trials Register; ISRCTN, International Standard Randomised Controlled Trial Number Register; IRCT, Iranian Registry of Clinical Trials; JPRN, Japan Primary Registries Network; NTR, The Netherlands National Trial Register; PACTR, Pan-African Clinical Trial Registry; REPEC, Peruvian Clinical Trials Registry; SLCTR, Sri Lanka Clinical Trials Registry; TCTR, Thai Clinical Trials Registry.

Values are given as number (percentage).

[a] Non-ClinicalTrials.gov included 16 registries besides ClinicalTrials.gov.

**Table 2.** Noninterventional studies registered on ClinicalTrials.gov vs. 16 other registries (Non-ClinicalTrials.gov) from 2014 to 2018

| Year | 2014 (*n* = 7347) | 2015 (*n* = 8106) | 2016 (*n* = 10,224) | 2017 (*n* = 12,611) | 2018 (*n* = 14,771) |
|---|---|---|---|---|---|
| ClinicalTrials.gov | 4844 (65.9) | 4891 (60.3) | 6194 (60.6) | 7000 (55.5) | 6764 (45.8) |
| Non-ClinicalTrials.gov[a] | 2503 (34.1) | 3215 (39.7) | 4030 (39.4) | 5611 (44.5) | 8007 (54.2) |
| ANZCTR | 148 (2.0) | 135 (1.7) | 236 (2.3) | 229 (1.8) | 305 (2.1) |
| ChiCTR | 633 (8.6) | 757 (9.3) | 1097 (10.7) | 1838 (14.6) | 2954 (20.0) |
| CRiS | 0 (0.0) | 1 (0.0) | 0 (0.0) | 1 (0.0) | 3 (0.0) |
| CTRI | 236 (3.2) | 269 (3.3) | 271 (2.7) | 903 (7.2) | 1714 (11.6) |
| DRKS | 315 (4.3) | 389 (4.8) | 445 (4.4) | 489 (3.9) | 584 (4.0) |
| IRCT | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 8 (0.1) |
| ISRCTN | 95 (1.3) | 163 (2.0) | 179 (1.8) | 218 (1.7) | 215 (1.5) |
| JPRN | 833 (11.3) | 1196 (14.8) | 1456 (14.2) | 1519 (12.1) | 1635 (11.1) |
| NTR | 195 (2.7) | 209 (2.6) | 208 (2.0) | 255 (2.0) | 307 (2.1) |
| ReBEC | 6 (0.1) | 24 (0.3) | 34 (0.3) | 26 (0.2) | 56 (0.4) |
| RPCEC | 0 (0.0) | 0 (0.0) | 1 (0.0) | 1 (0.0) | 1 (0.0) |
| TCTR | 42 (0.6) | 72 (0.9) | 103 (1.0) | 132 (1.1) | 225 (1.5) |

Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; ReBEC, Brazilian Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Registry; CRiS, Clinical Research Information Service Republic of Korea; CTRI, Clinical Trials Registry—India; RPCEC, Cuban Public Registry of Clinical Trials; EU-CTR, EU Clinical Trials Register; DRKS, German Clinical Trials Register; ISRCTN, International Standard Randomised Controlled Trial Number Register; IRCT, Iranian Registry of Clinical Trials; JPRN, Japan Primary Registries Network; NTR, The Netherlands National Trial Register; PACTR, Pan African Clinical Trial Registry; REPEC, Peruvian Clinical Trials Registry; SLCTR, Sri Lanka Clinical Trials Registry; TCTR, Thai Clinical Trials Registry.

Values are given as number (percentage).

We did not include four registries (EU-CTR, PACTR, REPEC, and SLCTR) in the table because the number of noninterventional studies registered on these registries from 2014 to 2018 was 0.

[a] Non-ClinicalTrials.gov included 16 registries besides ClinicalTrials.gov.

**Table 3.** Characteristics of studies registered on the International Clinical Trials Registry Platform (ICTRP) from 2014 to 2018

| Category | Interventional | | Noninterventional | |
|---|---|---|---|---|
| | ClinicalTrials.gov | Non-ClinicalTrials.gov | ClinicalTrials.gov | Non-ClinicalTrials.gov |
| Countries | | | | |
| 1st | United States 36260 (35.9) | Japan 16521 (20.2) | United States 6904 (23.3) | China 6959 (29.8) |
| 2nd | France 7215 (7.1) | Iran 14071 (17.2) | France 3336 (11.2) | Japan 6517 (27.9) |
| 3rd | China 6682 (6.6) | India 9448 (11.6) | China 1841 (6.2) | India 3419 (14.6) |
| 4th | Canada 6157 (6.1) | China 8844 (10.8) | Germany 1554 (5.2) | Germany 2206 (9.4) |
| 5th | United Kingdom 5308 (5.3) | Australia 6826 (8.4) | United Kingdom 1456 (4.9) | Netherland 1304 (5.6) |
| 6th | Germany 4581 (4.5) | Germany 6347 (7.8) | Italy 1178 (4.0) | Australia 812 (3.5) |
| 7th | Spain 3950 (3.9) | United Kingdom 4770 (5.8) | Canada 1039 (3.5) | United Kingdom 543 (2.3) |
| 8th | Korea 3635 (3.6) | Netherland 4408 (5.4) | Spain 908 (3.1) | Thailand 530 (2.3) |
| 9th | Italy 3440 (3.4) | Spain 3656 (4.5) | Korea 834 (2.8) | Brazil 187 (0.8) |
| 10th | Belgium 2590 (2.6) | United States 3560 (4.4) | Switzerland 776 (2.6) | Italy 168 (0.7) |
| Study phase | | | | |
| Phase 0 | 306 (0.3) | 190 (0.2) | 25 (0.1) | 23 (0.1) |

(*Continued*)

**Table 3.** Continued

| | Interventional | | Noninterventional | |
|---|---|---|---|---|
| **Category** | **ClinicalTrials.gov** | **Non-ClinicalTrials.gov** | **ClinicalTrials.gov** | **Non-ClinicalTrials.gov** |
| Phase I | 12,256 (12.1) | 3017 (3.7) | 2094 (7.1) | 574 (2.5) |
| Phase I and II | 3865 (3.8) | 1625 (2.0) | 824 (2.8) | 93 (0.4) |
| Phase I and II and III | 0 (0.0) | 6 (0.01) | | |
| Phase I and III | 0 (0.0) | 9 (0.01) | | |
| Phase I and IV | 0 (0.0) | 8 (0.01) | | |
| Phase II | 12,853 (12.7) | 8453 (10.3) | 2642 (8.9) | 312 (1.3) |
| Phase II and III | 1761 (1.7) | 2791 (3.4) | 249 (0.8) | 35 (0.2) |
| Phase II and IV | 0 (0.0) | 2 (0.0) | | |
| Phase III | 7924 (7.9) | 8372 (10.2) | 1752 (5.9) | 131 (0.6) |
| Phase III and IV | 0 (0.0) | 347 (0.4) | 0 (0.0) | 10 (0.04) |
| Phase IV | 8838 (8.8) | 4069 (5.0) | 1068 (3.6) | 461 (2.0) |
| Not specified | 53,185 (52.7) | 52,894 (64.7) | 21,039 (70.9) | 21,727 (93.0) |
| Target sample size | | | | |
| 1–9 | 3642 (3.6) | 1359 (1.7) | 539 (1.8) | 161 (0.7) |
| 10–99 | 57,908 (57.3) | 44,130 (54.0) | 10,162 (34.2) | 6265 (26.8) |
| 100–999 | 33,518 (33.2) | 22,248 (27.2) | 12,925 (43.5) | 7537 (32.3) |
| 1000 or more | 3689 (3.7) | 2338 (2.9) | 4946 (16.7) | 1964 (8.4) |
| Not specified | 2231 (2.2) | 11,708 (14.3) | 1121 (3.8) | 7439 (31.8) |
| Recruitment status | | | | |
| Ongoing | 58,807 (58.2) | 43,995 (53.8) | 17,253 (58.1) | 15,954 (68.3) |
| Completed | 34,993 (34.7) | 34,501 (42.2) | 10,002 (33.7) | 6957 (29.8) |
| Terminated | 4871 (4.8) | 198 (0.2) | 1357 (4.6) | 27 (0.1) |
| Unknown | 14 (0.01) | 2970 (3.6) | 4 (0.01) | 396 (1.7) |
| Enrollment by invitation | 2303 (2.3) | 119 (0.2) | 1077 (3.6) | 32 (0.1) |
| Retrospective registration | 22,304 (22.1) | 27,995 (34.2) | 9971 (33.6) | 8493 (36.4) |
| Total | 100988 | 81,783 | 29,693 | 23,366 |

*P*-values for the $\chi^2$ test were less than 0.001 in study phase, target sample size, recruitment status, and retrospective registration of interventional design and noninterventional design.

**Table 4.** Distribution of studies in each registry from the top five countries by number of registrations on the International Clinical Trials Registry Platform (ICTRP) from 2014 to 2018

| **Ranking** | **Countries** | **ClinicalTrials.gov** | **JPRN** | **ChiCTR** | **IRCT** | **EU-CTR** | **DRKS** |
|---|---|---|---|---|---|---|---|
| Interventional studies | | | | | | | |
| 1st | United States | 36,260 (91.1) | 1 (0.0) | 1 (0.0) | 0 (0.0) | 2329 (5.9) | 254 (0.6) |
| 2nd | Japan | 1715 (9.4) | 15,585 (85.5) | 0 (0.0) | 0 (0.0) | 554 (3.0) | 55 (0.3) |
| 3rd | China | 6682 (43.0) | 0 (0.0) | 8072 (52.0) | 0 (0.0) | 227 (1.5) | 70 (0.5) |
| 4th | Iran | 320 (2.2) | 0 (0.0) | 0 (0.0) | 13,964 (97.3) | 1 (0.01) | 0 (0.0) |
| 5th | Germany | 4581 (41.9) | 0 (0.0) | 1 (0.01) | 0 (0.0) | 2678 (24.5) | 2844 (26.0) |
| Non-interventional studies | | | | | | | |
| 1st | China | 1841 (20.9) | 0 (0.0) | 6863 (78.0) | 0 (0.0) | 0 (0.0) | 9 (0.1) |
| 2nd | United States | 6904 (98.5) | 0 (0.0) | 2 (0.03) | 0 (0.0) | 0 (0.0) | 34 (0.5) |
| 3rd | Japan | 316 (4.6) | 6482 (94.9) | 3 (0.04) | 0 (0.0) | 0 (0.0) | 6 (0.1) |
| 4th | Germany | 1554 (41.3) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 2114 (56.2) |
| 5th | India | 232 (6.4) | 0 (0.0) | 2 (0.1) | 0 (0.0) | 0 (0.0) | 8 (0.2) |

Abbreviations: ANZCTR, Australian New Zealand Clinical Trials Registry; ReBEC, Brazilian Clinical Trials Registry; ChiCTR, Chinese Clinical Trial Registry; CTRI, Clinical Trials Registry—India; EU-CTR, EU Clinical Trials Register; DRKS, German Clinical Trials Register; ISRCTN, International Standard Randomised Controlled Trial Number Register; IRCT, Iranian Registry of Clinical Trials; JPRN, Japan Primary Registries Network; PACTR, Pan African Clinical Trial Registry; REPEC, Peruvian Clinical Trials Registry; SLCTR, Sri Lanka Clinical Trials Registry; TCTR, Thai Clinical Trials Registry.

We show the registries in order of total studies of 10 countries in interventional design and noninterventional design.

We applied a prespecified protocol to perform this study [15]. We changed how to manage duplication compared with our protocol [15] and did not perform a sensitivity analysis of duplication as described in our protocol [15]. The reason for this change is that we focused on the actual numbers of planned studies, not the numbers of registered records in each registry.

### 2.5. Ethics

Because this was meta-research, ethics approval was not required.

## 3. Results

### 3.1. Search results

We initially identified a total of 537,425 studies (17 registries) from ICTRP. Figure 1 shows the inclusion flow. After excluding studies by year of registration, we identified 256,369 studies registered between 2014 and 2018, leaving a total of 235,830 studies (130,681 C-studies and 105,149 NC-studies) after excluding duplication. The NC-studies were registered in the following registries: Australian New Zealand Clinical Trials Registry, Brazilian Clinical Trials Registry, Chinese Clinical Trial Registry, Clinical Research Information Service—Republic of Korea, Clinical Trials Registry—India, Cuban Public Registry of Clinical Trials, EU Clinical Trials Register, German Clinical Trials Register, International Standard Randomised Controlled Trial Number Register, Iranian Registry of Clinical Trials, Japan Primary Registries Network, The Netherlands National Trial Register, Pan-African Clinical Trial Registry, Peruvian Clinical Trials Registry, Sri Lanka Clinical Trials Registry, and Thai Clinical Trials Registry.

### 3.2. The proportion of NC-studies from 2014 to 2018

Tables 1 and 2 show the trends of C-studies and NC-studies in the ICTRP from 2014 to 2018, classified by study design. The proportion of NC-studies among studies registered on ICTRP increased from 2014 to 2018 (38.3% to 53.3% overall, 39.3% to 53.0% for interventional design, and 34.1% to 54.2% for noninterventional design; $P$ for trend $< 0.001$). The proportion of NC-studies with a randomized design among all studies with a randomized design registered on ICTRP increased from 2014 to 2018 [43.9% (10,281/23,394) to 56.7% (20,656/36,406); $P$ for trend $< 0.001$].

### 3.3. Comparisons of characteristics between C-studies and NC-studies

Table 3 summarizes the characteristics of the included studies. More than one-third of C-studies were from the United States, whereas NC-studies were mainly from countries in Asia and the Pacific. Compared with C-studies, the study phase of NC-studies was more often unknown (interventional design: 52.7% in C-studies and 64.7% in NC-studies; noninterventional design: 70.9% in C-studies and 93.0% in NC-studies). Target sample sizes were similar in interventional design (C-studies: median [interquartile range {IQR}] = 60 [30–150], NC–studies: median [IQR] = 60 [33–120], $P = 0.24$, $z = 1.17$ in Mann-Whitney U test), whereas the size was larger in C-studies than NC-studies in noninterventional design (C-studies: median [IQR] = 150 [53–500], NC-studies: median

| CTRI | REPEC | ISRCTN | ANZCTR | TCTR | ReBec | SLCTR | PACTR | Total |
|---|---|---|---|---|---|---|---|---|
| | | | | | | | | |
| 203 (0.5) | 546 (1.4) | 118 (0.3) | 73 (0.2) | 1 (0.0) | 23 (0.06) | 5 (0.01) | 6 (0.02) | 39,820 (100) |
| 87 (0.5) | 203 (1.1) | 19 (0.1) | 11 (0.06) | 0 (0.0) | 5 (0.03) | 2 (0.01) | 0 (0.0) | 18,236 (100) |
| 80 (0.5) | 174 (1.1) | 112 (0.7) | 97 (0.6) | 4 (0.03) | 3 (0.02) | 5 (0.03) | 0 (0.0) | 15,526 (100) |
| 4 (0.03) | 7 (0.1) | 10 (0.1) | 9 (0.06) | 76 (0.5) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 14,391 (100) |
| 157 (1.4) | 479 (4.4) | 133 (1.2) | 27 (0.3) | 0 (0.0) | 24 (0.2) | 4 (0.04) | 0 (0.0) | 10,928 (100) |
| | | | | | | | | |
| 24 (0.3) | 0 (0.0) | 30 (0.3) | 19 (0.2) | 13 (0.2) | 1 (0.01) | 0 (0.0) | 0 (0.0) | 8800 (100) |
| 29 (0.4) | 0 (0.0) | 24 (0.3) | 16 (0.2) | 1 (0.01) | 3 (0.04) | 0 (0.0) | 0 (0.0) | 7013 (100) |
| 18 (0.3) | 0 (0.0) | 4 (0.1) | 3 (0.04) | 0 (0.0) | 1 (0.01) | 0 (0.0) | 0 (0.0) | 6833 (100) |
| 21 (0.6) | 0 (0.0) | 63 (1.7) | 7 (0.2) | 0 (0.0) | 1 (0.03) | 0 (0.0) | 0 (0.0) | 3760 (100) |
| 3387 (92.8) | 0 (0.0) | 13 (0.4) | 6 (0.2) | 3 (0.1) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 3651 (100) |

[IQR] = 100 [50–322], $P < 0.001$, $z = -13.52$ in Mann-Whitney U test). Compared with C-studies, the target sample sizes of NC-studies were more often unknown irrespective of the study design (interventional design: 2.2% in C-studies and 14.3% in NC-studies; noninterventional design: 3.8% in C-studies and 31.8% in NC-studies). Retrospective registration rate was higher in NC-studies than C-studies in interventional design but similar in noninterventional design (interventional design: 22.1% in C-studies and 34.2% in NC-studies; noninterventional design: 33.6% in C-studies and 36.4% in NC-studies). Proportions of interventional design in study design were similar in both groups (C-studies: 77.3%, NC-studies: 77.8%).

### 3.4. Distribution of studies in each registry from the top five countries in order of number of registrations

Table 4 shows the distribution of studies in each registry from the top five countries in numbers of registrations on ICTRP from 2014 to 2018. The top five countries for interventional design were the USA, Japan, China, Iran, and Germany, whereas the top five countries for noninterventional design were China, the USA, Japan, Germany, and India.

## 4. Discussion

### 4.1. Summary of findings

NC-studies among registered studies of the ICTRP made up an increasing proportion of protocol registrations regardless of study designs in the most recent 5 years. The results remained unchanged if we restricted the studies registered on ICTRP to those with randomized design. The increase in the proportion of noninterventional designs implies that systematic reviewers should search ICTRP in addition to ClinicalTrials.gov when conducting SRs of noninterventional designs than randomized controlled trials, such as SRs of diagnostic test accuracy or prognostic studies. The protocols of NC-studies were somewhat associated with low methodological quality, such as nonreporting of target sample size and retrospective registration.

### 4.2. Results in relation to prior studies

This study showed that the proportion of NC-studies having an interventional design among the studies registered on ICTRP has furthermore increased since 2014, as a previous study showed [4]. However, systematic reviewers often did not search ICTRP. Twenty-two percent of the SRs published in 2014 and 2015 searched only ClinicalTrials.gov to collect ongoing or unpublished studies [16]. Given our evidence that NC-studies have increased to more than half of the studies registered on ICTRP, searching only ClinicalTrial.gov may be inadequate for an SR. We therefore suggest that systematic reviewers should search ICTRP. Systematic reviewers should also search other registries than ICTRP such as ClinicalTrials.gov. Certain search terms detected more studies in ClinicalTrials.gov than in ICTRP [17].

The proportion of NC-studies with interventional design in 2013 was 50% in a previous study [4], whereas the proportion in 2014 was 39.3% in our study. The reason for this inconsistency was excluding duplicates from the data or not. We excluded the duplicates to estimate the precise number of NC-studies, but the previous study did not.

The ranking of countries in order of biomedical research publications differs from our ranking [18]. This might indicate that NC-studies have more unpublished records than C-studies [19]. Further work should assess the issue of the unpublished rate of studies in each registry.

The countries registering records in ICTRP that most contributed to our results were different from those of a previous study from 2011 to 2015 conducted in ICTRP [20]. These results are consistent with the change in country rankings of publications [18].

### 4.3. Limitations

The applicability of this study was limited because the data included only studies registered in the ICTRP. The registry included a representative data set of studies [2]. However, other, possibly low-quality, registered data of studies may be excluded. For example, studies registered in the South African National Clinical Trials Register and Hong Kong clinical trials register were not included in ICTRP [2]. The exclusion of these databases may have an insignificant impact on the results because Pan-African Clinical Trial Registry and Chinese Clinical Trial Registry, which were the primary registries in ICTRP, were representative registries for studies registered in South Africa and Hong Kong [2].

The post hoc sensitivity analysis restricting randomized controlled trials might suffer from misclassification because we judged studies to be randomized trials if they stated ‘‘randomization,’’ ‘‘randomisation,’’ ‘‘randomized,’’ or ‘‘randomised’’ in the ‘‘study design’’ section of their registration records.

## 5. Conclusion

Our study suggests a greater need for systematic reviewers to search ICTRP when searching for clinical trials registries irrespective of study design. Further investigation is required to establish an optimal registry that incorporates such important items as the study phase and target sample sizes of all the registered studies.

## CRediT authorship contribution statement

**Masahiro Banno:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Resources, Data

curation, Writing - original draft, Visualization, Project administration. **Yasushi Tsujimoto:** Conceptualization, Methodology, Validation, Writing - review & editing. **Yuki Kataoka:** Conceptualization, Methodology, Validation, Writing - review & editing, Supervision, Funding acquisition.

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