Attribution of non-ClinicalTrials.gov registries among WHO International Clinical Trials Registry Platform-registered trials from 2014 to 2018: A protocol for a meta-epidemiological study

Masahiro Banno[1,2], Yasushi Tsujimoto[3,4], Yuki Kataoka[5,6]

[1] Department of Psychiatry, Seichiryo Hospital, Nagoya City, Aichi Prefecture, Japan

[2] Department of Psychiatry, Nagoya University Graduate School of Medicine, Nagoya City, Aichi Prefecture, Japan

[3] Department of Healthcare Epidemiology, School of Public Health in the Graduate School of Medicine, Kyoto University, Kyoto City, Kyoto Prefecture, Japan

[4] Department of Nephrology and Dialysis, Kyoritsu Hospital, Kawanishi City, Hyogo Prefecture, Japan

[5] Hospital Care Research Unit, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki City, Hyogo Prefecture, Japan

[6] Department of Respiratory Medicine, Hyogo Prefectural Amagasaki General Medical Center, Amagasaki City, Hyogo Prefecture, Japan

Corresponding author:

Masahiro Banno[1, 2]

Email address: solvency@med.nagoya-u.ac.jp

Author name abbreviations: Masahiro Banno (MB), Yasushi Tsujimoto (YT), Yuki Kataoka (YK)

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ABSTRACT

Background. The attribution of non-ClinicalTrials.gov registries among registered trials of the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) had increased until 2013. However, the attribution after 2013 is unknown. Moreover, no study has investigated the usage of non-ClinicalTrials.gov registries after 2015 or compared the characteristics of trials under non-ClinicalTrials.gov and ClinicalTrials.gov registries.

Methods. This will be a meta-epidemiological study. It will include all trials registered on the ICTRP from January 1, 2014, to December 31, 2018. First, we will describe the total attribution of non-ClinicalTrials.gov registries among the ICTRP-registered trials for each year and each registry worldwide. Second, we will compare the recruitment status, target sample size, study type, study design, countries, prospective registration, funding, and study phase of the trials on ClinicalTrials.gov and other registries from 2014 to 2018. Third, we will report on the distribution of primary registries of trials from the top five countries in order of the quantity of registered trials on the ICTRP.

Ethics & Dissemination. Ethics approval is not required for this study. This protocol has been registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR). The findings will be published in a peer-reviewed journal and may be presented at conferences.

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Introduction

It is important to register clinical trials in order to avoid waste from inaccessibility of information on study methods and reduced publication bias, both of which may affect patient care and research (Chalmers & Glasziou, 2009; Chan et al., 2014). Over a decade, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) has developed as a registry and collected data of trials in national and regional registries all over the world since 2005 (Gulmezoglu et al., 2005; WHO International Clinical Trials Registry Platform (ICTRP), 2018). ClinicalTrials.gov was the largest of the 16 registries that supplied data to the ICTRP until 2013 (Viergever & Li, 2015) and had 119,840 records of drug trials before July, 2015 (Zwierzyna et al., 2018).

Attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials had increased from 30% to 50% between 2005 and 2013 (Viergever & Li, 2015). It might have been because of the small annual growth rate of medical research funding in the USA from 2004 to 2011 as compared to the global annual growth rate as the non-USA share of global medical research funding increased from 43% to 56% between 2004 and 2012 (Moses et al., 2015). The attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials is expected to further increase because another study (Zwierzyna et al., 2018) has reported a recent decrease in attribution of trials registered in the USA on ClinicalTrials.gov, which might be derived from a shift in which are officially the largest countries in terms of the number of registered trials for a decade (ClinicalTrials.gov is under the control of the USA). However, the current status of the attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials is unknown.

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We hypothesize that the attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials from 2014 to 2018 is higher than it previously was (from 2004 to 2013). This study will examine the attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials from 2014 to 2018.

Study Objectives

The primary purpose of this study is to investigate the total attribution of worldwide non-ClinicalTrials.gov registries among ICTRP-registered trials each year. The secondary objectives are to a) compare the characteristics of registered clinical trials on ClinicalTrials.gov and other registries among the ICTRP from 2014 to 2018 and b) describe the distribution of primary registries of trials from the top five countries, in order of the quantity of registered trials on the ICTRP.

Materials & Methods

Types of Studies to be Included

All clinical trials registered on the ICTRP from January 1, 2014, to December 31, 2018, will be included in the data set. Observational studies that incorporate "study type" in the data set will be excluded.

Search Methods

A search of the ICTRP will be conducted on February 1, 2019, for all trials registered from January 1, 2014, to December 31, 2018.

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About the Data Set

This study will use data downloaded from the ICTRP data set available on the server of the WHO. The following fields will be extracted: TrialID, Primary_sponsor, Date_registration, Date_registration3, Source_Register, Recruitment_Status, Date_enrollement, Target_size, Study_type, Study_design, Phase, Countries, Source_Support, and Retrospective_flag.

Data Analysis

First, the total attribution of non-ClinicalTrials.gov registries among ICTRP-registered trials for each year from 2014 to 2018 will be described. We will calculate the total attribution of non-ClinicalTrials.gov registries among the ICTRP-registered trials, dividing the number of registered clinical trials in non-ClinicalTrials.gov registries by the number of total registered clinical trials on the ICTRP. The Cochran-Armitage test will be performed to examine attribution trends.

Second, the attribution of each non-ClinicalTrials.gov registry among the ICTRP-registered trials for each year from 2014 to 2018 will be described. This will be carried out in the same manner as described above.

Third, the study will report on the recruitment status, target sample size, study type, study design, countries, prospective registration (Yes, No), funding (Yes, No), and study phase of the trials on ClinicalTrials.gov and other registries between 2014 and 2018. We will record a “Yes” for prospective registration if retrospective_flag is found to be “Yes,” and a “No” if retrospective_flag is found to be “No” or unclear. We will record a “Yes” for funding if

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source_support has any description of the funders, and a "No" if source_support has no descriptions of any funders (for example, empty, none, no funder, and so on).

Fourth, the distribution of primary registries of trials from the top five countries, in order of the quantity of registered trials on the ICTRP, will be reported on.

Ethics & Dissemination

Since this will be a meta-epidemiological study, an ethics approval is not required. The protocol used has been registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (Trial registration number: UMIN000034401). The planned completion date of the present study is December 31, 2019. The findings will be published in a peer-reviewed journal and may be presented at conferences.

Discussion

Strengths

To conduct a systematic review, authors are encouraged to search ongoing and unpublished studies that are registered on the ICTRP (Higgins & Green, 2011). However, a previous study has reported that only 40% and 24% of authors searched ClinicalTrials.gov and the ICTRP, respectively (Baudard et al., 2017). We hypothesize that more non-ClinicalTrials.gov registries have been attributed to the ICTRP since 2014. The results are expected to prove that a mere search on ClinicalTrials.gov is not sufficient, and to highlight the importance of searching the ICTRP to identify ongoing and unpublished studies. Moreover, this study will compare the characteristics of registered clinical trials on ClinicalTrials.gov and other registries. The results

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of the third analysis will suggest improvements for the registries. For example, many studies have pointed out a considerable number of retrospective registrations that may cause bias in estimation of treatment effect (Huic, Marusic & Marusic, 2011; Viergever et al., 2014; Scott, Rucklidge & Mulder, 2015; Viergever & Li, 2015; Harriman & Patel, 2016; Zarin et al., 2017). We will show and compare the proportion of retrospective registrations across the registries on the ICTRP. This may highlight implications for further research and help improve the registries. Furthermore, this study will mention the registries and countries that researchers should preferentially investigate, reflecting the top five countries in order of the quantity of registered trials on the ICTRP.

Limitations

The applicability of this study will be limited because the data include only clinical trials registered on the ICTRP. The registry has a representative data set of clinical trials (WHO International Clinical Trials Registry Platform (ICTRP), 2018). However, other, possibly low-quality, registered data of clinical trials may be excluded. For example, trials registered in the South African National Clinical Trials Register (SANCTR) will be excluded (WHO International Clinical Trials Registry Platform (ICTRP), 2018). It is expected that the exclusion of the SANCTR will have an insignificant impact on the overall results. All countries in Africa that join in the African Vaccine Regulatory Forum have agreed to regard the Pan African Clinical Trials Registry (PACTR), which supplies data to the ICTRP, as their primary registry (WHO International Clinical Trials Registry Platform (ICTRP), 2018).

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Author Contributions

All authors (MB, YT, and YK) have contributed to the conception and design of the research. MB was solely responsible for writing the protocol. All authors gave their final approval of the protocol before submission. It has been planned that after the publication of the protocol, MB, YT, and YK will screen the relevant records of the ICTRP, extract data, conduct the data analysis without being blind to the data, and write the manuscript.

Declaration of Competing Interests

Masahiro Banno has received speaker honoraria from Dainippon Sumitomo and travel fees from Yoshitomi Pharmaceutical Industries Ltd. The other authors have no competing interests to declare.

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