Author's response to reviews

Title: Review of the registration of clinical trials in UMIN-CTR from 2 June 2005 to 1 June 2010 - focus on Japan domestic, academic clinical trials

Authors:

Wentao Tang (twtreaher@gmail.com)  
Manabu Fukuzawa (manabu_fukuzawa@hotmail.com)  
Hirono Ishikawa (hirono-tky@umin.ac.jp)  
Kichiro Tsutani (tsutanik@gmail.com)  
Takahiro Kiuchi (tak-kiuchi@umin.ac.jp)

Version: 2 Date: 6 August 2013

Author's response to reviews: see over
Dear Editors,

On behalf of my coauthors, I am submitting the covering letter with a point-by-point description of the changes made to the manuscript entitled “Review of the registration of clinical trials in UMIN-CTR from 2 June 2005 to 1 June 2010 – focus on Japan domestic, academic clinical trials”. We have also uploaded the revised manuscript (all changes tracked and highlighted) and figures to the online submission system of Trials.

First, as the response to the requests of language editing from the editors of Trials and referee 2, we have made our manuscript proofread by the ASCA Cooperation (http://www.asca-co.com/english_site/about/service-policy.html), which is a company specialized in medical translations and proofreading by native English speakers. We have also adjusted the format of the manuscript in accordance with author instructions and the layout in the journal’s template.

Second, we have made the point-by-point revision according to the reviewer’s report from referee 1. The actions and locations for the revisions are provided as follows:

Reviewer’s report

Title: Review of the registration of clinical trials in UMIN-CTR from 2 June 2005 to 1 June 2010

Version: 1 Date: 3 June 2013

Reviewer: Tony Tse

Reviewer’s report:

This manuscript characterizes clinical trials registered at UMIN-CTR during its first five
years of operation and compares them to data sets downloaded from the ICTRP Search Portal and ClinicalTrials.gov. Although UMIN-CTR is an important trial registry (e.g., frequently cited in journal articles in compliance with the ICMJE “obligation to register clinical trials” policy), little has been published about it to date. This manuscript provides the first descriptive overview of the types of registered trials and the degree of overlap with trials conducted in Japan but not registered in UMIN-CTR.

Major Compulsory Revisions

1. Move information about UMIN-CTR and clinical trial registration policies from the Methods section (pp. 6 & 7) to Background. Also in the Background section, please provide more details about the registration policies that affect UMIN-CTR, some of which are currently described in Discussion section and Figure 2 (e.g., “Requirement for the application of Health and Labour Sciences Research Grants (Apr 2007),” “Ethical Guidelines for Clinical Research (Apr 09)”). Consolidating and expanding such information in the Background section and citing later, as appropriate, will give readers more context about the central role UMIN-CTR plays in supporting international and Japanese registration policies.

**Action:** We have moved the details of the registration policies affecting UMIN-CTR from the Discussion section to the Background section (location: paragraph beginning “To improve clinical trials registration in Japan, the Japanese government…”)

With regard to the introduction of UMIN-CTR, we still want to place this in the
Methods section. We feel that the Background section would become too heavy if the introduction of UMIN-CTR is incorporated. We found that the paper on ClinicalTrials.gov by Zarin et al. (2005) also introduced the registry in the Methods section.

2. p. 6. The authors state that they had intended to include all trials registered in UMIN-CTR during its 5 years, but then limited the actual analysis due to “possible differences in trial characteristics caused by different funding sources, and because most registered trials in UMIN-CTR were non-industry funded.” Please elaborate on this justification for limiting the analysis to “academic (non-industry-funded) clinical trials conducted only in Japan” (e.g., versus all trials registered in the first 5 years).

**Action:** First, we have added a subtitle: “focus on Japan domestic, academic clinical trials”.

Second, we have added information for preliminary research to the Background section as follows: “…while 98.2% (3,530/3,595) of registrations in UMIN-CTR are domestic clinical studies (conducted only in Japan).” We have also explained “and the major body of the registrations in UMIN-CTR is constituted by Japan domestic, academic clinical studies” in the same paragraph.

Finally, we have clarified the justification for limiting the analysis to Japan domestic, academic clinical trials in the Background section as follows: “The focus of our analyses was on Japan domestic, academic clinical trials because these studies constitute the major body of all the registrations in UMIN-CTR, and may have
considerably different trial characteristics from industry-funded or global studies. To reflect the main characteristics of the clinical trials registered in UMIN-CTR more precisely, we finally defined the object of our analyses as Japan domestic, academic clinical trials registered in UMIN-CTR in the first 5 years since its inception” (location: paragraph beginning with “More than 2,000 new registrations were received in UMIN-CTR in 2011…”).

3. p. 6. The authors need to explain the significance of research question 3: “How is the accessibility of trials registered in UMIN-CTR by people around the world through WHO-ICTRP?” The ICTRP Search Portal uses data submitted by primary registries/data providers themselves. Even though ICTRP lists JPRN as the data provider (p. 5), doesn’t JPRN obtain its data directly from UMIN-CTR? Why the authors might anticipate any differences in accessibility of trials registered in UMIN-CTR at the WHO ICTRP Search Portal should be explained.

Action: We have clarified the objective of research question 3 in the Background section as follows: “since UMIN-CTR was incorporated into JPRN as a part of the primary registry of ICTRP at 3 years after its establishment, the aspect of whether the clinical trials in UMIN-CTR, especially those trials registered before its incorporation into ICTRP, can be accessed successfully through ICTRP became our concern. Since this issue has not previously been investigated, we analyzed the accessibility of the clinical trials in UMIN-CTR to people around the world through ICTRP” (location:
paragraph beginning with “Moreover, since UMIN-CTR was incorporated into JPRN as…."

Although almost all people believe that all of the data in UMIN-CTR should be accessible from ICTRP, there is no confirmation of this accessibility. Therefore, we performed an analysis to confirm this aspect.

Minor Essential Revisions

1. Check references. For example: a. p. 4. “To address the problems stated above, registration of clinical trials has been proposed as a possible solution since the 1960s” only cites Levine et al. (1974). Note that registration to mitigate publication bias is widely attributed to Simes (1986).


b. p. 4. Add citation for “20-item WHO trial registration dataset” – i.e.,

Action: We have added the link to the webpage as Ref. [13].

c. p. 5. Provide references for Japic-CTI (currently Ref. [21]) and JMACCT (currently Ref. [22]) when mentioned initially.

Action: The references for Japic-CTI (currently Ref. [18]) and JMACCT (currently Ref. [19]) have been moved to where they appear initially in the Background section.

2. Throughout the manuscript. “Registries” is used to describe “records” or “registrations.” For example: p. 5: “More than 2,000 new registries were received in UMIN-CTR in 2011.” Review and replace “registries” with an appropriate term, as necessary.

Action: We have replaced “registries” with “registrations” where appropriate.

3. p. 7. “Reporting trial results in UMIN-CTR is optional…” Please provide additional details (e.g., structure of the UMIN-CTR results database) and a reference for details regarding trial results reporting at UMIN-CTR.

Action: The details of the trial results are provided in the Methods section as follows: “On the other hand, reporting of trial results in UMIN-CTR is optional, and no
results database has yet been established. Although the aspect of whether or not the trial results have been published must be chosen when registering a trial, the URL for published results and detailed trial results in text form are only optional items and are not mandated to be registered [23]” (location: Methods section → Registry → last paragraph).

4. p. 8. “We obtained the full data containing all the registered information of registries [records?] in UMIN-CTR from 2 June 2005 to 1 June 2010.” Please provide the date on which the UMIN center downloaded the registration information for analysis.

**Action:** We have provided the date of download as follows: “We obtained these data from the UMIN Center (downloaded on 18 January 2011), and imported them into an Excel file for screening.” (location: Methods section → Data and screening → first paragraph).

5. p. 9: How were the 15 “items of primary concern” and 13 “items of secondary concern” selected under research question 2? How do these selected 28 items from UMIN-CTR relate to the 20 items WHO Trial Registration Data Set (Version 1.2.1)? (There doesn’t appear to be a simple one-to-one mapping.) Are the definitions for each UMIN-CTR data item available in English? (Reference 16 provides a link to the Simple Glossary page at http://www.umin.ac.jp/ctr/UMIN-CTR_Yougo.htm, which is only available in the Japanese.)
The items of primary concern and secondary concern were decided from interviews and discussions with all the authors of this work. We have clarified in the Methods section that: “According to the local needs for information by Japanese clinicians and researchers, 15 items were analyzed with primary concern and are discussed in this article” (location: Methods section → Research question 2 → first paragraph).

Ref. [23] (Ref. [16] before revision) is a reference for data items in UMIN-CTR. The item names in Ref. [23] are available in English, but the definitions for the items are only in Japanese. We are sorry that there is currently no English reference for these definitions. We have reported this question to the UMIN Center, and they should develop an English version in the future.

6. p. 12. “We searched clinical studies conducted in Japan and registered from 2 June 2005 to 1 June 2010 in ClinicalTrials.gov.” Please clarify the following: (A) Does “conducted in Japan” refer to (1) studies with at least one listed site in Japan or (2) studies that only have sites listed in Japan? (B) Does “registered from” refer to the First Received date (i.e., initial registration at ClinicalTrials.gov)? (C) On what date was information downloaded from ClinicalTrials.gov?

Action: (A) “conducted in Japan” refers to studies with at least one listed site in Japan, and this has clarified in the manuscript where necessary.
(B) “registered from” refers to the First Received date in ClinicalTrials.gov, and this has been clarified in the Methods section (location: Methods section → Research question 4 → first paragraph).

(C) the data from ClinicalTrials.gov were downloaded on 29 November 2012. This has been clarified in the Methods section (location: Methods section → Research question 4 → first paragraph).

7. p. 13. “First 3,530 trials… were extracted. Then, we excluded industry-funded trials…” Replace “trials” with “studies” because these datasets include observational studies, which have not yet been excluded.

Action: The word “trials” has been replaced with “studies”.

8. Table 3. (A) For category 10 (“Type of intervention”), indicate that the number of trials include records that specify at least one of the listed interventions (i.e., values within this category are not mutually exclusive). (B) Elaborate on the definition of “Published” (e.g., journal article only?) and “Partially published” under category 13 (“Publication of results”). (C) Footnote #2: Define “last follow-up date” (e.g., same as study completion date or “last patient last visit”?)

Action: (A) We have clarified “values within this category are not mutually exclusive” as footnote #1 for Table 3
(B) “published” means that the final trial results are published regardless of the kind of publication form (journals, academic conferences, webpages, etc.). “Partially published” means that only the results of interim analyses are published. This has been clarified as footnote #3.

(C) footnote #2: “last follow-up date” refers to “date of last patient’s final visit”. This has been clarified in footnote #2.

9. p. 20. “Some obvious differences in the characteristics of registered clinical trials between UMIN-CTR, ICTRP and ClinicalTrials.gov were found.” Note that a limitation of this comparison is that the UMIN-CTR dataset consists of non-industry funded trials, whereas nearly a third of the data analyzed in Viergever & Ghersi (2011) and Califf et al. (2012) consisted of industry-funded trials (34% and 32%, respectively).

**Action:** We have added an explanation to the Discussion section as follows: “To explain the above differences in the trial characteristics between UMIN-CTR and ICTRP/ClinicalTrials.gov, it should be considered that all industry-funded trials were excluded from our analysis of UMIN-CTR, but included with a prevalence of 44.0% in the analyses of both ICTRP and ClinicalTrials.gov” (location: Discussion section → Research question 2 → fourth paragraph).

We checked the papers by Viergever & Ghersi (2011) and Califf et al. (2012) again, and found that the prevalences of industry-funded trials were both 44.0%.
Therefore, we wonder whether 34% and 32% refer to the prevalences of industry-sponsored trials.

10. Fig 1. Add “(n=2,779)” to the bottom box (“Clinical trials for research question 1 and 2”). Suggest indicating that the top box (“Registries [Records?] in UMIN-CTR from…”) serves as the sample for research question 3.

Action: We have added “clinical trials for research question 3” to the top box. The information of “(n=2,779)” is already in the bottom box.

11. Fig 2. Indicate the total number of trials represented to the title or legend. Provide citations for each of the four events listed.

Action: We have added the total number of trials (2,779) to the legend for Figure 2. Citations for each of the four events have also been added.

12. Fig 3. Add “by specialty” to the title to read: “Disease-classified registration number *by specialty* and control type”). Indicate the total number of trials represented (n=2,779?). Suggest highlighting or otherwise drawing attention to the 6 subcategories >50% discussed in the text.

Action: We have added “by specialty” and the total number of trials represented (n=2,779)
to the legend of Figure 3. We have highlighted the six subcategories with a prevalence of <50% for using an active control in pink.

Discretionary Revisions

1. p. 7. “…registration in Japanese is optional” at UMIN-CTR. But research question 4 addresses “accessibility of trials … in the Japanese language. (p. 6)”. Stating the number (%) of UMIN-CTR records that actually provide information in the Japanese language would be helpful background information for readers.

Action: According to the UMIN-CTR’s glossary

(http://www.umin.ac.jp/ctr/UMIN-CTR_Yougo.htm; only available in Japanese), we have added the following information to the Methods section: “According to the UMIN-CTR’s principle, if Japan is included in the countries of recruitment for a study, registration in both English and Japanese is required. Otherwise, registration in English only is acceptable” (location: Methods section → Registry → first paragraph).

Moreover, we have added a sentence to the Discussion section as follows: “On the other hand, if a clinical trial is conducted in Japan and intended to be registered in UMIN-CTR, in accordance with the UMIN-CTR’s principle introduced in the Methods section, it must be registered not only in English but also in Japanese” (location: Discussion section → Research question 4 → first paragraph).
2. p. 7. Clarify that, while FDAAA was enacted in September 2007, the submission of summary results data did not become mandatory until September 2008 – one year after enactment.

**Action:** We have clarified this issue in the Methods section as follows: “With respect to the reporting of trial results in a clinical trials registry, Section 801 of the Food and Drug Administration Amendments Act (FDAAA; enacted since September 2007) has mandated the submission of summary result data for certain trials of drugs, biologics, and devices to ClinicalTrials.gov (generally not later than 1 year after the Completion Date) since September 2008 [25].” (location: Methods section → Registry → third paragraph).

3. Table 2. Note that “NCT*” may be less precise than “NCT0*” as an “Identifiable string in study ID” for ClinicalTrials.gov. As of 3 June 13, “NCT*” retrieved 356 records and “NCT0*” retrieved 322 records at the ICTRP Search Portal.

**Action:** We have replaced “NCT” with “NCT0”. Although we used “NCT” in our search of UMIN-CTR for research question 4, we checked all the hits to see whether they were included in the dataset downloaded from ClinicalTrials.gov. Therefore, the final results for research question 4 are not considered to be changed by replacing “NCT” with “NCT0”.

For a general search strategy, “NCT0” may be more precise than “NCT”, so we
4. p. 17 and Table 4. Not clear that highlighting UMIN-registered trials by funder type is useful. The Background section established that over 92% of studies registered in “UMIN-CTR are academic (non-industry-funded) clinical studies. (p.5)” In fact, industry-funded studies were excluded from the samples analyzed for research questions 1 and 2 for this reason. Given that few trials registered in UMIN (and the 2 other Japanese trial registries) are funded by industry, it is difficult to interpret the significance of these numbers.

**Action:** In Table 4, we mainly want to show the prevalence of registration in Japanese registries according to each funder type. Providing the numbers of registrations in UMIN, Japic, and UMIN/Japic, respectively, in each funder category may help toward understanding of the different characteristics of registration in UMIN and Japic. We think this may be useful information for some Japanese and foreign researchers.

5. p.19. Do the authors attribute the increase in registration starting in July 2008 to the revised ICMJE policy, in part. Do they have any data supporting this as a primary factor (e.g., increase in percentage of “explanatory/pragmatic” studies registered at UMIN-CTR)?
We have calculated the ratio of explanatory/pragmatic studies registered in UMIN-CTR, using the data for 1 year before and after the revised ICMJE policy (July 2007 to June 2008 versus July 2008 to June 2009). We found there was actually an increase in the ratio of explanatory/pragmatic studies from 26.3% (July 2007 to June 2008) to 34.5% (July 2008 to June 2009). However, we noticed that for nearly half of the registered trials, the registration of explanatory/pragmatic is missed (it is only an optional item for registration). In addition, as we have mentioned in the Discussion section, the registration of explanatory/pragmatic is based on the registrant’s own judgments. Therefore, the reliability of such data remains in question, and the interpretation may be difficult.

We only took the revised ICMJE policy as one of the possible factors influencing the registration trend. Other possible factors, such as the New 5-Year Clinical Trial Activation Plan issued by the Japanese government and the formation of the Japan Primary Registries Network (JPRN) as a WHO ICTRP Primary Registry in October 2008, were also mentioned in the Discussion section. All of these three factors were clarified in Fig. 2.

6. p. 23. “The reason why study ‘C000000060’ were [sic] not found in the search on ICTRP remains unclear.” Have the authors contacted JPRN or ICTRP to determine what happened to this record? Note that this UMIN record was cited by Atagi et al (2012; Lancet Oncol): “This study is registered with UMIN Clinical Trials Registry, number C000000060, and ClinicalTrials.gov, number NCT00132665.” (see
Action: We made an enquiry for this issue to the technician of UMIN-CTR. However, he was also not very clear about the reason why study ‘C000000060’ was missed. An enquiry to ICTRP regarding this issue may be needed in the future.

Third, we have asked about the issue of competing interests in the cover letter submitted on 2 May 2013, however, we have got no response yet. Three authors of this paper (Wentao Tang, Manabu Fukuzawa and Kichiro Tsutani) are affiliated with Department of Drug Policy & Management, Graduate School of Pharmaceutical Sciences, the University of Tokyo. This department is endowed with Towa Pharmaceutical Co., Ltd. (a Japanese pharmaceutical company specialized in generic drugs). Although the three authors don’t think they have any competing interests in this paper after reading Trials’s instructions for authors carefully, we still want to ask for your opinion in order to make sure whether any potential competing interests should be declared. All the other authors declare that they have no competing interests in this research work. Provisionally we reported “All the authors declare they have no competing interests” in the manuscript, however, this may be revised based on your opinion.

Finally, we really appreciate the precious opinions about our manuscript from the editors of Trials and two peer reviewers. We have tried our best to improve the quality of the submitted manuscript as you expected. Hope to hear from you soon.
Best regards.

Yours sincerely,

Tang Wentao