Reviewer's report

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

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Reviewer: Tony Tse

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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.

2. p. 6. The authors state that they had intended to include all trials registered in UMIN-CTR during its first 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).

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.

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

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.

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.

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.

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.)

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?

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.

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”?)

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).

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.

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

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.

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.

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.

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.

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.

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)?
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 http://www.ncbi.nlm.nih.gov/pubmed/22622008)

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests.