CONTRIBUTED SESSION 18

ALL-CAUSE MORTALITY REPORTING IN CLINICALTRIALS.GOV COMPARED TO PUBLICATIONS.

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Description of Session:

Background: Incomplete reporting of deaths in a clinical trial can distort the evidence base for a studied treatment. Sponsors reporting clinical trial results information to ClinicalTrials.gov can include the frequency of deaths due to any cause in a standardized all-cause mortality (ACM) table. Prior to the table's introduction in January 2017, deaths were reported in different places in the ClinicalTrials.gov record. In this study, we aimed to assess the extent of mortality reporting in the new ACM table in ClinicalTrials.gov and compare this reporting to corresponding publications.

Methods: On March 1, 2018, we downloaded 1902 clinical trial records with results first posted in ClinicalTrials.gov between April 1 and June 30, 2017. Among a 20% random sample (380 records), we identified records with both published results in PubMed and posted ACM table information on ClinicalTrials.gov. Of these, we assessed whether ACM information reported in the two sources were concordant (i.e., same number of deaths, including by arm) or discordant (i.e., different numbers of deaths). Authors manually reviewed each eligible publication to categorize the reporting of deaths in the study. If more than one results publication was found, the one published earliest was used.

Results: Of 380 trials in our sample, 43.7% (166/380) had a results publication in PubMed (Figure 1). Of these, 47 trials had ACM table information in the ClinicalTrials.gov record - 26 trials with 0 deaths and 21 trials with ?1 deaths (Figure 1). Of those trials with 0 deaths in the record, 96% of corresponding publications (25/26) did not provide a specific death count, although 7 publications noted there were no adverse or serious adverse events; 1 publication specifically stated there were 0 deaths (Table 1). Of those trials with ?1 deaths, 61.9% (13/21) of publications were concordant, 23.8% (5/21) were discordant, and 14.3% (3/21) did not provide specific death counts (Table 1). The ClinicalTrials.gov record included more deaths than the publication for 3 of the discordant trials, including one study with 30 deaths in the record compared to 1 death in the publication. For the other 2 discordant trials, the total number of reported deaths was identical, but the specific arm information was inconsistent.

Conclusion: For those trials in our sample with results reported in both ClinicalTrials.gov and a publication, we found 60% (28/47) of trials reported a specific number of deaths (0 or ?1) in the ClinicalTrials.gov record but no specific number of deaths in the corresponding publication. This gap was most pronounced when the ClinicalTrials.gov record noted 0 deaths. The ClinicalTrials.gov record listed deaths in 3 trials that were not reported in the corresponding publication; there were no instances in which deaths were listed in the publication but not included in ClinicalTrials.gov. These findings suggest that standardized ACM reporting in ClinicalTrials.gov helps ensure that more complete mortality information is publicly available, including by explicitly stating when no deaths occurred.

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CONTRIBUTED SESSION 18

PROBLEMATIC REGISTRATION, RANDOMIZATION, AND ANALYSIS IN RANDOMIZED CONTROLLED TRIALS: SYSTEMATIC REVIEW OF OBSTETRICS AND GYNAECOLOGY STUDIES FROM AN AFRICAN COUNTRY (2013-2018)

Wentao Dr. Li
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Description of Session:

Background: Randomized controlled trials (RCTs) provide the most reliable information to guide clinical practice. In the view of the rapidly growing number of RCTs and a high proportion of RCTs yielding positive findings, it is critical to ensure the quality and data integrity of RCTs. Traditional assessment tools for RCTs are confined to the risk of bias, but do not assess RCTs regarding registration, randomization, and statistical analysis performed. As a sample to understand the prevalence of problematic registration, randomization, and analysis in RCTs, we systematically reviewed RCTs from one country published in top journals of Obstetrics and Gynaecology in the last five years.

Methods: We systematically identified RCTs from one African country published in the top 50 (Scimago Journal Rank) journals of Obstetrics and Gynaecology between 2013 and 2018. We checked the authenticity of trial registration. We calculated the probability of random sampling for baseline variables using Monte Carlo analysis (100,000 simulations), a screening tool that could indicate the presence of non-random data in RCTs from summary statistics for baseline variables. We then reviewed the statistical methods used in RCTs. Critical statistical issues were defined as follows: no description of the statistical method, sampling or conceptual error, and inconsistency between specified and actual statistical methods. Other statistical issues were defined as less critical ones. For the comparison of continuous variables using independent t test and one-way ANOVA, we computed p-values with corresponding mean, standard deviation, and the number of patients reported in papers. Harley's F test was performed to test the equality of variances before t test. We computed p-values with crosstabs in papers for the comparison of categorical variables that used univariable analysis. Odds ratios and risk ratios were also calculated in the case that they were reported. We evaluated the consistency between computed results and those published.

Results: We identified 52 RCTs. The proportion of studies with registration was 61.5% (32/52), among which 50.0% (16/32) registered over 6 months after the start of recruitment. The proportions of studies that had baseline variable(s) with a probability of random sampling lower than 0.1 and 0.05 were 37.3% (19/51) and 13.7% (7/51), respectively. Lack of appropriate registration was positively associated with problematic randomization (OR=3.5, 95% CI: 0.8-14.3). Regarding statistical analysis, 21.2% (11/52) had critical statistical issues and 73.1% (38/52) had less critical issues. For baseline characteristics, 80.8% (42/52) of RCTs performed statistical tests between arms to demonstrate the goodness of randomization, among which the proportions of studies with not repeatable tests for continuous and categorical variables were 68.8% (22/32) and 37.1% (13/35), respectively. The statistical results of primary outcome were not repeatable in 25.7% (9/35) of RCTs. The proportion of RCTs with not repeatable outcome(s) was 53.3% (24/45).

Conclusions and implications: In this systematically derived sample of RCTs, possible faulty registration, randomization, and statistical analysis are prevalent and likely associated. We suggest rigorous monitoring and comprehensive assessment during peer-review to ensure the reliability of RCTs. Methodological support should be available to some clinicians who conduct RCTs in this country.

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CONTRIBUTED SESSION 18

EVOLVING PRACTICES OF RESULTS REPORTING IN CLINICALTRIALS.GOV

Kehao Zhu
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Description of Session:

BACKGROUND: It is ethical and professional to disclose results of clinical trials to the public. In 2007, US Congress passed the Food and Drug Administration Amendments Act (FDAAA) that requires Applicable Clinical Trials (ACTs) to submit basic results to ClinicalTrials.gov (CT.gov) database independent of journal publication or conference presentation in timely fashion (normally within 1 year after primary completion date). However, the compliance was poor (Anderson et al. 2015). The final rule for FDAAA 801 was issued in 2016 to further clarify the results reporting requirements with the effective date on January 18, 2017. The goal of this project is to examine the results reporting in CT.gov over the past decade.

METHODS: We analyzed trials registered in CT.gov that completed or terminated in or after 2008 and defined likely applicable clinical trial (LACT) status for individual trial based on public available information in CT.gov. We plotted the cumulative percentages of trials that reported results after the primary completion date group by LACT status. We calculated the proportion of trials that reported results within 12 months interval group by LACT status and year of completion. Among the trials with results reported, the key result elements, including outcome measures, adverse events and baseline characteristics, were examined for completeness and interpretability.

RESULTS: Of 130,762 trials completed or terminated between 2008 and 2017, 26% of trials were flagged as LACT. Overall, 59% of LACTs and 15% of non-LACTs had reported results to date. For LACTs, the percentages of trials submitted results to CT.gov within one year after completion increased from 10% among trials completed in 2008 to 29% among trials completed in 2017. On the contrary, for non-LACTs, the percentages increased from 5% to 6% during the same period. The result elements reported on CT.gov became more informative regardless of the LACT status over the past decade, including specifying methods for adverse events collection, reporting all-cause mortality, summarizing the ethnicity / race background etc. More details and visualization of results will be presented at the meeting.

DISCUSSION: Since CT.gov released its results database in 2008 and the final rule was issued in 2016, reporting results at CT.gov has been gradually becoming a more popular practice, which is an important next step after the prospective trial registration and a prior step to sharing individual participant data (IPD). We hope the continuing improvement in universal results reporting practice brings more values to clinical trials for the societal advancement.

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DUPLICATE PATTERNS AND DUPLICATE PUBLICATION BIAS AMONG CHINESE-SPONSORED DRUG-RELATED RANDOMIZED CONTROLLED TRIALS

Yuanxi Jia
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Description of Session:

Objective Our study aims to evaluate the duplicate pattern and duplicate publication bias among Chinese-sponsored drug-related randomized trials (CS-D-RCTs). We hypothesized (1) the most prevailing duplicate pattern among CS-D-RCT was translation without cross-reference; (2) CS-D-RCTs with positive results are more likely to have duplicates than the ones with negative results.

Data source Trial registries: Chinese Clinical Trial Registry (ChiCTR), ClinicalTrials.gov (CT.gov), and Drug Clinical Trial Registry Platform (DCTRP). English bibliographic databases: PubMed, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL). Chinese bibliographic databases: the China National Knowledge Infrastructure (CNKI), the Wanfang Database (Wanfang), the VIP Information (VIP), and the Chinese Biomedical Literature Database (CBM).

Data collection We conducted a retrospective cohort study among CS-D-RCTs which were registered in the three trial registries and published as journal articles. A CS-D-RCT was defined as an RCT using the following criteria: (1) one of the experimental interventions is drug or biological; (2) at least one sponsor locates in the Mainland China; and (3) at least one recruitment center locates in the Mainland China. We retrieved eligible records of CS-D-RCTs conducted from January 1, 2008 to December 31, 2013 from the trial registries and mapped them to journal articles indexed in the seven bibliographic databases. The searching strategy was listed in (Table 1). The criteria to match registry records with corresponding articles were listed in Table 2.

Analysis plan The journal articles corresponding to one CS-D-RCT form a cluster. The main article of a CS-D-RCT was defined as the one with the largest sample size or the earlier publication date. A duplicate was an article overlapped with a previous one without cross-reference. We compared the participants, interventions, and outcomes between the main article and the duplicates to determine the duplicate pattern listed in Table XX. A CS-D-RCT was considered positive if at least one of the primary outcomes was positive. Logistic regression models were used to evaluate the duplicate publication bias adjusting for covariates such as sponsor type (domestic vs. international), sample size (<100 or ?100), number of recruitment centers (single-center vs. multi-center), and funding source (industry vs. non-industry).

Result There were 924 CS-D-RCTs registered in the three registries, 417 (51%) were published, 83 (19.8%) have at least one duplicate. Among the 550 journal articles, 133 (24.2%) were duplicates. Among the 83 clusters with duplicates, 26 were translations without cross-reference; 17, 8, 6 were SALAMI publications with a subset of outcomes, interventions, and participants from the main article, respectively; 14 and 6 were IMALAS publications with increasing sample size and interventions, respectively. Adjusting for covariates, the odds of having duplicates among CS-D-RCTs with positive results were 5.71 (95%CI: 4.34-6.67) times the odds among CS-D-RCTs with negative results.

Conclusion The three prevailing duplicate patterns among CS-D-RCTs are translations, SALAMI, and IMALAS publications. CS-D-RCTs with positive results were more likely to have duplicates. Systematic reviewers should be alert of the possible duplicates when including Chinese-sponsored RCTs.

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