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Completeness of Clinical Evidence Citation in Trial Protocols: A Cross-sectional Analysis

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Rationale/ Problem Statement	• Clinical trial protocols do not always provide a comprehensive and systematic evidence citation of previous research. • Such incompleteness of evidence in trial protocols causes a few concerns: ✓ Authorities such as the **ethics committee** will be difficult to evaluate the needs, risks, benefits, and ethical issues for a proposed study (1, 2). ✓ **Researchers** are unable to appreciate the significance of the trials. ✓ The practice of **healthcare providers** is not informed by clinical trials. ✓ Redundant trials may lead to waste of resources, causing financial implications to **policymakers, funders, and the public.** ✓ Unnecessary clinical trials may also expose **study participants** to unnecessary research burdens (3).
Study Objectives	• **Primary objective**: To assess the extent to which clinical trial protocols reflected all published and ongoing clinical trials addressing similar clinical hypotheses. • **Secondary objective**: To determine whether clinical trial protocols preferentially cite studies that are randomized, larger, or more similarly designed.
Methods	• **Study design**: Cross-sectional cohort study. • **Search strategies**: Firstly, clinical trial protocols published between 1st January 2018 and 23rd March 2020 was randomly selected from Clinical-Trials.gov database. Secondly, these clinical trial protocols were classified into industry- and non-industry-sponsored trials. Thirdly, using PubMed and ClinicalTrials.gov databases, reference searches were conducted to determine the extent to which the selected clinical trial protocols cited published and ongoing trials with identical intervention-indication pairings. • **Statistical analysis**: The primary outcome (comprehensiveness of citation within clinical trial protocols) was assessed via a) The proportion of clinical trial protocols that cited at least one published and/or ongoing trial of the same intervention-indication pairing; b) Median citation ratio, which was determined by dividing the number of cited trials by the number of citable trials. The secondary outcome (preferential citation) was assessed using Fischer's exact test or Mann-Whitney Test.
Results	• A total of 101 clinical trial protocols were selected from Clinical-Trials.gov database (50 industry-sponsored trials vs 51 non-industry-sponsored trials). • None of the protocols (from both industry- and non-industry-sponsored trials) mentioned that systematic search was conducted for published or ongoing trials of the same drug-indication pairing.

	Primary Outcome	• Of the 50 industry-sponsored trials, 23 (46.0%) cited at least one published trial and 33 (66.0%) cited at least one ongoing trial. Of these, 7 (30.4%) trial protocols did not cite any of the published trials involving the same intervention-indication pairing and 10 (30.3%) protocols did not cite any ongoing trials of the same intervention-indication pairing. The median citation ratio was 0.67. • Of the 51 non-industry-sponsored index trials, 28 (54.9%) cited at least one published trial and 19 (37.3%) cited at least one ongoing trial. Of these, 5 (17.9%) trial protocols did not cite any of the published trials involving the same intervention-indication pairing and 14 (73.7%) protocols did not cite any ongoing trials of the same intervention-indication pairing. The median citation ratio was 0.50. • Of the 73 trial protocols (both industry- and non-industry-sponsored trials) for which cited at least one citable published or ongoing trial involving the same intervention-indication pairing, 56.2% omitted at least one relevant trial and 41.1% did not cite the majority of easily accessible trials. Approximately one in five protocols (21.9%) did not cite any clinical trials that were captured in the reference searches.
	Secondary Outcome	• The selected clinical trial protocols did not preferentially cite trials that were randomized (83.3% of cited studies versus 66.7% of citable studies, p = .23) or trials that had larger sample sizes (median sample size of cited studies: 132.5 versus that of citable studies: 51.0, p = .08). • The selected clinical trials also did not have greater preference to cite studies with more similar design characteristics, including use of the same comparator (60.0% of cited studies versus 46.7% of citable studies, p = .44), same dose (83.3% of cited studies versus 80.0% of citable studies, p > .99), same disease stage (96.7% of cited studies versus 90.0% of citable studies, p = .61), or indication subpopulation (80.0% of cited studies versus 93.3% of citable studies, p = .25).
Conclusion	• Clinical trial protocols undercite relevant trials and do not document systematic searches for relevant clinical trials. • However, there is no preferred citation seen in both industry- and non-industry-sponsored trials.	
Limitations/ Caveats	• The reference searches were only performed using PubMed and ClinicalTrials.gov databases. A more exhaustive search is required using different databases and search strategies. • Some references may be excluded from the selected clinical trials based on scientific justifications (e.g., used irrelevant comparators, had different study designs). The exclusion of such irrelevant studies does not necessarily translate into incompleteness of evidence.	

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