Data reproducibility issues on evidence synthesis of adverse events associated with HER2-targeted antibody–drug conjugates

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Approximately 85% systematic reviews and meta-analyses of adverse events have been shown to have serious data reproducibility issues in terms of reproducibility of data extraction,\textsuperscript{1} making the corresponding meta-analytical results and associated conclusions questionable and unreliable. Therefore, it is important to figure out whether or not there are also data extraction errors in a new published systematic review and meta-analysis on adverse events (AEs), such as the meta-analysis of AEs of HER2-targeted antibody–drug conjugates (ACDs) presented recently.\textsuperscript{2}

After careful scrutiny of the original data sources of all 13 randomized controlled trials involved, we found numerous data extraction errors in Fu’s meta-analysis,\textsuperscript{3} rendering their meta-analysis less reliable.

First, there are many numerical errors in Fu’s Table 1.\textsuperscript{4} To name only a few, the correct number of all-grade AEs, grade ≥3 AEs, and serious AEs in Verma 2012\textsuperscript{5} were 470, 200, and 76, respectively, rather than 474, 233, and 91 used for Fu’s meta-analysis.\textsuperscript{2} Furthermore, the correct number of discontinuation due to AEs in Thungappa et al.\textsuperscript{6} was zero rather than 3 used for Fu’s meta-analysis.\textsuperscript{2} Also, the accurate number of grade ≥3 AEs in Tolaney 2021\textsuperscript{7} should be 61 rather than 62 used.

Second, Fu and colleagues\textsuperscript{2} failed to distinguish between treatment-emergent adverse events (TEAEs) and drug-related TEAEs in their Table 1. In the study by Cortés 2022 (Cortés’ Table S5),\textsuperscript{8} in trastuzumab deruxtecan (T-DXd) group, TEAEs for all-grade AEs, grade ≥3 AEs, serious AEs were reported to be 256, 134, 49, respectively, and drug-related TEAEs for all-grade AEs, drug-related grade ≥3 AEs, drug-related serious AEs were 252, 116, 28, respectively; however, the authors of the systematic review extracted the number 252 (drug-related TEAE), 134 (TEAE), 49 (TEAE). Moreover, in trastuzumab emtansine (T-DM1) group in the Cortés’ Table S5,\textsuperscript{8} TEAEs for all-grade AEs, grade ≥3 AEs, serious AEs, discontinuation due to AEs were reported to be 249, 126, 47, 19, respectively, and drug-related TEAEs for all-grade AEs, drug-related grade ≥3 AEs, drug related serious AEs, discontinuation due to drug-related AEs were 226, 104, 16, 13; however, the authors of the systematic review extracted the data of drug-related TEAEs instead of TEAEs, making the data of TEAEs extracted from the study by Cortés 2022\textsuperscript{8} inconsistent highly with those abstracted from the other randomized controlled trials included.

Third, many of their extracted data (in their Table 1)\textsuperscript{2} cannot be reproduced from all original sources of corresponding references. For example, the number of serious AEs in Perez 2019\textsuperscript{9} and number of all-grade AEs in Krop 2017\textsuperscript{10} cannot be found in all available sources of original literature\textsuperscript{9,10}; however, Fu et al.\textsuperscript{1} used 164 and 371, respectively, in their meta-analysis. Moreover, there was no information on grade ≥3 AEs in the original report of Thungappa et al.;\textsuperscript{6} however, Fu et al.\textsuperscript{1} claimed the number to be 20. Also, the number of all-grade AEs in Tolaney et al.\textsuperscript{7} was not reported; however, Fu et al.\textsuperscript{1} claimed the number to be 383.

Other than these data extraction errors identified in the extraction of adverse events from randomized controlled trials included in the systematic review, a lot of information pertaining to study types in Fu’s Table 1\textsuperscript{2} was wrong, which should be specified to be a randomized controlled trial, a single-arm trial, or others rather than a “Yes” or “No”. Overall, we have examined all the 13 randomized controlled trials involved in their systematic review and found remarkable data reproducibility issues, necessitating clarifications and a further self-scrutiny of the other data obtained from the 24 single-arm trials included.

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Abbreviations: ACDs, antibody-drug conjugates; AEs, adverse events; HER2, human epidermal growth factor receptor 2; TEAEs, treatment-emergent adverse events

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Declaration of interests
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