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Obtaining confidential protocols to increase the completeness and accuracy of risk of bias assessments for RCTs: an example from recombinant human bone-morphogenetic protein-2 (rhBMP-2) for spinal fusion

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Background: Risk of bias assessment is an integral part of a systematic review. The Cochrane risk of bias tool covers selection, performance, detection, attrition, and reporting biases.[1] Trials are classed as having "high", "low", or "unclear" risk of bias. The ability to assess a trial confidently as having a "high" or "low" risk of bias is often hindered by poor reporting of methodology in publications.

Objective: To explore whether access to trial protocols provides more definitive assessments of risk of bias than use of publications and conference abstracts.

Methods: As part of a systematic review and meta-analysis investigating the effectiveness of rhBMP-2 in spinal fusion, we conducted risk of bias assessments for 12 published RCTs.[2,3] We compared judgements about selection bias, performance bias, and detection bias for each trial based on information from three sources: (1) trial publications and abstracts; (2) publicly available summary protocols and; (3) detailed confidential trial protocols. Original detailed (in this case confidential) trial protocols were made available to us by the manufacturer of the product or through contacting study authors.

Results: Eleven RCTs were conducted by the manufacturer of rhBMP-2, and one was conducted independently. When confidential trial protocols were used, 45 of 48 risk of bias judgements were definitive ("low" or "high"). Risk of bias assessment based on publications and abstracts resulted in 28 of 48 definitive judgements (Figure 1). This was due to non-reporting of randomisation and allocation concealment details in the publicly available sources (Figure 2). Publicly available protocols from trial registers produced no definitive judgments; the risk of bias was judged to be "unclear" for all trials across all domains.

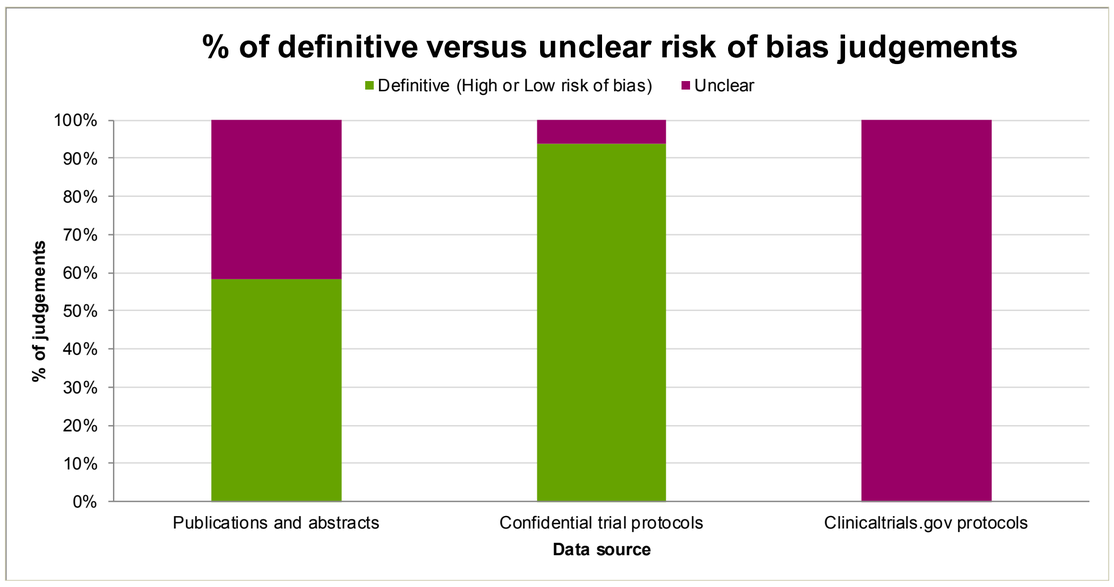

Figure 1: Proportion of definitive versus unclear risk of bias judgements by data source

Conclusions: Reviewers can reduce uncertainty in risk of bias judgements by obtaining detailed trial protocols either from journals or directly from investigators or sponsors. Protocols exclusively from trial registers are unlikely to be adequate for this purpose.

References:

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3. Simmonds MC, Brown JV, Heirs MK, Higgins JP, Mannion RJ, Rodgers MA, Stewart LA. Safety and Effectiveness of Recombinant Human Bone Morphogenetic Protein-2 for Spinal Fusion: A Meta-analysis of Individual-Participant Data. *Ann Intern Med*. 2013;158(12):877-89.

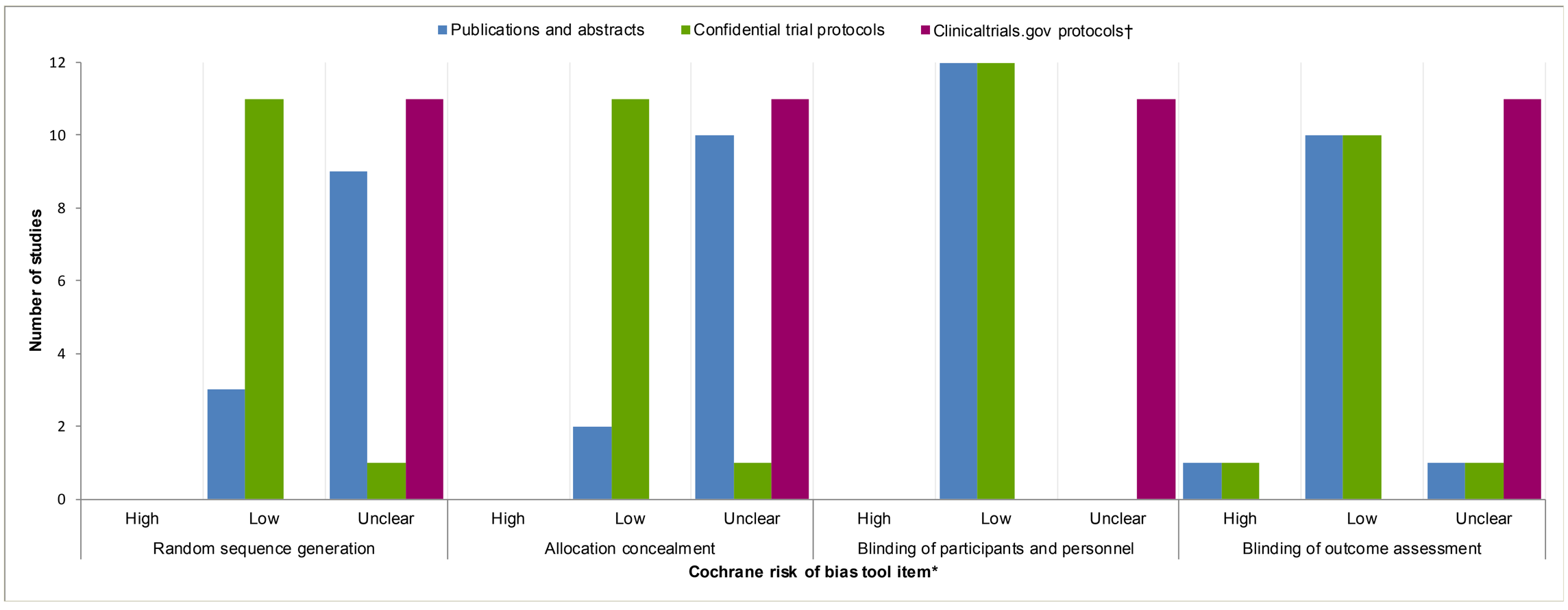

Figure 2: Risk of bias judgements based on three different data source
*Items on withdrawals and reporting of outcomes were not applicable to protocols † A clinicaltrials.gov protocol was unavailable for one trial

This research was funded by the Yale University Open Data Access project. The views expressed in here are those of the authors and not necessarily those of the funders.

CRD is funded by the National Institute for Health Research, England; the Department of Health, Public Health Agency, Northern Ireland; and the National Institute for Social Care and Health Research, Welsh Assembly Government.