

What to do with a clinical trial with conflicts of interest

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Financial considerations, personal conviction and concerns about academic careers may influence how research is designed, conducted and reported.¹ This has recently been highlighted in the case of harms from transvaginal mesh devices and cases of research misconduct where pressure to ensure funding and academic prestige have compromised science.^{2–4} Less dramatic examples are the overinterpretation of study findings or downplaying of harms.^{5,6} Such practices may be caused by conflicts of interest which can be defined as circumstances that create a risk that professional judgement or actions regarding a primary interest will be unduly influenced by a secondary interest.¹

Concern for conflicts of interest are particularly important in clinical trials, as trials play a central role in clinical practice, by providing the basis for regulatory drug and device approval and by producing evidence to guide clinical decision-making and clinical guideline recommendations.¹ About 40% of clinical trials and 70% of drug trials are commercially funded, and a similar proportion of drug trials have authors with industry ties, though there is large variation across medical specialties.^{7,8} Both industry funding and investigator ties are associated with more favourable trial outcomes^{8,9} and cases revealing ‘spin’ and reporting biases in industry trials have been described.¹⁰

There is wide debate about how associations between financial conflicts of interest and favourable trial outcomes should be interpreted.^{9,11} Some have argued that there is more pronounced bias in the estimated treatment effects generated by trials with conflicts of interest, while others have argued that this association may be explained by underlying differences in the type of hypotheses tested and the design used in such trials compared with independent trials, for example, differences in choice of participants, comparators or outcomes.⁹

In addition, independent academic trials that are free from commercial influence are not necessarily problem free. Investigators may have other non-financial conflicts of interest, for example, strong specialty interests or personal beliefs¹² and this may shape how trials are designed, analysed or reported. Accordingly, disclosure of both financial and non-financial conflicts of interest is considered important by journals^{1,13} and trials with disclosed conflicts are generally perceived as being less reliable by journal readers.¹⁴

It is currently unclear how disclosed conflicts of interest should be most appropriately interpreted when appraising trial reports—either

as reader of a journal article or in the context of conducting a systematic review. Roseman and colleagues found that only 2 of 29 non-Cochrane systematic reviews of drug trials reported trial funding sources, and none of the reviews included information on trial authors’ conflicts of interest.¹⁵ Another study reported that around 30% of Cochrane reviews incorporated trial funding or author conflicts of interest directly in the risk of bias assessment.¹⁶ However, the Cochrane Handbook discourages this practice as any bias from conflicts of interest should already be captured by the domains included in the Cochrane Risk of Bias Tool (eg, selective reporting).¹⁶ Nevertheless, there is currently little practical guidance for how to tackle conflicts of interest and there is therefore a clear need for a broader consensus on how information on trial funding and authors’ conflicts of interest should be addressed in systematic reviews.

In 2015, members of the Cochrane Bias Methods Group, responsible for updating the Cochrane risk of bias tool, agreed that further guidance was needed and assembled a group to develop this. The group includes researchers with experience in trial and systematic review methodology, industry involvement, journal editors, as well as experts in conflicts of interest research. The aim is to develop a Tool for Addressing Conflicts of Interest in Trials (TACIT) to help systematic review authors address the potential influence of conflicts of interest in their review.

TACIT facilitates gathering and processing information about conflicts of interest which may be used to: (1) conduct risk of bias assessment of an individual trial; (2) assess risk of bias due to missing results in a meta-analysis; (3) as a guide for secondary meta-analyses (subgroup or sensitivity analyses) and (4) inform reflections on variability and applicability of meta-analytical result.¹¹ TACIT development is underpinned by a systematic review of how critical appraisal tools address conflicts of interest and by a survey and qualitative interview study of experienced trialists. TACIT is planned to be pilot tested by expected end users. The framework of TACIT is also included in the chapter on bias and conflicts of interest in the upcoming version of the Cochrane Handbook.¹⁷ Updates on tool development can be found on the TACIT website (www.tacit.one) and the tool is expected to be released in 2020. The tool is intended primarily for systematic review authors but may

also be useful for peer reviewers, editors, guideline authors or other readers of trial reports.

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Competing interests All authors are members of the TACIT steering group. We declare that we have no other competing interests.

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