# Tool for Addressing Conflicts of Interest in Trials (TACIT) - background and rationale

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# Main themes

- Introduction to Conflicts of Interest in trials
- Debate about commercial funding as source of bias
- Challenges in dealing with conflicts of interests in trials included in Cochrane Reviews
- The proposed way forwards: TACIT

# Conflicts of interest in trials

The Institute of Medicine *(2009)* defined conflicts of interest as: *"a set of circumstances that creates a risk that professional judgment or actions regarding a primary interest will be unduly influenced by a secondary interest"*

- Industry funding
  - 40% of trials in general, 69% of drug trials
- Author financial conflicts of interest
  - 57% of trials in general, 68% of drug trials
- Author non-financial conflicts of interest
  - 2% of trials in general

*Ahn BMJ 2017*
*Hakoum BMJ Open 2017*
*Hakoum J Clin Epidemiol 2017*

# Conflicts of interest and trial outcomes

## Cochrane review on industry sponsorship – *Lundh CDSR 2017*

| Outcome | Papers | Studies | Statistical method | Effect estimate | Heterogeneity (%) |
|---|---|---|---|---|---|
| Favorable efficacy results | 25 | 2923 | Risk ratio (M–H, random, 95% CI) | 1.27 [1.17–1.37] | 28 |
| Favorable conclusions | 29 | 4583 | Risk ratio (M–H, random, 95% CI) | 1.34 [1.19–1.51] | 92 |

- Effect size estimates – mixed results
- Risk of bias – no difference

## Study of PI manufacturer ties and trial results – *Ahn BMJ 2017*

- 195 drug trials
- Adjusted OR: 3.57 (95% CI: 1.65 to 7.7)

# What should review authors do?

*It is important that information about vested interests is collected and presented when relevant. However, review authors should provide this information in the 'Characteristics of included studies' table (see Section 11.2.2). The 'Risk of bias' table should be used to assess specific aspects of methodology ….. choice of a particularly low dose of a comparator drug, should be addressed as a source of heterogeneity rather than through the 'Risk of bias' tool, since they do not impact directly on the internal validity of the findings.*

Cochrane Handbook 2011

| | | | |
|---|---|---|---|
| R69 | *Table of 'Characteristics of included studies': funding source* | ***Mandatory*** | |
| | Include details of funding sources for the study, where available. | Details of funding sources should be placed in this table rather than as part of the 'Risk of bias' table. Including an extra row in the table of 'Characteristics of included studies' is encouraged. | Cochrane Training resource: collecting data<br><br>CIL: module 4 - selecting studies and collecting data |
| R70 | *Table of 'Characteristics of included studies': declarations of interest* | ***Mandatory*** | |
| | Include details of any declarations of interest among the primary researchers. | Declarations of interest should be placed in this table rather than as part of the 'Risk of bias' table. Including an extra row in the table of 'Characteristics of included studies' is encouraged. | Cochrane Training resource: collecting data<br><br>CIL: module 4 - selecting studies and collecting data |

**MECIR** criteria
**27 June 2016**

# How to address COI in trials in systematic reviews?

## Why the Cochrane risk of bias tool should include funding source as a standard item

Lisa A Bero
20 December 2013

## Why the Cochrane risk of bias tool should not include funding source as a standard item

Jonathan AC Sterne
20 December 2013

# Bias and its many meanings

- Bias = **departure from the truth** in a trial result
  - Low internal validity

- Bias = a methodological or clinical **problem** with the trial
  - Low internal validity
  - Low external validity
  - Low precission

- Bias = a **lack of neutrality** in a person (planning, conducting, analysing, or reporting a trial)

# Conflicts of interest and its many meanings

- CoI = **commercial funding + author ties to producer of drug/device + lack of neutrality for non-commercial reasons**

- CoI = author ties to commercial funder (e.g. producer of drug/device)
- CoI = author ties to commercial funder (e.g. producer of drug/device) + lack of neutrality for non-commercial reasons

- TACIT terminology
  - Commercial conflicts of interest = funder/sponsor + author ties

# Risk of bias tool principles

- Domains defined by **core mechanisms** (Cochrane risk of bias tool 2)
  - **Bias arising from randomisation process**
  - **Bias due to deviation from the intended intervention**
  - **Bias due to missing outcome data**
  - **Bias in measurement of the outcome**
  - **Bias in selection of the reported outcome**

- Domains defined empirically/pragmatically
  - Trial size, country of origin, single-center status, funding, …
- Other principles
  - Non-domain based, tradition, simplicity, causes, etc

# How to address COI in trials when doing Cohrane Reviews?

Underreporting in Cochrane reviews

- 46 of 151 (30%) reported trial funding
- 16 of 151 (11%) reported author conflicts of interest

*BMJ* 2012;345:e5155 doi: 10.1136/bmj.e5155 (Published 21 August 2012)


RESEARCH

## Reporting of conflicts of interest from drug trials in Cochrane reviews: cross sectional study

OPEN ACCESS

Michelle Roseman *master's student*[1], Erick H Turner *assistant professor*[2], Joel Lexchin *professor*[3], James C Coyne *professor*[4], Lisa A Bero *professor*[5], Brett D Thombs *associate professor*[1]

# Inconsistent and problematic use of risk of bias tool

Incorporation of commercial funding source in the Risk of bias tool

| | |
|---|---|
| -includes in “Other bias option”: | 27 of 100 reviews |
| -adds another domain: | 5 of 100 reviews |
| Total | **32%** |

Jørgensen *et al. Systematic Reviews* (2016) 5:80
DOI 10.1186/s13643-016-0259-8

Systematic Reviews

RESEARCH Open Access

CrossMark

## Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews

Lars Jørgensen[1*], Asger S. Paludan-Müller[1], David R. T. Laursen[1], Jelena Savović[2,3], Isabelle Boutron[4], Jonathan A. C. Sterne[2,3], Julian P. T. Higgins[2,3] and Asbjørn Hróbjartsson[1,5]

## Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis

Andrea Cipriani, Toshi A Furukawa*, Georgia Salanti*, Anna Chaimani, Lauren Z Atkinson, Yusuke Ogawa, Stefan Leucht, Henricus G Ruhe, Erick H Turner, Julian P T Higgins, Matthias Egger, Nozomi Takeshima, Yu Hayasaka, Hissei Imai, Kiyomi Shinohara, Aran Tajika, John P A Ioannidis, John R Geddes

Summary

**Funding:** "In our analyses, **funding by industry was not associated with substantial differences in terms of response or dropout rates.** However, non-industry funded trials were few and many trials did not report or disclose any funding."

**The certainty of evidence** for the relative treatment effects of efficacy and acceptability **varied**; it was **moderate** for most of the comparisons involving agomelatine, escitalopram, citalopram …

**Author conflicts of interest:** not addressed.

BMC Psychiatry

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**Selective serotonin reuptake inhibitors versus placebo in patients with major depressive disorder. A systematic review with meta-analysis and Trial Sequential Analysis**

Janus Christian Jakobsen, Kiran Kumar Katakam, Anne Schou, Signe Gade Hellmuth, Sandra Elkjær Stallknecht, Katja Leth-Møller, Maria Iversen, Marianne Bjørnø Banke, Iggiannguaq Juhl Petersen, Sarah Louise Klingenberg, Jesper Krogh, Sebastian Elgaard Ebert, Anne Timm, Jane Lindschou and Christian Gluud

*BMC Psychiatry* BMC series – open, inclusive and trusted 2017 **17**:58
https://doi.org/10.1186/s12888-016-1173-2 | © The Author(s). 2017
**Received:** 15 March 2016 | **Accepted:** 20 December 2016 | **Published:** 8 February 2017

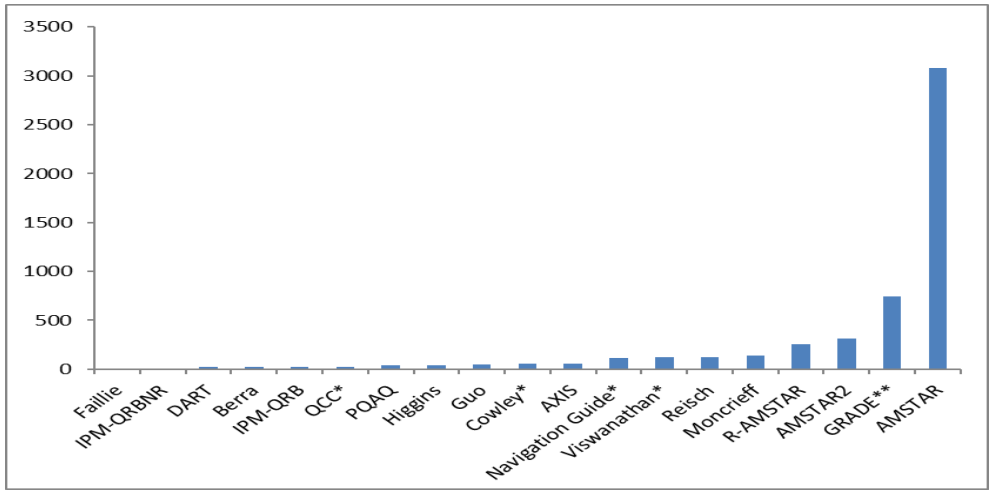
**Funding:** "All [131] trials had high risk of bias". **All industry trials rated as high risk of bias.**

"GRADE assessments show that due to the high risks of bias **the quality of the evidence** must be regarded as **very low**"

**Author conflicts of interest:** not addressed.

# Review of appraisal tools with items on CoI

Figure 2. Total number of citations of appraisal tools with items on conflicts of interest (Lund 2019, unpublished)




19 appraisal tools included items on conflicts of interest: 1-2 items

| | |
|---|---|
| Declaration only: | AMSTAR |
| Presence: | Cowley-RCT |
| Interpretation: | PQAQ, AMSTAR2 |

Conclusion: many tools address CoI superficailly without clear guidance as to what to do with a trial with CoI

# Summary

- Conflicts of interest are important
  - interpretation of reliability and relevance of trial results

- Cochrane Reviews,
  - extraction of information on conflicts of interest is expected
  - Paradoxical praxis: simultaneous underreporting and over-interpretation

- We need a structured approach
  - Addresses role of funding and author ties
  - Distinguishes between cause for ”concern” and risk of ”bias”
  - Transparent, systematic, evidence-based
  - Integration with existing tools (Rob 2), GRADE and expected future tools (Rob-ME)

# TACIT aim

To develop a tool that facilitates a **systematic and transparent assessment** of **“notable concern”** for conflicts of interest of key trial stakeholders (funders, authors and collaborators) of randomised clinical trials included in systematic reviews.

Facilitate that conflicts of interest are more often addressed and addressed appropriately.

-subgroup analyses

-external validity (comparator, setting, outcome, timing, etc)

-risk of bias (tool 2.0)

-risk of bias due to missing evidence (RoB-ME)

# Non-financial conflicts of interest (Cochrane Handbook, chapter 8, 2019)

- Characterizations of non-financial conflicts of interest will typically distinguish between conflicts mainly related to an
  - individual (e.g. **adherence to a theory or ideology**),
  - relationships to other individuals (e.g. **loyalty to friends, family members or close colleagues**),
  - relationship to groups (e.g. **work place or professional groups**).

- It is useful to differentiate between non-financial conflicts of interest of a trial researcher and the basic interests and hopes involved in doing good trial research. Most researchers conducting a trial will have an interest in the scientific problem addressed, a well-articulated theoretical position, anticipation for a specific trial result, and hopes for publication in a respectable journal. This is not a conflict of interest but a basic condition for doing clinical research.

# What are review authors doing?

- **Roseman BMJ 2012 - 151 Cochrane reviews**
  - 46 (30%) reported trial funding sources
  - 16 (11%) reported trial authors' conflicts of interest

- **Jørgensen Syst Rev 2016 – 100 Cochrane reviews**
  - 5 added separate funding or conflicts of interest domain
  - 23 addressed funding or conflicts of interest as part of 'other' domain

# How to address COI in trials in systematic reviews?

## Why the Cochrane risk of bias tool should include funding source as a standard item

Lisa A Bero
20 December 2013

"Bias related to funding source can results from systematic influences on how the study is actually conducted, the methodology of the study, whether the full results and analyses of the study are published, or a combination of these mechanisms.

"Drug study results can be biased to maximise efficacy and minimise harm through such mechanisms as choice of inferior comparators (either by dose, drug or administration route), biased coding of outcomes, bias in how data are analysed, and selective outcome reporting and publication bias".

# How to address COI in trials in systematic reviews?

**Why the Cochrane risk of bias tool should not include funding source as a standard item**

Jonathan AC Sterne
20 December 2013

"There are particular **problems associated with pharmaceutical industry-funded research**, but these should be dealt with by: (1) reporting and **commenting on conflicts of interest as a standard component of Cochrane systematic reviews**; (2) better procedures and an **improved tool to assess reporting biases**; and (3) more extensive use of mixed treatment comparisons. "