Tool for Addressing Conflicts of Interest in Trials (TACIT)

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CEBMO
Centre for Evidence-Based Medicine Odense

Cochrane Methods
Bias

SDU

Region of Southern Denmark
OUH
Odense
University Hospital

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**

- Authors of systematic reviews handle conflicts of interest in trials inconsistently and paradoxically
  - Underreporting of source of funding and authors' conflicts of interest
  - In some cases overinterpretation of the role of funding

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

TACIT aim

To provide a framework for addressing conflicts of interest in trials included in Cochrane Reviews and other systematic reviews

- a systematic retrieval and processing of information relevant for conflicts of interest (funding + author conflicts of interest)
- a reasoned and transparent judgement for whether there is cause for 'notable concern' about conflicts of interest in a trial
- prioritize
  - ease of use
  - integration with other tools
  - build on Cochrane standards

TACIT working process

- Methods
  - Development of prototype by core team
  - Iterative feedback by working group
  - Evidence building supportive projects
  - Pilottesting

- Working group
  - **Andreas Lundh, Asbjørn Hróbjartsson, Isabelle Boutron, Lesley Stewart,** Alastair Matheson, Angela Webster, An-Wen Chan, Brett Thombs, Elie Akl, Holger Schünemann, Jesse Berlin, Jonathan Sterne, Julian Higgins, Kerry Dwan, Lisa Bero, Matthew Page, Tom Jefferson, and Wim Weber

TACIT Grid

Step 3. Judge concern about conflicts of interest for each trial stage.

3.1 For each trial stage: Did a funder, sponsor or their employees with important conflicts of interest have an important role in that trial stage?
Commercial funders, sponsors or their employees are generally considered to have important conflicts of interest. The conflicts of interest of non-commercial funders may in some cases be judged as unimportant (see guidance documents for details).
See examples in step 3.3. below for which roles are considered important.

□ Yes. Judge stage as 'notable concern' about conflicts of interest in step 3.3 below, describe reason for judgement and repeat step 3.1 for next trial stage.

□ No. Proceed to step 3.2.

3.2 Did any of the primary academic researchers with important conflicts of interest have an important role in that trial stage?
In some cases the conflicts of interest of primary academic researchers may be considered unimportant (see guidance documents and Table 5 for details and examples of relationships that may be considered unimportant conflicts of interest).
See examples in step 3.3. below for which roles are considered important.

□ Yes. Judge stage as 'notable concern' about conflicts of interest in step 3.3 below, describe reason for judgement and repeat step 3.1 for next trial stage.

□ No. Judge stage as 'no notable concern' about conflicts of interest in step 3.3 below, describe reason for judgement and repeat step 3.1 for next trial stage.

3.3. Record concern about conflicts of interest in each trial stage.

Trial stage	Examples of important roles	Judgement of concern about conflicts of interest (if party with important conflicts of interest had an important role in the trial)	Describe reasons for judgement	How concern about conflicts of interest may inform assessment of risk of bias in the trial and applicability of results. For example, as assessed by other review tools.
Design	Writing trial protocol.	□ Notable concern □ No notable concern		**Assessment of applicability of trial results.**
Conduct	Participant enrolment and randomisation, administration of interventions and co-interventions, database management, outcome ascertainment or decisions about exclusion from trial.	□ Notable concern □ No notable concern		**Risk of bias due to how the trial was conducted:** e.g. assessed using the RoB 2 tool on trial level.
Analysis and reporting	Statistical analysis or writing of trial manuscripts.	□ Notable concern		**Risk of bias due to how analyses were done or reported**: e.g. assessed using the RoB 2 tool's domain selection of reported results on trial level and the RoB-ME tool on trial level.

- Step 1. Identify funders, sponsors and any employees with conflicts of interest and their role in the trial
- Step 2. Identify primary academic researchers with conflicts of interest and their role in the trial
- Step 3. Judge concern about conflicts of interest for each trial stage
- Step 4. Judge overall concern about conflicts of interest on trial level

TACIT end products

- Assessment of notable concern for conflicts of interest informative for
  - sensitivity analysis (robustness exploration)
  - subgroup analysis (heterogeneity exploration)

- TACIT information relevant for other tools and general interpretation of results
  - risk of bias assessment: RoB2
  - RoB-ME
  - assessments of applicability of trial results (e.g. relevant for indirectness and inconsistency)

Supporting TACIT subprojects

- **Project 1**: Systematic review of critical appraisal tools addressing conflicts of interest in biomedical studies

  J Clin Epidem December 2019

- **Project 2**: Qualitative interview of trialists on how COI may influence design, conduct, analysis and reporting of trials

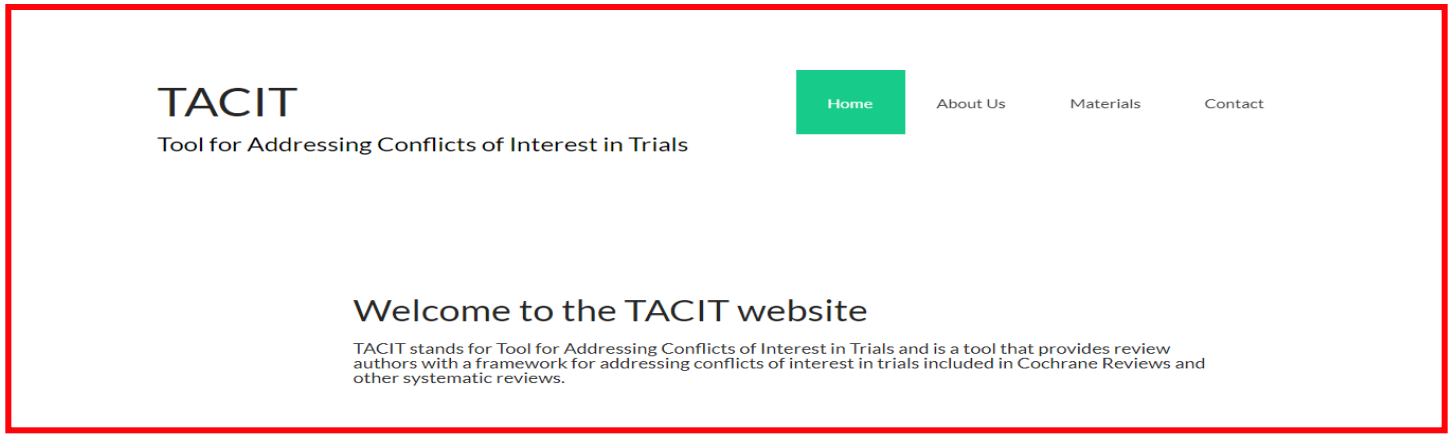
  BMJ October 2020

- **Project 3**: Pilot-testing, incl. inter-observer variation study

  Next step

Thanks for your time

www.tacit.one



Challenges

- Ensure as simple as approach as possible
  - Another tool (RoB, RoB-ME, GRADE)
  - Simplicity (time, decisions)
  - Tool reliability
- Cope with incomplete information
- Deal with the threshold problem: ‘Degree’ of conflicts of interest
- Non-financial conflicts of interest

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)

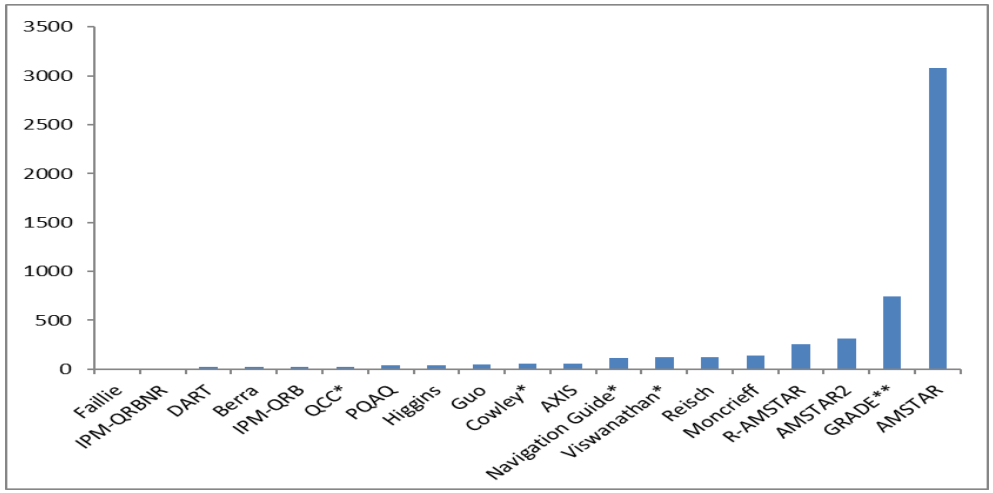
Non-financial conflicts of interest (Cochrane Handbook, chapter 8, 2019)

- 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.

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

How to address COI in trials when doing Cohrane Reviews?

Underreporting in Cochrane reviews

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

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

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

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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.