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COMMENTARY

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Blinding of interventions in clinical trials helps to prevent selection bias by making the allocation sequence difficult to decipher

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1 | COMMENTARY

Many risks of bias tools were developed to facilitate the appraisal of medical literature and enhance readers' perception of the limitations of published studies.

Most of these tools are developed specifically for one type of study design and are therefore structured on relevant domains that would screen limitations on methodologic aspects relevant to the specific scenario. For instance, the first version of Cochrane risk of bias tool[1] has six specific domains that encompass important biases relevant for randomized controlled trials (see Table 1) and one additional domain that would be used to highlight other methodological problems.

Although the domain-based critical appraisal facilitates the implementation of risk of bias assessment, some relevant limitations of the study design may be lost. In the updated version (Cochrane risk of bias tool 2), the additional domain was removed, as the developers wanted to focus only on the covered domains.[2]

Several biases and threats to validity have now been catalogued,[3,4] and the perception that study aspects may be multi-layered and not static is important in widening the perception of study limitations outside the traditional tools.

In this commentary, we aim to discuss how intervention blinding may prevent selection bias, an aspect that is not explicitly covered in any risk of bias tool.

2 | RANDOMIZING TO PREVENT RESEARCHER'S INFLUENCE ON TREATMENT ASSIGNMENTS

Randomizing the allocation sequence in a clinical trial reassures that the allocation process was performed in good faith.[5] The famous 1948 Medical Research Council (MRC) streptomycin trial used treatment allocation based on random numbers to prevent the influence of researchers in "imputing" patients from the allocation process.[6] Chalmers[6] argued against the notion that the initiation of randomization procedures was based on a statistical theoretical background but mainly on the notion to promote a fair comparison.

With the 1948 MRC trial example, we can see that the notion that procedures would need to be taken to "compare like with like" in

TABLE 1 Domains and biases addressed by Cochrane risk of bias tool for randomized controlled trials

Domain	Type of bias
Sequence generation	Selection
Allocation concealment	
Blinding of participants and personnel	Performance
Blinding of outcome assessment	Detection
Incomplete outcome data	Attrition
Selective outcome report	Reporting bias
Risk of bias due to problems not covered elsewhere in the table	Other sources of bias

trials goes as far as the very early usage of randomization in medicine. Also, it was previously established that generating a random sequence is not enough as trialists could still manipulate the order of assignment during enrolment.

3 | ALLOCATION CONCEALMENT: PROTECTING THE RANDOMIZATION SEQUENCE

As perceived by the 1948 MRC trialists, generating an allocation sequence by chance alone would not be sufficient to prevent the influence of the researcher on the allocation process.

The term "allocation concealment" was introduced in 1994[7] to replace the already used term "randomization blinding." This decision was made to avoid confusion with the concept of intervention blinding using placebos, for example.

The definition of allocation concealment was proposed based on concealing assignments until the point of allocation,[7] following the rationale that "the reduction of bias in trials depends crucially upon preventing foreknowledge of treatment assignment."

Methods that make allocation concealment possible include "central randomization" (or the allocation through a central system), "central independent pharmacy," and "sealed, opaque and sequentially numbered envelopes."[7]

As we can see, the introduction of the term allocation concealment was made intentionally to distinguish this process from intervention blinding. In fact, even open-label trials may implement reasonable techniques to avoid problems related to the foreknowledge of treatment assignment, such as allocation through a central system.

4 | BLINDING OF INTERVENTIONS: PROTECTING ALLOCATION CONCEALMENT

Although different processes, intervention blinding and allocation concealment are related. We will now discuss an example where the lack of intervention blinding facilitated the violation of allocation concealment, thus introducing important selection bias to the study design.

In a multicenter, open-label trial, outpatients with suspected sepsis were randomized after screening by ambulance teams to receive antibiotics immediately or in the hospital.[8] The study could have used a double-dummy approach to permit the blinding of participants, personnel, and outcome assessors. However, this was not implemented.

The allocation occurred through "centrally generated and consecutively numbered indistinguishable envelopes containing a note with the group assignment (intervention or usual care)." The envelopes were "put in all participating ambulances by the local research team."[8]

Theoretically, the allocation method prevents foreknowledge of treatment assignment, reducing the risk of selection bias. However, a major protocol violation occurred, resulting in "more patients being included in the intervention group."

This happened because ambulance teams wanted to treat as many patients as possible and therefore would "open envelopes until they found an envelope instructing randomization to the intervention group."[8] The authors reported that "at the end of the study the total number of patients in the intervention group outnumbered the patients in the usual care group by 398."

Because the sealed envelopes guarded unblinded treatment labels, the trial personnel were able to violate the allocation sequence. If the envelopes had blinded treatment labels (for instance, unique numerical/encoded labels macheted with the drug recipients), this violation would be much more difficult – if not impossible. The violation would also not have happened if allocation was made centrally and not with envelopes.

5 | RECOGNIZING FURTHER BENEFITS OF INTERVENTION BLINDING AND IMPLICATIONS TO THE STUDY OF RISK OF BIAS IN CLINICAL TRIALS

We discussed an example where lack of intervention blinding resulted in an increased risk of selection bias, one aspect that is not explicitly covered in the Cochrane risk of bias tool.[1] It is important to highlight, therefore, that intervention blinding has more benefits than just preventing performance and detection biases.

It is obvious that critical appraisal tools would never encompass all potential threats to validity as that would not be feasible. These tools must be structured considering the most common and impactful methodological aspects relevant to each study design. This is important as some threats may be missed in uncommon cases; therefore, general knowledge of different biases is complementary to knowledge of critical appraisal tools.

More importantly, the domains of risk of bias tools should not be used to guide the design of future trials. Methodological prevention steps, such as intervention blinding, should always be implemented when possible.

6 | CONCLUSION

We discussed how blinding of interventions in clinical trials helps to prevent selection bias. Critical appraisal tools have an inherent limitation of not encompassing all relevant threats to validity. General knowledge of biases is complementary to the use of common tools. More importantly, critical appraisal tools should not be used as the only guide to developing future trials – instead, robust methods should be implemented whenever possible.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are not available.

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