Double-blind, single-blind, observer-blind: when and how

Siri Giacomo

E.O. Ospedale Galliera - Genova
Dip. di Matematica - Università degli Studi di Genova

giacomo.siri03@gmail.com
//sites.google.com/site/giacomosiripersonalwebpage/home

10th October 2019
### Evidences on blinding in RCTs (1)

A review of 20571 RCTs from 1990 to 2015 showed:

- 38% used inadequate methods for blinding participants and personnel.
- 20% used inadequate methods for blinding of outcome assessment.

#### Figure 2

Number and proportion of RCTs at low risk of bias, high risk of bias and unclear risk of bias (N=20,571). RCTs, randomised controlled trials.

**Catillon, 2019**
A review of 20571 RCTs from 1990 to 2015 showed that: [1]

- 38% used inadequate methods for blinding participants and personnel
- 20% used inadequate methods for blinding of outcome assessment
Evidences on blinding in RCTs (2)

- The proportion of RCTs using inadequate methods for blinding of participants and personnel increased from 32.5% to 43.0%.
- The proportion of RCTs using adequate methods for blinding of outcome assessment increased from 35.7% to 51.2%.
- Better blinding of participants and personnel was found in industry-related RCTs ($p < 0.05$).

Catillon, 2019
the proportion of RCTs using **inadequate** methods for blinding of participants and personnel is increased from 32.5% to 43.0%
Evidences on blinding in RCTs (2)

- The proportion of RCTs using inadequate methods for blinding of participants and personnel is increased from 32.5% to 43.0%.
- The proportion of RCTs using adequate methods for blinding of outcome assessment is increased from 35.7% to 51.2%.

Catillon, 2019
the proportion of RCTs using *inadequate* methods for blinding of participants and personnel is increased from 32.5% to 43.0%

the proportion of RCTs using *adequate* methods for blinding of outcome assessment is increased from 35.7% to 51.2%

better blinding of participants and personnel was found in *industry-related RCTs* \((p < 0.05)\)

«Human behaviour is influenced by what we know or believe. In research there is a particular risk of expectation influencing findings, most obviously when there is some subjectivity in assessment, leading to biased results. Blinding (sometimes called masking) is used to try to eliminate such bias». 

«Human behaviour is influenced by what we know or believe. In research there is a particular risk of expectation influencing findings, most obviously when there is some subjectivity in assessment, leading to biased results. Blinding (sometimes called masking) is used to try to eliminate such bias».


«Since there is no way of eliminating the prospect of bias in data collection, the researcher has to be content with controlling bias».

«Bias [...] is controlled if it is the same across the treatment groups being compared-controlled because, whatever the bias, its effect is removed by comparing differences between treatment groups and, thus, removing the bias by subtraction». 
Blinding or masking?

Blinding terminology emerged when Benjamin Franklin (18th century) and colleagues actually blindfolded participants to shield them from knowledge in their assessments of the therapeutic claims made for Mesmerism.
Blinding terminology emerged when Benjamin Franklin (18th century) and colleagues actually blindfolded participants to shield them from knowledge in their assessments of the therapeutic claims made for Mesmerism.

### pros Blinding
- suggests a more secure procedure because is a strong imagery

### pros Masking
- more appropriate in trials that involve participants who have impaired vision, and could be less confusing in trials in which blindness is an outcome
Definition of blinding

Definition from ICH-E9 guidelines [14]

«The most important design techniques for avoiding bias in clinical trials are blinding and randomisation. [...] Blinding [...] is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on...»
Definition of blinding

Definition from ICH-E9 guidelines [14]

«The most important design techniques for avoiding bias in clinical trials are blinding and randomisation. [...] Blinding [...] is intended to limit the occurrence of conscious and unconscious bias in the conduct and interpretation of a clinical trial arising from the influence which the knowledge of treatment may have on. . . »
Who needs to be blinded and potential benefits? (1)

Participants [10]

- less likely to have biased psychological or physical response to treatment
- more likely to comply with trial regimens
- less likely to seek additional adjunct interventions
- less likely to leave trial without providing outcome data, leading to lost to follow-up
- ...
Who needs to be blinded and potential benefits? (2)

Healthcare providers [10]

- less likely to transfer their inclinations or attitudes to participants
- less likely to differentially administer co-interventions or adjust dose
- less likely to differentially withdraw participants
- less likely to differentially encourage or discourage participants to continue trial
- . . .
Outcome assessors [10]

- less likely to have biases affect their ascertainment of outcomes, especially with subjective outcomes of interest

...
Who needs to be blinded and potential benefits? (4)

Biostatisticians [9, 13]

- more likely to choose strategies of analysis (e.g. tests and models) adequate to the distribution of variables
- more likely to include all possible confounders in a multiple model
- less likely to keep or remove patients from the analysis (e.g. outliers or recovery of missing data)
- less likely to do subgroup analysis on selected patients
- ...
Who needs to be blinded and potential benefits? (5)

Others
- data safety and monitoring committee
- manuscript writers [13]
- general practitioners and caregivers [3]
Confusion on blinding terminology

A study of 200 RCTs reported as "double-blind" found 18 different combinations of groups blinded, and about one in every five of these trials – reported as "double-blind" – did not blind participants, healthcare providers, or data collectors [9].

A sample of 91 physicians showed 10, 17, and 15 unique interpretations of single-, double- and triple-blinding, respectively [11]. The agreement for a most common interpretation falls down from 75%, to 38%, and to 18% when passing from single-, to double-, and to triple-blind respectively [11].

CONSORT2010 recommends that the terms "single-blind", "double-blind", and "triple-blind" be abandoned and, instead, blinded RCTs should only detail who was blinded after treatment allocation and how [9].
Confusion on blinding terminology

- A study of 200 RCTs reported as “double-blind” found **18 different combinations** of groups blinded, and about one in every five of these trials – reported as “double-blind”– did not blind participants, health care providers, or data collectors [9]
A study of 200 RCTs reported as “double-blind” found **18 different combinations** of groups blinded, and about one in every five of these trials – reported as “double-blind”– did not blind participants, healthcare providers, or data collectors [9].

A sample of 91 physicians showed 10, 17 and 15 unique interpretations of single-, double- and triple-blinding, respectively [11].
Confusion on blinding terminology

- A study of 200 RCTs reported as “double-blind” found 18 different combinations of groups blinded, and about one in every five of these trials – reported as “double-blind”– did not blind participants, healthcare providers, or data collectors [9]

- A sample of 91 physicians showed 10, 17 and 15 unique interpretations of single-, double- and triple-blinding, respectively [11]

- The agreement for a most common interpretation falls down from 75%, to 38%, and to 18% when passing from single-, to double-, and to triple-blind respectively [11]
Confusion on blinding terminology

- A study of 200 RCTs reported as “double-blind” found 18 different combinations of groups blinded, and about one in every five of these trials – reported as “double-blind” – did not blind participants, health care providers, or data collectors [9]

- A sample of 91 physicians showed 10, 17 and 15 unique interpretations of single-, double- and triple-blinding, respectively [11]

- The agreement for a most common interpretation falls down from 75%, to 38%, and to 18% when passing from single-, to double-, and to triple-blind respectively [11]

- CONSORT2010 recommends that the terms “single-blind”, “double-blind”, and “triple-blind” be abandoned and, instead, blinded RCTs should only detail who was blinded after treatment allocation and how [9]
Double-blind, single-blind and so on...(1)

Were subjects blinded to treatment assignment?

- No: Not a “blinded study”. List other groups that were blinded, if any.
- Yes: Were investigators (including those who administer treatment) and outcome assessors blinded to treatment assignment?

  - No: Single-blind study. List other groups that were blinded, if any.
  - Yes: Were data managers and biostatisticians blinded to treatment assignment?

    - No: Double-blind study
    - Yes: Triple-blind study.
      List other groups that were blinded, if any.

Miller, 2011
### Double-blind, single-blind and so on… (2)

<table>
<thead>
<tr>
<th>RCTs open access from September 2018</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>double blind</td>
<td>251</td>
<td>77.71%</td>
</tr>
<tr>
<td>single blind</td>
<td>30</td>
<td>9.29%</td>
</tr>
<tr>
<td>blind</td>
<td>20</td>
<td>6.19%</td>
</tr>
<tr>
<td>triple blind</td>
<td>6</td>
<td>1.86%</td>
</tr>
<tr>
<td>others</td>
<td>16</td>
<td>4.95%</td>
</tr>
<tr>
<td>assessor blind</td>
<td>6</td>
<td>1.86%</td>
</tr>
<tr>
<td>observer blind</td>
<td>2</td>
<td>0.62%</td>
</tr>
<tr>
<td>patient assessor blind</td>
<td>2</td>
<td>0.62%</td>
</tr>
<tr>
<td>patient blind</td>
<td>1</td>
<td>0.31%</td>
</tr>
<tr>
<td>investigator blind</td>
<td>1</td>
<td>0.31%</td>
</tr>
<tr>
<td>analyst blind</td>
<td>1</td>
<td>0.31%</td>
</tr>
<tr>
<td>open label - blinded endpoint</td>
<td>1</td>
<td>0.31%</td>
</tr>
<tr>
<td>non-blind</td>
<td>2</td>
<td>0.62%</td>
</tr>
</tbody>
</table>
Main types of bias due to absence of blinding

- **PERFORMANCE BIAS**
- **DETECTION BIAS**
- **ATTRITION BIAS**
- **REPORTING BIAS**

Awareness of the treatment assigned to patients can introduce...
Main types of bias due to absence of blinding (1)

- **PERFORMANCE BIAS**: Awareness of the treatment assigned to patients can introduce...
  - **DETECTION BIAS**
  - **ATTRITION BIAS**
  - **REPORTING BIAS**

Systematic differences between groups in the care that is provided, or in exposure to factors other than the interventions of interest [6]

- more attention
- ancillary treatment
- diagnostic investigations
- ...
Main types of bias due to absence of blinding (2)

systematic differences between groups in how outcomes are determined or assessed [6]
- under-/over-estimation of the gravity of event
- more likely to round up/down a measurement scale (e.g. blood pressure measures, medical images, ...)
Main types of bias due to absence of blinding (3)

systematic differences between groups in withdrawals from a study [6]

- exclusion refer to situations in which some participants are omitted from reports of analyses, despite outcome data being available to the trialists
- attrition refers to situations in which outcome data are not available
  
  ...
Main types of bias due to absence of blinding (4)

- **systematic differences between reported and unreported findings** [2]
  - omitting outcomes unfavourable or statistically insignificant
  - adding or changing outcomes based on collected data to favour statistical significance
  - including only a subset of data in the published study
  - failing to report data that was analysed in the trial (e.g. adverse events, ...)
  - ...
When to blind and under what conditions? (1)

When?

Blinding is highly recommended when outcome measures involve some subjectivity (e.g. pain, quality of life, psychological outcome, ...) and becomes less to reduce bias for objective criteria (e.g. death).
When to blind and under what conditions? (1)

When?

Blinding is highly recommended when outcome measures involve some **subjectivity** (e.g. pain, quality of life, psychological outcome, ...) and becomes less to reduce bias for objective criteria (e.g. death).

Blinding of patients or healthcare providers is impossible, impractical or ill-advised when...

- the trial involves different treatment modalities (e.g. pharmacological and surgical)
- dose adjustments are required on the basis of some measurements (e.g. biomarkers)
- the treatment or follow-up visit schedule differs depending on treatment assignment
- the blinding requires lying to patients
- the blinding expose the patients to risks of harm or misadventure
When to blind and under what conditions? (2)

However . . . [9]

- blinding of data collectors and outcomes assessors is often achievable
- in particular if the endpoints are assessed on diagnostic tests and not directly on the unblinded patient, who could influence the clinician
Blinding in pharmacological trials: with placebos

(active-) placebo should be administered, whenever possible, to controls when assessing the effects of a proposed new treatment for a condition for which no effective treatment already exists

- one must ensure the placebo matches the sensory (on all human senses) specifications to that of the medicine under test
- requiring to the original manufacturer of medicine the placebo used in authorization trials
  - cons: usually produced in limited quantity for authorization trial, disappointing to the independent researchers
- manufacturing the matching placebo elsewhere
  - cons: use of the same ingredients as those in its active counterpart does not always guarantee a satisfactory level of sensory equivalence and this involves reformulating also the active treatment from its licensed form but this actually means manufacturing a new product with problems of bioequivalence
if a proven effective standard treatment exists (pills)

- over-encapsulation (with possible addition of excipients) of the two pills to achieve the similarity
  cons: increasing in size of the original dosage; to prove the bioequivalence between the encapsulated and original product

- bespoke manufacturing of both treatments to control the visual appearance
  cons: equivalent bioequivalence

- double-dummy methods with more placebos, one for each treatment, also in case of different formulation form
  cons: it requires to participant to take two (or more) study medications and this could raise the questions of the potential risk of non-compliance
Blinding in pharmacological trials: with active controls (2)

if a proven effective standard treatment exists (infusion therapy)

- using opaque tubes or covering the infusion bag with plastic sleeve
- cons: poor robustness unless accepting the unblinded status of those administering the treatment
Surgical treatments often result in incisions and scars that may differ between groups. Moreover, conceal treatment arm from at least some individuals involved in the trial is usually impossible

- sham surgery could be unethical;
- if the trial involves 2 similar procedures (e.g. a comparison of division vs nondivision of the short gastric vessels during laparoscopic Nissen fundoplications), trialists may not inform patients of their treatment allocation (obviously surgeon is not blinded)
- if the comparison is between a surgical technique and a no, patients can only be blinded with ethically questionable sham surgery
even if these methodological precautions are adopted, the researchers should report the limitations and potential bias due to the lack of an adequate blinding in the discussion section.
### Conclusions

Blinding should be used, whenever possible, to avoid bias, in particular when the outcome measures could be affected by some subjectivity. If blinding is used in a clinical trials, researchers should try to avoid terms such as "single-blind", "double-blind" or "triple-blind" in favour of "blind" only. Researchers should therefore explain carefully in the methods who was blinded, and how, to allow the reader to assess by himself the goodness of methods used to achieve blinding. A further step should be to incorporate a measurement of the success of the blinding.
Blinding should be used, whenever possible, to avoid bias, in particular when the outcome measures could be affected by some subjectivity.
Blinding should be used, whenever possible, to avoid bias, in particular when the outcome measures could be affected by some subjectivity.

If blinding is used in a clinical trials, researchers should try to avoid terms such as “single-blind”, “double-blind” or “triple-blind” in favour of “blind” only.
Conclusions

- Blinding should be used, whenever possible, to avoid bias, in particular when the outcome measures could be affected by some subjectivity.

- If blinding is used in a clinical trials, researchers should try to avoid terms such as “single-blind”, “double-blind” or “triple-blind” in favour of “blind” only.

- Researchers should therefore explain carefully in the methods who was blinded, and how, to allow the reader to assess by himself the goodness of methods used to achieve blinding.
Conclusions

- Blinding should be used, whenever possible, to avoid bias, in particular when the outcome measures could be affected by some subjectivity.

- If blinding is used in a clinical trials, researchers should try to avoid terms such as “single-blind”, “double-blind” or “triple-blind” in favour of “blind” only.

- Researchers should therefore explain carefully in the methods who was blinded, and how, to allow the reader to assess by himself the goodness of methods used to achieve blinding.

- A further step should be to incorporate a measurement of the success of the blinding.
Thanks for your attention
References I


References II


