Bias in clinical trials

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What is bias?
What is bias?

Random error

Systematic error (bias)
Bias

- a systematic error
- a systematic disposition of certain trial designs to produce results consistently better or worse than other trial designs (Bandolier extra)
- a tendency of an estimate to deviate in one direction from a true value (Centre for EBIntvention)
- a threat to internal validity of the study
Bias

- at any part of study
- an inadequate design, misconduct of the research methodology, the inadequate analysis of data
- David Sackett - 35 types of bias
Validity of the study

- confidence that an estimate of an effect is near the true value for an outcome
- prevention of systematic errors (bias)
- internal validity - risk of bias within a study
- external validity - applicability of study results to other patients or settings
Types of bias

- Cochrane handbook
  - Selection bias
  - Performance bias
  - Detection bias
  - Attrition bias
  - Reporting bias
Selection bias

- a process of identification of the participants (sample selection bias)
- a process of allocation of participants to the groups (allocation bias)
- factors influencing participation in the study (attrition)
Selection bias (allocation)

• **Routine clinical practice:**
  - patients receive treatment according to the discretion of the physician (the groups compared may differ in a systematic way)
  - different prognosis and different treatment

• **What can be done**
  - Randomisation
  - Allocation concealment
Laparoscopic resection of esophageal cancer

- One patient operated and dies in the peri-operative period. Surgeon is upset.
  - *case-report*
  - why did this patient die?
- Five patients operated. After six months 80% is dead (4/5). Surgeon is worried?
  - *case-series*
  - why did these patients die?
  - Factors influencing the outcome, yet not dependent on the subject of interest = *confounders*
10 patients underwent surgery. 
- After 6 months follow up 50% died. 
- Surgeon compared this group with another group of patients of similar size and disease severity who underwent open surgery (by his colleague) in another hospital (40% died).

Why they died? 
- Cohort study
10 patients operated laparoscopically, after 6 months 30% dead.

Compared with another similar 10 patients operated by the same surgeon using open surgery during previous year (40% mortality)

cohort study with historical control
  - Are patients identical? Is their care the same?
  - Factors influencing the outcome, yet not dependent on the subject of interest = *confounders*

Imbalance of confounders = results systematically different from the truth (not valid, biased)
Confounders

- Factors, other than study subject, which influence outcome (cause or prevent it), "get in the way",

- Confounders not balanced between the groups
  - The results are biased
Evidence Assessment of validity

- How to get a comparable control group?

- Achieve a situation where comparable groups are, before treatment, similar (identical) in respect to confounders

- Achieve a situation where getting or not getting treatment depends only on chance

- Achieve a situation where each patient entering the experiment has the same probability to enter experimental or control group as any other patient entering study (definition of randomization).
Unbalanced confounders

How we can get comparable groups?
Regarding known confounders - study design
  ▶ matching
  ▶ stratification
  ▶ restriction
Regarding known and unknown factors - study design
  ▶ Randomisation

Cochrane Handbook
Randomised controlled trial

Cohort study

Randomised controlled trial
Goal: comparable groups should be similar in respect to prognostic factors

Mechanism: each patient entering the experiment has the same probability to enter experimental or control group as any other patient entering study
Methodology of RCT
randomization

- Patients with cholecystitis. RCT comparing open vs. laparoscopic technique. It is difficult to organize laparoscopic surgery at night.

- Randomization code in envelopes. Patient admitted at night → checking the envelopes → if open surgery, patient in, if laparoscopic → patient out or a new envelope

- In effect, most (all) patients admitted at night got into ‘open’ group.
  - Are patients admitted at night similar to those admitted during the day?
  - Are surgeons the same?
  - How could it influence the results?
RCT methods

Review of 811 RCTs

- Studies with inadequate/unclear sequence generation - 10% exaggeration of treatment effect
- Studies with inadequate/unclear allocation concealment - 11% exaggeration of treatment effect

Performance bias

- differences in care provided to comparison groups other than the intervention of interest (attention, co-interventions, diagnostic tests)

- What can be done?
  - blinding
Studies without / unclear double blinding - 14% exaggeration of treatment effect
Measurement bias

- Also called: detection bias, information bias
- Bias when measuring the outcomes
- Systematic differences between groups in how outcomes are determined

- What can be done?
  - blinding of outcome assessors
Attrition bias

- differences between groups in withdrawals from the study (due to discontinuation of treatment, cross-over to other treatment, poor compliance, adverse experiences)

- What can be done?
  - intention-to-treat analysis, sensitivity analysis
Attrition bias

Treatment

100 patients

20 non-tolerant

80 tolerant

Control

100 patients

100 patients
Methods

Intent to treat analysis

Treatment

100 patients

20 non-tolerant

80 tolerant

Control

100 patients

“per protocol” comparison

“intention to treat” comparison
Comparison of surgical vs. conservative medical treatment

All methodological requirements are met

Outcome: mortality

During the year from randomization 10% of ‘medical’ patients died.

During a year after hospital discharge 5% of ‘surgical’ patients died.

Surgical treatment is associated with lower mortality
Methods

completeness of follow-up

Surgery

100 patients

20 status unknown

80 status known, 5% mortality

Medical Tx

100 patients

10% mortality

"comparing those who are followed"

mortality?
Reporting bias

- Dissemination of the research results influenced by its nature and direction

Examples:
- Publication bias (file drawer problem)
- Time lag
- Duplicate publication
- Location bias
- Citation
- Language
- Outcome reporting
Publication bias
### Table 4. Pooled Odds Ratio for Outcome Reporting Bias (Fully vs Incompletely Reported Outcomes), by Study Design and Sensitivity Analyses

<table>
<thead>
<tr>
<th>Trial Population</th>
<th>Efficacy Outcomes</th>
<th>Harm Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Trials*</td>
<td>OR (95% CI)†</td>
</tr>
<tr>
<td>All trials</td>
<td>50</td>
<td>2.4 (1.4-4.0)</td>
</tr>
<tr>
<td>Parallel-group trials</td>
<td>38</td>
<td>2.8 (1.5-5.4)</td>
</tr>
<tr>
<td>Crossover trials</td>
<td>11</td>
<td>1.4 (0.63-3.2)</td>
</tr>
<tr>
<td>Excluding survey nonresponders</td>
<td>16</td>
<td>1.8 (0.73-4.7)</td>
</tr>
<tr>
<td>Excluding physiologic/pharmacokinetic trials</td>
<td>45</td>
<td>2.7 (1.6-4.8)</td>
</tr>
<tr>
<td>Fully/partially reported vs qualitatively/unreported outcomes</td>
<td>35</td>
<td>3.1 (1.7-5.9)§</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; NA, not available; OR, odds ratio.

*Trials were excluded if an odds ratio could not be calculated due to entire rows or columns being empty in the 2 × 2 table.

†Except for the bottom row, an OR > 1 indicates that statistically significant outcomes (P < .05) have higher odds of being fully reported compared with nonsignificant outcomes.

‡Cannot be calculated.

§An OR > 1 indicates that statistically significant outcomes (P < .05) have a higher odds of being fully or partially reported compared with nonsignificant outcomes.
Outcome reporting bias

- Higher odds of being fully reported for statistically significant outcomes compared with nonsignificant outcomes
  - for efficacy (OR 2.4 [95% CI, 1.4-4.0])
  - for harm (OR 4.7 [95% CI, 1.8-12.0])
- Published articles vs protocols
  - 62% of trials - at least 1 primary outcome that was changed, introduced, or omitted

*JAMA. 2004;291:2457-2465*
Other types of selection bias

- confounding by indication - patients allocated to the intervention or control group on the basis of patient and investigator preferences, patient characteristics, and clinical history
- participation bias (healthy worker, self-selection, survival, non-response)
- ascertainment bias (referral, surveillance)

Am J Epidemiol 2006; 163(6):
In observational studies

- Other types of information bias:
  - bias due to periodical changes, recall bias,
  - interviewer bias
  - Misclassifiation - a systematic difference in the way information concerning the measured parameter is collected for the groups being compared
    - non-differential (random) - the same probability of being misclassified for all study subjects
    - differential - the error rate or probability of being misclassified differs across groups of study subjects (BP measurement in heavy vs light using the same cuff size)