Seven Deadly Sins: Bias in Trauma Outcomes and Comparative Effectiveness Research

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The Original 7 Deadly Sins

1. Lust
2. Gluttony
3. Sloth
4. Envy
5. Pride
6. Greed
7. Wrath

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Specific Aims

1. Help explain conflicting trauma research findings (beyond chance) across observational studies and randomized clinical trials (RCTs)

2. Improve the validity & reproducibility of trauma outcomes and comparative effectiveness research (CER)
7 Deadly Sins in Trauma Outcomes Research\(^1\)

Overlooking or ignoring sources of bias:

1. Indications for treatment

2. Collider Bias

3. Survivorship bias

4. **Time-varying**, dynamic treatment regimes

5. **Time-dependent** confounding

6. Non-uniform effects over **time**

7. Non-random, non-ignorable missing values
1. Indication Bias

Definition:
In an observational CER study of interventions A & B, patients receiving intervention A ≠ patients receiving the alternate intervention B. Unlike in a randomized trial, the eligibility criteria and indications for interventions A & B may differ substantially.
1. Indication Bias continued

Example:

Plasma early vs. later in resuscitating bleeding trauma patients?

- Trauma patients are extremely heterogeneous in injury and bleeding severity and in their need for life-saving resuscitation interventions.
- Patients who needed plasma early but died before it could be administered get counted in the same later group as those who actually got plasma later and those who never got or needed any plasma at all.
1. Indication Bias continued

Resolution:
1. Capture data on as many important pre-intervention baseline covariates as possible.

2. Use stratification, propensity score matching or modeling (e.g., regression) to appropriately adjust for the pre-intervention baseline covariates.
2. Collider Bias

Definition:
Prevalent in trauma research, collider bias results from subgrouping or adjusting analyses by a covariate that is a consequence (collider) rather than a cause (confounder) of both the treatment and outcome.
2. Collider Bias continued

Example:
Randomized trials of prehospital hypertonic saline vs. standard-of-care resuscitation fluids subgrouped patient data by a well-known surrogate for bleeding severity: >10 PRBC units/24hrs or “massive transfusion”, MT
2. Collider Bias continued

Resolution:

1. Early in the design phase, thoroughly evaluate covariates, especially surrogates, with causal diagrams (Directed Acyclic Graphs or DAGs).^7

2. Replace colliders with valid pre-intervention (or pre-randomization) baseline covariates and conduct the most rigorous subgroup or adjusted analyses possible.
3. Survival Bias

**Definition:** Failure to exclude the antecedent survival time that the intervention (or alternate condition) could not possibly affect
3. Survival Bias continued

Example:
For bleeding trauma patients, does a 1:1:1:1 balanced transfusion ratio of plasma:platelets:PRBC over the first 24 hours save more lives than an unbalanced ratio < 1:1:2

The longer a bleeding trauma patient survives, the more likely s/he will eventually receive units of plasma and platelets to balance a rapid sequence of PRBC units transfused. But many bleeding trauma patients die before having the chance to receive anything but PRBCs.
3. Survival Bias continued

Resolution:

1. Use time-dependent covariate analysis (e.g., Cox proportional hazards regression modeling)\(^3\)

2. Use logistic regression with appropriate time intervals conditioned on survival\(^4\)
4. Time Varying Treatment

Definition:
Interventions are often dynamic regimens that may dramatically fluctuate in both complexity and intensity (e.g., dose) over time. A single cumulative summary or mid-point average can be misleading for patients in different phases.
### 4. Time Varying Treatment cont2

**Example:** Time interval-specific and cumulative ratios (plasma:platelets:PRBCs)

<table>
<thead>
<tr>
<th>Time</th>
<th>Patient A</th>
<th>Patient B</th>
<th>Patient C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Interval</td>
<td>Cumulative</td>
<td>Interval</td>
</tr>
<tr>
<td>15 m</td>
<td>1:6:1</td>
<td>1:6:1</td>
<td>0:0:0</td>
</tr>
<tr>
<td>30 m</td>
<td>2:0:2</td>
<td>3:6:3</td>
<td>0:0:0</td>
</tr>
<tr>
<td>45 m</td>
<td>1:0:1</td>
<td>4:6:4</td>
<td>0:0:0</td>
</tr>
<tr>
<td>60 m</td>
<td>1:0:1</td>
<td>5:6:5</td>
<td>0:0:0</td>
</tr>
</tbody>
</table>

Patient A got platelets early and nearly equal amounts of plasma and RBCs throughout. Patient B got all RBCs, plasma and platelets in the last time interval. Patient C got RBCs early, plasma in a later time interval and platelets in the last interval.
4. Time Varying Treatment cont3

Resolution:
1. Accurately and completely capture the timing and characteristics of dynamic and complex interventions with meaningful granularity over a broad range.
2. Capture data on the short, intermediate and long-term outcomes.
3. Use time-dependent covariate analysis if appropriate
5. Time-dependent Confounding

Definition and Example:
In a dynamic treatment regimen (e.g., blood product transfusion), when a covariate (platelet transfusion) predicts future treatment (plasma transfusion) and outcome (survival) and is itself predicted by past treatment (plasma), time-dependent covariate adjustment can fail to produce unbiased estimates of the treatment (plasma) effect.
5. Time-dependent Confounding continued

Resolution:

1. Marginal structural models using inverse probability of treatment weighting offers a more complex but potentially more valid approach.\(^5\)

2. Stratification by treatment sequence within defined time windows is another approach if sample size allows.\(^4\)
6. Non-uniform Intervention Effects Over Time continued

PROMMTT³ provided a striking example. Primary causes of death, mortality rates and RRs changed over time.

<table>
<thead>
<tr>
<th>Time interval after ED admission</th>
<th>Deaths (cause)</th>
<th>Hours at Risk</th>
<th>Mortality Rate (RR of association)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Within 6 hours</td>
<td>88 (hemorrhage)</td>
<td>3,590</td>
<td>0.0245 (1:1:2&gt;1:1:1)</td>
</tr>
<tr>
<td>From &gt;6 hours to 24 hours</td>
<td>34 (head injury)</td>
<td>14,039</td>
<td>0.0024 (1:1:2=1:1:1)</td>
</tr>
<tr>
<td>From &gt;24 hours to 30 days</td>
<td>84 (complication)</td>
<td>491,618</td>
<td>0.0002 (1:1:2=1:1:1)</td>
</tr>
</tbody>
</table>
6. Non-uniform Effects Over Time continued

Resolution:

1. Stratification by time periods should be routinely examined to identify potentially differential short, intermediate and long-term effects.

2. Data analysis should include standard statistical tests for homogeneity of effects across strata or appropriate modeling with the inclusion of treatment by time interaction terms.
7. Non-random Missing Values

Definition:
Missing values in trauma research data imply 1 of 3 underlying mechanisms (best case to worst): missing completely at random (MCAR), missing at random (MAR), and missing not at random (MNAR).
7. Non-random missing values continued

- Missing Completely at Random (MCAR) is assumed in Complete Case Analysis (CCA), which excludes patients with missing values.

- Missing at Random (MAR) is assumed in analyses using multiple imputation.

- Missing Not at Random (MNAR) cannot be refuted or confirmed; it can only be explored in sensitivity analyses with hypothetical scenarios.
7. Non-random Missing Values continued

Example:
- Trauma data are notorious for missing covariate values.
- Patients at the two opposite extremes of severity are the most likely to have missing data raising concern for the standard approach, CCA, that assumes MCAR as well as for multiple imputation that assumes MAR.\(^6\)
7. Non-random Missing Values continued

Resolution:
1. Consider multiple imputation with the less restrictive MAR assumptions and compare results with CCA.
2. Seek expert advice to explore various worst-case scenarios with sensitivity analysis, the only MNAR option.
Conclusions

Multi-disciplinary Trauma Research Teams can rid trauma research of the 7 deadly sins.
References: