The Net Benefit of a treatment should take the correlation between benefits and harms into account

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Problem

Benefit / risk assessments use *marginal* estimates of benefits and risks

Such assessments do not account for the correlation between the outcomes

Positive correlation

*Example*: skin rash in patients with EGFR-mutated advanced lung cancer receiving inhibitors of EGFR

No correlation

*Example*: cardiac toxicity in frail patients with advanced breast receiving anthracyclines

Negative correlation

*Example*: toxicities leading to treatment stop in enzyme-deficient patients with advanced colorectal cancer receiving irinotecan

*Ref*: Buyse et al. J Clin Epidemiol, 2021
Generalized pairwise comparisons of prioritized outcomes in the two-sample problem

Marc Buyse$^{a,b,*}$
Pairwise Comparisons

TREATMENT GROUP

CONTROL GROUP

$X_i > Y_j$ (WIN)

$X_i < Y_j$ (LOSS)

$X_i = Y_j$ (TIE)

$X_i$ or $Y_j$ missing (uninformative)

WINS $X_i > Y_j$

LOSSES $X_i < Y_j$

TIES $X_i = Y_j$

(UNINFORMATIVE)

All Pairwise Comparisons

Net Benefit

\[
\text{Net Benefit} = \frac{\#\text{Wins} - \#\text{Losses}}{\#\text{Pairs}}
\]

-1 < Net Benefit < 1

Win Ratio

\[ \text{Win Ratio} = \frac{\#\text{Wins}}{\#\text{Losses}} \]

\(0 < \text{Win Ratio} < \infty\)

Ref: Pocock et al. Eur Heart J, 2012;33:176
The Net Benefit is a U-statistic

\[ X_i \ (i = 1, \ldots, m) \]
\[ Y_j \ (j = 1, \ldots, n) \]
\[ u_{ij} = \begin{cases} 
+1 & \text{if } (X_i, Y_j) \text{ pair is a win} \\
-1 & \text{if } (X_i, Y_j) \text{ pair is a loss} \\
0 & \text{otherwise} 
\end{cases} \]

\[ U = \frac{1}{m \cdot n} \sum_{i=1}^{n} \sum_{j=1}^{m} u_{ij} \]

\(U\) (the Net Benefit) is unbiased and efficient in situations of practical interest

Ref: Verbeeck et al. SMMR, 2021;30:747
Thresholds of Clinical Relevance

Threshold of clinical relevance $\delta$

- **WINS**: $X_i - Y_j > \delta$
- **LOSSES**: $X_i - Y_j < -\delta$
- **TIES**: $|X_i - Y_j| < \delta$

Multiple Prioritized Outcomes

Multiple outcomes can often be prioritized

<table>
<thead>
<tr>
<th>Prioritized outcome 1</th>
<th>Prioritized outcome 2</th>
<th>Pairwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>win</td>
<td>ignored</td>
<td>win</td>
</tr>
<tr>
<td>loss</td>
<td>ignored</td>
<td>loss</td>
</tr>
<tr>
<td>uninformative or tie</td>
<td>win</td>
<td>win</td>
</tr>
<tr>
<td>uninformative or tie</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td>uninformative or tie</td>
<td>tie</td>
<td>tie</td>
</tr>
<tr>
<td>uninformative or tie</td>
<td>uninformative</td>
<td>uninformative</td>
</tr>
</tbody>
</table>

Benefit / Risk Analyses

Erlotinib
569 advanced pancreatic cancers

Gemcitabine + erlotinib
285
R
Gemcitabine + placebo
284

FOLFORINOX
342 advanced pancreatic cancers

R
171
FOLFIRINOX
171
Gemcitabine

Nab-Paclitaxel
861 advanced pancreatic cancers

R
431
Gemcitabine + nab-paclitaxel
430
Gemcitabine

Refs: Moore et al. JCO 2007; Conroy et al. NEJM, 2011; Von Hoff et al. NEJM, 2013
Benefit: Longer OS

Erlotinib
- Erlotinib group
- Placebo group
- HR = 0.82
- 95% CI (0.69 - 0.99)
- P = 0.036

Erlotinib (n=285)
- Median survival = 6.37 months

Placebo (n=284)
- Median survival = 5.91 months

FOLFORINOX
- FOLFIROINOX group
- Gemcitabine group
- HR = 0.57
- 95% CI (0.45 - 0.73)
- P < 0.001

FOLFIROINOX (n=171)
- Median survival = 11.1 months

Gemcitabine (n=171)
- Median survival = 8.8 months

Nab-Paclitaxel
- Hazard ratio for death, 0.72 (95% CI, 0.62–0.83)
- P < 0.001 by stratified log-rank test
## Risk: Severe Toxicity

<table>
<thead>
<tr>
<th>Worst Toxicity</th>
<th>Erlotinib</th>
<th>Gem</th>
<th>FOLFORINOX</th>
<th>Gem</th>
<th>Gem+NabP</th>
<th>Gem</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>10%</td>
<td>23%</td>
<td>4%</td>
<td>1%</td>
<td>9%</td>
<td>22%</td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>59%</td>
<td>57%</td>
<td>27%</td>
<td>39%</td>
<td>36%</td>
<td>54%</td>
</tr>
<tr>
<td>Grade 3-5</td>
<td>31%</td>
<td>20%</td>
<td>69%</td>
<td>60%</td>
<td>55%</td>
<td>24%</td>
</tr>
</tbody>
</table>

Prioritized Outcomes OS / Toxicity

<table>
<thead>
<tr>
<th>Survival</th>
<th>Worst Toxicity (Grade 3-5)</th>
<th>Pair is a</th>
</tr>
</thead>
<tbody>
<tr>
<td>win</td>
<td>-</td>
<td>win</td>
</tr>
<tr>
<td>loss</td>
<td>-</td>
<td>loss</td>
</tr>
<tr>
<td>tie</td>
<td>win</td>
<td>win</td>
</tr>
<tr>
<td>tie</td>
<td>loss</td>
<td>loss</td>
</tr>
<tr>
<td>tie</td>
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<td>tie</td>
</tr>
</tbody>
</table>

*Ref: Buyse & Péron, In: Piantadosi & Meinert (eds.), Principles and Practice of Clinical Trials, 2021*
Prioritized Outcomes OS Threshold / Toxicity

<table>
<thead>
<tr>
<th>Survival (threshold $m$ months)</th>
<th>Worst Toxicity (Grade 3-5)</th>
<th>Pair is a</th>
</tr>
</thead>
<tbody>
<tr>
<td>win</td>
<td>-</td>
<td>win</td>
</tr>
<tr>
<td>loss</td>
<td>-</td>
<td>loss</td>
</tr>
<tr>
<td>tie</td>
<td>win</td>
<td>win</td>
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<td>tie</td>
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*Ref: Buyse & Péron, In: Piantadosi & Meinert (eds.), Principles and Practice of Clinical Trials, 2021*
Sensitivity Analysis of Benefit / Risk

Ref: Buyse & Péron, In: Piantadosi & Meinert (eds.), Principles and Practice of Clinical Trials, 2021
Conclusions

GPC provide a flexible and mathematically sound tool to explore multivariate outcomes.

The Net Benefit with prioritized outcomes naturally accounts for the correlation between these outcomes.

GPC are also useful in other contexts:

- Composite time to most relevant outcome
- Multidimensional analyses, *e.g.*, of quality of life data (O’Brien test)
- Non standard situations, *e.g.*, non proportional hazards