Moving the statistical analysis of randomized trials from a single endpoint to a patient-centric benefit-risk assessment

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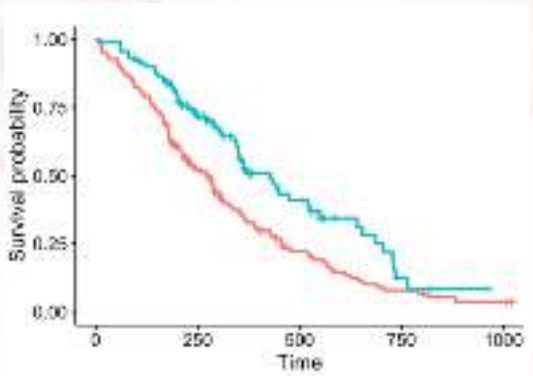
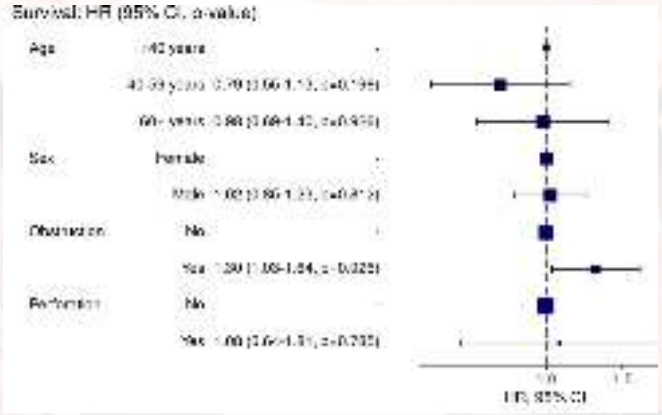
Statistical analysis of randomized trials





USUAL STATISTICS

Survival curves,
forest plots,
hazard ratios,
odd ratios,
and so on…

What matters to patients?

SEVERAL CONCRETE QUESTIONS

- How much longer can I live?
- Will treatment be painful?
- What will my symptoms look like?
- What is my chance of doing better on treatment than on control?

Benefits

Risks

Overall assessment

What matters to patients?

What outcomes matter most to patients?

PRIORITIES

Outcomes prioritized according to patient preferences, e.g.

- Time to death (Duration)
- Pain (Yes/No)
- Selected symptoms, e.g. severe neuropathy (Yes/No)
- Etc.

What differences in outcomes matter to patients?

THRESHOLDS

Thresholds of clinival relevance, e.g.

- Time to death (Difference in duration found to be worthwile)
- Pain (Intensity)
- Selected symptoms, e.g. neuropathy (Severity)
- Etc.

Research Article

Statistics in Medicine

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Generalized pairwise comparisons of prioritized outcomes in the two-sample problem

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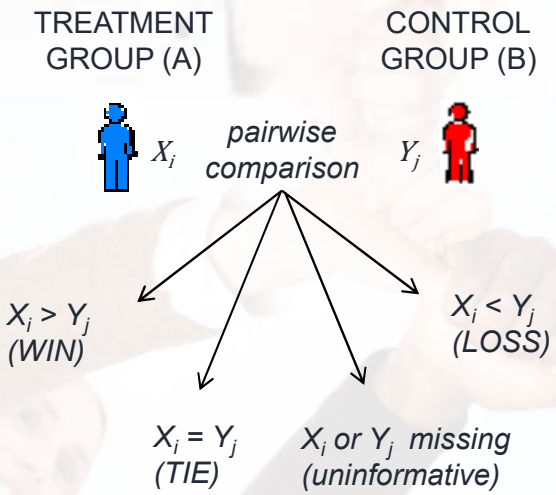
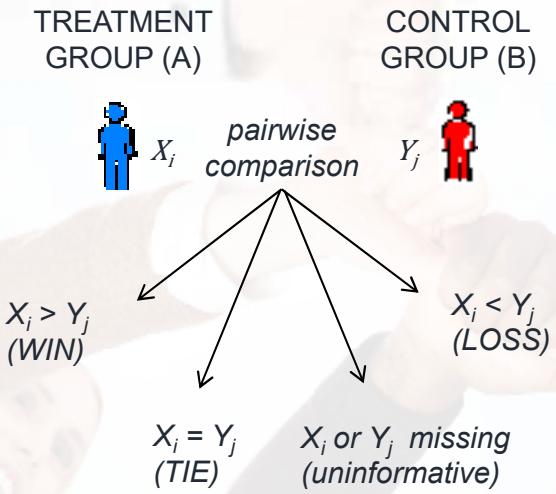
Pairwise Comparisons

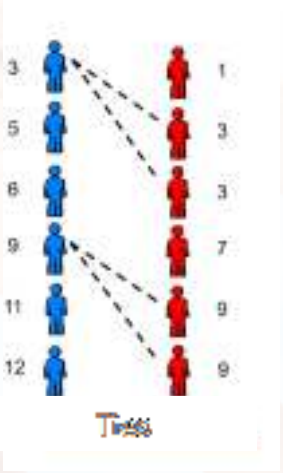


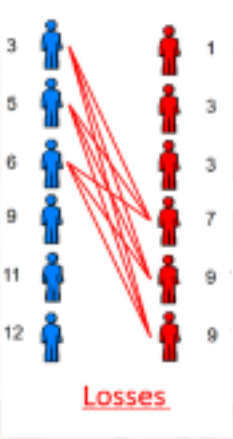
WINS	$X_i > Y_j$
LOSSES	$X_i < Y_j$
TIES	$X_i = Y_j$

(UNINFORMATIVE)

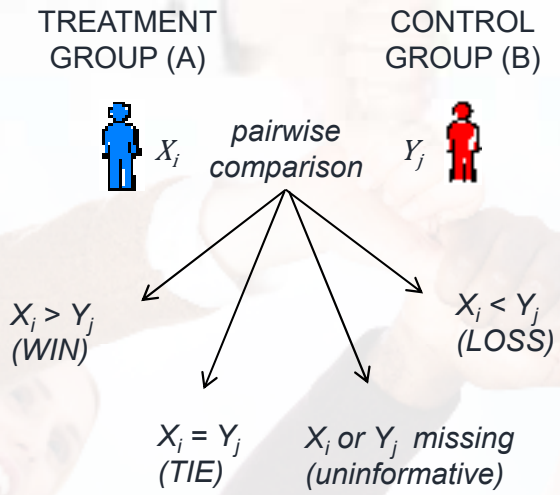
All Pairwise Comparisons







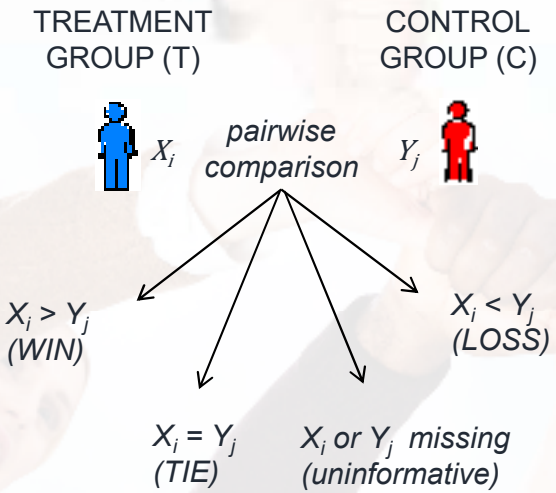
Thresholds of Clinical Relevance



Threshold of clinical relevance (δ)

WINS	$X_i - Y_j > \delta$
LOSSES	$X_i - Y_j < -\delta$
TIES	$\lvert X_i - Y_j \rvert < \delta$

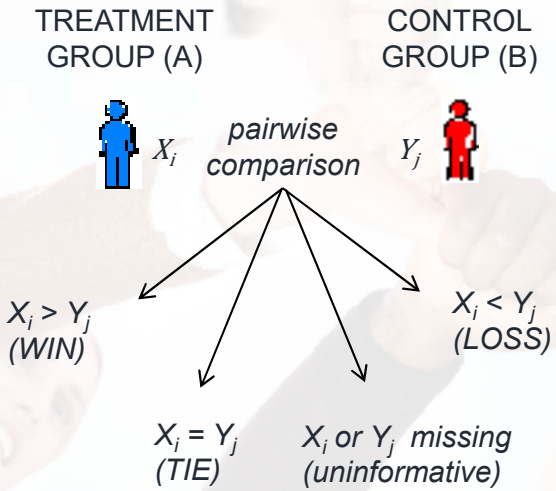
Multiple Prioritized Outcomes



Multiple outcomes can be assessed in order of priority

Prioritized outcome 1	Prioritized outcome 2	Pairwise comparison
win	ignored	win
loss	ignored	loss
uninformative or tie	win	win
uninformative or tie	loss	loss
uninformative or tie	tie	tie
uninformative or tie	uninformative	uninformative

Net Benefit



$$Net\ Benefit = (\#\ Wins - \#\ Losses) / \#\ Pairs$$

$$-100\% < Net\ Benefit < 100\%$$

Advantages of GPC

- GPC is a non-parametric approach to account for multiple outcomes of any type representative of several dimensions :
  - Efficacy
  - Safety
  - Quality of Life
- GPC permits a mathematically rigorous benefit/risk assessment when outcomes are correlated
- The Net Benefit is a universal measure of treatment effect that has a straightforward probabilistic interpretation
- Prioritizing outcomes is natural and patient-centric

Applications of GPC

- Thresholds of clinical relevance
  (*e.g.*, survival better by at least *m* months)
- Non standard situations
  (*e.g.*, non-proportional hazards with immunotherapy in oncology)
- Time to most relevant event, rather than time to first outcome
  (*e.g.*, time to death more important than time to progression)
- Mixed outcomes
  (*e.g.*, time to event and early biomarker such as circulating tumor DNA)
- Multidmensional scales
  (*e.g.*, quality of life)
- Highly multidimensional data
  (*e.g.*, gene expression profiles)

Potential Users of GPC

	Patients	Clinicians	Regulatory Agencies	HTA & Payers	Pharma Market Access	Pharma R&D
Thresholds of clinical relevance	⊕	+		⊕	⊕	
Non standard situations (e.g. non PH)			+			⊕
Time to most relevant outcome	+	+	⊕	+	+	+
Mixed outcomes (e.g. benefit / risk)	⊕	+		+	+	
Multidimensional scales	+	⊕		+	+	

Consumers Regulators Producers