THE USE OF GENERALIZED PAIRWISE COMPARISONS FOR DESIGNING TRIALS THAT ARE TAILORED TO PATIENTS' WISHES AND NEEDS

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Overview

Structure

1. Motivating examples
2. Non-inferiority criticism
3. Generalized Pairwise Comparisons
4. Application

1. MOTIVATING EXAMPLES

1. Motivating examples

Example 1

Context

- Disease: locally advanced rectal cancer
- Population of interest: elderly ($\geq$ 70 years)
- Standard of care: short course radiotherapy + cycles of chemotherapy

Motivation

- Elderly population is more fragile
- The benefits from the additional chemotherapy may be overthrown by its harms in toxicity
- New suggested treatment: only radiotherapy

  $\rightarrow$ Context for a **non-inferiority trial**?

Example 1

Assumptions of the non-inferiority trial

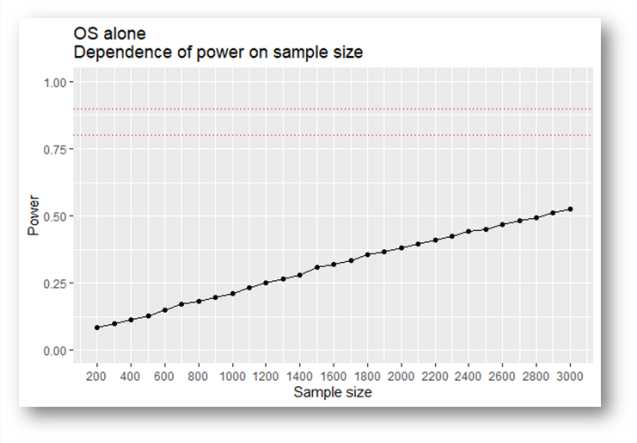
$$\begin{cases} \text{Trt: Short course radiotherapy (SCRT)} \\ \text{Ctr: Rapido - SCRT + 6 capox} \end{cases}$$

- Potential endpoints of interest:
  - T_1: overall survival at 36 months
  - T_2: disease recurrence at 36 months
- Proportions of events at 36 months:

	Trt	Ctr
T_1	15%	11%
T_2	32%	24%

Example 1 - Questions

1. Is the trial feasible?



2. How to include patients' voices in the design?

Example 2

Context

- Disease: low and intermediate risk acute promyelocytic leukemia
- Standard of care: full dose of ATRA (all-trans retinoic acid)

Motivation

- Full dose induces much toxicities
- Reported real world data shows that a reduced dose may provide similar efficacy
- New suggested treatment: lowered dose

  → Context for a **non-inferiority trial**?

Example 2

Assumptions of the non-inferiority trial

$$\begin{cases} \text{Trt: Reduced ATRA dose} \\ \text{Ctr: Full ATRA dose} \end{cases}$$

- Potential endpoints of interest:
  - T_1: event-free survival at 24 months
- Proportions of events at 24 months:

	Trt	Ctr
T_1	10%	8%

Example 2 - Questions

1. Is the trial feasible?

Outcome	Value in Control Arm*	Value in Experimental Arm**	Difference (Control – Experimental)	Non-inferiority margin	Approximate Sample Size
EFS at 2 years non-inferior	0.92	0.92	0.0	0.05	1000
	0.92	0.91	0.01	0.05	1500
	0.92	0.90	0.02	0.05	2900

2. How to include patients' voices in the design?

2. NON-INFERIORITY CRITICISM

2. Non-inferiority criticism

Context

- Our trials are infeasible in terms of sample size and leave no room to the voice of patients.
- But there are other regular criticism towards non-inferiority trials:
  - Composite objective (acceptable deterioration is compensated), yet benefits are either (i) not shown, or (ii) analyzed separately with disregard of dependencies

Toxicity	
Absence	Presence
50%	50%

Survival	
Do worse	Do better
50%	50%

?

?

		Survival	
		Do worse	Do better
Toxicity	Absence	50%	0%
	Presence	0%	50%

		Survival	
		Do worse	Do better
Toxicity	Absence	0%	50%
	Presence	50%	0%

2. Non-inferiority criticism

Context

- There are other regular criticism towards non-inferiority (NI) trials:
  - Assay sensitivity (capacity of a trial to distinguish an effective therapy from one that is not effective); NI trials are biased towards positive results if they are poorly designed and conducted.
    Review study of Wangge et al. (2010): 1/3 of the 232 PubMed registered trials did not use blinding.
  - Choice of population: ITT may bias towards positive result, while per protocol has smaller size
  - Choice of the margin: no statistical consensus, prone to 'cherry-picking', and not easy to include patients' voices
  - 'biocreep' phenomenon

$\Rightarrow$ Can we address these concerns with a statistically sound procedure?

3. GENERALIZED PAIRWISE COMPARISONS

Context and Motivation

Consider a randomized clinical trial with a treatment and a control group:

- Let Y^t be the continuous outcome of interest in the treatment group.
- Let Y^c be the continuous outcome of interest in the control group.
- We observe Y_i^ℓ, $i = 1, \ldots, n^\ell$, $\ell \in \{t, c\}$.
- Question of the trial: is there a treatment effect?
- One way to assess: the Mann-Whitney form of the Wilcoxon test

$$U_{ij} = \begin{cases} 1 & \text{if } Y_i^t > Y_j^c \\ 1/2 & \text{if } Y_i^t = Y_j^c \\ 0 & \text{if } Y_i^t < Y_j^c \end{cases}$$

Test is then based on

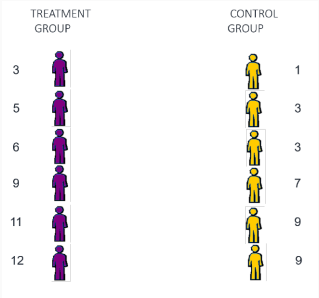
$$U = \frac{1}{n^t n^c} \sum_{i=1}^{n^t} \sum_{j=1}^{n^c} U_{ij}.$$

Context

$$U = \frac{1}{n^t n^c} \sum_{i=1}^{n^t} \sum_{j=1}^{n^c} U_{ij}.$$

Way of reading:

- Simple idea of comparing pairs of patients: win, loss, neutral
- Besides test, effect size measured is $\mathbb{P}(Y^t > Y^c) + 1/2\,\mathbb{P}(Y^t = Y^c)$



Idea

Generalize the pairwise comparisons:

- 'Classify' for all ordinal types of outcomes, e.g.
  - Binary: patient alive is better than dead.
  - Continuous: e.g. win if outlive for at least τ months, $Y_i^t \geq Y_j^c + \tau$.
- Include multiple outcomes to keep classifying pairs:

First priority outcome	Second priority outcome	Classification
Win	-	Win
Loss	-	Loss
Tie/uninformative	Win	Win
Tie/uninformative	Loss	Loss
Tie/uninformative	Tie/uninformative	Tie/uninformative

The Net Treatment Benefit

- Let Y_i^t and Y_j^c be possibly multivariate:

$$U_{ij} = \begin{cases} +1 & \text{if } Y_i^t \succ Y_j^c \\ -1 & \text{if } Y_i^t \prec Y_j^c \\ 0 & \text{otherwise.} \end{cases}$$

  where $\succ$ and $\prec$ define wins and losses according to the context.

- Generalized Pairwise Comparisons:

$$\widehat{\Delta}_\tau := \frac{1}{n^t n^c} \sum_{i=1}^{n^t} \sum_{j=1}^{n^c} U_{ij},$$

  is an estimator of $\Delta_\tau := \mathbb{P}(Y^t \succ Y^c) - \mathbb{P}(Y^t \prec Y^c)$, called the Net Treatment Benefit.

- Other GPC statistics:

  Win Ratio $:= \mathbb{P}(Y^t \succ Y^c) \,/\, \mathbb{P}(Y^t \prec Y^c)$
  Win Odds $:= \{\mathbb{P}(Y^t \succ Y^c) + 1/2\mathbb{P}(Y^t \asymp Y^c)\} \,/\, \{\mathbb{P}(Y^t \prec Y^c) + 1/2\mathbb{P}(Y^t \asymp Y^c)\}$

Theoretical Developments

GPC-based statistics have known many theoretical developments that make them now available for designing practical trials. For instance (non-exhaustive list):

- Adaptations to nuisances / particularities in the data:
  - Censoring: Gehan (1965), Efron (1967), Péron et al. (2016), Deltuvaite-Thomas et al. (2022)
  - Missing Data: Deltuvaite-Thomas and Burzykowski (2022)
  - Competing Risks: Cantagallo et al. (2020)
- Inferential procedures:
  - Asymptotic procedures: Bebu and Lachin (2016), Ozenne et al. (2022)
  - Resampling procedures: Buyse (2010), Pocock et al. (2012), Chung and Romano (2016), Anderson and Verbeeck (2019)

4. APPLICATION

Example 1

- Endpoints of interest:
  - T_1: Survival, time to death from any cause.
  - T_2: Time to disease recurrence.
  - X_1: Any grade ≥ 2 neurological toxicity ($0 \succ 1$).
  - X_2: Any grade ≥ 3 toxicities during pre-operative treatment ($0 \succ 1$).

Natural prioritization: efficacy $\succ$ toxicities

- Incorporating the voice of patients:
  - Prioritization of interest:

$$T_2 \succ T_1 \succ X_1 \succ X_2$$

  - For toxicities to be ignored, need a efficacy gains of at least 12 months
  - Final prioritization:

$$T_2[12] \succ T_1[12] \succ X_1 \succ X_2$$

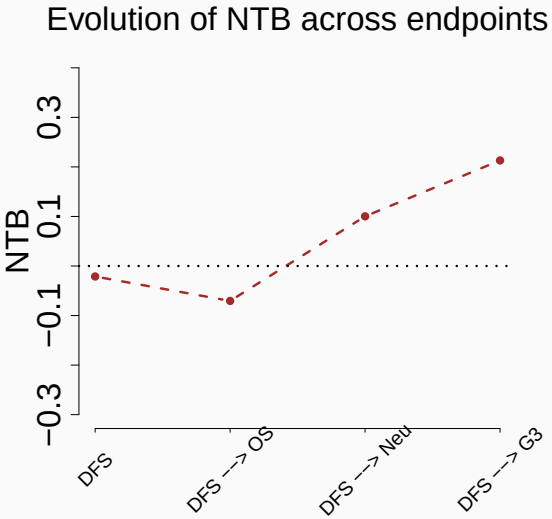
Example 1 - assumptions

1. Proportions of events at 36 months:

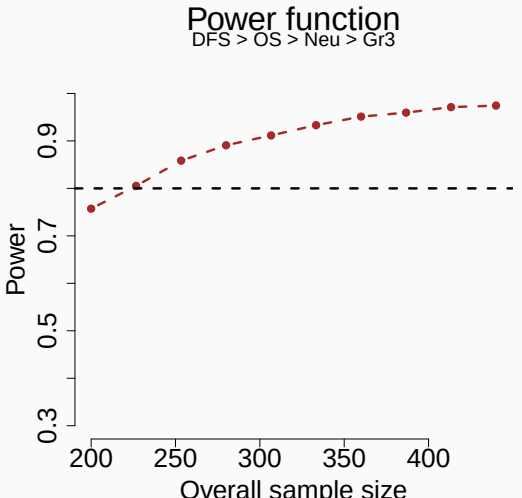
	Trt	Ctr
T_1: death at 36 months	15%	11%
T_2: disease recurrence at 36 months	32%	24%
X_1: $P(X_1 = 1)$ (lower better)	5%	35%
X_2: $P(X_2 = 1)$ (lower better)	24%	55%

2. $T_1, T_2 \sim Exp(\cdot)$
3. $X_1, X_2 \sim Bernoulli(\cdot)$
4. Same dependence structure for the two groups

Example 1 - Net Treatment Benefit

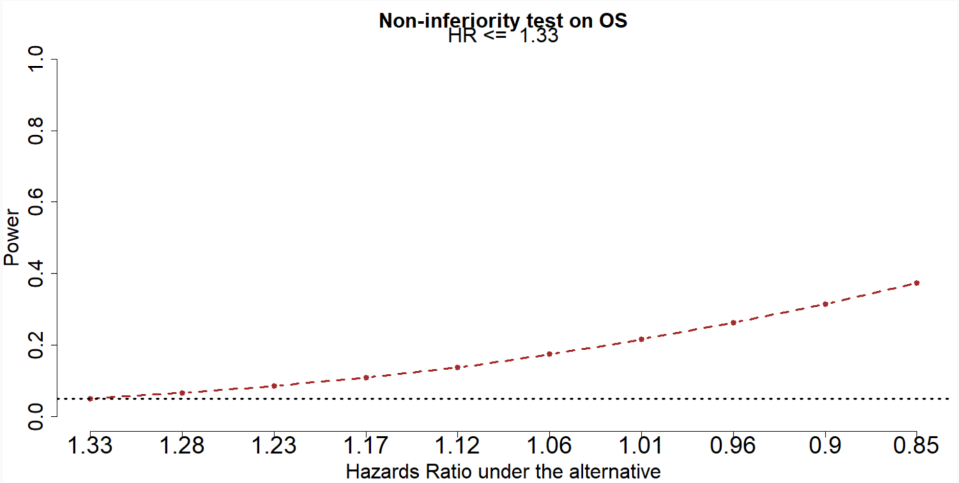


Example 1 - Sample size



Example 1 - Comparing with a conventional NI trial

Using the sample size obtained by the GPC-based design:



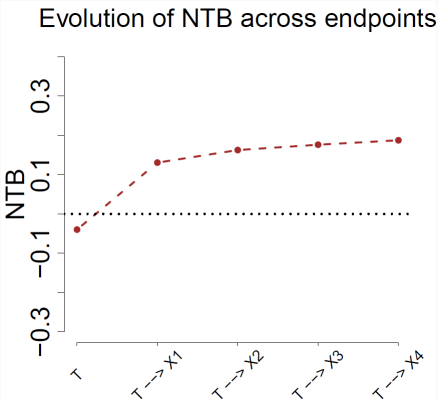
Example 1 - Lessons

- Non-inferiority concerns:
  - ✓ sample size
  - ✓ voice of patients
  - ✓ composite objective
  - ✓ population of interest
  - ✓ choice of margin
  - ✓ biocreep
  - assay sensitivity: can we prevent bias towards positive results for sloppy trials?

Example 2

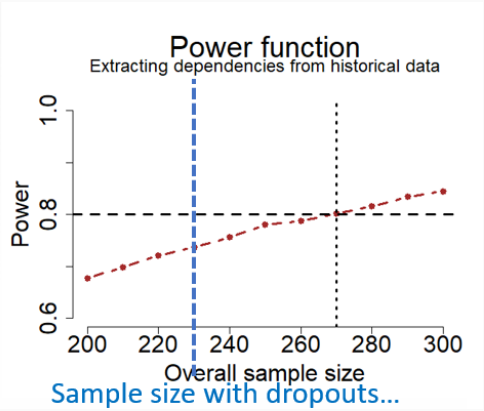
- Endpoints of interest:
  - T_1: EFS, binary ($0 \succ 1$).
  - X_1 till X_4: toxicities ($0 \succ 1$).

Natural prioritization: $T_1 \succ$ toxicities



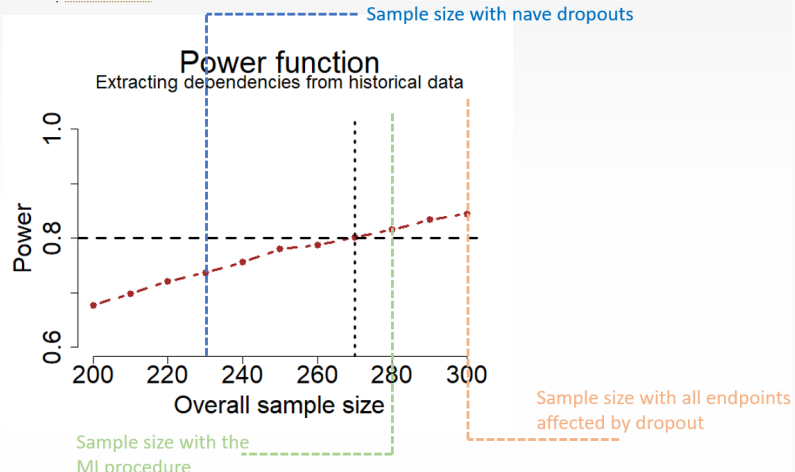
Example 2

- The impact of time:
  - Toxicities (in favor of the treatment) are measured early on
  - EFS (in favor of the control) is measured at end of trial
  - If naive handling of drop-outs:



Example 2

- The impact of time:
  - We may enforce the penalization of sloppy data collection, hence avoiding assay sensitivity issues:



5. CONCLUSION

Conclusion

- Generalized Pairwise Comparisons provide a simple tool for designing trials with:
  - realistic sample sizes
  - explicit composite objective
  - incorporation of the voice of patients
- Recent theoretical developments provide the framework for these designs in many situations, but challenges remain:
  - modelling of dependence structures
  - consideration of more complex designs (interim analysis etc)

Thanks!
Questions?