



4th KCE TRIALS SYMPOSIUM

HOT TOPICS AND METHODS IN PUBLICLY FUNDED
CLINICAL TRIALS



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Pacheco centre Brussels

MULTIPLE PRIORITIZED OUTCOMES IN CLINICAL TRIALS

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OUTLINE

1. Issues with a single primary outcome
2. 4' video about multiple outcomes
3. The « Net Treatment Benefit »
4. Two examples in oncology

ISSUES WITH A SINGLE PRIMARY OUTCOME

OUTCOMES MEASURES IN ONCOLOGY

- Overall survival OS
- Quality of life QoL
- Time to cancer progression TTP
- Tumor response (measurable disease) ORR
- Biomarkers

OUTCOMES MEASURES vs. GOAL OF THERAPY

The goal of cancer therapy is to improve the duration and/or quality of life

Yet, overall survival (OS) and quality of life (QoL) are rarely primary endpoints for clinical trials:

- OS takes too long to be observed, is statistically insensitive and confounded by second-line treatments and by causes of death unrelated to cancer or treatment ¹
- QoL is insufficiently used as supportive outcome measure, let alone as primary outcome measure ²

PRIMARY ENDPOINT

The outcome measure of greatest clinical interest is the « primary endpoint »

The sample size is calculated to provide high power ($\geq 80\%$) to detect a treatment effect on the primary endpoint

What about other endpoints ?

- Secondary endpoints
- Patient-reported outcomes
- Safety endpoints
- Exploratory / translational / biological endpoints

CHOICE OF A PRIMARY ENDPOINT

1. Patient-relevant

A clinical endpoint measures *how a patient feels, functions or survives*

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Early assessment enables interim analyses for futility / efficacy

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A clinical endpoint measures *how a patient feels, functions or survives*

2. Measured without bias

Blinding or central review are effective ways of reducing bias

3. Measured early

Early assessment enables interim analyses for futility / efficacy

4. Sensitive to treatment effects

Power depends on number of observations / events / follow-up time

CHOICE OF A PRIMARY ENDPOINT

	Relevance	Bias	Timing	Power
OS				
QoL				
TTP				
ORR				
Biomarker				

CHOICE OF A PRIMARY ENDPOINT

	Relevance	Bias	Timing	Power
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4' VIDEO ABOUT MULTIPLE OUTCOMES

MULTIPLE OUTCOMES CAN BE ANALYSED USING GENERALIZED PAIRWISE COMPARISONS

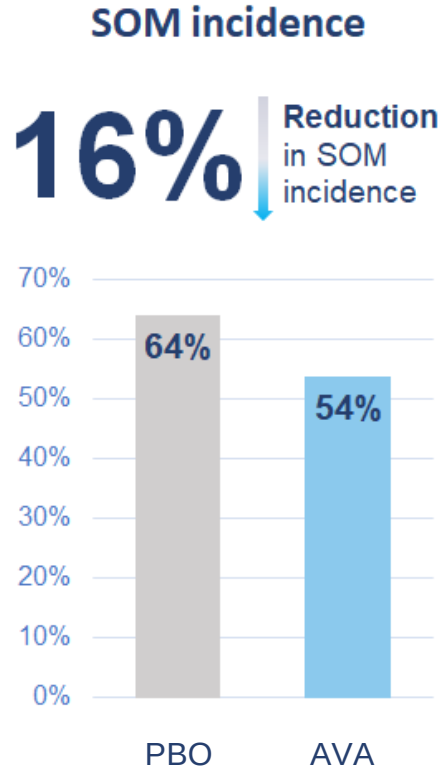
- Simultaneous analysis of several outcomes, **prioritized by importance**
- All pairs of patients are formed with one patient from the treated group and one patient from the control group
- For all pairs, the prioritized outcomes are compared to find which patient has a better outcome
- The Net Treatment Benefit NTB is the net probability that a random treated patient has a better outcome than a random control patient

IMPROVING PATIENT RELEVANCE
AND
STATISTICAL SENSITIVITY

PREVENTION OF SEVERE ORAL MUCOSITIS

- Clinical trial of investigational drug avasopasem manganese (AVA) for patients with locally advanced head & neck cancer receiving IMRT + cisplatin
- 70% of patients develop severe oral mucositis (SOM, WHO grade 3-4)
- Clinical trial randomized 241 patients to 90 mg/day AVA vs. 166 to placebo

CONVENTIONAL ANALYSIS



Relative effect of AVA : $1 - 54\% / 64\% = 16\%$

Absolute effect of AVA : $64\% - 54\% = 10\%$

Number needed to treat : $1 / 10\% = 10$

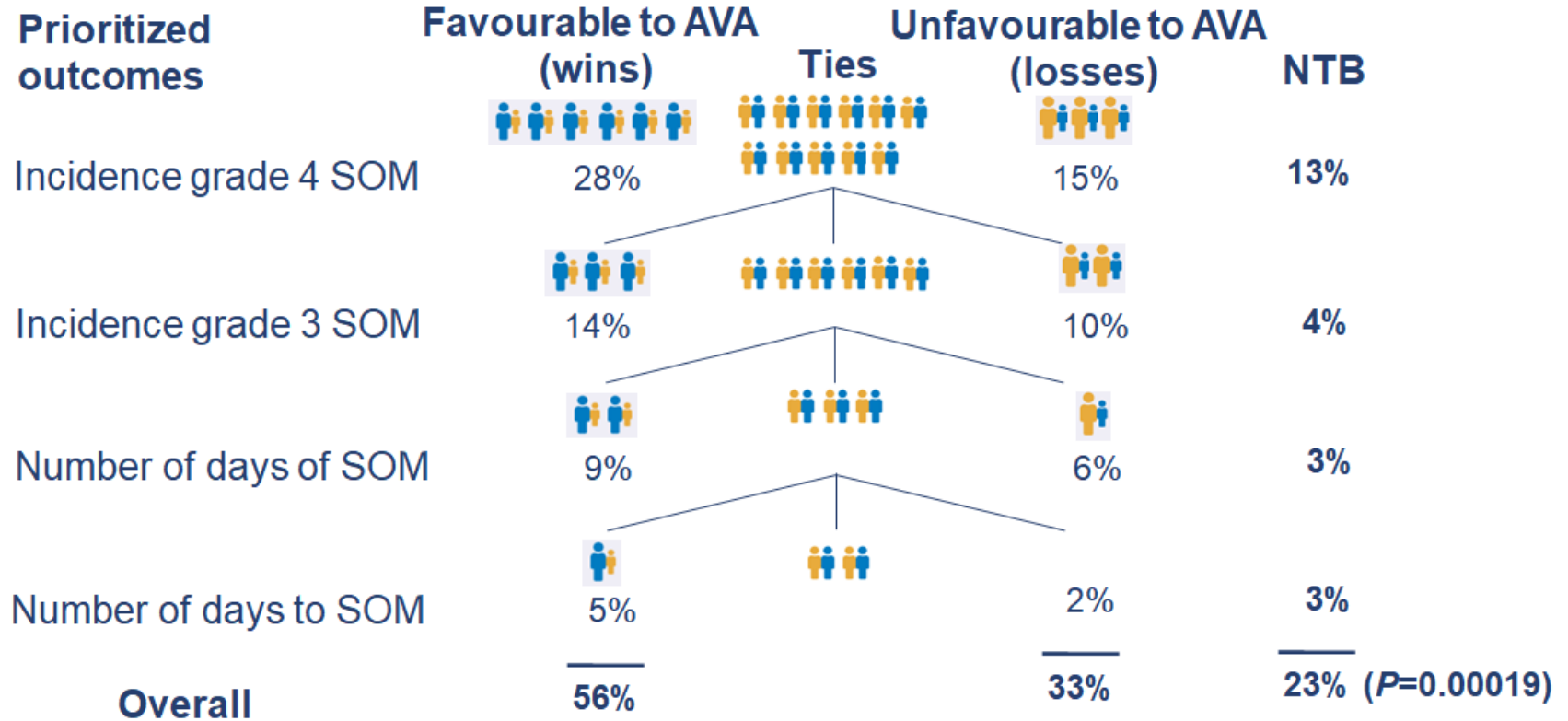
GENERALIZED PAIRWISE COMPARISONS

Prioritized Outcomes:

1. Incidence of WHO grade 4 SOM
2. Incidence of WHO grade 3 SOM
3. Number of days of SOM through IMRT *
4. Number of days to onset of SOM *

** Difference of at least 7 days defined as clinically relevant*

GENERALIZED PAIRWISE COMPARISONS



GENERALIZED PAIRWISE COMPARISONS

Interpretation

- 56% probability that a random AVA patient has a better outcome than a random placebo patient
- 33% probability that a random AVA patient has a worse outcome than a random placebo patient
- $\text{NTB} = 56\% - 33\% = 23\%$ ($P=0.00019$)

Number needed to treat = $1/23\% = 4.3$ patients

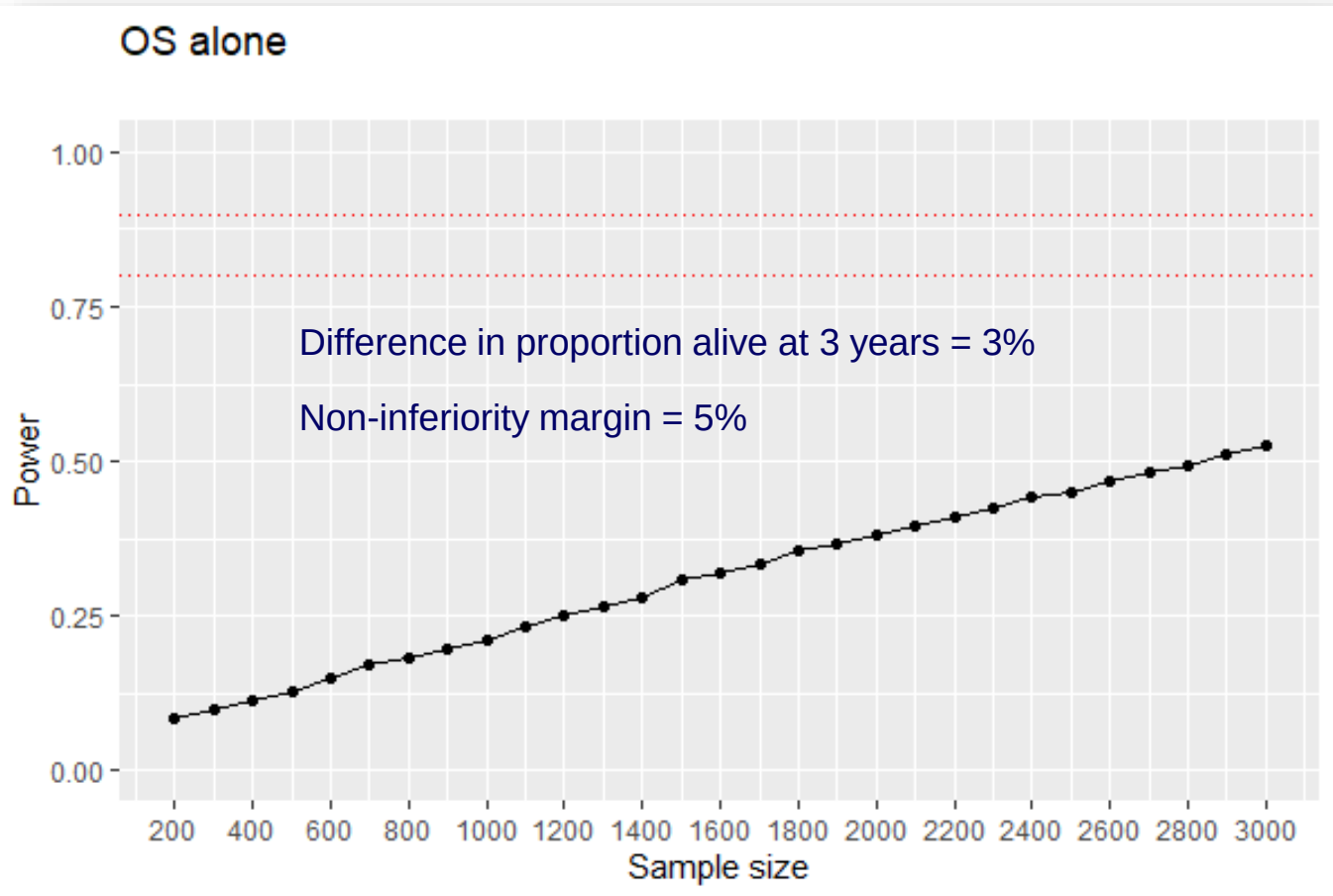
REPLACING SURVIVAL NON-INFERIORITY
BY A
NET BENEFIT SUPERIORITY

DESIGN OF TRIAL FOR REDUCED INTENSITY

- Clinical trial of neo-adjuvant radio-chemotherapy in elderly patients with rectal cancer: standard of care for young and fit patients is SCRT + 6 courses of chemotherapy: can chemotherapy be omitted in the elderly?

At 3-year follow-up:	SCRT + chemo	SCRT
Proportion alive	88%	85%
Proportion progression-free and alive	24%	32%
Proportion with grade ≥ 2 neurotoxicity	35%	5%
Proportion with grade ≥ 3 toxicities during neo-adjuvant therapy	55%	24%

SAMPLE SIZE REQUIRED TO SHOW NON-INFERIORITY OF OS



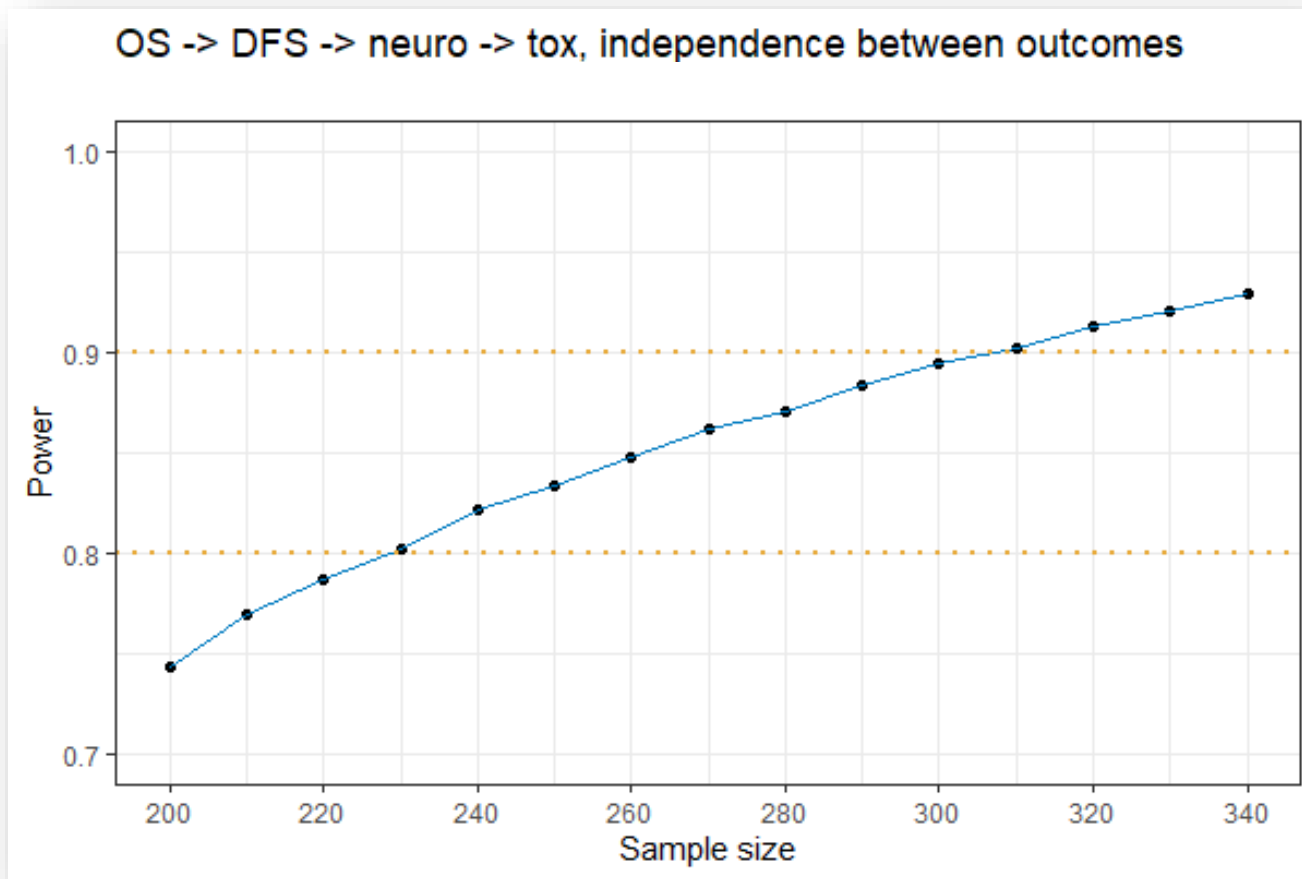
GENERALIZED PAIRWISE COMPARISONS

Prioritized Outcomes:

1. Time to death *
2. Time to disease recurrence *
3. Occurrence of grade ≥ 2 neurotoxicity
4. Occurrence of grade ≥ 3 toxicities during neo-adjuvant therapy

** Difference of at least 12 months considered to be patient relevant*

SAMPLE SIZE REQUIRED TO SHOW SUPERIORITY OF NTB



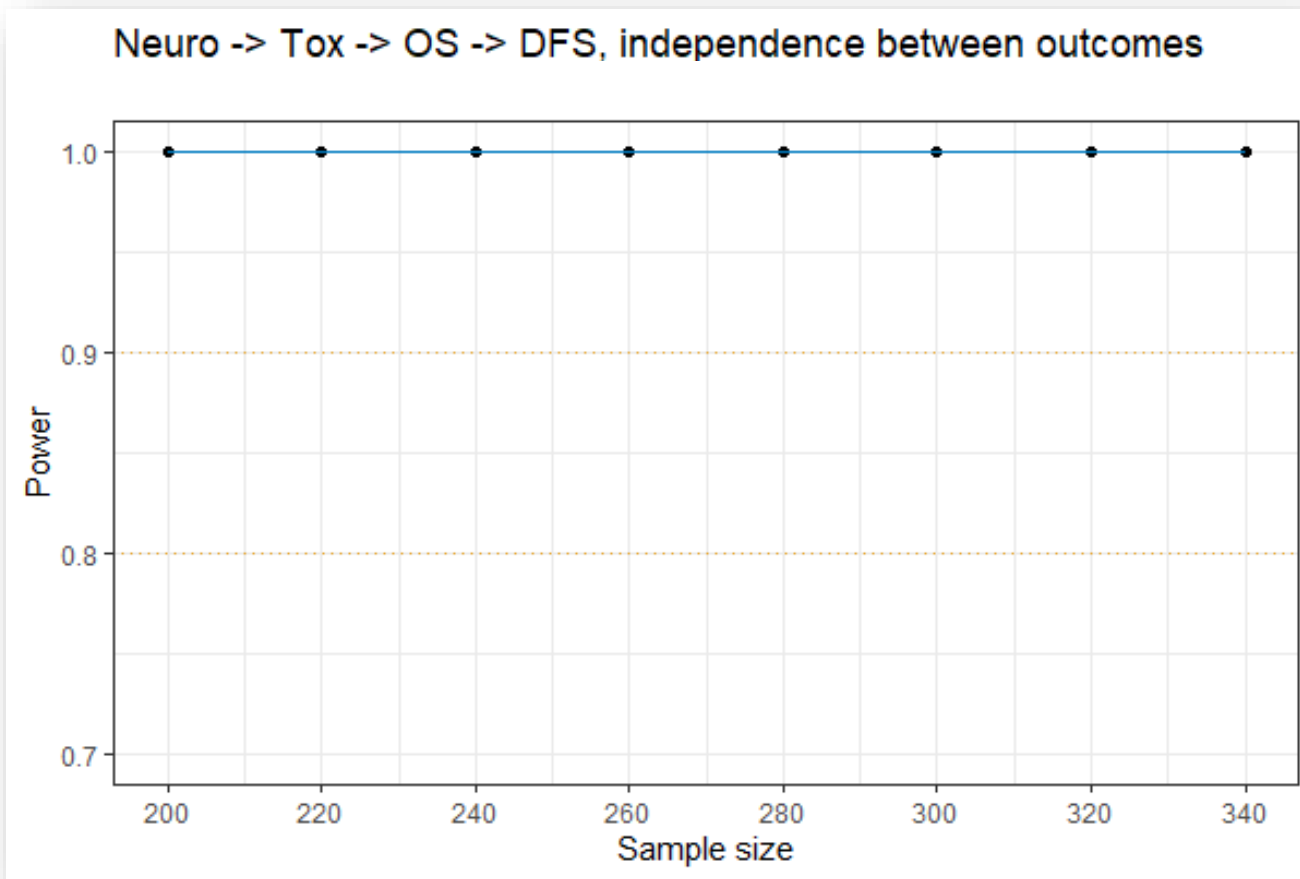
GENERALIZED PAIRWISE COMPARISONS

Prioritized Outcomes:

1. Occurrence of grade ≥ 2 neurotoxicity
2. Occurrence of grade ≥ 3 toxicities during neo-adjuvant therapy
3. Time to death *
4. Time to disease recurrence *

** Difference of at least 12 months defined as clinically relevant*

SAMPLE SIZE REQUIRED TO SHOW SUPERIORITY OF NTB



CONCLUSIONS

- GPC can analyze time to *worst* (most patient-relevant) outcome rather than time to *first* outcome
- GPC can incorporate as many outcomes of any type as desired
- GPC can combine clinical outcomes and patient-reported outcomes
- Priorities of outcomes and thresholds of clinical relevance can be individualized according to each patient's preferences