Composite endpoints including patient relevant endpoints (Quality of Life)

UHASSELT

I-BioStat

KU LEUVEN

Interuniversity Institute for Biostatistics and statistical Bioinformatics

EUROPEAN JOINT PROGRAMME RARE DISEASES

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Content

- Composite endpoints in clinical trials
- Generalized Pairwise Comparisons (GPC)
  - Effect measure
  - Characteristics
  - Inference for small samples
- Example: Epidermolysis bullosa
- Conclusions

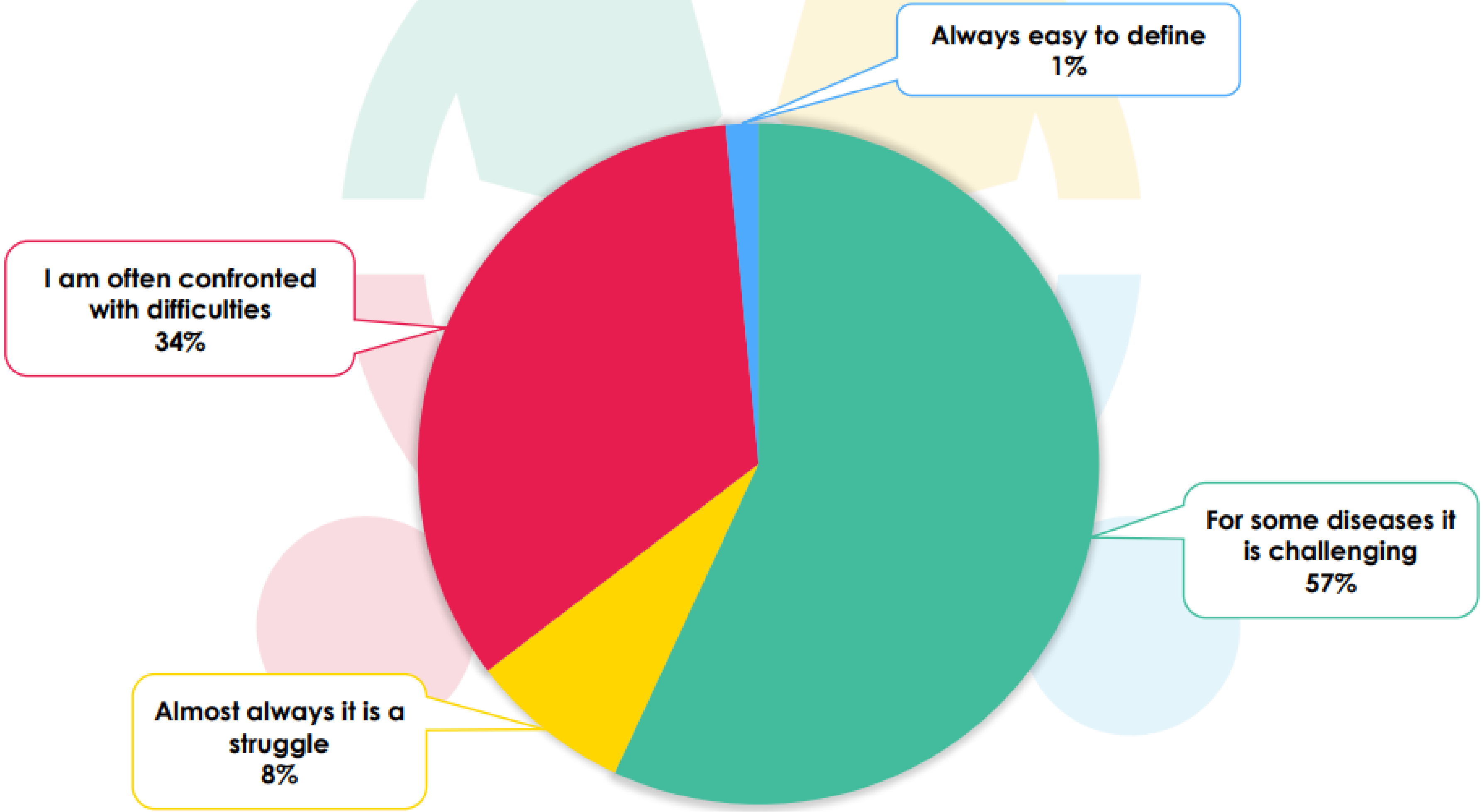
Composite endpoints in clinical trials

Multivariate endpoints

- International Conference Council on Harmonisation recommends to select a **single meaningful endpoint**.

International Conference on Harmonisation
E9 Expert Working Group (1998)

What is your experience to define a single meaningful endpoint for the study of a disease?



Multivariate endpoints

- It is **not always easy to choose** or define a meaningful single endpoint
- A single endpoint is **often not sufficient** to reflect the full clinical benefit of a treatment in multifaceted diseases
- **Combination** of several clinical meaningful endpoints

Combination of endpoints of different data type in small sample trials

International Conference on Harmonisation
E9 Expert Working Group (1998)

Multivariate endpoints methodologies

Combining endpoints on:

- **subject level:**
  - Reduce per subject multivariate to univariate endpoint: f.e. clinical indices, composite endpoints (time to first event)

    Cox proportional hazard model[1] and its extensions (Anderson-Gill[2],...)

    longrank test and its extension (weighted composite endpoint[3])

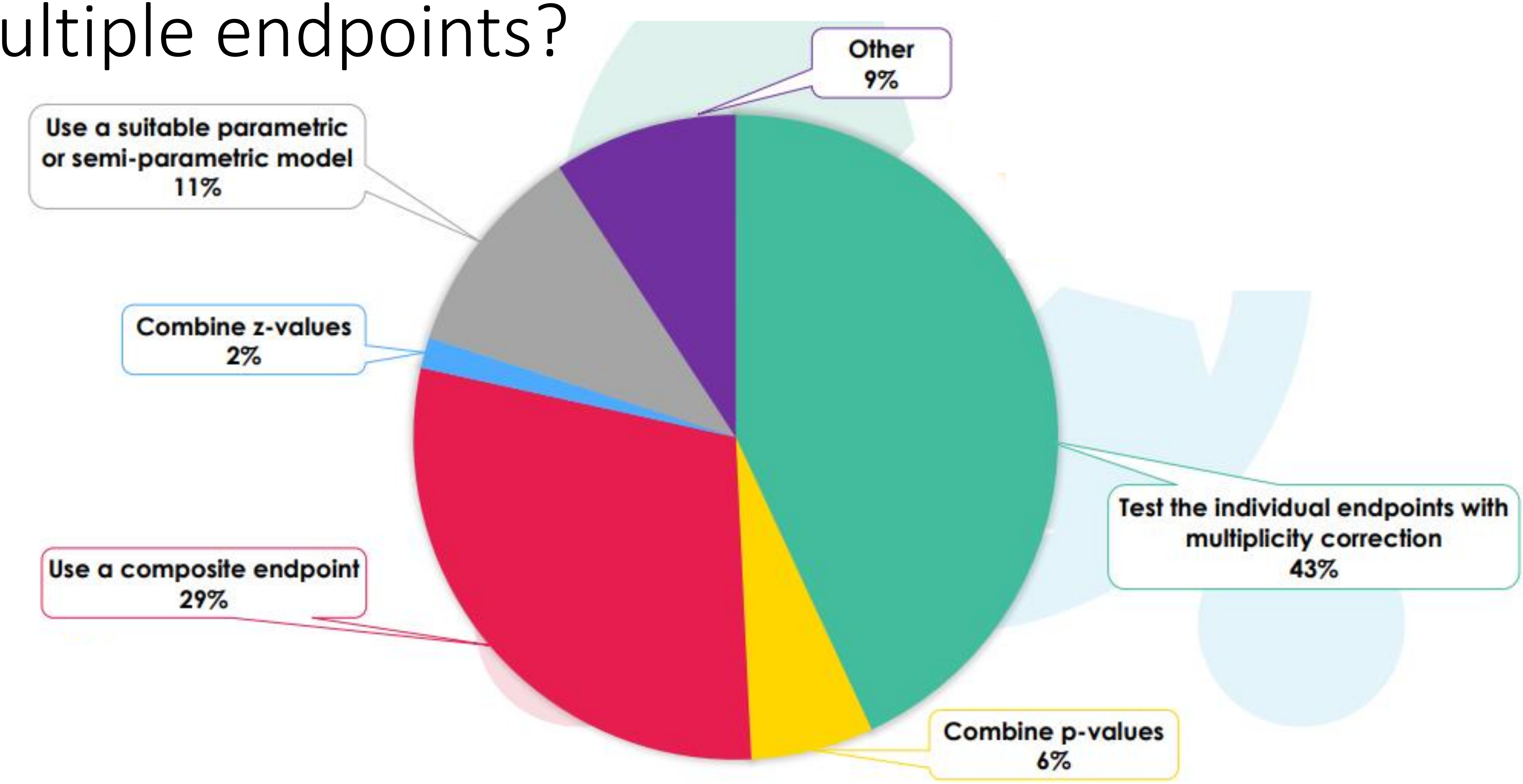
  - Joint frailty models[4],…

are limited:

- In the number and type of endpoints that can be combined
- Poor small sample properties

1. Cox (1972)
2. Andersen and Gill (1982)
3. Armstrong et al. (2011)
4. Rondeau et al. (2007)

What is your preferred method to handle multiple endpoints?



EJP RD

Multivariate endpoints methodologies

Combining endpoints on:

- **subject level:**
  - Reduce per subject multivariate to univariate endpoint: f.e. clinical indices, composite endpoints
  - joint models

- **test statistics level:** Combine univariate z-or t-statistics

  - combine t-statistics[1]: accounts for correlation, but only allows for continuous endpoints

  - average z-scores[2]: allows all types of endpoints, but ignores correlation

- **level of p-values:** Combine p-values of endpoint corresponding test

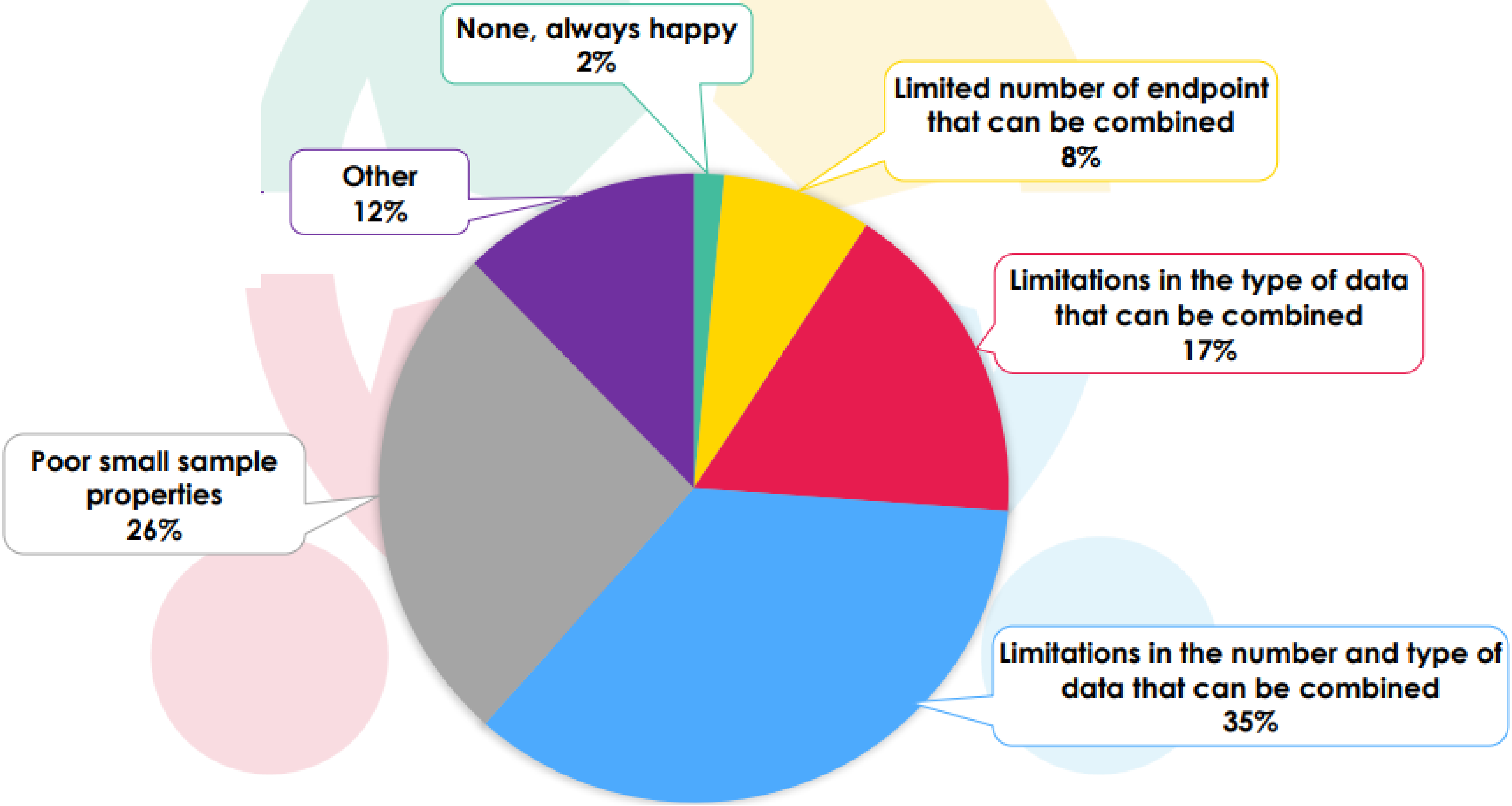
  f.e. Lancaster[3], Dai[4] procedures, multiple testing procedures[5] : correlation?

1. O'Brien (1984)
2. Sun et al. (2012)
3. Lancaster (1961)
4. Dai et al. (2014)
5. Dmitrienko et al. (2010)

Limitations of multivariate methods

- Ignore the correlation between the endpoints
- Limited to one type of endpoints
- Treats every endpoint as equally important
- No straightforward effect sizes measure to quantify the effect of the treatment is available
- Small sample properties

What are the limitations you encounter with multiple endpoint analyses?



EJP RD

Novel non-parametric methods

- **Based on ranks**:

  Global rank[1], Desirability of Outcome Ranking (DOOR)[2]; unambiguous ranks are not possible for multivariate censored outcomes

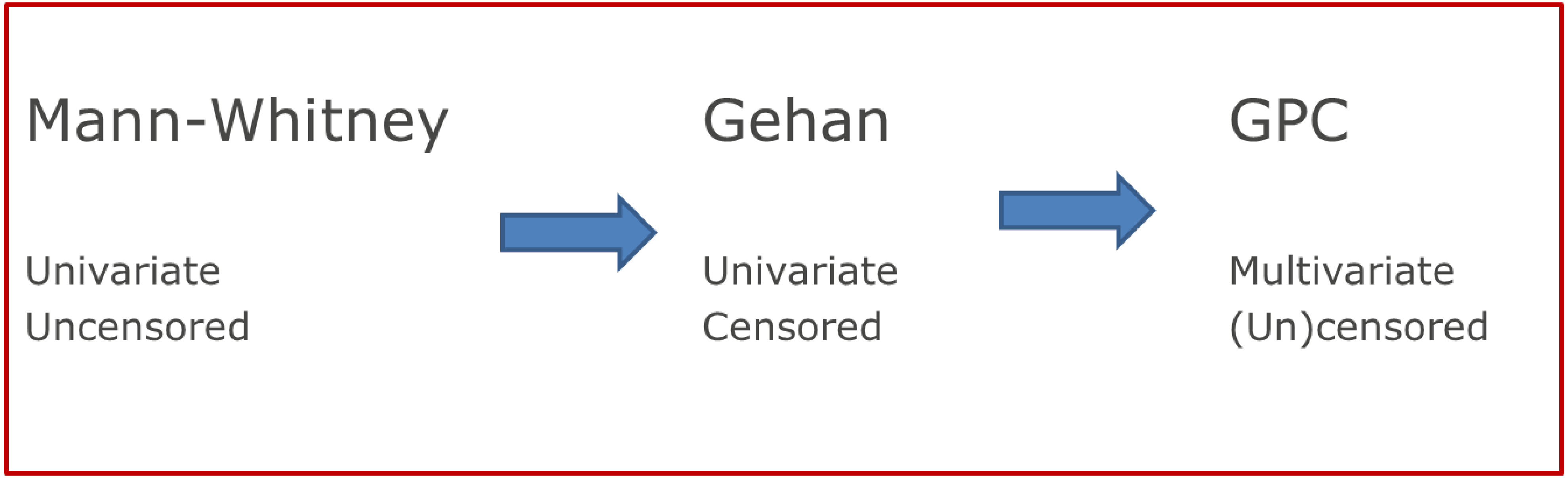
- **Extension of Mann-Whitney test** :

  Generalized Pairwise Comparisons[3] (or win statistics[4])

1. Felker and Maisel (2010)
2. Evans et al. (2015)
3. Buyse (2010)
4. Dong et al. (2021)

Generalized Pairwise Comparisons (GPC)

Family of GPC



Mann-Whitney

Univariate
Uncensored

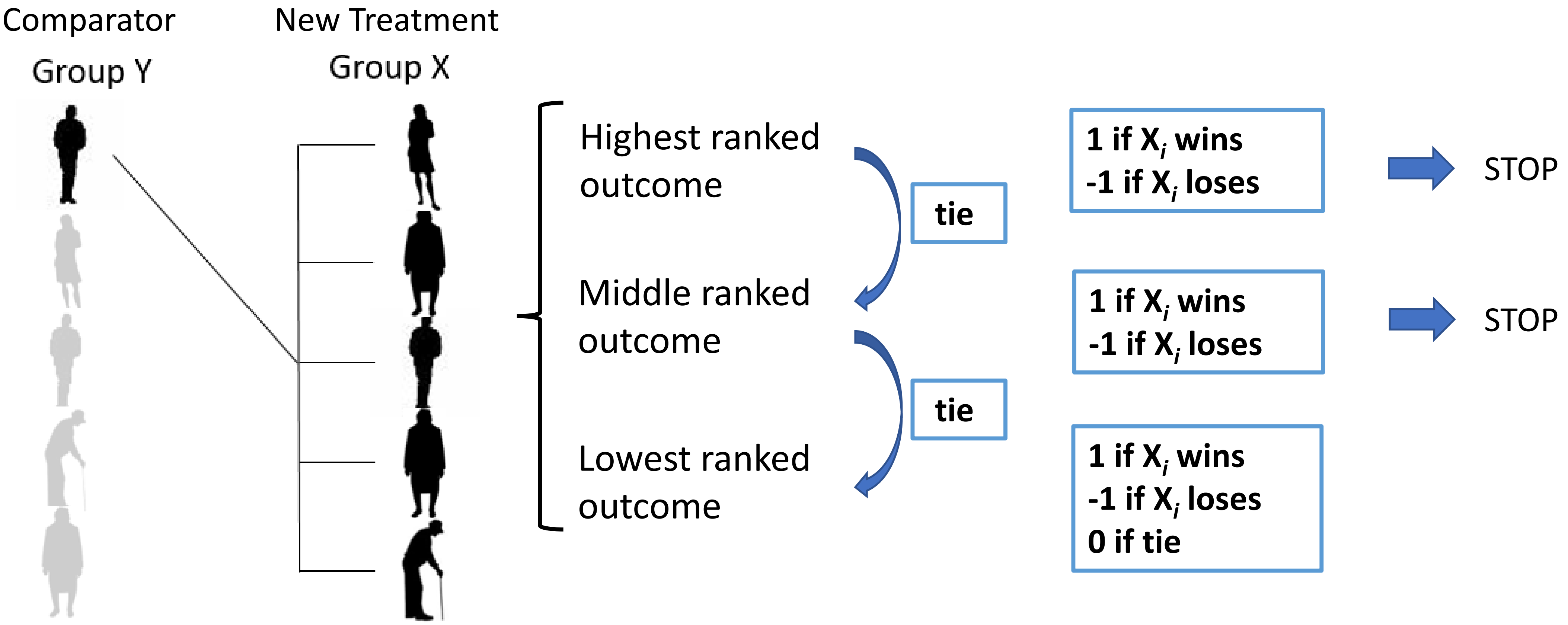
Gehan

Univariate
Censored

GPC

Multivariate
(Un)censored

Generalized Pairwise Comparison (GPC) methodology



Comparator

Group Y

New Treatment

Group X

Highest ranked outcome

tie

1 if X_i wins
-1 if X_i loses

STOP

Middle ranked outcome

tie

1 if X_i wins
-1 if X_i loses

STOP

Lowest ranked outcome

1 if X_i wins
-1 if X_i loses
0 if tie

Finkelstein et al. (1999)
Buyse (2010)
Pocock et al (2012)

GPC statistics

$$\text{Net (treatment) benefit} = \frac{N_X - N_Y}{nm}$$

Amount of pairs

Number of wins for the treatment subjects

Number of wins for the control subjects

Net benefit (Δ): values between [-1, 1]
$\Delta = P(X>Y) - P(X<Y)$

= U-statistic

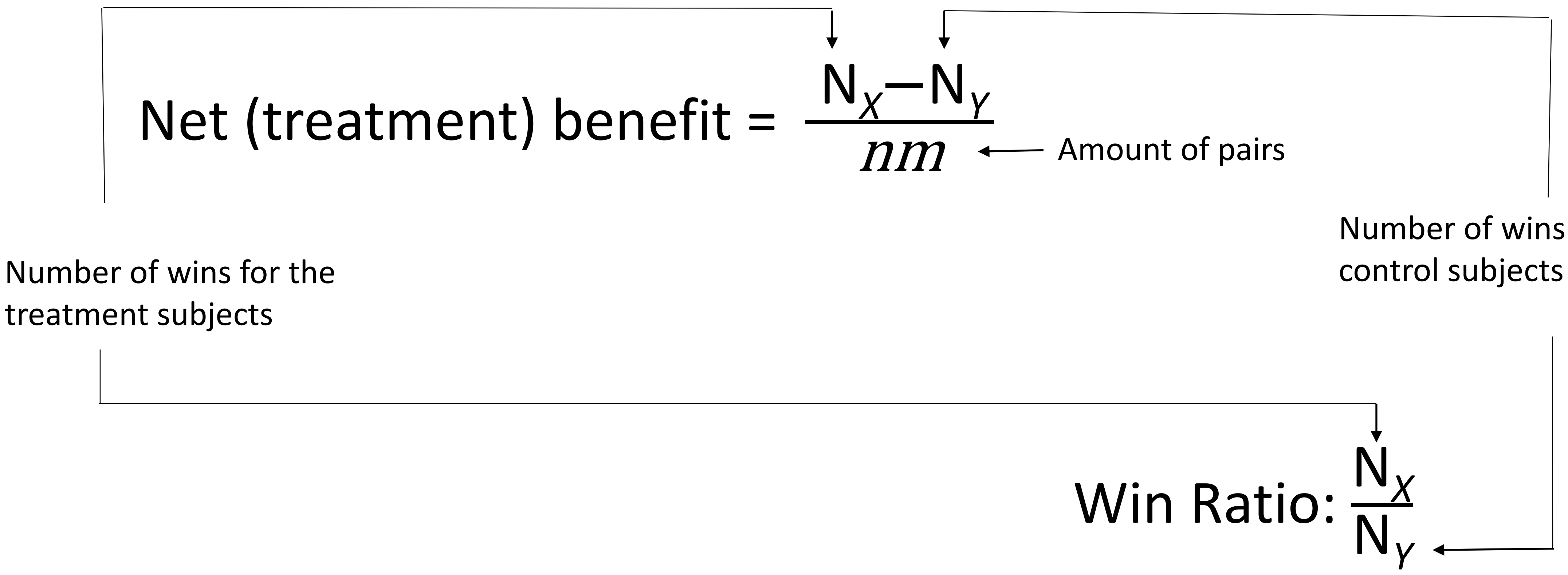
Related to probabilistic index, relative effect,… (θ):

$$\theta = P(X>Y) + 1/2\, P(X=Y)$$

$$\Delta = 2\theta - 1$$

Buyse (2010)

GPC statistics



Net (treatment) benefit = $\frac{N_X - N_Y}{nm}$

Amount of pairs

Number of wins for the treatment subjects

Number of wins for the control subjects

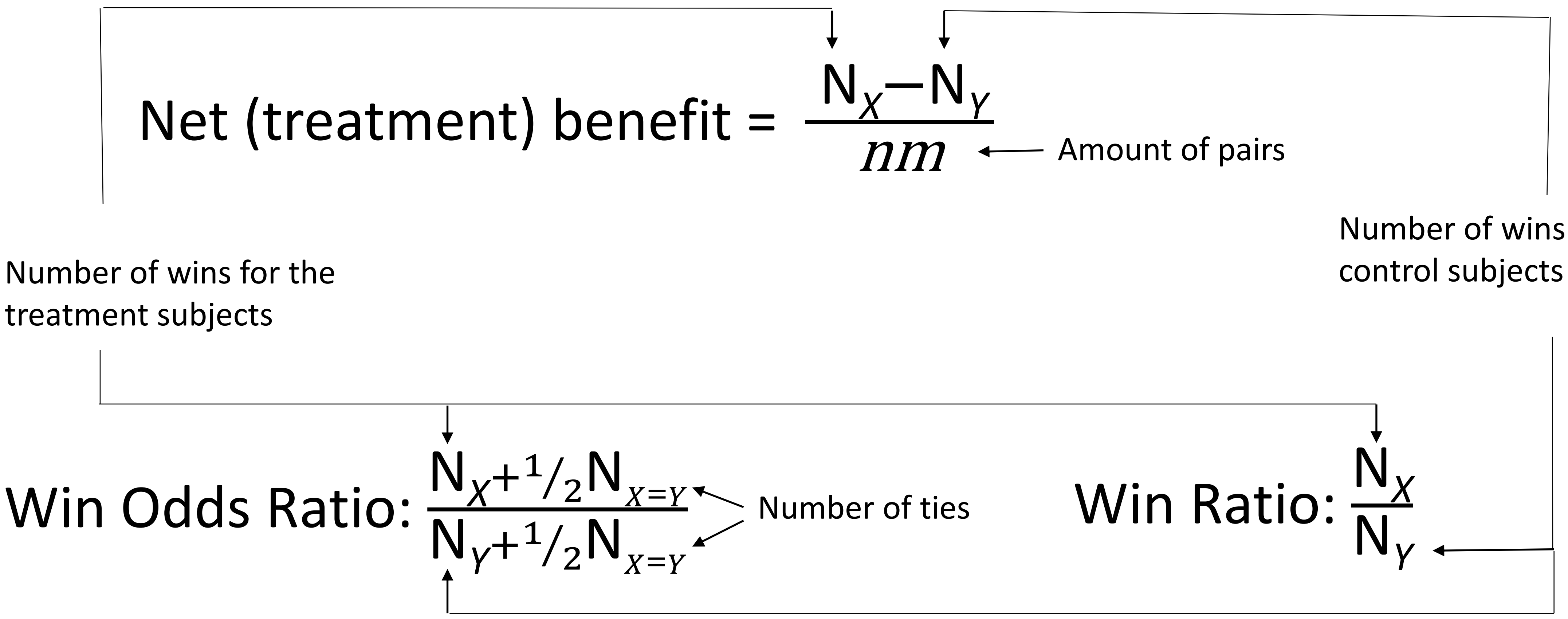
Win Ratio: $\frac{N_X}{N_Y}$

Values between [0,∞ [

Ignores ties

Pocock et al. (2012)

GPC statistics



Net (treatment) benefit = $\frac{\mathrm{N}_X - \mathrm{N}_Y}{nm}$

Amount of pairs

Number of wins for the treatment subjects

Number of wins for the control subjects

Win Odds Ratio: $\frac{\mathrm{N}_X + {}^1\!/_2\mathrm{N}_{X=Y}}{\mathrm{N}_Y + {}^1\!/_2\mathrm{N}_{X=Y}}$

Number of ties

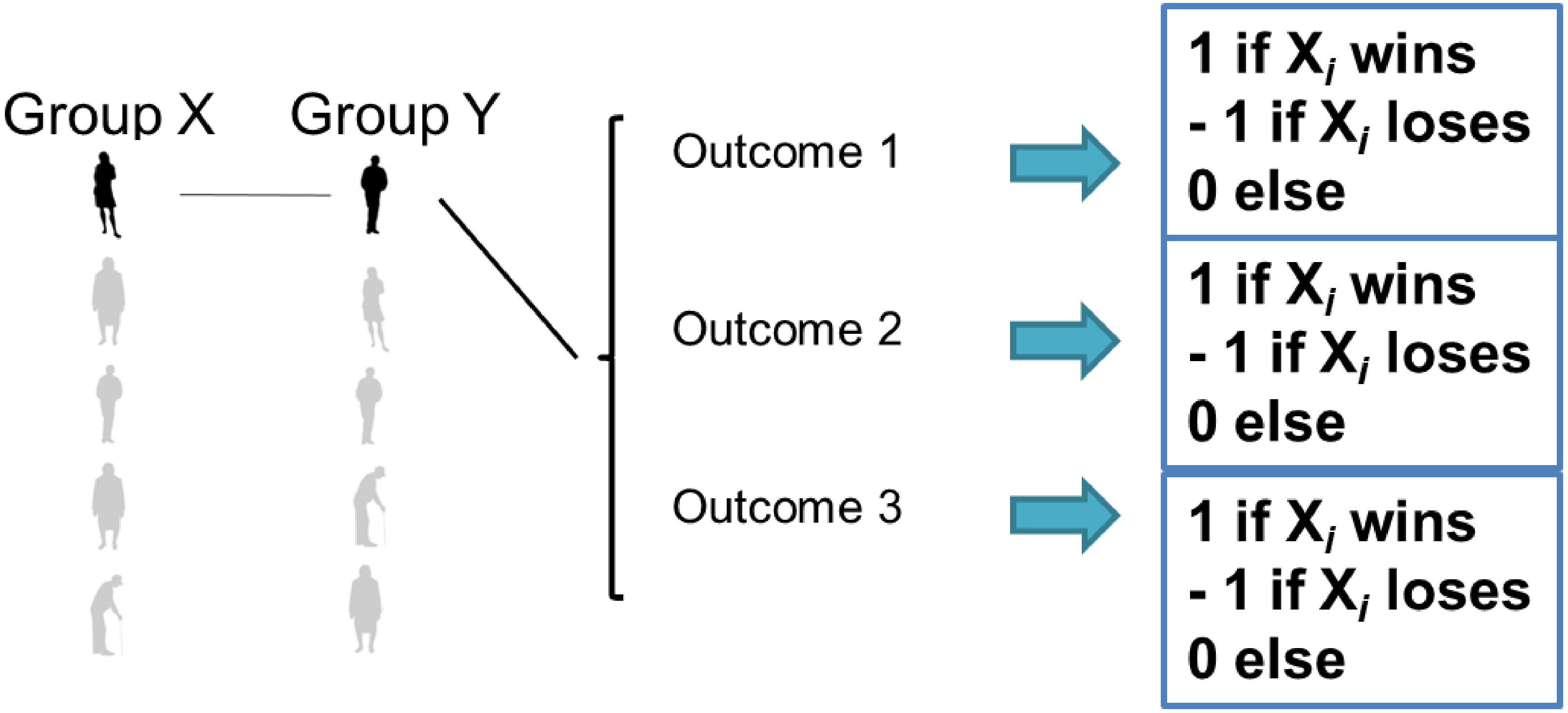
Win Ratio: $\frac{\mathrm{N}_X}{\mathrm{N}_Y}$

Values between [0,∞ [

$$= \frac{1+\Delta}{1-\Delta}$$

Dong et al. (2020)
Brunner et al. (2021)

Non-prioritized GPC



Group X

Group Y

Outcome 1

Outcome 2

Outcome 3

1 if X_i wins
- 1 if X_i loses
0 else

1 if X_i wins
- 1 if X_i loses
0 else

1 if X_i wins
- 1 if X_i loses
0 else

$$\Delta = \frac{N_X - N_Y}{nm\textcolor{red}{k}}$$

with *k* the number of outcomes

O'Brien (1984)
Ramchandani et al. (2016)
Verbeeck et al. (2019)

Flexible framework of GPC

- Prioritized/non-prioritized[1,2]
- Matched/unmatched pairwise comparisons[3]
- Threshold of clinical relevance (τ)[4]

[1] Ramchandani et al. (2016)
[2] Verbeeck et al. (2019)
[3] Pocock et al. (2012)
[4] Buyse (2010)

Characteristics of GPC

- **Univariate uncensored:** unbiased and efficient in clinical trials scenarios[1]

- **Univariate censored**: drop-out bias can be corrected[2]

- **Multivariate:** correlation between outcomes affects prioritized and non-prioritized GPC differently[3]

1. Verbeeck et al. (2021)
2. Deltuvaite-Thomas et al. *Submitted*
3. Verbeeck et al. (2019)

Inference with GPC

Net benefit	Win ratio	Win odds
Re-sampling permutation test	Re-sampling bootstrap test	Rank-based test
Asymptotic Normal U-statistic	Asymptotic Lognormal U-statistic	

Theoretically shown that GPC test with net benefit, win ratio and win odds are approximately equal

Small sample behavior?

Verbeeck et al. (2020)

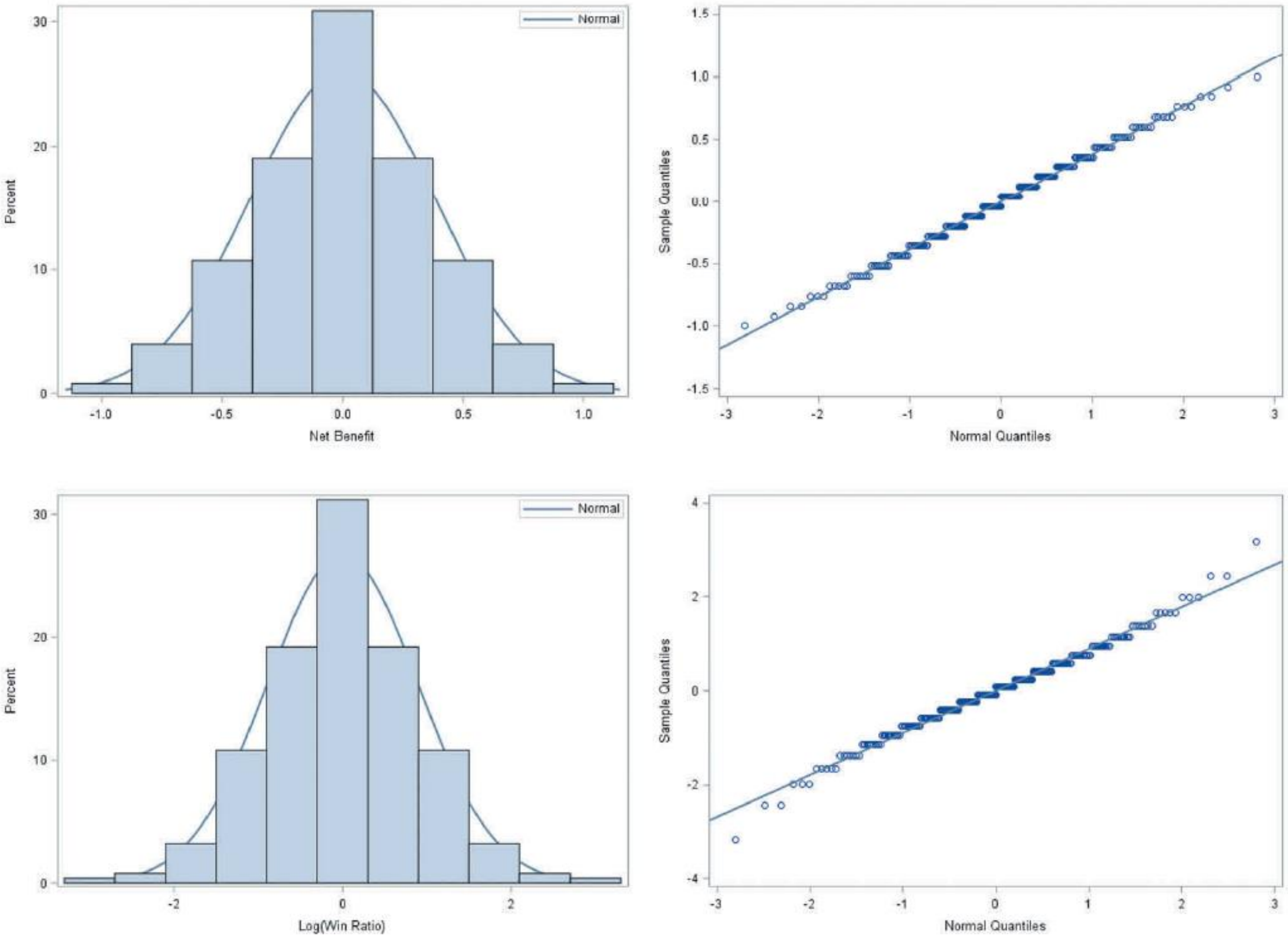
Small sample inference with GPC

- Extend **exact permutation test** of Gehan and Gilbert to win ratio, to bootstrap test and non-prioritized GPC.

- The null distribution of the GPC statistic in every possible permutation (bootstrap) sample is standard normally distributed.

Verbeeck et al. (2020)

Small sample inference with GPC

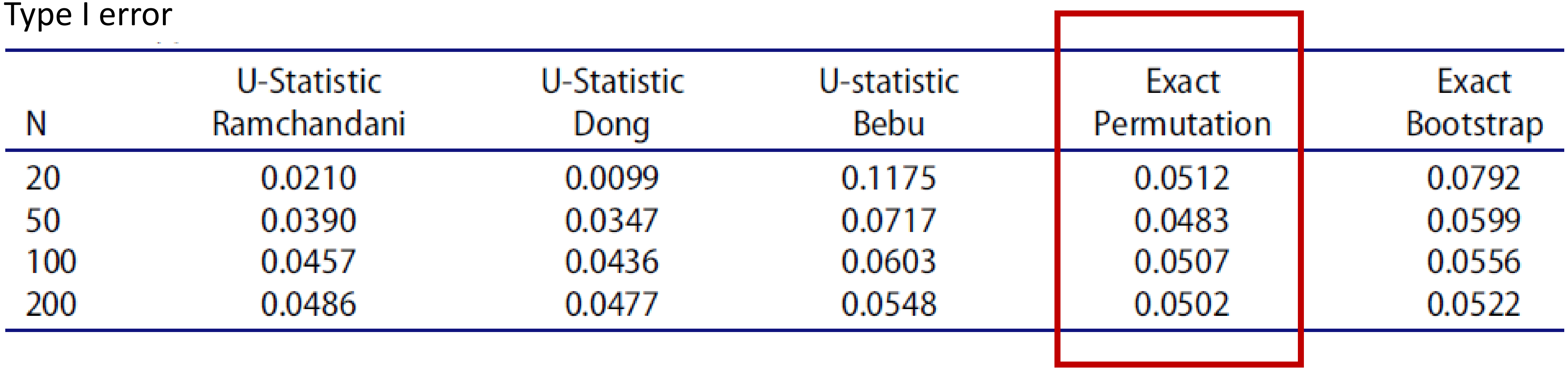


Histogram with fitted normal density curve (left) and normal Q-Q plot (right) of the exact permutation distribution of the net benefit (top row) and the logarithm of the win ratio (bottom row) for a simulation of **five subjects per arm**.

Verbeeck et al. (2020)

Small sample inference with GPC

Type I error



N	U-Statistic Ramchandani	U-Statistic Dong	U-statistic Bebu	Exact Permutation	Exact Bootstrap
20	0.0210	0.0099	0.1175	0.0512	0.0792
50	0.0390	0.0347	0.0717	0.0483	0.0599
100	0.0457	0.0436	0.0603	0.0507	0.0556
200	0.0486	0.0477	0.0548	0.0502	0.0522

Verbeeck et al. (2020)

GPC corrects all limitations of multivariate methods

- Captures correlation between the endpoints
- Allows any number and type of endpoints
- Allows priority ranking of endpoints by severity
- Straightforward effect sizes measure to quantify the effect of the treatment
- Good small sample properties

GPC method accepted by regulatory authorities

- Amyloid cardiomyopathy (ATTR-CM)
- Prevalence <1/100,000 in EU
- Accumulation of misfolded transthyretin amyloid fibrils in the myocardium, leading to restrictive cardiomyopathy and heart failure.

- Drug approval Vyndaqel (tafamidis) by FDA (May 2019) and EMA (Feb 2020) based on ATTR-ACT trial:
  - 441 patients
  - **Primary endpoint: GPC** with all-cause mortality, followed by cardiovascular-related hospitalizations

Maurer et al. (2018)

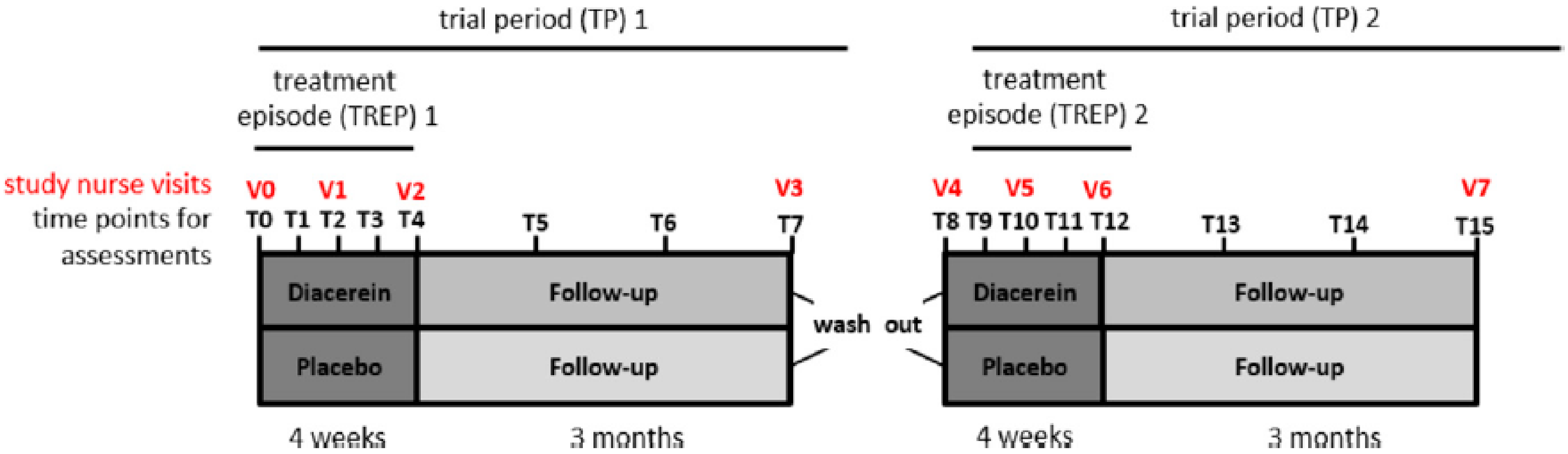
Example: Epidermolysis bullosa

European Joint Programme on Rare Diseases:
“Demonstration projects on existing statistical methodologies to improve RD clinical trials”

EBStatMax project (Salzburg, Hasselt, Uppsala)

EB trial design

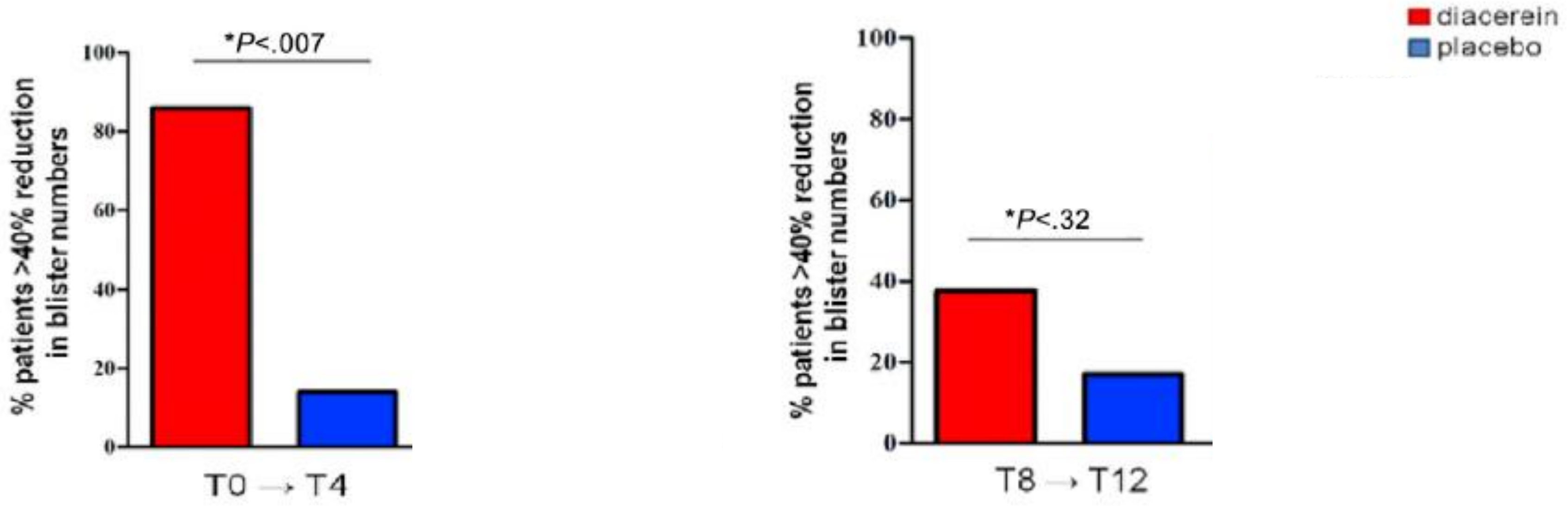
- Rare skin disease: Epidermolysis bullosa simplex
- Formation of blisters under low mechanical stress
- 15 pediatric subjects (with missing data) treated with placebo and diacerin cream in a longitudinal cross-over trial



Wally et al. (2018)

Inconclusive results primary endpoint analysis

- Primary endpoint: >40% reduction in blister count compared to baseline (binary outcome) at week 4; Barnard test (~Fisher exact test 2x2 table)



Wally et al. (2018)

But…..

- Barnard test ignores:
  - Cross-over design
  - Longitudinal data: blister count measurement: 2, 4, weeks and 3 months
  - Patient relevant outcomes: QoL: baseline and post-treatment visit 4 weeks

- Question:

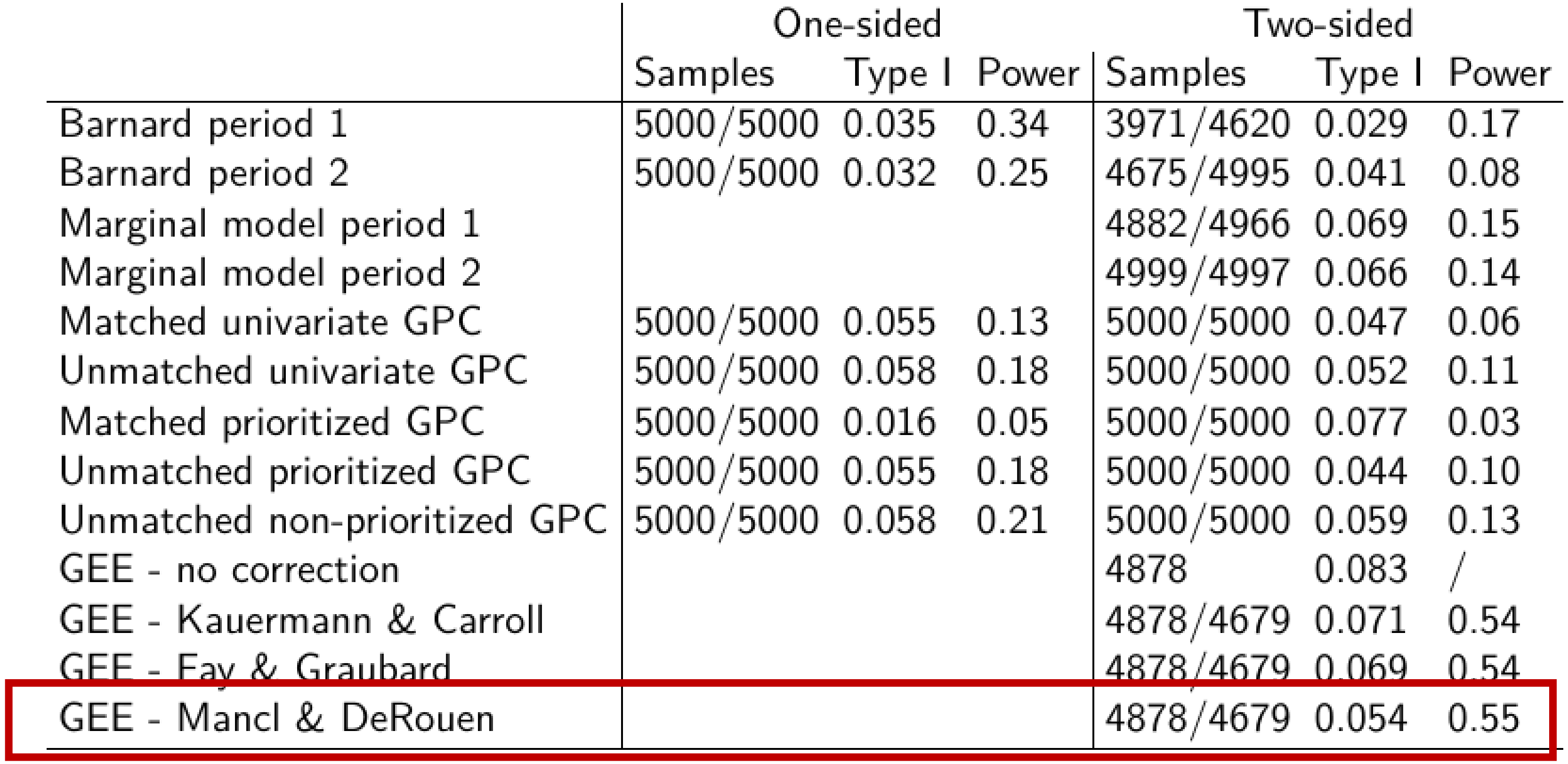
“Is there a powerful test, accounting for the cross-over design and longitudinal information? ”

Wide array of tests are being evaluated for blister outcome

- Non-parametric:
  - Rank-based marginal model for longitudinal data (nparLD)
  - GPC
- Semi-parametric
  - GEE-type model with small sample corrections
- Parametric
  - Model averaging

Verbeeck et al. *In prep*

GEE-type model performs best for cross-over longitudinal measures



	One-sided			Two-sided		
	Samples	Type I	Power	Samples	Type I	Power
Barnard period 1	5000/5000	0.035	0.34	3971/4620	0.029	0.17
Barnard period 2	5000/5000	0.032	0.25	4675/4995	0.041	0.08
Marginal model period 1				4882/4966	0.069	0.15
Marginal model period 2				4999/4997	0.066	0.14
Matched univariate GPC	5000/5000	0.055	0.13	5000/5000	0.047	0.06
Unmatched univariate GPC	5000/5000	0.058	0.18	5000/5000	0.052	0.11
Matched prioritized GPC	5000/5000	0.016	0.05	5000/5000	0.077	0.03
Unmatched prioritized GPC	5000/5000	0.055	0.18	5000/5000	0.044	0.10
Unmatched non-prioritized GPC	5000/5000	0.058	0.21	5000/5000	0.059	0.13
GEE - no correction				4878	0.083	/
GEE - Kauermann & Carroll				4878/4679	0.071	0.54
GEE - Fay & Graubard				4878/4679	0.069	0.54
GEE - Mancl & DeRouen				4878/4679	0.054	0.55

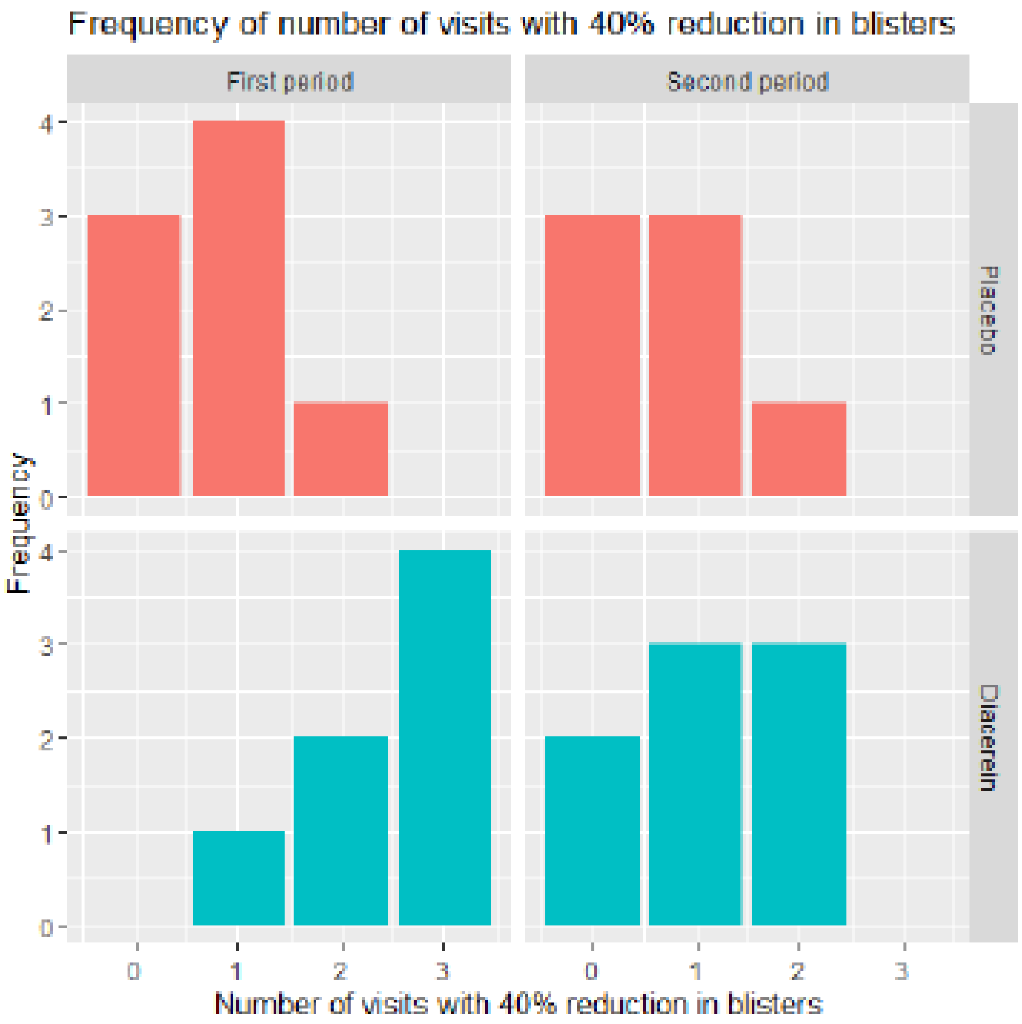
$$\mathrm{logit}(\pi_{ist}) = \beta_0 + \beta_1 G_{is} + \beta_2 P_i + \sum \beta_j T_{ist},$$

Verbeeck et al. *In prep*

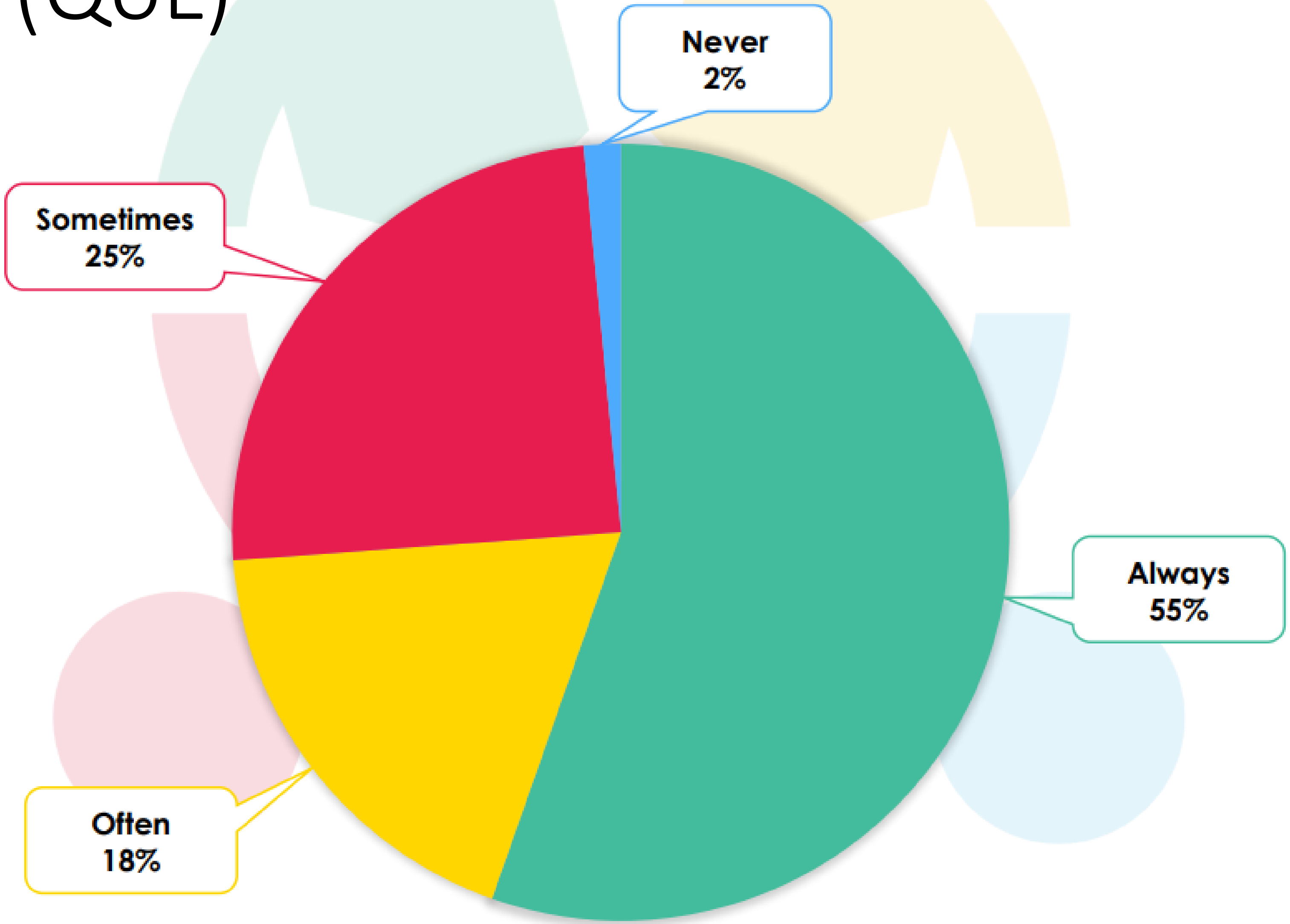
Diacerin improves blister outcome

The **odds ratio** of a 40% reduction in the number of blisters between diacerein and placebo is **5.73 (95%CI: 1.50–21.91; *p-value* = 0.0125)**, which is mainly due to the effect in the first period.

The odds ratio of a 40% reduction in the number of blisters in period 1 versus period 2 is 4.34 (95% CI: 1.12–16.84; *p-value* =0.0350).



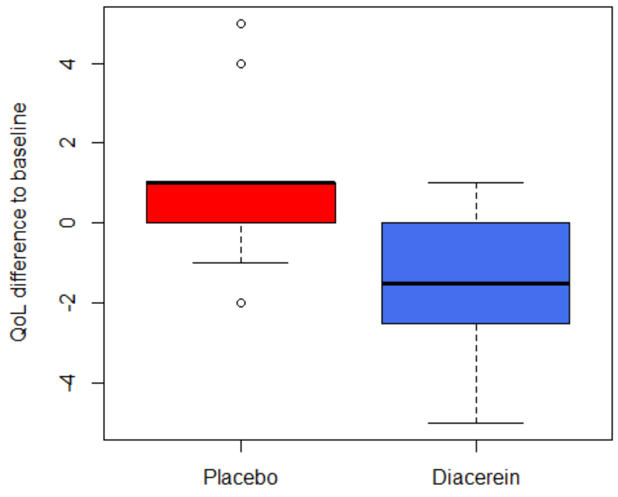
Multivariate outcome with patient reported outcome (QoL)



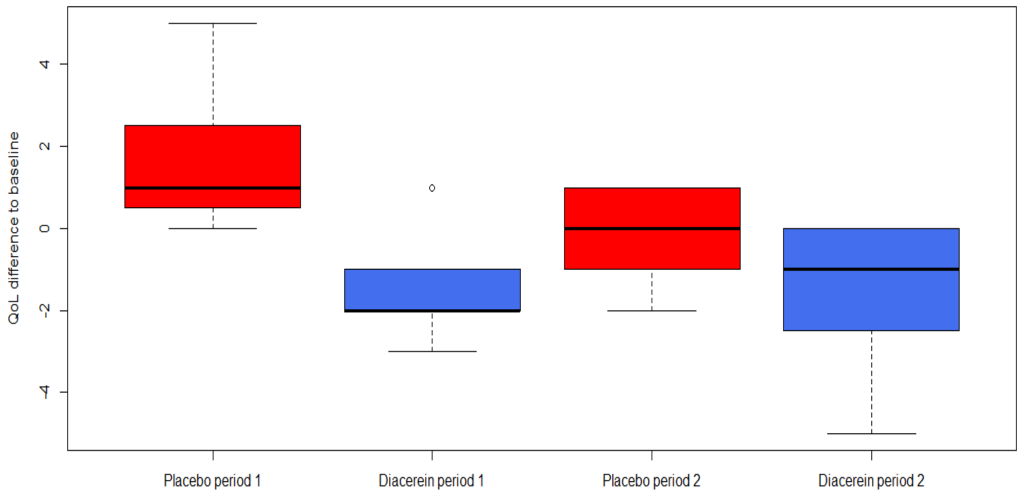
Multivariate outcome with patient reported outcome (QoL)

QoL questionnaire on hindrance daily activities:

- 8 questions
- Each scored:
  0 (no hindrance)-3 (very much hindrance)
- Maximum of 24 points



Since QoL is measured only at baseline and post-treatment visit, we ignore the longitudinal profile of the blister outcome



Multivariate outcome with patient reported outcome (QoL)

- Non-parametric:
  - Rank-based marginal model for longitudinal data (nparLD)
  - GPC

- Semi-parametric
  - GEE-type model with small sample corrections

- Parametric
  - Model averaging

Variants of GPC

- (Unmatched) Prioritized GPC:
  - 40% blister reduction
  - QoL difference to baseline
- (Unmatched) Non-prioritized GPC
- Matched prioritized GPC

Matched GPC inference

- Conditional sign test:

$$Z_m = \frac{N_X - N_Y}{\sqrt{N_X + N_Y}} \sim N(0,1)$$

Uniformly most powerful test

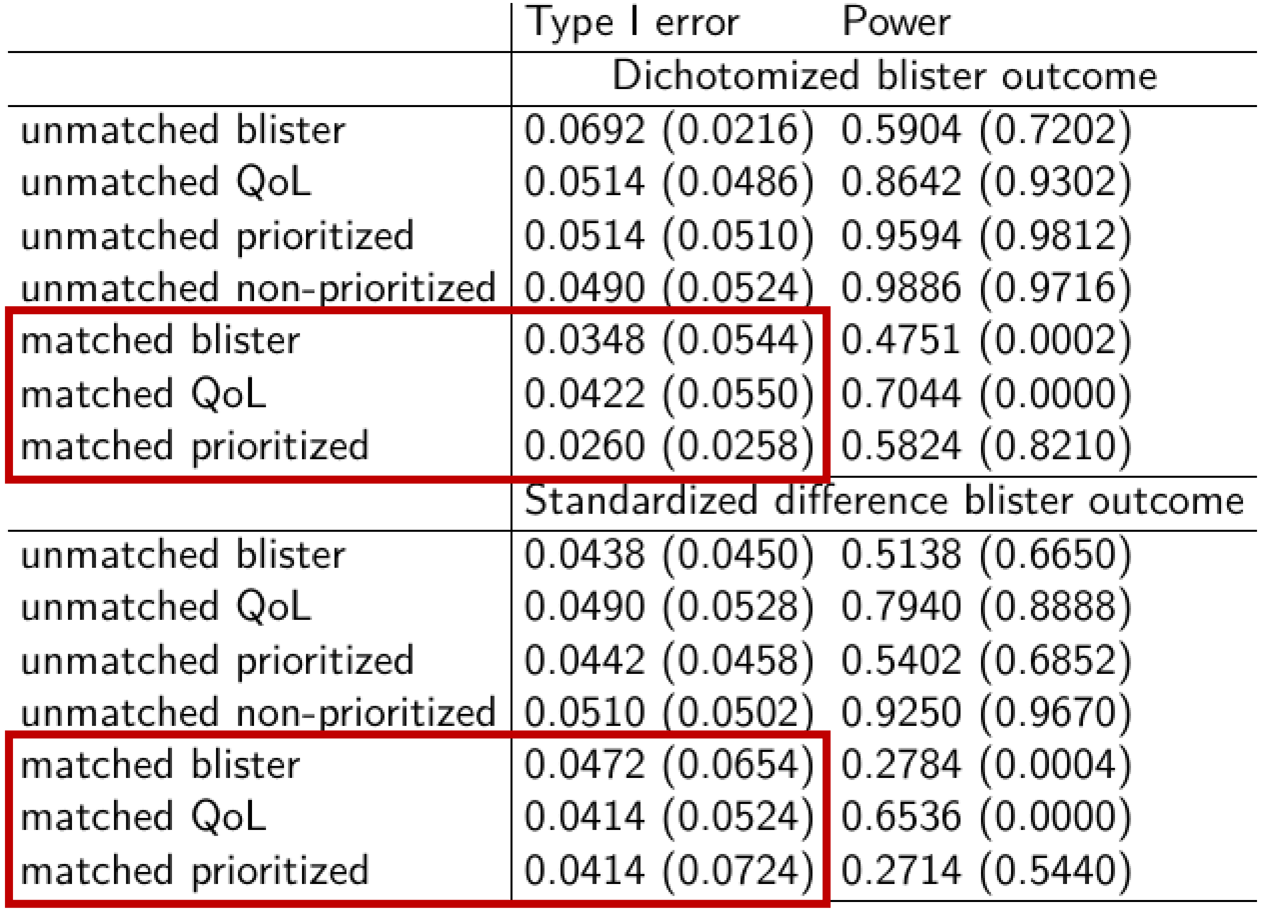
- But:
  - requires at least 15-20 (paired) subjects
  - ignores number of ties
  - Konietschke and Pauly (2012) motivate that under certain conditions (applicable for the exact permutation test) the paired design can be ignored.

Coakley et al. (1996)
Fagerland et al. (2013)

Simulation set-up

- Permute EB trial blister count and QoL over treatment arms 5000 times
- Add a random Poisson(λ=3) treatment effect for both the placebo blister count and QoL for the placebo arm
- Dichotomized blister count (40% reduction) and standardized difference with baseline ($\frac{y_0 - y_4}{y_0}$)

Matched GPC: often uncontrolled type I error



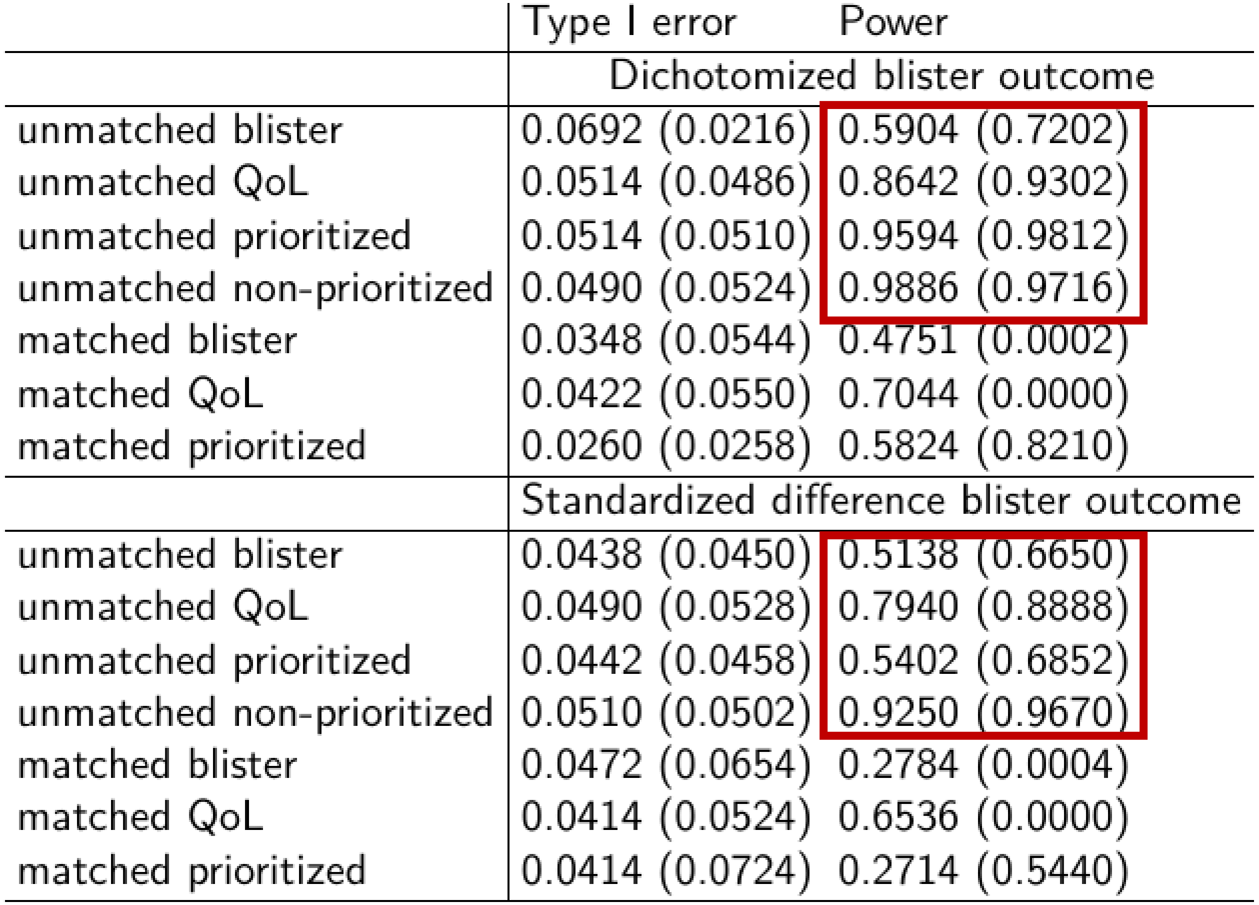
	Type I error	Power
	Dichotomized blister outcome	
unmatched blister	0.0692 (0.0216)	0.5904 (0.7202)
unmatched QoL	0.0514 (0.0486)	0.8642 (0.9302)
unmatched prioritized	0.0514 (0.0510)	0.9594 (0.9812)
unmatched non-prioritized	0.0490 (0.0524)	0.9886 (0.9716)
matched blister	0.0348 (0.0544)	0.4751 (0.0002)
matched QoL	0.0422 (0.0550)	0.7044 (0.0000)
matched prioritized	0.0260 (0.0258)	0.5824 (0.8210)
	Standardized difference blister outcome	
unmatched blister	0.0438 (0.0450)	0.5138 (0.6650)
unmatched QoL	0.0490 (0.0528)	0.7940 (0.8888)
unmatched prioritized	0.0442 (0.0458)	0.5402 (0.6852)
unmatched non-prioritized	0.0510 (0.0502)	0.9250 (0.9670)
matched blister	0.0472 (0.0654)	0.2784 (0.0004)
matched QoL	0.0414 (0.0524)	0.6536 (0.0000)
matched prioritized	0.0414 (0.0724)	0.2714 (0.5440)

N=13

N=12

Two-sided (one-sided) type I error and power

Adding QoL to blister increases power,…



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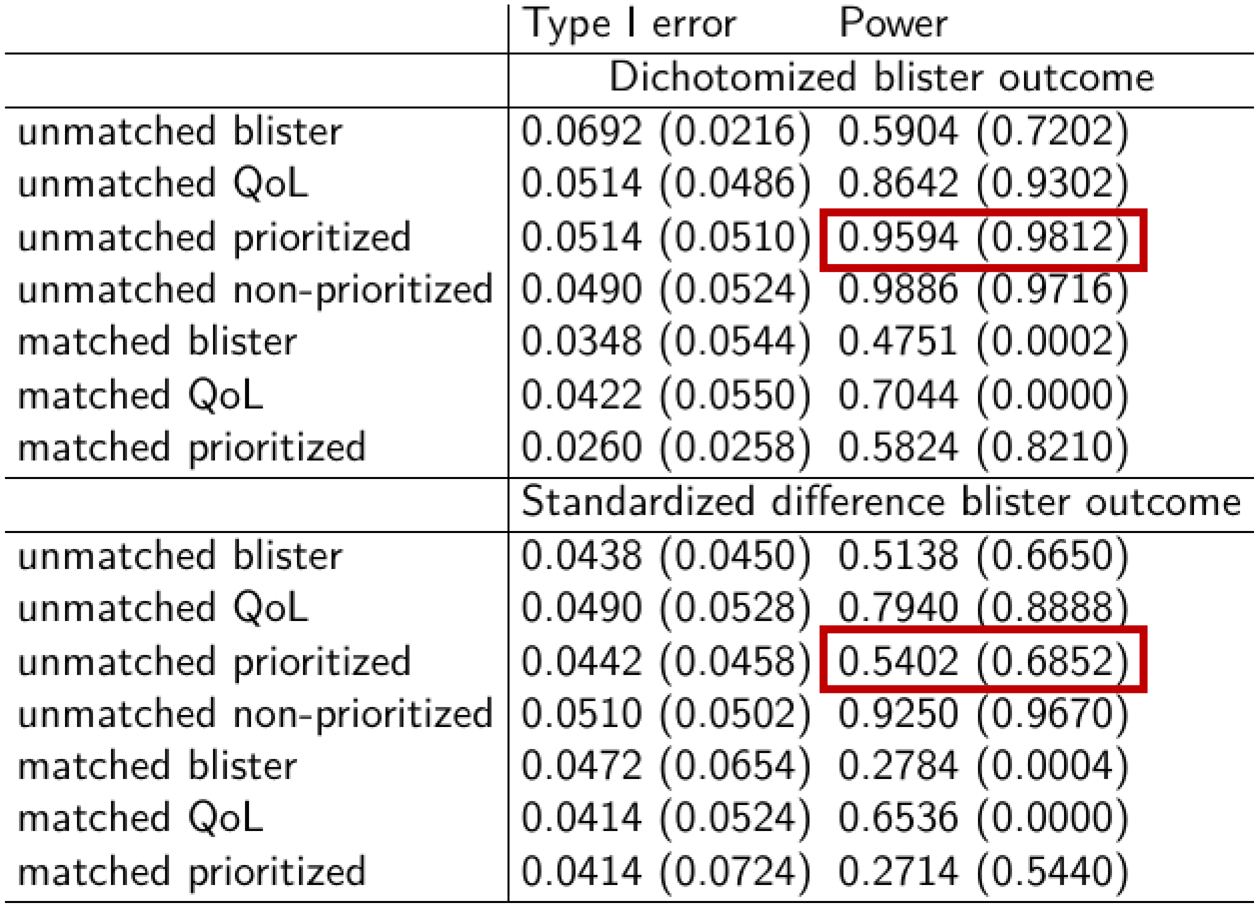
N=15x15

N=14x14

Two-sided (one-sided) type I error and power

… but less so for the prioritized continuous outcome



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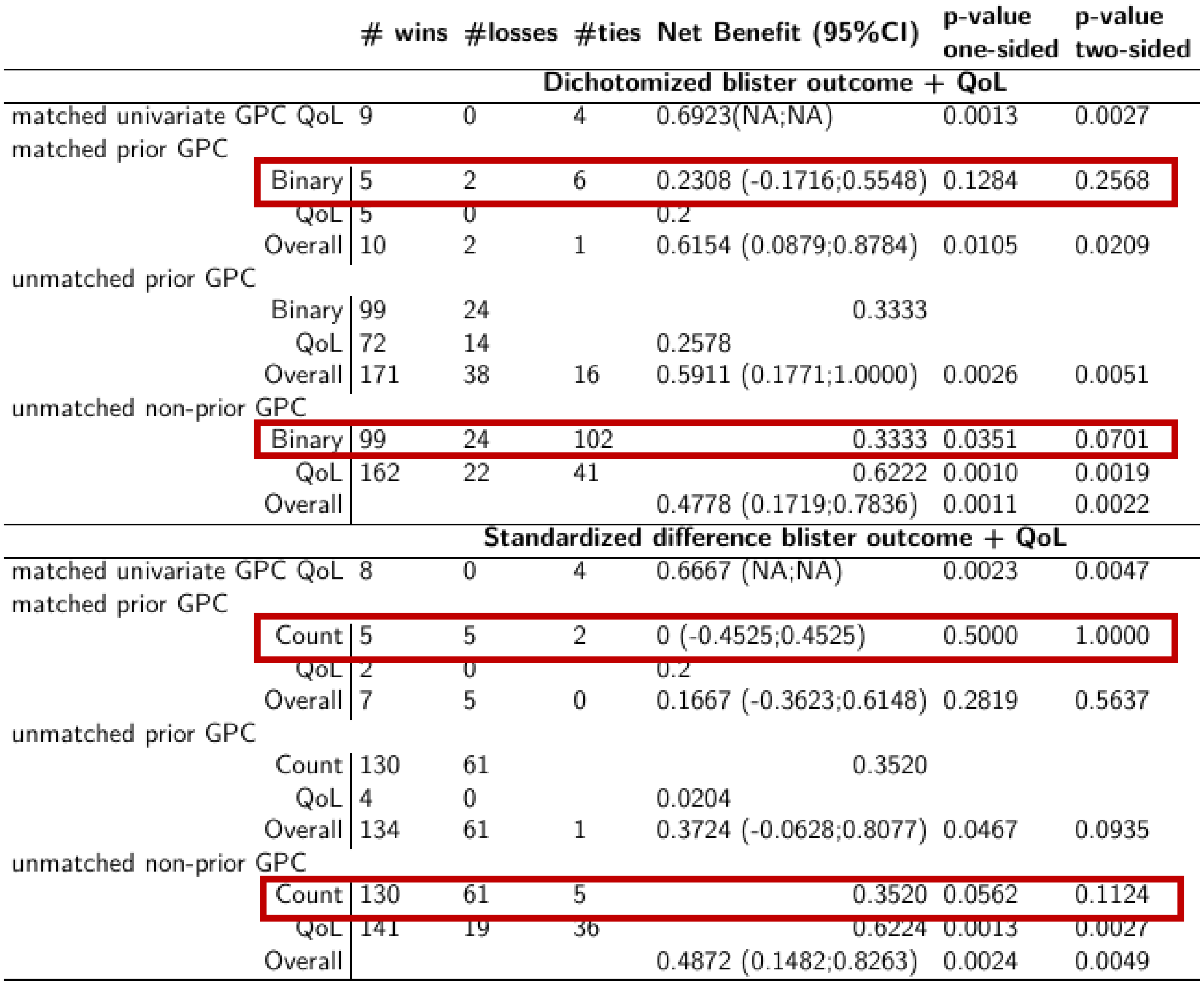
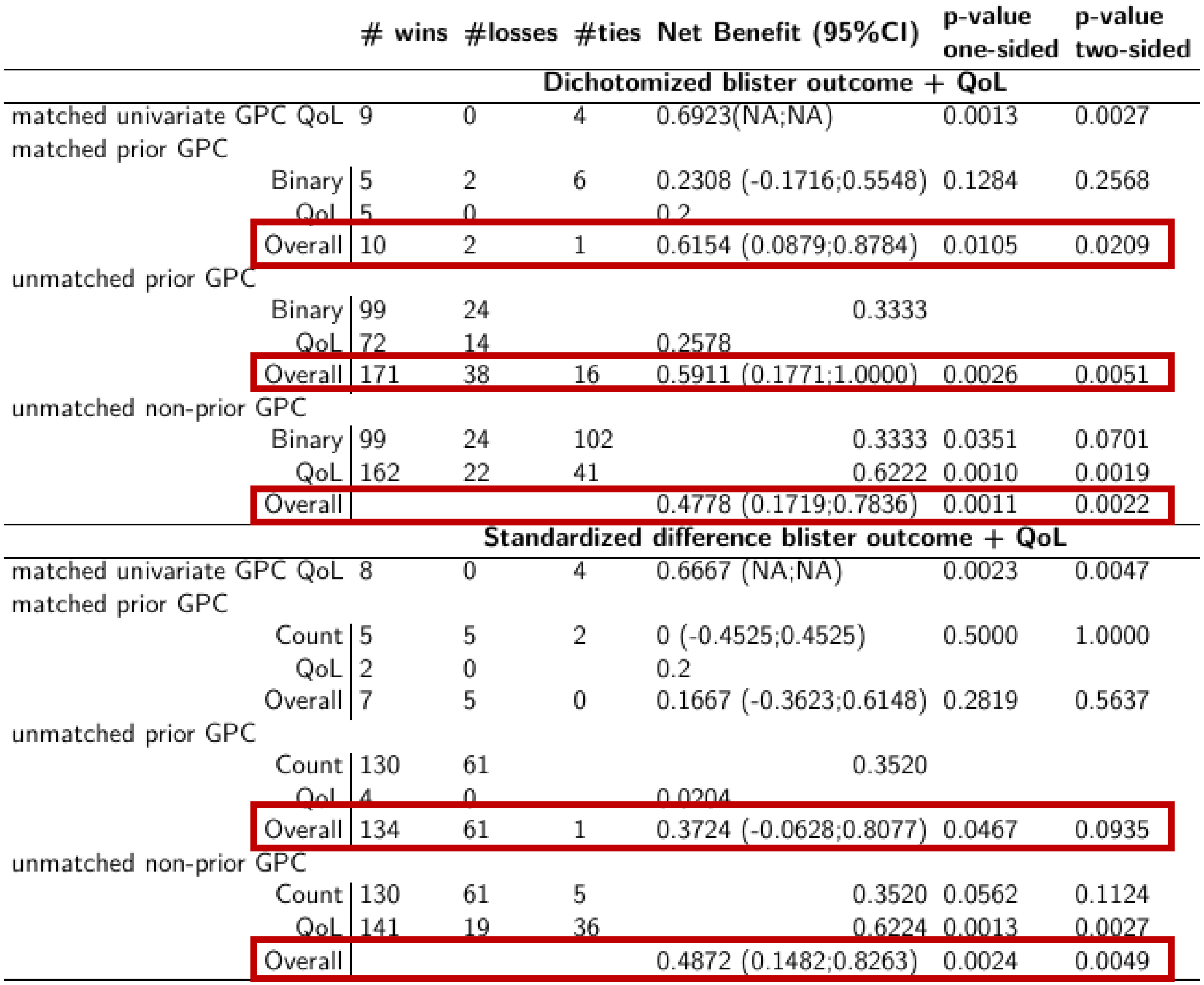
Two-sided (one-sided) type I error and power

Univariately: little evidence of a treatment effect



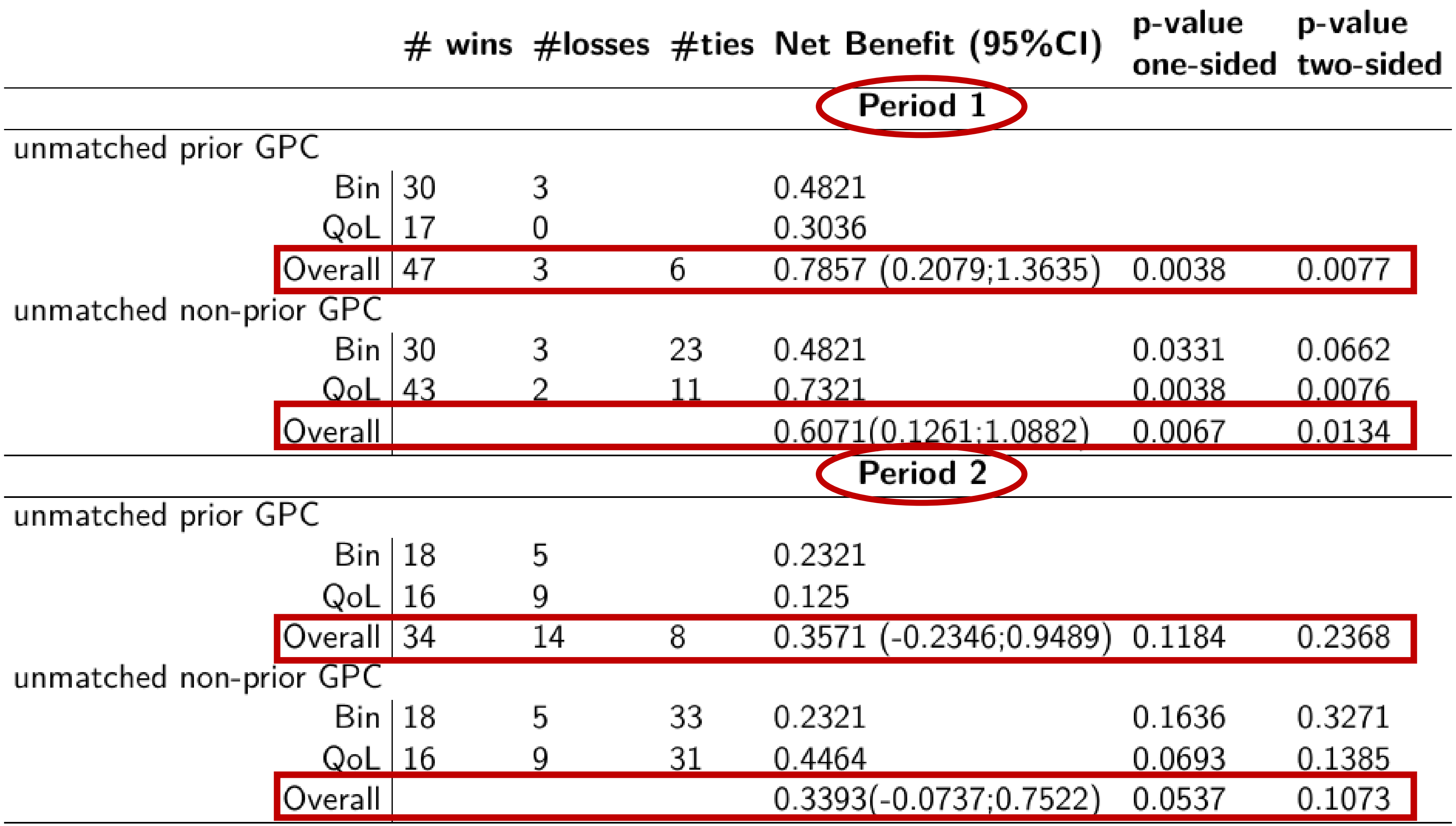
		# wins	#losses	#ties	Net Benefit (95%CI)	p-value	p-value
						one-sided	two-sided
Dichotomized blister outcome + QoL							
matched univariate GPC QoL		9	0	4	0.6923(NA;NA)	0.0013	0.0027
matched prior GPC							
	Binary	5	2	6	0.2308 (-0.1716;0.5548)	0.1284	0.2568
	QoL	5	0		0.2		
	Overall	10	2	1	0.6154 (0.0879;0.8784)	0.0105	0.0209
unmatched prior GPC							
	Binary	99	24		0.3333		
	QoL	72	14		0.2578		
	Overall	171	38	16	0.5911 (0.1771;1.0000)	0.0026	0.0051
unmatched non-prior GPC							
	Binary	99	24	102	0.3333	0.0351	0.0701
	QoL	162	22	41	0.6222	0.0010	0.0019
	Overall				0.4778 (0.1719;0.7836)	0.0011	0.0022
Standardized difference blister outcome + QoL							
matched univariate GPC QoL		8	0	4	0.6667 (NA;NA)	0.0023	0.0047
matched prior GPC							
	Count	5	5	2	0 (-0.4525;0.4525)	0.5000	1.0000
	QoL	2	0		0.2		
	Overall	7	5	0	0.1667 (-0.3623;0.6148)	0.2819	0.5637
unmatched prior GPC							
	Count	130	61		0.3520		
	QoL	4	0		0.0204		
	Overall	134	61	1	0.3724 (-0.0628;0.8077)	0.0467	0.0935
unmatched non-prior GPC							
	Count	130	61	5	0.3520	0.0562	0.1124
	QoL	141	19	36	0.6224	0.0013	0.0027
	Overall				0.4872 (0.1482;0.8263)	0.0024	0.0049

Multivariately: evidence of a treatment effect,…



		# wins	#losses	#ties	Net Benefit (95%CI)	p-value one-sided	p-value two-sided
					Dichotomized blister outcome + QoL		
matched univariate GPC QoL		9	0	4	0.6923(NA;NA)	0.0013	0.0027
matched prior GPC							
	Binary	5	2	6	0.2308 (-0.1716;0.5548)	0.1284	0.2568
	QoL	5	0		0.2		
	Overall	10	2	1	0.6154 (0.0879;0.8784)	0.0105	0.0209
unmatched prior GPC							
	Binary	99	24		0.3333		
	QoL	72	14		0.2578		
	Overall	171	38	16	0.5911 (0.1771;1.0000)	0.0026	0.0051
unmatched non-prior GPC							
	Binary	99	24	102	0.3333	0.0351	0.0701
	QoL	162	22	41	0.6222	0.0010	0.0019
	Overall				0.4778 (0.1719;0.7836)	0.0011	0.0022
					Standardized difference blister outcome + QoL		
matched univariate GPC QoL		8	0	4	0.6667 (NA;NA)	0.0023	0.0047
matched prior GPC							
	Count	5	5	2	0 (-0.4525;0.4525)	0.5000	1.0000
	QoL	2	0		0.2		
	Overall	7	5	0	0.1667 (-0.3623;0.6148)	0.2819	0.5637
unmatched prior GPC							
	Count	130	61		0.3520		
	QoL	4	0		0.0204		
	Overall	134	61	1	0.3724 (-0.0628;0.8077)	0.0467	0.0935
unmatched non-prior GPC							
	Count	130	61	5	0.3520	0.0562	0.1124
	QoL	141	19	36	0.6224	0.0013	0.0027
	Overall				0.4872 (0.1482;0.8263)	0.0024	0.0049

… mainly in first treatment period



	# wins	#losses	#ties	Net Benefit (95%CI)	p-value one-sided	p-value two-sided
				Period 1		
unmatched prior GPC						
Bin	30	3		0.4821		
QoL	17	0		0.3036		
Overall	47	3	6	0.7857 (0.2079;1.3635)	0.0038	0.0077
unmatched non-prior GPC						
Bin	30	3	23	0.4821	0.0331	0.0662
QoL	43	2	11	0.7321	0.0038	0.0076
Overall				0.6071(0.1261;1.0882)	0.0067	0.0134
				Period 2		
unmatched prior GPC						
Bin	18	5		0.2321		
QoL	16	9		0.125		
Overall	34	14	8	0.3571 (-0.2346;0.9489)	0.1184	0.2368
unmatched non-prior GPC						
Bin	18	5	33	0.2321	0.1636	0.3271
QoL	16	9	31	0.4464	0.0693	0.1385
Overall				0.3393(-0.0737;0.7522)	0.0537	0.1073

EJP RD

Conclusions

EJP RD

Conclusions

- The GPC methodology is very flexible.

- It allows for a combination of any type and any number of outcomes, including patient relevant outcomes.

- Takes account of the correlation between outcomes.

- May increase power, compared to a univariate outcome.

- Allows for an easy interpretable treatment effect and gives insight into the partial contribution of outcomes to the overall result.

- The exact permutation is easy, fast and precise even in very small samples (Available in SAS, R and under development in Python).

Questions ?

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