One-step validation method for surrogate endpoints in multiple randomized cancer clinical trials with failure-time endpoints

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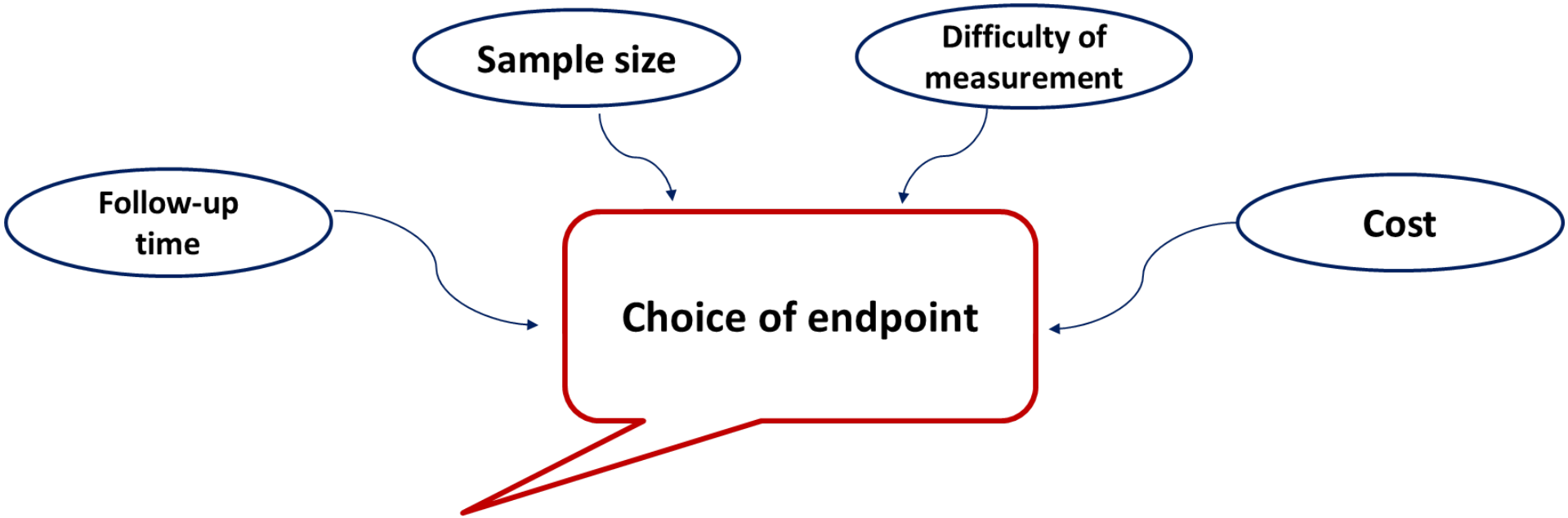
Setting up clinical trials



Surrogate endpoint

- Might be measured earlier, more conveniently, or more frequently
- But, need to be validated based on appropriate methods

Burzykowski et al. 2005, Fleming 1996, Ellenberg and Hamilton 1989, Fleming and DeMets 1996

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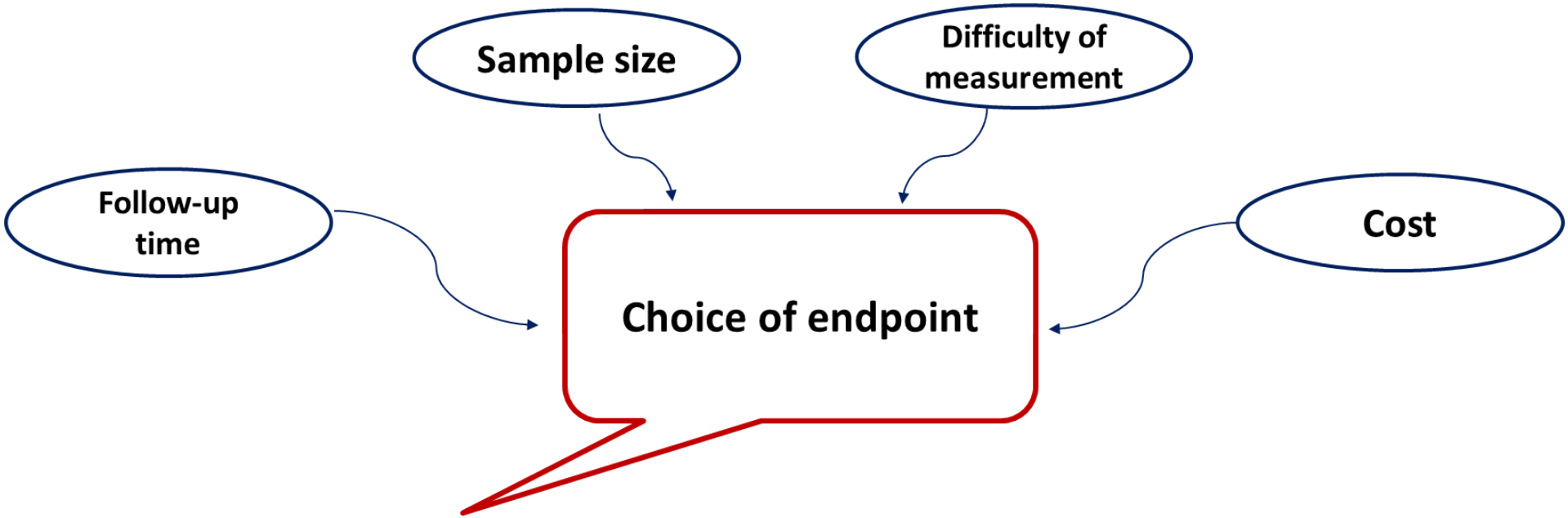

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Surrogate endpoint assessment

Related works: (**S** = surrogate et **T** = True endpoint)

- **S** must capture the full effect of treatment upon the **T**, Prentice (1)
- Validation (1): two-stage model - population and individual level

  $\Rightarrow$ Large number of observations, meta-analysis

Current consensus: two failure-time endpoints

- Individual level, association between S and T: Copula model
- Trial-level, prediction: random effect model, adjusted R^2 ($R^2_{trial,adj}$)
- Methods based on a two-step hierarchical analysis strategy

  Main problem: $R^2_{trial,adj}$ not always available

Prentice 1989, Freedman et al. 1992, Burzykowski et al. 2001, Renfro et al. 2012, Li et al. 2011

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Main Objectif

To propose a surrogate endpoint one-step validation method, based on a joint frailty model

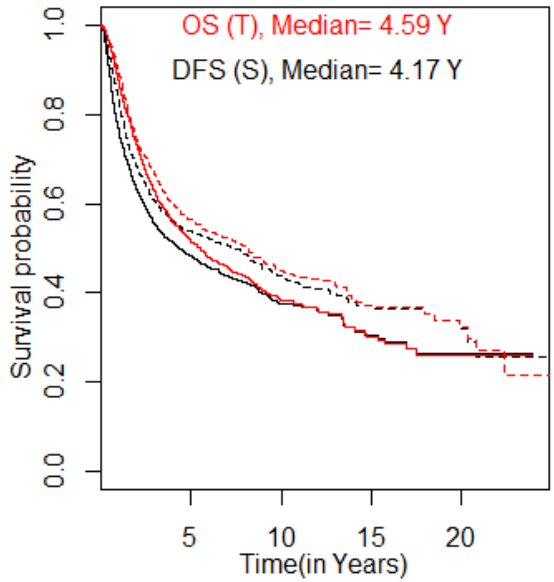
Motivating example

Data source

Individual patient data meta analysis in gastric cancer, from The GASTRIC group: evaluation of an adjuvant therapy, in term of DFS and OS

Data description

- DFS: minimum(relapse, death)
- Included 3288 patients in 14 trials
- Subjects per trial: 6.5 (IQR: 5.5-8.2)%
- Randomized patients: 48%
- 1763 (54%) DFS vs 1705 (52%) OS



Model definition

Assume S_{ij} and T_{ij}, the event-times associated with S and T for subject $j \in$ trial i

$$\begin{cases} \lambda_{S_{ij}}(t|\omega_{ij}, u_i, v_{S_i}, Z_{ij1}) = \lambda_{0S}(t)\exp(\omega_{ij} + u_i + v_{S_i}Z_{ij1} + \beta_S Z_{ij1}) \\ \lambda_{T_{ij}}(t|\omega_{ij}, u_i, v_{T_i}, Z_{ij1}) = \lambda_{0T}(t)\exp(\zeta\omega_{ij} + \alpha u_i + v_{T_i}Z_{ij1} + \beta_T Z_{ij1}) \end{cases}$$

where

$$\omega_{ij} \sim N(0,\theta) \quad u_i \sim N(0,\gamma) \quad \begin{pmatrix} v_{S_i} \\ v_{T_i} \end{pmatrix} \sim MVN\left(\mathbf{0}, \Sigma\right), \quad \Sigma = \begin{pmatrix} \sigma_S^2 & \sigma_{ST} \\ \sigma_{ST} & \sigma_T^2 \end{pmatrix}$$

- ω_{ij}, heterogeneity: correlation between S and T at the individual-level
- u_i trial random effect associated with the baseline risk function
- ζ and α, to distinguish heterogeneities between end-points
- v_{S_i} and v_{T_i}, correlated random treatment by trial interaction
- v_{S_i} and v_{T_i}: assess the prediction of treatment effect on T

Model estimation

Marginal log-likelihood : $l(\Phi)$

$$l(\Phi) = \log \left\{ \prod_{i=1}^{G} \int_U \left[\prod_{j=1}^{ni} \int_{\omega_{ij}} \lambda_{Sij}^{\delta_{ij}} \cdot S(S_{ij}) \cdot \lambda_{Tij}^{\delta_{ij}^*} \cdot S(T_{ij}) f(\omega_{ij}) d\omega_{ij} \right] f(v_{S_i}, v_{T_i}) f(u_i) dU \right\}$$

where

- $\Phi = (\hat{\sigma}^2_{v_S}, \hat{\sigma}^2_{v_T}, \hat{\sigma}_{v_{ST}}, \hat{\theta}, \hat{\gamma}, \hat{\lambda}_{0T}(.), \hat{\lambda}_{0S}(.), \hat{\beta}_S, \hat{\beta}_T)$
- U=(u_i, v_{S_i}, v_{T_i})

Parameters estimation

1. $\hat{\lambda}_{0S}(.)$ and $\hat{\lambda}_{0T}(.)$ approximated using splines, smoothing functions
2. Maximization of the penalized Log-likelihood using Marquardt algorithm
3. Numeric integration with Monte-Carlo and Gaussian Hermite quadrature

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where

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Surrogacy Evaluation and simulations

Individual and Trial-level surrogacy

- New definition of Kendall's $\tau = f(\theta, \zeta, \gamma, \alpha)$
- Trial-level evaluation by $R^2_{trial} = \frac{\sigma^2_{ST}}{\sigma^2_S \sigma^2_T}$
- Standard error of R^2_{trial} by the delta method, bootstrap for Kendall's τ

Simulations

- Data generation using the surrogate joint-model (1)
- Event-times associated to S and T followed a Weibull distribution
- Scale and shape parameters: $\gamma_T = 3.0$, $\rho_T = 0.0025$, $\gamma_S = 1.8$, $\rho_S = 0.0045$
- We assumed S_{ij} censored by T_{ij} with $S_{ij} < T_{ij}$ in case of no censorship

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Integration methods and model assessment

	True	N=600 subjects; G=30 trials			
		Mean	SD	SE	CP
		MC-GH, Cens∼40%			
θ	1.000	1.209	0.491	0.505	96
ζ	1.000	0.995	0.374	0.384	90
γ	0.800	0.934	0.390	0.329	93
α	1.000	0.989	0.182	0.204	95
σ_S^2	0.700	0.760	0.414	0.379	90
σ_T^2	0.700	0.730	0.459	0.366	90
σ_{ST}	0.630	0.649	0.352	0.295	90
β_S	-1.250	-1.245	0.273	0.244	91
β_T	-1.250	-1.210	0.241	0.236	91
R^2_{trial}	0.810	0.817	0.186	0.185	75
τ	0.378	0.385	0.037	-	93

N_sim = 500, N_{MC} = 300 samples, N_{GH} = 20 points

1. Integration assessment
   - Good parameters' estimation
   - MC, PGH, MC-GH, MC-PGH
   - Comparable results found
2. Variation of data parameters
   - N=1000, G=10, Cens=70%
   - Robust. evaluation criteria
   - Improved CP of R2 when N ↑

Comparison with two-steps approach

Parameters	True	600 subjects; 30 trials Mean	Biais	MSE	NC:n(%)	600 subjects; 10 trials Mean	Biais	MSE	NC:n(%)
High individual-level and trial-level associations									
Clayton†					266(53)				10(2)
Kendall's τ	0.614	0.565	0.049	0.003		0.543	0.071	0.006	
$R^2_{trial,adj}$	0.810	0.742	0.068	0.082		0.833	-0.023	0.061	
Plackett†					274(55)				14(3)
Kendall's τ	0.614	0.559	0.055	0.004		0.538	0.076	0.006	
$R^2_{trial,adj}$	0.810	0.811	-0.001	0.069		0.844	-0.034	0.062	
Joint Surrogate‡					1(0)				4(1)
Kendall's τ	0.614	0.613	0.001	0.002		0.614	<10-3	0.001	
R^2_{trial}	0.810	0.817	-0.007	0.057		0.816	-0.006	0.061	
Weak individual-level and trial-level associations									
Clayton†					236(47)				8(2)
Kendall's τ	0.378	0.277	0.101	0.011		0.257	0.121	0.016	
$R^2_{trial,adj}$	0.360	0.446	-0.086	0.105		0.525	-0.165	0.139	
Plackett†					238(48)				10(2)
Kendall's τ	0.378	0.278	0.100	0.011		0.271	0.107	0.012	
$R^2_{trial,adj}$	0.360	0.511	-0.151	0.124		0.512	-0.152	0.139	
Joint Surrogate‡					0(0)				0(0)
Kendall's τ	0.378	0.382	-0.004	0.001		0.375	0.003	0.004	
R^2_{trial}	0.360	0.442	-0.082	0.08		0.478	-0.118	0.106	

† Two-step approaches, ‡ One-step approaches, NC = did Not converged, N_sim = 500 simulated dataset

- Convergence issues with the two-step approaches
- underestimation of Kendall's τ

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- Better estimation of the R^2_{trial} by the proposed approach
- High bias on R^2_{trial} in case of weak trial level association

Evaluation of DFS as surrogate endpoint for OS

Questions

1. Are DFS and OS correlated at the individual-level? Kendall's τ
2. Does the treatment effect on DFS reliably predict the treat. effect on OS?, R^2_{trial}

DFS Evaluation

Parameters	R^2_{trial}	Kendall's τ
One step approach		
Proposed joint surrogate	0.99 (0.84-1.14)	0.68 (0.65-0.70)
Poisson	1.00 (0.08–1.00)	0.74 (0.73–0.76)
Two steps approach using R		
Clayton adj	0.97 (0.46–1.00)	0.81 (0.80–0.91)
Plackett adj	1.00 (0.69–1.00)	0.82 (0.81–0.83)
Hougaard adj	0.94 (0.08–1.00)	0.18 (0.17–0.19)

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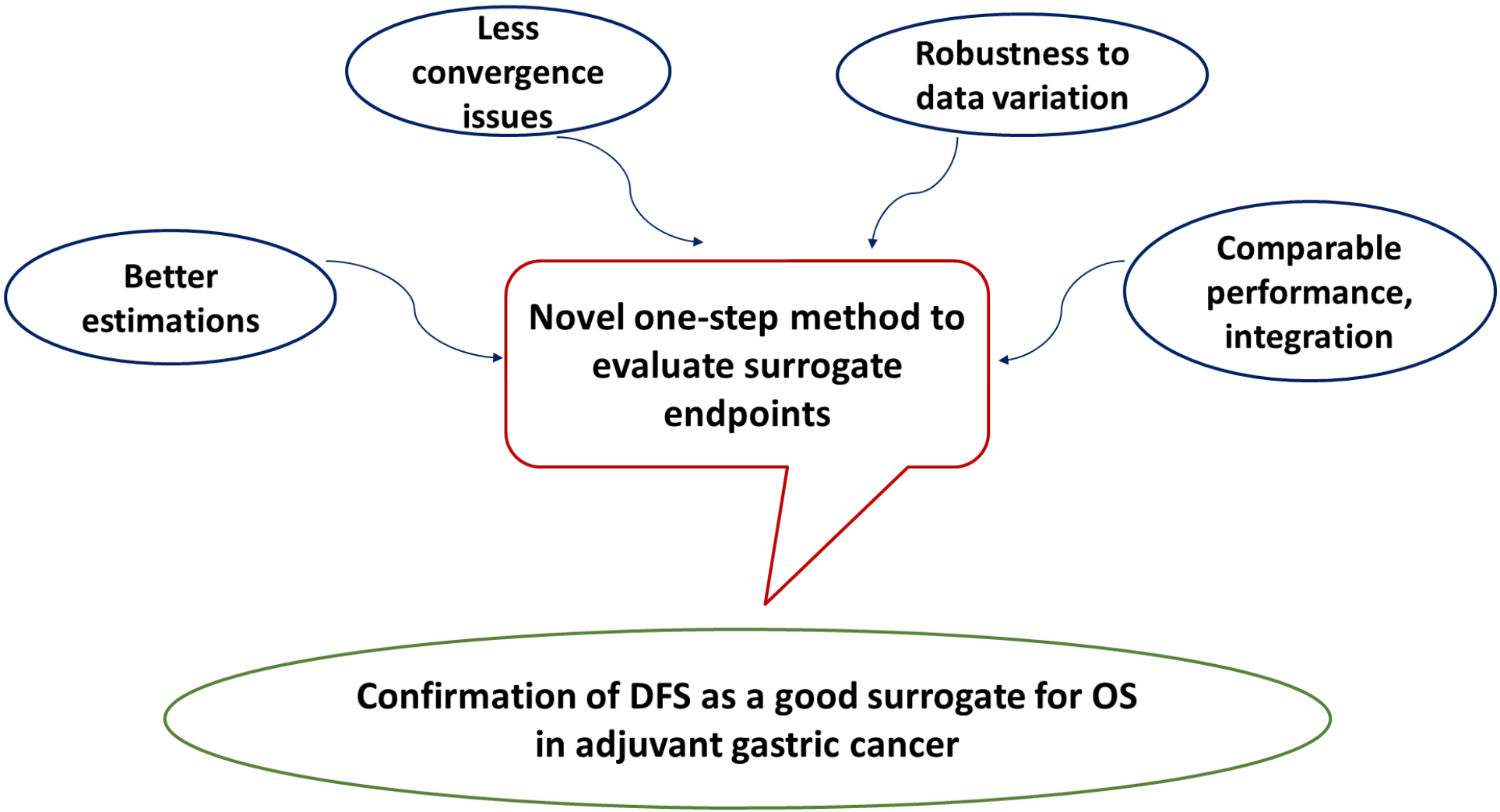
Conclusion


Less convergence issues
Robustness to data variation
Better estimations
Novel one-step method to evaluate surrogate endpoints
Comparable performance, integration
Confirmation of DFS as a good surrogate for OS in adjuvant gastric cancer

Funding :

RÉGION Nouvelle-Aquitaine

Inserm
La science pour la santé
From science to health

Association pour la Recherche sur le Cancer
Reconnue d'utilité publique

INSTITUT NATIONAL DU CANCER

Thanks for your kind attention

The semi-parametric penalized likelihood approach

Parameters estimation

- The baseline hazard function were approximated using cubic M-splines
- $\sigma^2_{v_S}$, $\sigma^2_{v_T}$, $\sigma_{v_{ST}}$, θ, γ, β^S, β^T, $\lambda_{0S}(t)$ and $\lambda_{0T}(t)$ estimated based on a semi parametric penalized likelihood approach.
- The penalized log-likelihood were defined by:

$$pl(\Phi) = l(\Phi) - k_1 \int_0^\infty \lambda''^2_{0S}(t)dt - k_2 \int_0^\infty \lambda''^2_{0T}(t)dt$$

- The smoothing parameters k_1 and k_2 were obtained by cross validation
- Estimated parameters were obtained by the robust Marquardt algorithm
- Transformation applied to spline coefficient, variance parameters, ≥ 0
- Standard errors of transformed parameters based on Delta-method

Individual-level surrogacy

- New definition of Kendall's τ to evaluate the individual level surrogacy.
- $\tau \in$ [-1,1], assumes a zero value when S_{ij} and T_{ij} are independent.
- One can show that

$$\tau = 2 \int_{u_i} \int_{\omega_{ij}} \int_{u_{i'}} \int_{\omega_{i'j'}} \frac{\exp(\omega_{ij} + u_i + \zeta\omega_{ij} + \alpha u_i) + \exp(\omega_{i'j'} + u_{i'} + \zeta\omega_{i'j'} + \alpha u_{i'})}{(\exp(\omega_{i'j'} + u_{i'}) + \exp(\omega_{ij} + u_i))(\exp(\zeta\omega_{i'j'} + \alpha u_{i'}) + \exp(\zeta\omega_{ij} + \alpha u_i))} \frac{1}{\sqrt{2\pi\theta}} \exp\left[-\frac{1}{2}\frac{\omega_{i'j'}^2}{\theta}\right] \frac{1}{\sqrt{2\pi\gamma}} \exp\left[-\frac{1}{2}\frac{u_{i'}^2}{\gamma}\right] d\omega_{i'j'} du_{i'} \frac{1}{\sqrt{2\pi\theta}} \exp\left[-\frac{1}{2}\frac{\omega_{ij}^2}{\theta}\right] \frac{1}{\sqrt{2\pi\gamma}} \exp\left[-\frac{1}{2}\frac{u_i^2}{\gamma}\right] d\omega_{ij} du_i - 1$$

α and ζ set to 1, n_i and randomized subject per trial variables

Parameters	True value	Mean	Empirical SE	Mean SE	CP(%)
		N=1000 subjects G=14 trials C=48%			
θ	3.500	3.407	0.638	0.343	88
γ	2.500	2.733	1.994	0.651	59
σ_S^2	0.700	0.663	0.451	0.338	79
σ_T^2	0.700	0.669	0.451	0.350	77
σ_{ST}	0.630	0.593	0.417	0.309	77
β_S	-1.250	-1.211	0.328	0.250	88
β_T	-1.250	-1.208	0.333	0.259	85
R^2_{trial}	0.810	0.816	0.217	0.189	69
Kendall's τ	0.584	0.583	0.055	-	69
NC : n(%)	-	6(1)	-	-	-

Initial values quite far from true simulation values

Parameters	True value	Mean	Empirical SE	Mean SE	CP(%)
		N=1000 subjects G=30 trials C=38%			
θ	3.500	3.474	0.808	0.609	84
ζ	1.000	1.110	0.456	0.187	84
γ	2.500	2.627	0.933	0.640	84
α	1.000	1.058	0.230	0.139	86
σ_S^2	0.700	0.692	0.420	0.354	84
σ_T^2	0.700	0.716	0.477	0.390	89
σ_{ST}	0.630	0.618	0.373	0.321	86
β_S	-1.250	-1.177	0.291	0.219	87
β_T	-1.250	-1.190	0.314	0.239	91
R^2_{trial}	0.810	0.811	0.196	0.204	80
Kendall's τ	0.597	0.595	0.029	-	84
NC : n(%)	-	0(0)	-	-	-

Parameters	True	N=600 subjects; G=30 trials Mean	SD	SE	CP	N=600 subjects; G=30 trials Mean	SD	SE	CP
		Full MC				Full PGH			
θ	1.000	1.122	0.305	0.242	97	1.025	0.418	0.370	89
ζ	1.000	0.990	0.367	0.379	91	1.385	1.490	0.373	87
γ	0.800	0.957	0.493	0.343	92	0.762	0.255	0.273	91
α	1.000	0.982	0.185	0.202	95	1.082	0.310	0.192	92
σ_S^2	0.700	0.787	0.540	0.397	90	0.638	0.341	0.319	83
σ_T^2	0.700	0.723	0.450	0.361	89	0.726	0.495	0.360	84
σ_{ST}	0.630	0.652	0.355	0.296	89	0.581	0.293	0.287	87
β_S	-1.250	-1.259	0.312	0.250	91	-1.253	0.249	0.222	92
β_T	-1.250	-1.205	0.236	0.234	92	-1.305	0.345	0.236	91
R^2_{trial}	0.810	0.817	0.186	0.183	76	0.829	0.195	0.139	55
Kendall's τ	0.378	0.382	0.039	-	90	0.369	0.041	-	88
		MC-GH				MC-PGH			
θ	1.000	1.209	0.491	0.505	96	1.228	0.552	0.529	95
ζ	1.000	0.995	0.374	0.384	90	1.020	0.644	0.381	90
γ	0.800	0.934	0.390	0.329	93	0.939	0.402	0.336	93
α	1.000	0.989	0.182	0.204	95	0.985	0.188	0.204	95
σ_S^2	0.700	0.760	0.414	0.379	90	0.766	0.428	0.385	90
σ_T^2	0.700	0.730	0.459	0.366	90	0.739	0.499	0.367	89
σ_{ST}	0.630	0.649	0.352	0.295	90	0.653	0.355	0.297	90
β_S	-1.250	-1.245	0.273	0.244	91	-1.247	0.280	0.247	91
β_T	-1.250	-1.210	0.241	0.236	91	-1.208	0.241	0.236	91
R^2_{trial}	0.810	0.817	0.186	0.185	75	0.818	0.186	0.184	76
Kendall's τ	0.378	0.385	0.037	-	93	0.384	0.039	-	92

N_sim = 350 simulated dataset, N_{MC} = 300 samples, $N_{FullPGH}$ = 12 points and 20 points elsewhere

Parameters	True	Mean	SD	SE	CP	Mean	SD	SE	CP
		Reference(N=600, G=30, C=∼40%)				G=10 trials			
θ	3.500	3.397	0.528	0.526	94	3.372	0.456	0.534	95
ζ	1.500	1.583	0.324	0.319	85	1.594	0.318	0.337	88
γ	2.500	2.666	0.971	0.753	88	2.617	1.644	0.834	68
α	1.000	1.041	0.192	0.187	87	1.048	0.197	0.203	90
σ^2_S	0.700	0.731	0.518	0.481	88	0.714	0.601	0.442	81
σ^2_T	0.700	0.850	0.753	0.704	91	0.820	0.791	0.648	84
σ_{ST}	0.630	0.690	0.550	0.515	90	0.672	0.613	0.470	84
β_S	-1.250	-1.183	0.274	0.255	92	-1.197	0.351	0.314	91
β_T	-1.250	-1.229	0.386	0.360	94	-1.227	0.450	0.419	92
R^2_{trial}	0.810	0.826	0.232	0.356	71	0.814	0.254	0.307	64
Kendall's τ	0.614	0.614	0.025	-	91	0.612	0.032	-	82
NC* : n(%)	-	1(0)	-	-	-	4(1)	-	-	-
		N=1000 subjects				Censoring = 70%			
θ	3.500	3.547	0.629	0.525	93	3.777	0.850	1.124	97
ζ	1.500	1.601	1.026	0.271	85	1.577	1.101	0.651	91
γ	2.500	2.591	0.819	0.629	89	2.832	1.117	0.995	92
α	1.000	1.016	0.210	0.154	86	0.989	0.211	0.353	93
σ^2_S	0.700	0.708	0.433	0.367	87	0.817	0.696	0.628	88
σ^2_T	0.700	0.733	0.572	0.478	87	0.952	1.110	1.023	86
σ_{ST}	0.630	0.627	0.401	0.369	88	0.738	0.679	0.651	88
β_S	-1.250	-1.198	0.244	0.218	91	-1.230	0.322	0.323	94
β_T	-1.250	-1.199	0.294	0.292	93	-1.237	0.417	0.502	95
R^2_{trial}	0.81	0.812	0.206	0.259	78	0.806	0.264	0.858	71
Kendall's τ	0.614	0.613	0.041	-	91	0.617	0.047	-	93
NC* : n(%)	-	1(0)	-	-	-	52(10)	-	-	-

* *NC* =did Not converged, N_sim = 500 simulated dataset, N_{MC} = 300 samples, N_{GH} = 20 or 32 points