The Statistical Evaluation of Surrogate Endpoints in Clinical Trials

Geert Molenberghs

geert.molenberghs@uhasselt.be

Hasselt University, Diepenbeek, Belgium

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Research Team

Ariel Alonso Abad (UH)	Geert Molenberghs (UH)
Tomasz Burzykowski (UH)	Pascal Piedbois (Paris)
José Cortiñas Abrahantes (UH)	Didier Renard (Eli Lilly and UH)
Marc Buyse (IDDI and UH)	Ziv Shkedy (UH)
Helena Geys (J&J PRD and UH)	Fabián Tibaldi (Eli Lilly and UH)

Motivation

- ***Primary motivation***
  - True endpoint is rare and/or distant
  - Surrogate endpoint is frequent and/or close in time
- ***Secondary motivation***: True endpoint is
  - invasive
  - uncomfortable
  - costly
  - confounded by secondary treatments and/or competing risks

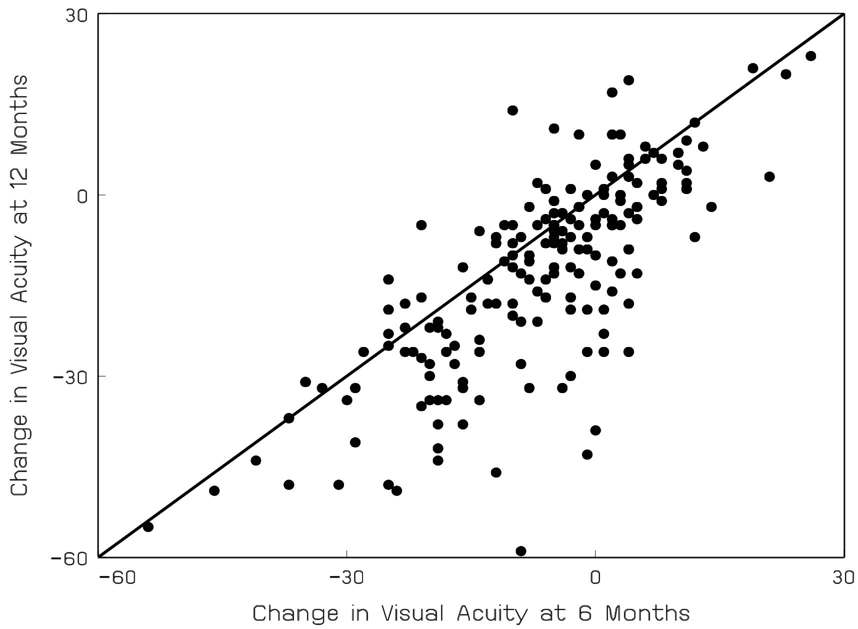
Age-Related Macular Degeneration

Pharmacological Therapy for Macular Degeneration Study Group (1997)

Z: ***Interferon-α***

S: ***Visual acuity at 6 months***

T: ***Visual acuity at 1 year***



N: 190 patients in 36 centers (# patients/center $\in$[2;18])

Definition and Single-Unit Model

Prentice (Bcs 1989)

"A test of H_0 of no effect of treatment on surrogate is equivalent to a test of H_0 of no effect of treatment on true endpoint."

$$\begin{aligned} S_j &= \mu_S + \alpha Z_j + \varepsilon_{Sj} \\ T_j &= \mu_T + \beta Z_j + \varepsilon_{Tj} \end{aligned} \qquad \Sigma = \begin{pmatrix} \sigma_{SS} & \sigma_{ST} \\ & \sigma_{ST} \end{pmatrix}$$

$$T_j = \mu + \gamma S_j + \varepsilon_j$$

Prentice's Criteria and Measures

Prentice (1989), Freedman *et al* (1992)

	Quantity	Estimate	Test
1	Effect of Z on T	β	$(T\|Z) \neq (T)$
2	Effect of Z on S	α	$(S\|Z) \neq (S)$
3	Effect of S on T	γ	$(T\|S) \neq (T)$
4	Effect of Z on T, given S	β_S	$(T\|Z,S) = (T\|S)$

$\downarrow$

Proportion explained

$$PE = \frac{\beta - \beta_S}{\beta}$$

$\swarrow$ $\searrow$

Relative Effect

$$RE = \frac{\beta}{\alpha}$$

Adjusted Association

$$\rho_Z = \text{Corr}(S, T|Z)$$

Prentice's Criteria and Measures

Prentice (1989), Freedman *et al* (1992)

	Quantity	Estimate	Test
1	Effect of Z on T	$\widehat{\beta} = 4.12(2.32)$	$p = 0.079$
2	Effect of Z on S	$\widehat{\alpha} = 2.83(1.86)$	$p = 0.13$
3	Effect of S on T	$\widehat{\gamma} = 0.95(0.06)$	$p < 0.0001$
4	Effect of Z on T, given S	$\widehat{\beta_S}$	

$\downarrow$

Proportion explained

$$\widehat{PE} = 0.65 \quad [-0.22; 1.51]$$

$\swarrow$ $\searrow$

Relative Effect

$$\widehat{RE} = 1.45 \quad [-0.48; 3.39]$$

Adjusted Association

$$\widehat{\rho}_Z = 0.75 \quad [0.69; 0.82]$$

Analysis Based on Several Trials

- **Context:**
  - multicenter trials
  - meta analysis
  - several meta-analyses

- **Extensions:**
  - ***Relative Effect*** $\longrightarrow$ ***Trial-Level Surrogacy***

    How close is the relationship between the treatment effects on the surrogate and true endpoints, based on the various trials (units)?
  - ***Adjusted Association*** $\longrightarrow$ ***Individual-Level Surrogacy***

    How close is the relationship between the surrogate and true outcome, after accounting for trial and treatment effects?

Statistical Model

- ***Model:***

$$\begin{aligned} S_{ij} &= \mu_{Si} + \alpha_i Z_{ij} + \varepsilon_{Sij} \\ T_{ij} &= \mu_{Ti} + \beta_i Z_{ij} + \varepsilon_{Tij} \end{aligned}$$

- ***Error structure:***

$$\Sigma = \begin{pmatrix} \sigma_{SS} & \sigma_{ST} \\ & \sigma_{TT} \end{pmatrix}$$

Statistical Model

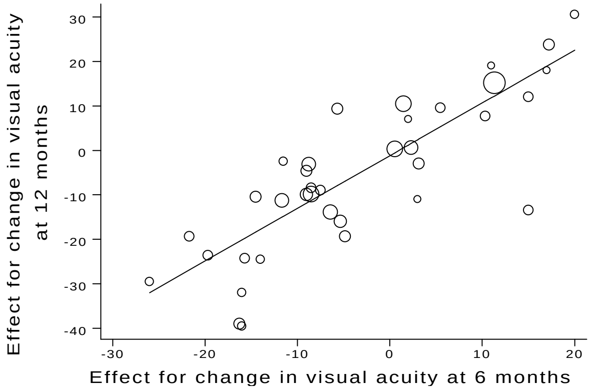
- ***Model:***

$$
\begin{aligned}
S_{ij} &= \mu_{Si} + \alpha_i Z_{ij} + \varepsilon_{Sij} \\
T_{ij} &= \mu_{Ti} + \beta_i Z_{ij} + \varepsilon_{Tij}
\end{aligned}
$$

- ***Trial-specific effects:***

$$
\begin{pmatrix} \mu_{Si} \\ \mu_{Ti} \\ \alpha_i \\ \beta_i \end{pmatrix} = \begin{pmatrix} \mu_S \\ \mu_T \\ \alpha \\ \beta \end{pmatrix} + \begin{pmatrix} m_{Si} \\ m_{Ti} \\ a_i \\ b_i \end{pmatrix} \qquad D = \begin{pmatrix} d_{SS} & d_{ST} & d_{Sa} & d_{Sb} \\ & d_{TT} & d_{Ta} & d_{Tb} \\ & & d_{aa} & d_{ab} \\ & & & d_{bb} \end{pmatrix}
$$

ARMD: Trial-Level Surrogacy



- ***Prediction:***
  - *What do we expect ?*

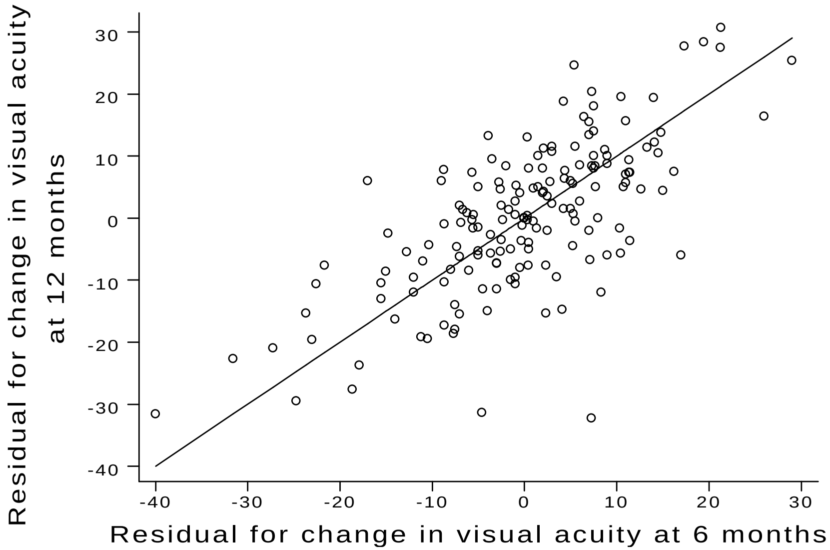
$$E(\beta + b_0 | m_{S0}, a_0)$$

  - *How precisely can we estimate it ?*

$$\text{Var}(\beta + b_0 | m_{S0}, a_0)$$

- ***Estimate:***
  - $R^2_{\text{trial}} = 0.692$ (95% C.I. $[0.52; 0.86]$)

ARMD: Individual-Level Surrogacy



- ***Individual-level association:***

  $\rho_Z = R_{\text{indiv}} = \text{Corr}(\varepsilon_{Ti}, \varepsilon_{Si})$

- ***Estimate:***
  - $R^2_{\text{indiv}} = 0.483$ (95% C.I. $[0.38; 0.59]$)
  - $R_{\text{indiv}} = 0.69$ (95% C.I. $[0.62; 0.77]$)
  - Recall $\rho_Z = 0.75$ (95% C.I. $[0.69; 0.82]$)

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A Number of Case Studies

	Age-related macular degeneration	Advanced ovarian cancer	Advanced colorectal cancer
Surrogate	Vis. Ac. (6 months)	Progr.-free surv.	Progr.-free surv.
True	Vis. Ac. (1 year)	Overall surv.	Overall surv.
Prentice Criteria 1–3 (p value)			
Association (Z, S)	0.31	0.013	0.90
Association (Z, T)	0.22	0.08	0.86
Association (S, T)	< 0.001	< 0.001	< 0.001
Single-Unit Validation Measures (estimate and 95% C.I.)			
Proportion Explained	$0.61[-0.19; 1.41]$	$1.34[0.73; 1.95]$	$0.51[-4.97; 5.99]$
Relative Effect	$1.51[-0.46; 3.49]$	$0.65[0.36; 0.95]$	$1.59[-15.49, 18.67]$
Adjusted Association	$0.74[0.68; 0.81]$	$0.94[0.94; 0.95]$	$0.73[0.70, 0.76]$
Multiple-Unit Validation Measures (estimate and 95% C.I.)			
R^2_{trial}	$0.69[0.52; 0.86]$	$0.94[0.91; 0.97]$	$0.57[0.41, 0.72]$
R^2_{indiv}	$0.48[0.38; 0.59]$	$0.89[0.87; 0.90]$	$0.57[0.52, 0.62]$

Overview: Case Studies

	Schizoph. Study I (138 units)	Schizoph. Study I (29 units)	Schizoph. Study II
Surrogate	— PANSS —		
True	— CGI —		
Prentice Criteria 1–3 (p value)			
Association (Z, S)	0.016		0.835
Association (Z, T)	0.007		0.792
Association (S, T)	< 0.001		< 0.001
Single-Unit Validation Measures (estimate and 95% C.I.)			
Proportion Explained	$0.81[0.46; 1.67]$		$-0.94[\infty]$
Relative Effect	$0.055[0.01; 0.16]$		$-0.03[\infty]$
Adjusted Association	$0.72[0.69; 0.75]$		$0.74[0.69; 0.79]$
Multiple-Unit Validation Measures (estimate and 95% C.I.)			
R^2_{trial}	$0.56[0.43; 0.68]$	$0.58[0.45; 0.71]$	$0.70[0.44; 0.96]$
R^2_{indiv}	$0.51[0.47; 0.55]$	$0.52[0.48; 0.56]$	$0.55[0.47; 0.62]$

Two Longitudinal Endpoints

First Stage

$$\begin{aligned} T_{ijt} &= \mu_{T_i} + \beta_i Z_{ij} + \theta_{T_i} t_{ijt} + \varepsilon_{T_{ijt}} \\ S_{ijt} &= \mu_{S_i} + \alpha_i Z_{ij} + \theta_{S_i} t_{ijt} + \varepsilon_{S_{ijt}} \end{aligned}$$

$$\Sigma_i = \begin{pmatrix} \sigma_{TTi} & \sigma_{STi} \\ \sigma_{STi} & \sigma_{SSi} \end{pmatrix} \otimes R_i$$

Two Longitudinal Endpoints

Second Stage

$$\begin{pmatrix} \mu_{S_i} \\ \mu_{T_i} \\ \alpha_i \\ \beta_i \\ \theta_{S_i} \\ \theta_{T_i} \end{pmatrix} = \begin{pmatrix} \mu_S \\ \mu_T \\ \alpha \\ \beta \\ \theta_S \\ \theta_T \end{pmatrix} + \begin{pmatrix} m_{S_i} \\ m_{T_i} \\ a_i \\ b_i \\ \tau_{S_i} \\ \tau_{T_i} \end{pmatrix}$$

Evaluation Measures?

A Sequence of Measures

- Variance Reduction Factor VRF:

$$VRF = \frac{\sum_i \{\text{tr}(\Sigma_{TTi}) - \text{tr}(\Sigma_{(T|S)i})\}}{\sum_i \text{tr}(\Sigma_{TTi})}$$

- Canonical-correlation Root-statistic Based Measure θ_p:

$$\theta_p = \sum_i \frac{1}{Np_i} \text{tr} \left\{ \left(\Sigma_{TTi} - \Sigma_{(T|S)i} \right) \Sigma_{TTi}^{-1} \right\}$$

A Sequence of Measures

- Canonical-correlation Root-statistic Based Measure R^2_Λ:

$$R^2_\Lambda = \frac{1}{N} \sum_i (1 - \Lambda_i),$$

where

$$\Lambda_i = \frac{|\Sigma_i|}{|\Sigma_{TTi}|\,|\Sigma_{SSi}|}$$

A Sequence of Measures

- The Likelihood Reduction Factor LRF:
  - Consider a pair of models:

$$
\begin{aligned}
g_T(T_{ij}) &= \mu_{T_i} + \beta_i Z_{ij} \\
g_T(T_{ij}) &= \theta_{0_i} + \theta_{1i} Z_{ij} + \theta_{2i} S_{ij}
\end{aligned}
$$

  - G_i^2 log-likelihood ratio for comparison of both models
  - The proposed measure:

$$
\text{LRF} = 1 - \frac{1}{N} \sum_i \exp\left(-\frac{G_i^2}{n_i}\right)
$$

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An Information-theoretic Approach

- Can we unify all previous proposals?
- Shannon (1916–2001) defined entropy of a distribution:

$$h(Y) = E[-\log(f(Y))]$$

- Conditional version:

$$h(Y|X = x) = E_{Y|X}[\log f_{Y|X}(Y|X = x)]$$

and

$$I(Y|X) = E_X[h(Y|X = x)]$$

An Information-theoretic Approach

- The amount of uncertainty (entropy) that is expected to be removed if the value of X is known:

$$I(X, y) = h(Y) - h(Y|X)$$

- Informational measure of association R_h^2:

$$R_h^2 = R_h^2 = \frac{EP(Y) - EP(Y|X)}{EP(Y)}$$

with

$$EP(X) = \frac{1}{(2\pi e)^n} e^{2h(X)}$$

An Information-theoretic Approach

- Version for N trials:

$$R_h^2 = \sum_{i=1}^{N_q} \alpha_i R_{hi}^2 = 1 - \sum_{i=1}^{N_q} \alpha_i e^{-2I_i(S_i,T_i)},$$

where the α_i form a convex combination.

Relationships With Previous Definitions

- All have desirable behavior within $[0, 1]$ for continuous endpoints
- All can be embedded within a family
- θ_p is symmetric in S and T whereas the VRF is not
- θ_p is invariant w.r.t. linear bijective transformations; VRF only when they are orthogonal
- R^2_Λ and later ones also apply to non-Gaussian settings
- Later ones specialize to earlier ones

Relationships With Previous Definitions

- They all reduce to the R^2_{indiv} for cross-sectional Gaussian outcomes
- Longitudinal normal setting:

$$R^2_h = R^2_\Lambda \qquad \text{if} \qquad \alpha_i = N_q^{-1}$$

- General setting:

$$\text{LRF} \xrightarrow{P} R^2_h$$

when the number of subjects per trial approaches ∞

Other Implications

- Relationship with Prentice's main criterion and the Data Processing Inequality:

$$f(T|Z,S) = F(T|S) \quad \Rightarrow \quad Z \rightarrow S \rightarrow T$$

$$\Rightarrow \quad I(T,Z|S) = 0$$

$$\Rightarrow \quad I(Z,S) \geq I(Z,T)$$

- PE and R_h^2:

$$\text{PE} = 1 - \frac{\beta_S}{\beta} \quad \longleftrightarrow \quad R_h^2 = 1 - \frac{\text{EP}(\beta_i|\alpha_i)}{\text{EP}(\beta_i)}$$

Fano's Inequality

- Fano's Inequality:

$$E\left[(T - g(S))^2\right] \quad \geq \quad EP(T)(1 - R_h^2)$$

  - Left hand side is prediction error
  - Applies regardless of distributional form and predictor function $g(\cdot)$
  - "How large does R_h^2 have to be?" $\longleftarrow$ The answer depend crucially on the power entropy of T

Schizophrenia Trial: Continuous Outcomes

- $VRF_{\text{ind}} = 0.39$ with 95% C.I. $[0.36; 0.41]$

- $R^2_{\text{trial}} = 0.85$ with 95% C.I. $[0.68; 0.95]$

Schizophrenia Trial: Binary Outcomes

Parameter	Estimate	95% C.I.
Trial-level R^2_{trial} measures		
1.1 Information-Theoretic	0.49	[0.21,0.81]
1.2 Probit	0.51	[0.18,0.78]
1.3 Plackett-Dale	0.51	[0.21,0.81]
Individual-level measures		
R^2_h	0.27	[0.24,0.33]
R^2_hmax	0.39	[0.35,0.48]
Probit	0.67	[0.55,0.76]
Plackett-Dale ψ	25.12	[14.66;43.02]
Fano's lower-bound	0.08	

Age-related Macular Degeneration Trial

- Both outcomes considered binary

Parameter	Estimate	[95% C.I.]
R^2_{trial}	0.3845	[0.1494;0.6144]
R^2_h	0.2648	[0.2213;0.3705]
$R^2_{h\text{max}}$	0.4955	[0.3252;0.6044]

Advanced Colorectal Cancer

S: Time to progression/death

T: Time to death

- Models:

$$\begin{aligned} h_{ij}(t) &= h_{i0}(t)\text{exp}\{\beta_i Z_{ij}\} \\ h_{ij}(t) &= h_{i0}(t)\text{exp}\{\beta_{Si} Z_{ij} + \gamma_i S_{ij}(t)\} \end{aligned}$$

Advanced Colorectal Cancer: First Dataset

Parameter	Estimate (95% C.I.)
Trial-level measures	
$\hat{R}^2_{\text{trial}}$ (separate models)	0.82 [0.40;0.95]
$\hat{R}^2_{\text{trial}}$ (Clayton copula)	0.88 [0.59;0.98]
Individual-level measures	
$\hat{R}^2_h$	0.84 [0.82;0.85]
Percentage of censoring	19%

Advanced Colorectal Cancer: Second Dataset

Parameter	Estimate (95% C.I.)
Trial-level measures	
$\hat{R}^2_{\text{trial}}$ (separate models)	0.85 [0.53;0.96]
$\hat{R}^2_{\text{trial}}$ (Clayton copula)	0.82 [0.43;0.95]
$\hat{R}^2_{\text{trial}}$ (Hougaard copula)	0.75 [0.00;1.00]
Individual-level measures	
$\hat{R}^2_h$	0.83 [0.82;0.85]
Percentage of censoring	55%

Prediction in a New Trial

- Consider a new trial $i = 0$:

$$S_{0j} = \mu_{S0} + \alpha_0 Z_{0j} + \varepsilon_{S0j}$$

- Prediction variance:

$$\text{Var}(\beta + b_0 | \mu_{S0}, \alpha_0, \vartheta) \approx f\{\text{Var}(\widehat{\mu}_{S0}, \widehat{\alpha}_0)\} + f\{\text{Var}(\widehat{\vartheta})\} + (1 - R^2_{\text{trial}})\text{Var}(b_0)$$

- where
  - $f(\cdot)$ are appropriate functions of the parameters involved
  - ϑ contains all fixed effects

Prediction in a New Trial

- Meaning of the three terms:
  - **Estimation error in both the meta-analysis and the new trial:**

    all three terms apply

  - **Estimation error in the meta-analysis only:**

$$\text{Var}(\beta + b_0 | \mu_{S0}, \alpha_0, \vartheta) \approx f\{\text{Var}(\widehat{\vartheta})\} + (1 - R^2_{\text{trial}})\text{Var}(b_0)$$

  - **No estimation error:**

$$\text{Var}(\beta + b_0 | m_{S0}, a_0) = (1 - R^2_{\text{trial}})\text{Var}(b_0)$$

The Surrogate Threshold Effect

- STE: The smallest treatment effect upon the surrogate that predicts a significant treatment effect on the true endpoint

- Various versions:
  - $\text{STE}_{N,n}$: STE for a finite meta-analysis and a finite new trial
  - $\text{STE}_{N,\infty}$: STE for a finite meta-analysis and an infinite new trial
  - $\text{STE}_{\infty,\infty}$: STE when both the meta-analysis and the new trial are infinitely large

Practical Conclusions

- *Are surrogate endpoints useful in practice?*
- An investigator wants to be able to predict the effect of treatment on T, based on the observed effect of treatment on S.
- R^2_{trial}, R^2_{indiv}, (ψ, τ), VRF, θ_p, R^2_Λ LRF, R^2_h, . . . : quantification of surrogacy in a meta-analytic setting
- Prediction: useful in a *new* trial

Methodological Conclusions

- ***Basis for new assessment strategy***
  - trial-level surrogacy
  - individual-level surrogacy
- ***Requires***
  - joint model for surrogate and true endpoint
  - acknowledgment of the hierarchical structure

Methodological Conclusions

- ***Methodological work needed for, e.g.,***
  - joint modeling for all combinations of surrogate and true endpoint
  - efficient estimation methods
  - flexible implementation
  - specific settings, such as microarrays, etc.-
  - Bayesian paradigm