Causal-inference and Meta-analytic Approaches to Surrogate Endpoint Validation

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Outline

- Motivation
- Meta-analytic approach
- Causal paradigms
- Principal surrogacy
- Causal-association & the meta-analytic approach

Terminology

- Clinical endpoint:
  a characteristic or variable that reflects how a patient feels, functions, or survives
- Biomarker:
  a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention
- Surrogate endpoint:
  a biomarker that is intended to substitute for a clinical endpoint. A surrogate endpoint is expected to predict clinical benefit (or harm or lack of benefit or harm)

Refs: Biomarkers Definition Working Group, Clin Pharmacol Ther 2001, 69: 89;
De Gruttola et al, Controlled Clin Trials 2001, 22: 485.

Why Do We Need Surrogates?

- Practicality of studies:
  - Shorter duration
  - Smaller sample size (?)
- Availability of biomarkers:
  - Tissue, cellular, hormonal factors, etc.
  - Imaging techniques
  - Genomics, proteomics, other -omics

Ref: Schatzkin and Gail, Nature Reviews (Cancer) 2001, **3**

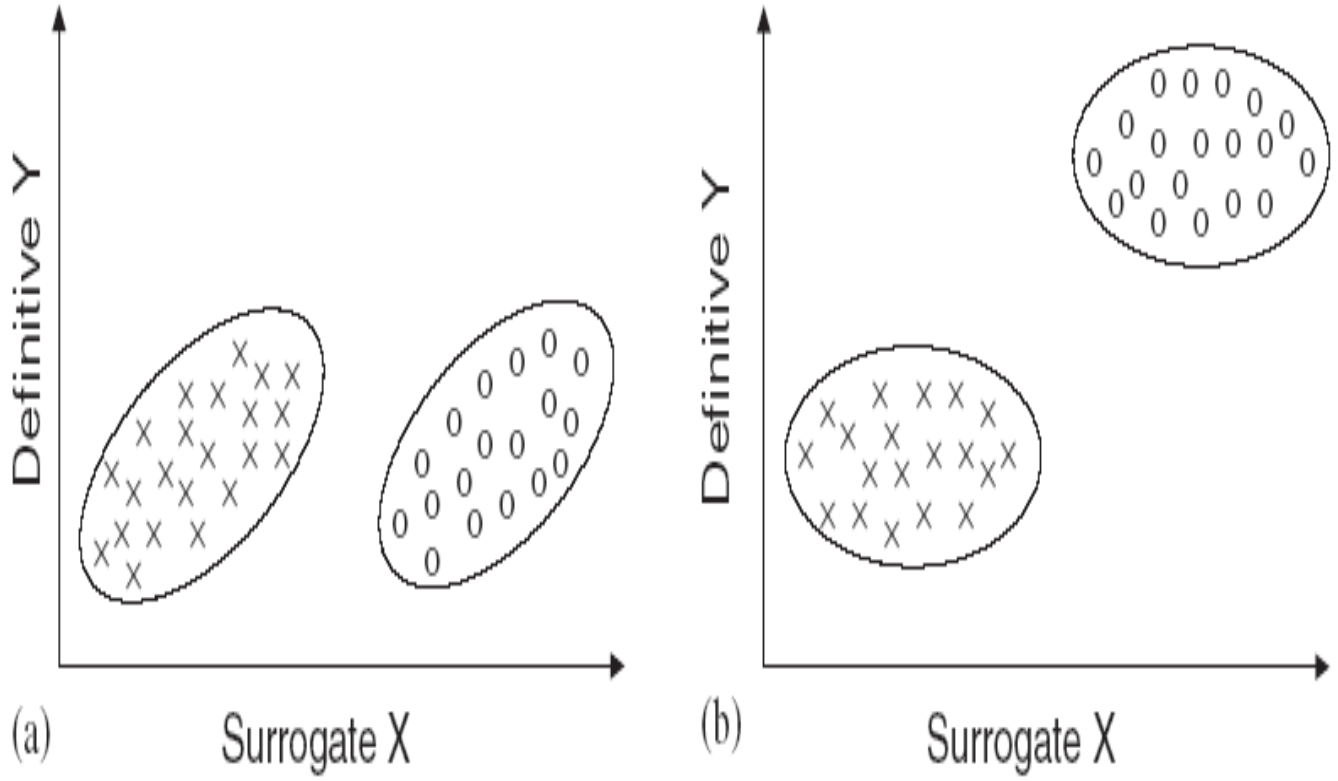
How To Define a Surrogate?

Key point: "A correlate does not a surrogate make"

$\Rightarrow$ correlation between *S(urrogate)* and *T(rue endpoint)* is not a sufficient condition for validity

Ref: Fleming and DeMets, Ann Intern Med 1996, **125**: 605.

A Correlate Does not a Surrogate Make



Ref: Korn, Albert & McShane, Statist Med 2005;**24**:163

Validation Based on the Precision of Prediction

"The effect of treatment on a surrogate endpoint must be reasonably likely to predict clinical benefit"

Ref: Biomarkers Definition Working Group, Clin Pharmacol Ther 2001, 69: 89.

Meta-analytic Approach

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

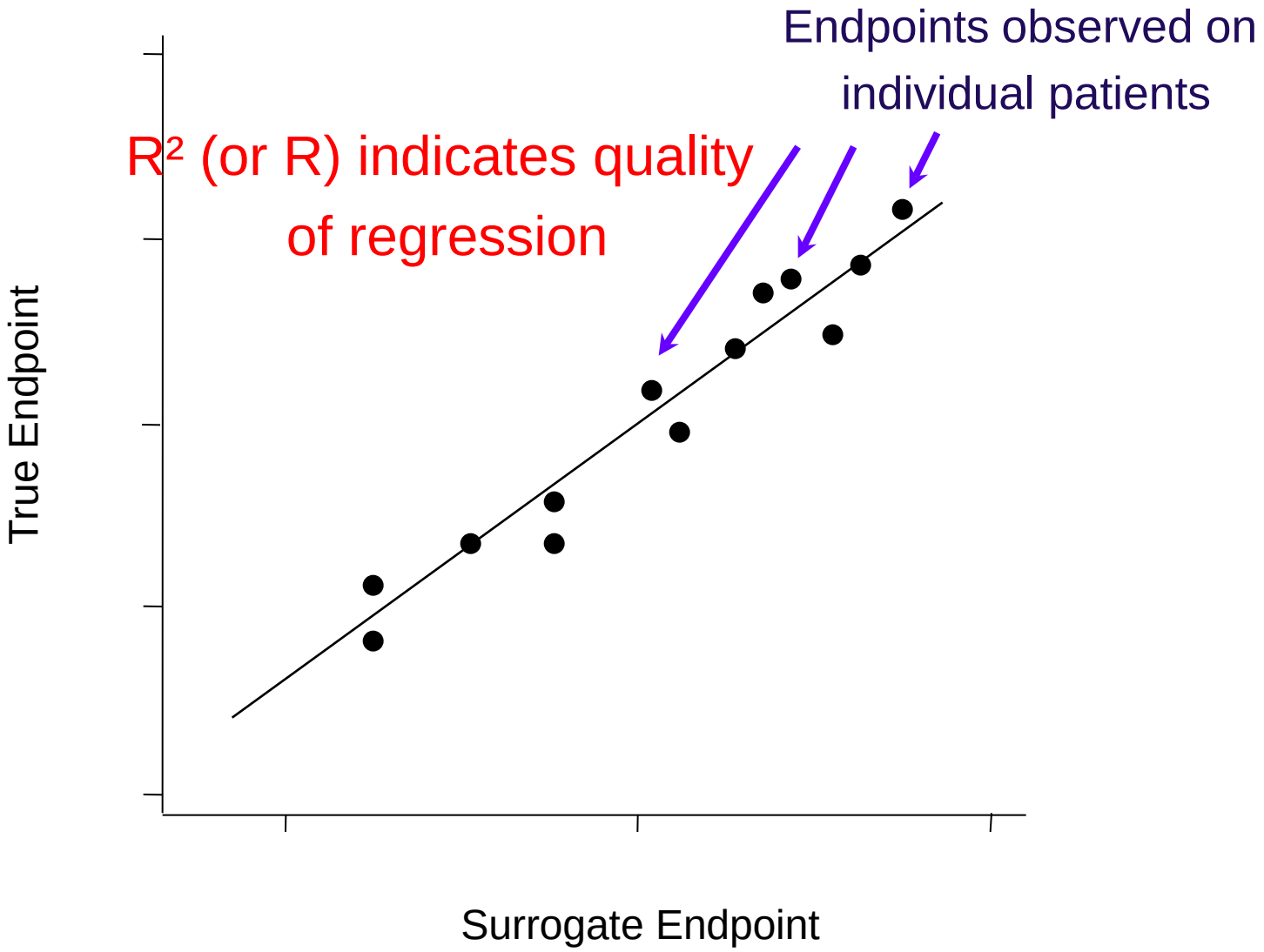
Assume $(\varepsilon_{Tij}, \varepsilon_{Sij})' \sim N_2(\mathbf{0}, \mathbf{\Sigma}_e)$, with $\mathbf{\Sigma}_e = \begin{pmatrix} \sigma_{TT} & \sigma_{TS} \\ \sigma_{TS} & \sigma_{SS} \end{pmatrix}$

Let $(\mu_{Si}, \mu_{Ti}, \beta_i, \alpha_i)' \sim$ normal.

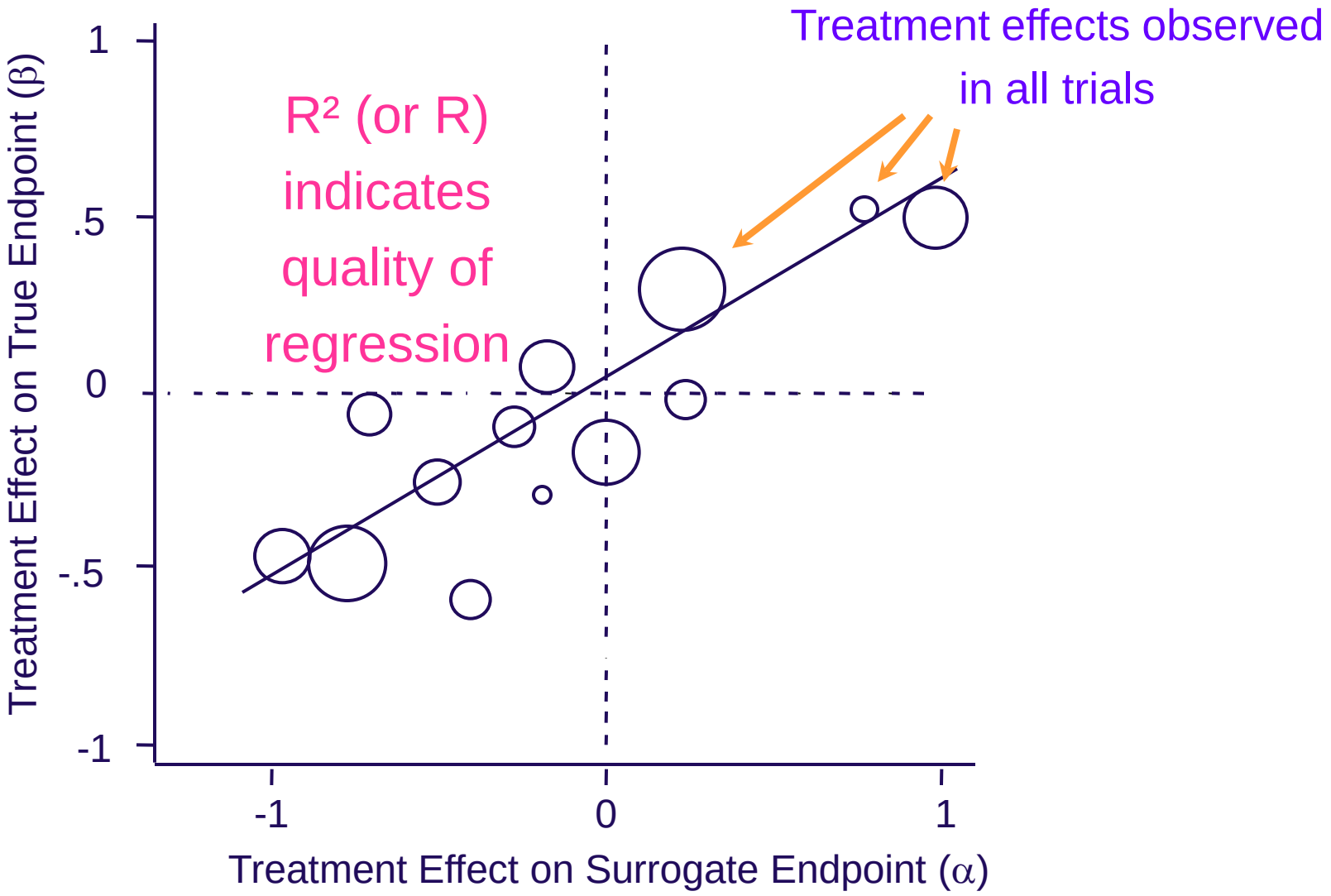
Define $\boldsymbol{\mu}_{\Delta i} = (\beta_i, \alpha_i)' \sim N_2(\boldsymbol{\mu}^*_{\Delta}, \mathbf{D}_{\Delta})$, with $\boldsymbol{D}_{\Delta} = \begin{pmatrix} d_{aa} & d_{ab} \\ d_{ab} & d_{bb} \end{pmatrix}$

Ref: Buyse et al, Biostatistics 2000

Prediction of True Endpoint From Surrogate



Prediction of Treatment Effect: Multiple Trials



Meta-analytic Approach

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

$(\varepsilon_{Tij}, \varepsilon_{Sij})' \sim N_2(\mathbf{0}, \mathbf{\Sigma}_e)$, with $\mathbf{\Sigma}_e = \begin{pmatrix} \sigma_{TT} & \sigma_{TS} \\ \sigma_{TS} & \sigma_{SS} \end{pmatrix}$

Define $R_{\text{ind}} = \sigma_{TS}/(\sigma_{TT}\sigma_{SS})^{0.5}$; if $R_{\text{ind}} \approx \pm 1$, surrogate valid at the individual-level

$\boldsymbol{\mu}_{\Delta i} = (\beta_i, \alpha_i)' \sim N_2(\boldsymbol{\mu}^*_{\Delta}, \mathbf{D}_{\Delta})$, with $\boldsymbol{D}_{\Delta} = \begin{pmatrix} d_{aa} & d_{ab} \\ d_{ab} & d_{bb} \end{pmatrix}$

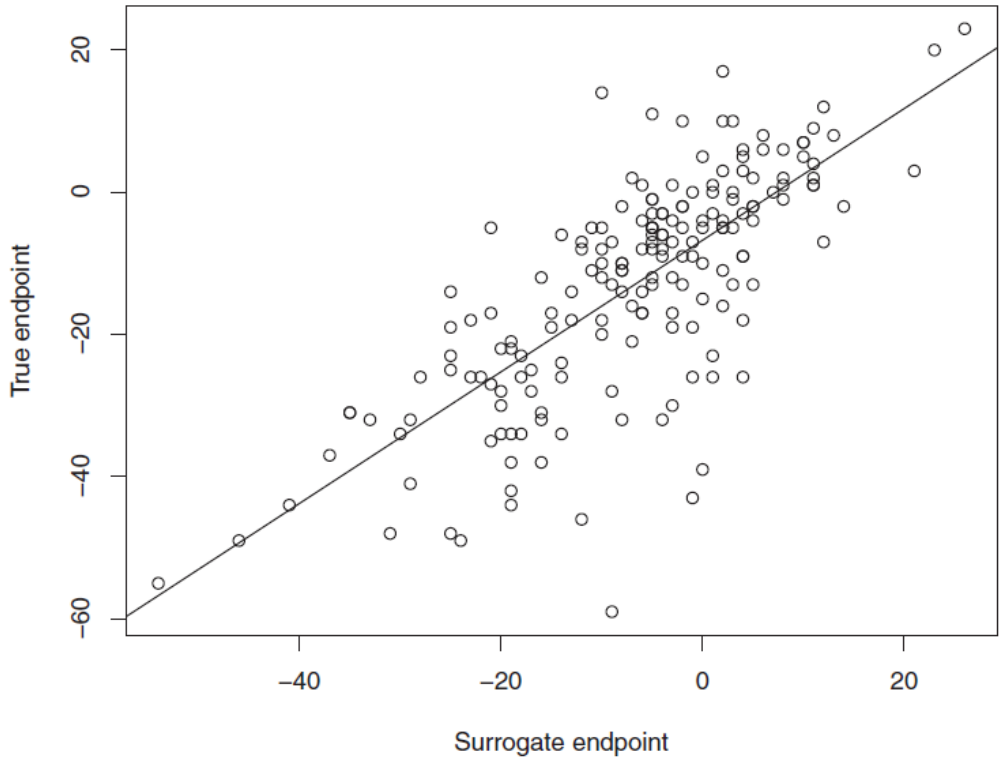
Define $R_{\text{trial}} = d_{ab}/(d_{aa}d_{bb})^{0.5}$; if $R_{\text{trial}} \approx \pm 1$, surrogate valid at the trial-level

Ref: Buyse et al, Biostatistics 2000

Example: Age-related Macular Degeneration

181 patients form 36 centers; placebo vs. interferon-α

S: change in visual acuity at 6 mths; T: change at 1 year



$$\widehat{\rho}_{S0T0} = 0.7693$$

$$\widehat{\rho}_{S1T1} = 0.7118$$

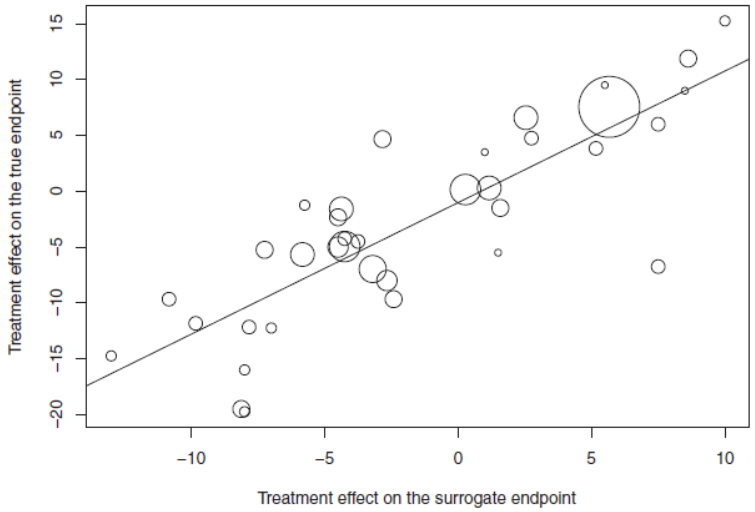
$$0.7450 \ (\mathrm{CI}_{95\%} = [0.6721,\ 0.8035])$$

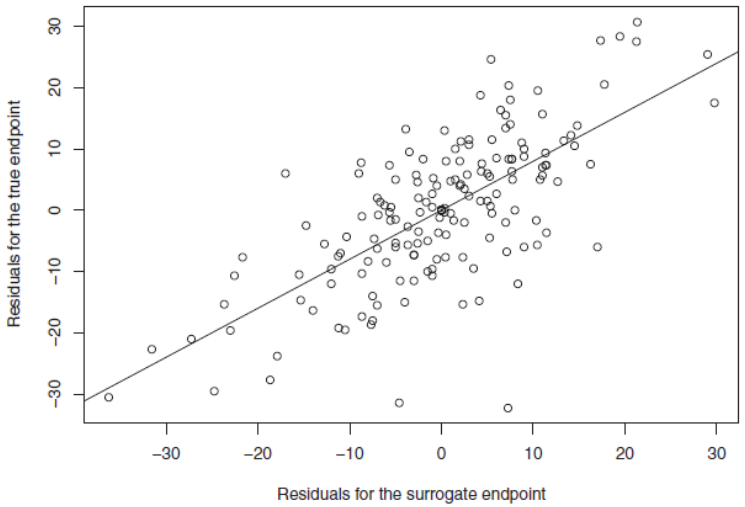
Ref: Buyse et al, Biostatistics 2000; Alonso et al, Biometrics 2015

Example: Age-related Macular Degeneration

	Trial level	
	Unweighted	Weighted
$\widehat{R}_{\text{trial}}$	0.831	0.837
$\widehat{R}_{\text{trial}}$ CI	(0.691, 0.911)	(0.702, 0.914)
$\widehat{d}_{aa}, \widehat{d}_{bb}$	37.75, 75.89	

	Individual level
$\widehat{R}_{\text{ind}}$ and CI	0.698, CI=(0.479, 0.835)





Ref: Alonso et al, Biometrics 2015

Causal-inference and Validation of Surrogate Endpoints

- Principal stratification (Frangakis & Rubin, *Biometrics* 2002)
- Causal inference links for "proportion explained" (Taylor et al, *Biometrics* 2005)
- Causal necessity and sufficiency (Gilbert & Hudgens, *Biometrics* 2008)
- Causal paradigms (Joffe & Greene, *Biometrics* 2009)
- Bayesian model, single trial (Li *et al.*, *Biometrics* 2010)
- Bayesian model, multiple trials (Li *et al.*, *Biostatistics* 2011)
- Principal stratification, normal endpoints (Conlon *et al.*, *Biostatistics* 2013)
- "Surrogate paradox" (VanderWeele, *Biometrics* 2013)
- Link to the meta-analytic approach (Alonso *et al.*, *Biometrics* 2015)

Causal Inference: Potential Outcomes and Counterfactuals

Each subject has two *potential outcomes* for T: T_{0j} and T_{1j}, corresponding to the two treatments ($Z = 0,1$). Likewise for S.

Only one of these outcomes is observed, the other is *counterfactual*.

Example: binary data

Subject j	Z_j	T_{0j}	T_{1j}	S_{0j}	S_{1j}
1	0	1	?	1	?
2	1	?	1	?	1
3	1	?	0	?	0
4	0	0	?	1	?
5	1	?	1	?	1
…					

Causal Inference: Individual Causal Effects

The causal treatment effect on T for subject j is $\Delta_{Tj} = T_{1j} - T_{0j}$.

The causal treatment effect on S for subject j is $\Delta_{Sj} = S_{1j} - S_{0j}$.

The effects are unobservable, unless special designs, e.g., a cross-over trial, are considered.

Causal Inference: Expected (Average) Causal Effects

The expected (average) causal effect on T is $\beta = \mathrm{E}(T_{1j} - T_{0j}) = \mathrm{E}(\Delta_{Tj})$.

The expected (average) causal effect on S is $\alpha = \mathrm{E}(S_{1j} - S_{0j}) = \mathrm{E}(\Delta_{Sj})$.

Under Stable Unit Treatment Value Assumption (SUTVA), and if $Z_j \perp (T_{0j}, T_{1j}, S_{0j}, S_{1j})$ (plausible under randomization), then

$\beta = \mathrm{E}(T_j|Z_j = 1) - \mathrm{E}(T_j|Z_j = 0)$ and $\alpha = \mathrm{E}(S_j|Z_j = 1) - \mathrm{E}(S_j|Z_j = 0)$

$\mathrm{E}(T_j|Z_j = 1)$, etc., can be estimated by the sample means.

Hence, the meta-analytic approach can be seen as the analysis of the association of the expected causal effects.

Causal-inference Paradigms for Validation of Surrogate Endpoints

Two paradigms:

-The causal-effects (CE) paradigm, in which knowledge of the effects of the treatment on the surrogate and of the surrogate on the clinical outcome is used to predict the effect of the treatment on the clinical outcome.

Examples: Prentice (1989); Taylor et al (2005)

-The causal-association (CA) paradigm, in which the effect of treatment on the surrogate is associated, across studies or population subgroups, with its effect on the clinical outcome, so allowing prediction of the effect on the clinical outcome from the effect on the surrogate

Examples: Frangakis & Rubin (2002); Buyse et al (2000)

Ref: Joffee & Greene, Biometrics 2009

The Causal-effects Paradigm

Uses concepts of the direct and indirect effects.

Applicable in a single-trial setting.

Explains the treatment effect on T "mechanistically".

Drawbacks:
-Requires (untestable) assumptions.
-Lacks power.
- Effects defined in terms of manipulation of the putative surrogate, but in pracitce interventions do not directly manipulate the surrogate.

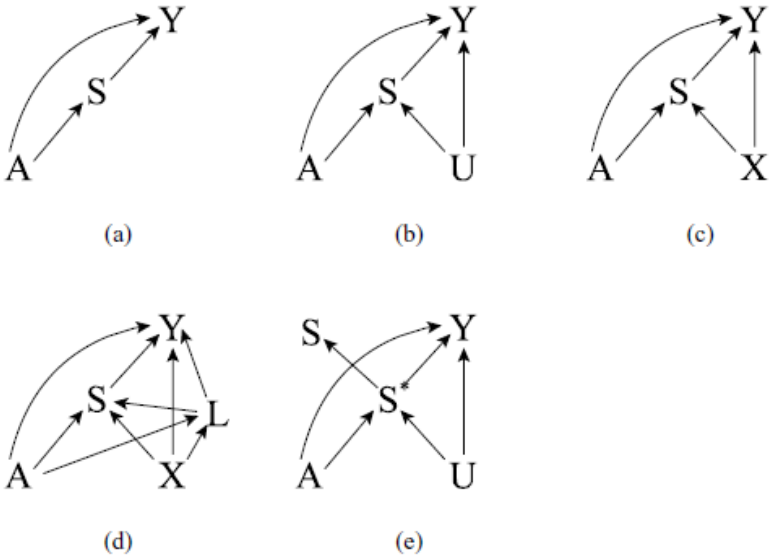


Figure 1. Causal diagrams for surrogate outcomes. (a) naive causal relationship; (b) general causal surrogate; (c) strong sequential ignorability (equations (7) and (8)); (d) weak sequential ignorability (equations (7) and (9)); and (e) proxy surrogate.

Ref: Joffee & Greene, Biometrics 2009

The Causal-association Paradigm

Considers association between expected causal effects.

Natural for the meta-analytic seting, though can be considered in a single-trial setting (principal surrogacy).

In the meta-analytic setting, applicable using the observable quantities.

More powerful than the CE paradigm.

Drawbacks:
- Does not "explain" the treatment effect on T; rather, evaluates its co-variation with the effect on S.

Ref: Joffee & Greene, Biometrics 2009

Principal Surrogate (1)

Frangakis & Rubin (2002): if no causal effect on S, then no effect on T.

Average causal necessity: $\mathrm{E}(\Delta_{Tj}|\Delta_{Sj} = 0) = 0$

Note: values of Δ_{Sj} define unobservable *principal strata*

Example: binary data

	(T_{0j}, T_{1j})				
(S_{0j}, S_{1j})	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	p_{11}	p_{12}	p_{13}	p_{14}	Never responders
(0,1)	p_{21}	p_{22}	p_{23}	p_{24}	Improved
(1,1)	p_{31}	p_{32}	p_{33}	p_{34}	Always responders
(1,0)	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

Ref: Frangakis & Rubin, Biometrics 2002; Gilbert and Hudgens, Biometrics 2008; Joffe & Greene, 2009

Principal Surrogate (2)

Frangakis & Rubin (2002): if no causal effect on S, then no effect on T.

Average causal necessity: $\mathrm{E}(\Delta_{Tj}|\Delta_{Sj} = 0) = 0$

Note: values of Δ_{Sj} define unobservable *principal strata*

Example: binary data

	(T_{0j}, T_{1j})				
(S_{0j}, S_{1j})	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	p_{11}	0	p_{13}	0	Never responders
(0,1)	p_{21}	p_{22}	p_{23}	p_{24}	Improved
(1,1)	p_{31}	0	p_{33}	0	Always responders
(1,0)	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

Ref: Frangakis & Rubin, Biometrics 2002; Gilbert and Hudgens, Biometrics 2008; Joffe & Greene, 2009

Principal Surrogate (3)

Frangakis & Rubin (2002): if no causal effect on S, then no effect on T.

Average causal necessity: $\mathrm{E}(\Delta_{Tj}|\Delta_{Sj}=0)=0$

Gilbert & Hudgens (2008): PS if average causal necessity and

Average causal sufficiency: $\exists\ \omega$ such that $\mathrm{E}(\Delta_{Tj}\mid\Delta_{Sj}>\omega)>0$

Ref: Frangakis & Rubin, Biometrics 2002; Gilbert and Hudgens, Biometrics 2008;

Dissociative & Associative Proportion

The *causal effect on T* is $CET = p_{+2} - p_{+4}$

The *dissociative proportion* is defined as $DP=((p_{12}-p_{14}) + (p_{32}-p_{34})) / CET$

The *associative proportion* is defined as $AP=((p_{22}-p_{24}) + (p_{42}-p_{44})) / CET$

	(T_{0j}, T_{1j})				
(S_{0j}, S_{1j})	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	p_{11}	p_{12}	p_{13}	p_{14}	Never responders
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(1,1)	p_{31}	p_{32}	p_{33}	p_{34}	Always responders
(1,0)	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

Note : the "proportions" are ratios of differences; their values span $[-\infty, +\infty]$ which is undesirable for a proportion

Ref: Li et al, Biostatistics 2011;12:478.

Dissociative & Associative Proportion for a Principal Surrogate

The *dissociative proportion* should be 0.

Additionally, for a "perfect" principal surrogate, we would like p_{24} and p_{42} to be 0. Hence, the *associative proportion* should be 1.

	(T_{0j}, T_{1j})				
(S_{0j}, S_{1j})	(0,0)	(0,1)	(1,1)	(1,0)	Principal stratification
(0,0)	p_{11}	0	p_{13}	0	Never responders
(0,1)	p_{21}	p_{22}	p_{23}	p_{24}	Improved
(1,1)	p_{31}	0	p_{33}	0	Always responders
(1,0)	p_{41}	p_{42}	p_{43}	p_{44}	Harmed

What Is Observed?

		T	
Z	S	0	1
0	0	$p_{11}+p_{12}+p_{21}+p_{22}$	$p_{13}+p_{14}+p_{23}+p_{24}$
	1	$p_{31}+p_{32}+p_{41}+p_{42}$	$p_{33}+p_{34}+p_{43}+p_{44}$
1	0	$p_{11}+p_{14}+p_{41}+p_{44}$	$p_{12}+p_{13}+p_{42}+p_{43}$
	1	$p_{21}+p_{24}+p_{31}+p_{34}$	$p_{22}+p_{23}+p_{32}+p_{33}$

- 15 “free” parameters, 6 supported by data
- Estimation of , e.g., DP & AP requires (untestable) identifying restrictions.
  - For instance, montonicity ($p_{41}=p_{42}=p_{43}=p_{44}=p_{14}=p_{24}=p_{34}=0$) reduces the number of “free” parameters to 8
  - Extra assumptions in a form of, e.g., priors in a Bayesian approach

Normally-distributed Endpoints, Single-trial Setting

Consider $\boldsymbol{Y}_j=(T_{0j}, T_{1j}, S_{0j}, S_{1j})' \sim N_4(\boldsymbol{\mu}, \boldsymbol{\Sigma})$ with $\boldsymbol{\mu}=(\mu_{T0}, \mu_{T1}, \mu_{S0}, \mu_{S1})'$ and

$$\boldsymbol{\Sigma} = \left(\begin{array}{cc|cc} \sigma_{T0T0} & \sigma_{T0T1} & \sigma_{T0S0} & \sigma_{T0S1} \\ \sigma_{T0T1} & \sigma_{T1T1} & \sigma_{T1S0} & \sigma_{T1S1} \\ \hline \sigma_{T0S0} & \sigma_{T1S0} & \sigma_{S0S0} & \sigma_{S0S1} \\ \sigma_{T0S1} & \sigma_{T1S1} & \sigma_{S0S1} & \sigma_{S1S1} \end{array}\right)$$

Consider *individual-causal effects*: $\boldsymbol{\Delta}_j = \mathbf{A}\boldsymbol{Y}_j = \begin{pmatrix} T_{1j} - T_{0j} \\ S_{1j} - S_{0j} \end{pmatrix} \sim N(\boldsymbol{\mu}_\Delta, \boldsymbol{\Sigma}_\Delta)$.

with $\boldsymbol{\Sigma}_\Delta = \mathbf{A}\boldsymbol{\Sigma}\mathbf{A}'$, $\boldsymbol{\mu}_\Delta=(\beta, \alpha)'$, $\beta = \mathrm{E}(\Delta_{Tj}) = \mu_{T1}-\mu_{T0}$, $\alpha = \mathrm{E}(\Delta_{Sj}) = \mu_{S1}-\mu_{S0}$.

Define *Individual Causal Association (ICA)*, $\rho_\Delta = \mathrm{Corr}(\Delta_{Tj}, \Delta_{sj})$. Then:

$$\rho_\Delta = \frac{\sqrt{\sigma_{T0T0}\sigma_{S0S0}}\rho_{T0S0} + \sqrt{\sigma_{T1T1}\sigma_{S1S1}}\rho_{T1S1} - \sqrt{\sigma_{T1T1}\sigma_{S0S0}}\rho_{T1S0} - \sqrt{\sigma_{T0T0}\sigma_{S1S1}}\rho_{T0S1}}{\sqrt{(\sigma_{T0T0} + \sigma_{T1T1} - 2\sqrt{\sigma_{T0T0}\sigma_{T1T1}}\rho_{T0T1})(\sigma_{S0S0} + \sigma_{S1S1} - 2\sqrt{\sigma_{S0S0}\sigma_{S1S1}}\rho_{S0S1})}}$$

Ref: Alonso et al, Biometrics 2015

Non-identifiability of ICA

Assume $\sigma_{T0} = \sigma_{T1} = \sigma_T$ and $\sigma_{S0} = \sigma_{S1} = \sigma_S$. Then

$$\rho_\Delta = \frac{\rho_{T0S0} + \rho_{T1S1} - \rho_{T1S0} - \rho_{T0S1}}{2\sqrt{(1-\rho_{T0T1})(1-\rho_{S0S1})}}.$$

Only ρ_{T0S0} and ρ_{T1S1} are identifiable.

Hence, ICA is non-identifiable without making untestable assumptions. The assumptions influence the value of ρ_Δ.

Ref: Alonso et al, Biometrics 2015

Average Causal Necessity

Average causal necessity: $\mathrm{E}(\Delta_{Tj}|\Delta_{Sj}=0)=0$

But

$$\Delta_{Tj}|\Delta_{Sj} \sim N\left[\beta+\sqrt{\frac{\sigma_T}{\sigma_S}\left(\frac{1-\rho_{T0T1}}{1-\rho_{S0S1}}\right)}\rho_{\Delta}(\Delta_{Sj}-\alpha),\ 2\sigma_T(1-\rho_{\Delta}^2)(1-\rho_{T0T1})\right]$$

Thus, even if $\rho_{\Delta}{}^2=1$, $E\left(\Delta_{Tj}|\Delta_{Sj}=0\right)=\ \beta\pm\sqrt{\frac{\sigma_T}{\sigma_S}\left(\frac{1-\rho_{T0T1}}{1-\rho_{S0S1}}\right)}\alpha\neq 0$

Hence, causal necessity is not satisfied, unless we assume $\beta=\alpha=0$.

Ref: Alonso et al, Biometrics 2015

Average Causal Sufficiency

Average causal sufficiency: $\exists\ \omega$ such that $E(\Delta_{Tj} \mid \Delta_{Sj} > \omega) > 0$

For truncated bivariate-normal

$$E(\Delta_{Tj}|\Delta_{Sj} > w) = \mu_{T|w} = \beta + \rho_\Delta \sqrt{2\sigma_T\,(1-\rho_{T0T1})}\,\lambda \times \left(\frac{w-\alpha}{\sqrt{2\sigma_S\,(1-\rho_{S0S1})}} \right)$$

with $\lambda(u)=\varphi(u)/(1-\Phi(u))$, $\lambda(u)>0$.

The average causal sufficiency is satisfied iff $\rho_\Delta > 0$.

Ref: Alonso et al, Biometrics 2015

Individual Causal Effects in a Meta-analytic Setting

Conider the individual causal effects in a multiple-trial setting. Let

$$\boldsymbol{\Delta}_{ij}=(T_{1ij}-T_{0ij},\ S_{1ij}-S_{0ij}) \sim \mathrm{N}_2(\boldsymbol{\mu}_{\Delta i},\boldsymbol{\Sigma}_{\Delta}) \text{ and } \boldsymbol{\mu}_{\Delta i} \sim \mathrm{N}_2(\boldsymbol{\mu}^*_{\Delta},\mathbf{D}_{\Delta}).$$

Then

$$\begin{cases} \Delta_{Tij} = \beta_i + \varepsilon_{\Delta Tij} \\ \Delta_{Sij} = \alpha_i + \varepsilon_{\Delta Sij} \end{cases}$$

with $(\varepsilon_{\Delta Tij},\ \varepsilon_{\Delta Sij})' \sim \mathrm{N}_2(\mathbf{0}, \boldsymbol{\Sigma}_{\Delta})$.

Define the *meta-analytic individual causal association* $\mathrm{MICA} = \mathrm{Corr}(\Delta_{Tij}, \Delta_{Sij})$.

It is equal to

$$\rho_M = \frac{\sqrt{\lambda_T \lambda_S}\, R_{\text{trial}} + 2\sqrt{(1-\rho_{T0T1})(1-\rho_{S0S1})}\,\rho_{\Delta}}{\sqrt{\lambda_T\lambda_S + 2\lambda_T(1-\rho_{S0S1}) + 2\lambda_S(1-\rho_{T0T1}) + 4(1-\rho_{T0T1})(1-\rho_{S0S1})}}$$

with $\lambda_T = d_{bb}/\sigma_{TT}$, $\lambda_S = d_{bb}/\sigma_{SS}$

Ref: Alonso et al, Biometrics 2015

Some Properties of MICA (1)

$$\rho_M = \frac{\sqrt{\lambda_T \lambda_S}\, R_{\text{trial}} + 2\sqrt{(1-\rho_{T0T1})(1-\rho_{S0S1})}\,\rho_\Delta}{\sqrt{\lambda_T\lambda_S + 2\lambda_T(1-\rho_{S0S1}) + 2\lambda_S(1-\rho_{T0T1}) + 4(1-\rho_{T0T1})(1-\rho_{S0S1})}}$$

If $\lambda_T \to +\infty$ and $\lambda_S \to +\infty$, then $\rho_M = R_{\text{trial}}$

(large between-trial variation → association between *expected* CA's captured)

If $\lambda_T \to 0$ and $\lambda_S \to 0$, then $\rho_M = \rho_\Delta$

(small between-trial variation → association between *individual* CA's captured)

Hence, MICA (ρ_M) evaluates validity of a surrogate across similar, but different populations (external validity). ICA (ρ_Δ) does it only for a single, fixed population (internal validity).

Ref: Alonso et al, Biometrics 2015

Some Properties of MICA (2)

Let $\rho_{T0T1} = \rho_{S0S1} = 0$. Then

$$\rho_M = \frac{\sqrt{d_{bb} d_{aa}}\, R_{\text{trial}} + 2\sqrt{\sigma_T \sigma_S}\, \rho_\Delta}{\sqrt{(d_{bb} + 2\sigma_T)(d_{aa} + 2\sigma_S)}}$$

If R_{ind} large, then $\rho_\Delta \approx R_{\text{ind}}$. Hence, choosing a surrogate with large $R_{\text{trial}} > 0$ and $R_{\text{ind}} > 0$ likely leads to a large ρ_M.

Thus, surrogates valid in the meta-analytic approach may also be valid in the causal-inference framework.

Ref: Alonso et al, Biometrics 2015

Some Properties of MICA (3)

$$\rho_M = \frac{\sqrt{\lambda_T \lambda_S}\, R_{\text{trial}} + 2\sqrt{(1-\rho_{T0T1})(1-\rho_{S0S1})}\,\rho_\Delta}{\sqrt{\lambda_T \lambda_S + 2\lambda_T(1-\rho_{S0S1}) + 2\lambda_S(1-\rho_{T0T1}) + 4(1-\rho_{T0T1})(1-\rho_{S0S1})}}$$

Large ρ_Δ (single-trial) may still give a low ρ_M (meta-analytic) if between-trial heterogeneity is larger than the within-trial one and expected causal association is low (small R_{trial}).

Note that, as ICA, MICA is also not identifiable, unless untestable assumptions are made.

Ref: Alonso et al, Biometrics 2015

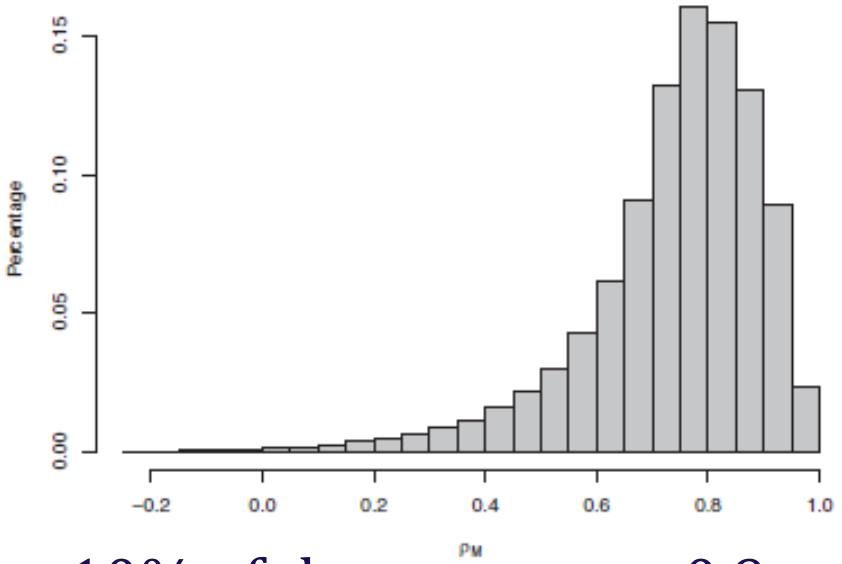
Example: Age-related Macular Degeneration

ρ_{S0T0}, ρ_{S1T1}, σ_{S0S0}, σ_{S1S1}, σ_{T0T0}, σ_{T1T1} fixed at the estimated values

Correlations in $\boldsymbol{\Sigma}$ fixed at values from {-1,-0.95,...,0, 0.05, ...,1}

41^4 matrices, leading to ρ_M

Substantial impact of the unidentified correlations



In 50% of the cases, ρ_M>0.77. In <10% of the cases, ρ_M>0.9. Similar (inconclusive) results as for the MA approach.

Ref: Alonso et al, Biometrics 2015

Causal-association & Meta-analytic Approach

Attention shifted to the association of expected causal effects.

Surrogate successfully evaluated at the trial and individual-level in a meta-analytic context, may likely also successfully pass a validation exercise based on individual causal effects.

A surrogate successfully evaluated in a single trial using ICEs may fail to pass a similar evaluation in a meta-analytic context.

Three main advantages of the MA approach :

(1) it has a causal interpretation (Joffe and Greene (2009)) ,
(2) it is identifiable under randomization;
(3) it may be more appealing to regulatory authorities and, therefore, more useful for drug approval.

Ref: Alonso et al, Biometrics 2015