

Investigating Validity of Psychiatric Symptom Scales and Surrogate Markers

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Outline

- Psychiatric disorders: Brief description of the challenge
- Validation of scales: A quick summary
- Surrogate marker methodology: Brief historical introduction
- Example in schizophrenia
- Repeated measurements:
 - Collapse of the traditional concepts: VRF
 - Canonical Correlation point of view: θ_p
 - Looking for a unifying approach: R_{Λ}^2 and LRF
 - Conclusions

Psychiatric Disorders

Lee Robins, a psychiatric epidemiologist at Columbia University, first reported the following findings in 1984:

- At any given time 15 to 23 percent of the U.S. population has a diagnosable mental disorder.
- Ten to 20 percent of people will have an episode of clinical depression.
- At some point in their lives, between 28 and 38 percent of people will develop a mental disorder.
- Each year at least 30,000 people will commit suicide.
- An additional 3,000 to 15,000 deaths per year can be attributed to other causes stemming from suicide attempts.

The United States loses more than \$185 billion each year, with the annual cost of mental health treatment being \$20 billion to \$50 billion.

Famous People With Mental Illness

- Abraham Lincoln: the revered 16th President suffered from severe, incapacitating and occasionally suicidal depressions
- Virginia Woolf: The British novelist who wrote *To The Lighthouse* and *Orlando* experienced manic depressive disorder
- Ludwig von Beethoven: experienced manic depressive disorder
- Leo Tolstoy: author of *War and Peace*, Tolstoy revealed the extent of his own mental illness in *My Confession*
- Vincent Van Gogh: experienced manic depressive disorder
- Charles Dickens: one of the greatest authors in English language suffered from clinical depression
- John Nash: Mathematician/Nobel Prize Winner experienced Schizophrenia

Schizophrenia

In 1911, Eugen Bleuler, first used the word "schizophrenia". The term schizophrenia comes from the Greek words "schizo" (=split) and "phrenia" (=mind)

schizophrenia = split + mind

Schizophrenia: Get the Facts

- Schizophrenia is a disease that strikes young people in their prime. Usual age of onset is between 16 and 25.
- It affects 1 in 100 people worldwide no mattering races in cultures and social classes.
- The disease distorts the senses, making it very difficult for the individual to tell what is real from what is not real.

Scales in Schizophrenia

- Positive And Negative Syndrome Scale (PANSS)
 - 30 items,
 - 1 (not present) to 7 (extremely severe).
 - Range: 30 to 210; the higher, the worse.
- CGI: Clinician's Global Impression (7 points)
 - 1= Very much improved
 - ⋮
 - 4=No change
 - ⋮
 - 7=Very much worsened

Validation of Scales

1. **Reliability:** Measures the reproducibility of an empirical measure

1.1 *Internal Consistency:*

Cronbach alpha, Kuder-Richardson and Factor analysis.

1.2 *Test-retest and Inter-rater reliability.*

Reflects the extent to which the instrument can differentiate among individuals.

2. **Validity**

2.1 *Content Validity:* samples all relevant contents.

2.2 *Criterion Validity:* relationship with “criterion” .

2.3 *Construct Validity:* relation with theoretical concepts.

Determine the degree of confidence we can place on inferences based on the scores.

Validation of Scales: Criterion Validity

Correlation of a scale with some other trait or disorder under study:

- **Concurrent validity:** correlates the new scale with the criterion measure, both given at the same time
- **Predictive validity:** criterion will not be available until some time in the future

—→ Surrogate marker methodology can offer more insight

Definition of Surrogate Endpoint

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.”

$$(S|\text{treated}) = (S|\text{control})$$



$$(T|\text{treated}) = (T|\text{control})$$

Prentice's Criteria

Criterion 1:

Treatment Z is prognostic for true endpoint T

$$T_j = \mu_T + \beta Z_j + \varepsilon_{Tj}$$

Criterion 2:

Treatment Z is prognostic for surrogate S

$$S_j = \mu_S + \alpha Z_j + \varepsilon_{Sj}$$

Criterion 3:

Surrogate S is prognostic for true endpoint T

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

Criterion 4:

The full effect of the treatment Z on the true endpoint T is explained by S

$$T_j = \mu_{T|S} + \beta_S Z_j + \gamma_Z S_j + \varepsilon_{T|Sj}$$

Other Proposals

Fourth Criterion



Proportion explained

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



Relative Effect

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



Adjusted Association

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

Analysis Based on Several Trials

Statistical Model

- **Model:**

$$T_{ij} = \mu_{Ti} + \beta_i Z_{ij} + \varepsilon_{Tij}$$

$$S_{ij} = \mu_{Si} + \alpha_i Z_{ij} + \varepsilon_{Sij}$$

- **Error structure:**

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

- **Trial-specific effects:**

$$\begin{pmatrix} \mu_{Si} \\ \mu_{Ti} \\ \alpha_i \\ \beta_i \end{pmatrix} = \begin{pmatrix} \mu_S \\ \mu_T \\ \alpha \\ \beta \end{pmatrix} + \begin{pmatrix} m_{Si} \\ m_{Ti} \\ a_i \\ b_i \end{pmatrix}$$

- **Error structure of random effects:**

$$D = \begin{pmatrix} d_{SS} & d_{ST} & d_{Sa} & d_{Sb} \\ d_{ST} & d_{TT} & d_{Ta} & d_{Tb} \\ d_{Sa} & d_{Ta} & d_{aa} & d_{ab} \\ d_{Sb} & d_{Tb} & d_{ab} & d_{bb} \end{pmatrix}$$

Trial-Level Surrogacy

To assess surrogacy at the trial level the following coefficient of determination is proposed:

$$R_{\text{trial}}^2 = R_{b_i | m_{S_i}, a_i}^2 = \frac{1}{d_{bb}} \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}^T \begin{pmatrix} d_{SS} & d_{Sa} \\ d_{Sa} & d_{aa} \end{pmatrix}^{-1} \begin{pmatrix} d_{Sb} \\ d_{ab} \end{pmatrix}$$

Individual-Level Validity

$$R_{\text{ind}}^2 = R_{\varepsilon_{T_i} | \varepsilon_{S_i}}^2 = \frac{\sigma_{TS}^2}{\sigma_{TS}\sigma_{SS}}$$

Scale Validation: Cross-sectional Setting

- (1) Traditional psychometric techniques limit themselves to the calculation of simple Pearson correlation coefficients.
- (2) Due to the hierarchical nature of the data, one is able to distinguish between trial-level and individual-level validity.
- (3) At the trial-level, treatment effects on aggregate scores can be translated to effects on more understandable measures.
- (4) Psychiatric studies: symmetry in the triplet (S_1, S_2, Z) :

$$R^2_{\text{trial}S_1S_2} \iff R^2_{\text{trial}S_2S_1}$$

- (5) The individual-level agreement addresses non-trial and non-treatment specific correlation between measurements at the level of the individual patient.

Repeated Measurements

Assumptions made so far

- (1) Both endpoints could be characterized by a univariate random variable.
- (2) Only one potential surrogate and one true endpoint were available for the analysis and only two treatments groups were considered.
- (3) Treatment effect on both responses was assumed to be constant over time and characterized by a single parameter.
- (4) The covariance structure of the error terms was homogeneous over the different trials.

Technically, we need (1) a model for bivariate longitudinal outcomes, and (2) new measures that let us evaluate surrogacy when longitudinal data are available.

Example

- ★ Meta-analysis of 5 double-blind randomized clinical trials on chronic schizophrenia comparing Risperidone with conventional neuroleptics.
- ★ Trial duration: 4 to 8 weeks. The analysis and only two treatments groups were considered.
- ★ Unit of Analysis: country within trial.

Country Id	1	2	3	4	5	6	7	8	9	10
# Patients	31	29	26	44	44	9	37	32	68	49

Country Id	11	12	13	14	15	16	17	18	19	20
# Patients	43	21	25	39	36	17	33	69	30	128

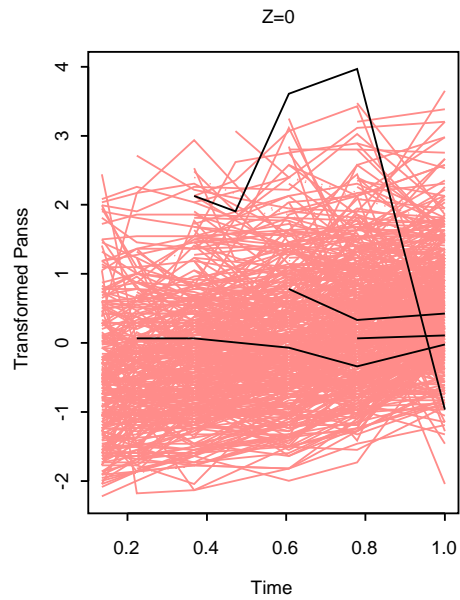
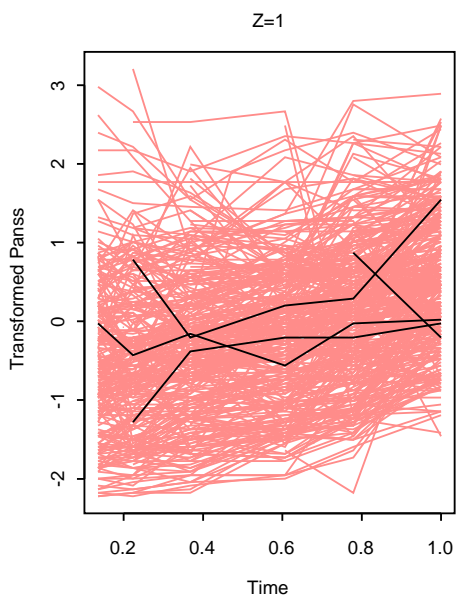
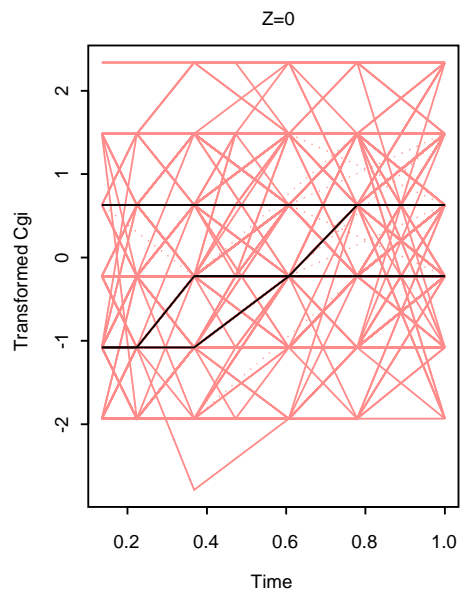
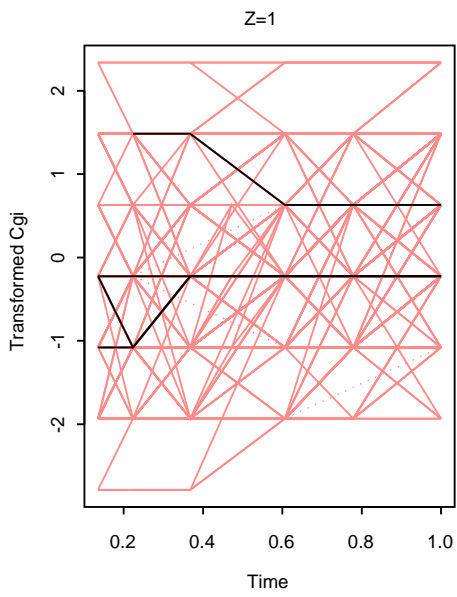
- New variables

$$T = -3.63495 + 0.8538 \cdot \text{CGI}$$

$$S = -3.5675 + 0.04484 \cdot \text{PANSS}$$

$$t_{new} = e^{-t/4}$$

Individual Profiles



Model Formulation

In each trial we will consider the model:

$$\begin{cases} T_{ijt} = \mu_{T_i} + \beta_i \cdot Z_{ij} + g_{Tij}(t_{ij}) + \varepsilon_{T_{ijt}} \\ S_{ijt} = \mu_{S_i} + \alpha_i \cdot Z_{ij} + g_{Sij}(t_{ij}) + \varepsilon_{S_{ijt}} \end{cases}$$

$$\Sigma_i = \begin{pmatrix} \sigma_{TTi} & \sigma_{TSi} \\ \sigma_{TSi} & \sigma_{SSi} \end{pmatrix} \otimes \begin{pmatrix} 1 & \rho_i & \cdots & \rho_i^{d_{1p_i}} \\ \vdots & \vdots & \vdots & \vdots \\ \rho_i^{d_{1p_i}} & \rho_i^{d_{1p_i}-1} & \cdots & 1 \end{pmatrix}$$

Four different models were fitted. Here $k = \{T, S\}$

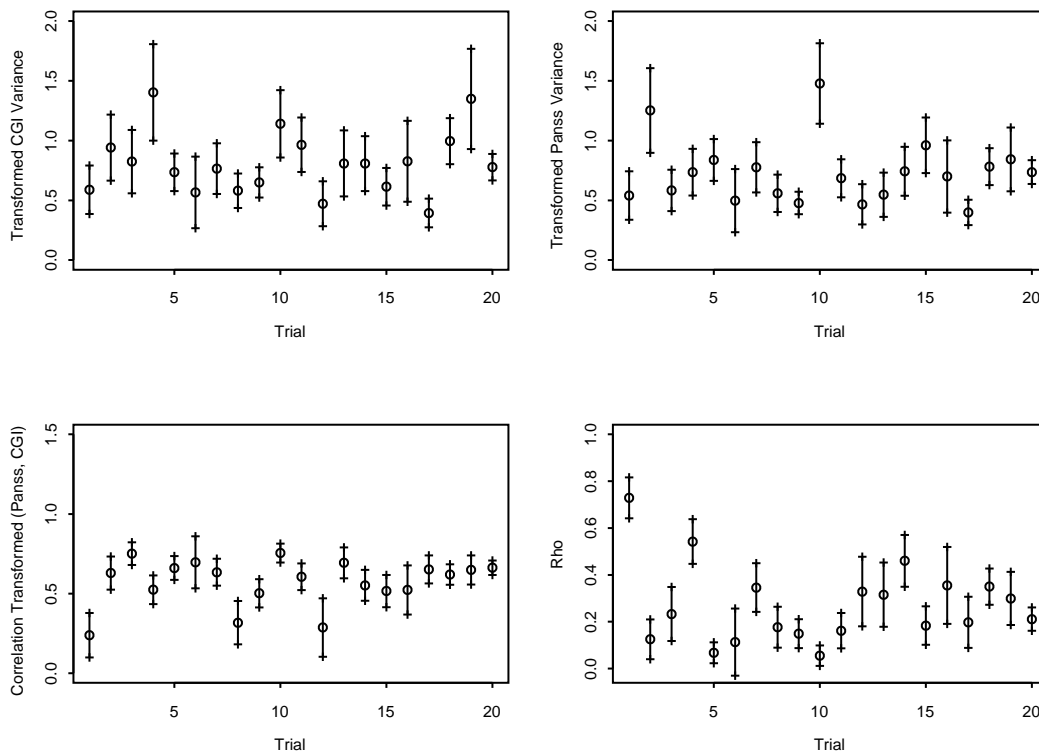
1. Linear trend over time and treatment-by-time interaction: $g_{kij}(t_{ij}) = \delta_{ki}Z_{ij}t_{ij} + \theta_{ki}t_{ij}$.
2. Linear trend over time: $g_{kij}(t_{ij}) = \theta_{ki}t_{ij}$.
3. Random intercept: $g_{kij}(t) = \theta_{ki}t_{ij} + b_{kij}$.
4. General trend over time modelled using splines via random effects as proposed by Verbyla *et al* (1999), $g_{ki}(t) = \text{lin}_{ki}(t) + \text{spl}_{ki}(t)$.

Evaluating Criterion Validity

a) Trial Level:

Parameter	Value	CI
$R^2_{\text{trial}}(T, S)$	0.866	(0.668, 0.942)
$R^2_{\text{trial}}(S, T)$	0.820	(0.611, 0.920)

b) Individual Level: Original approach inapplicable



Variance Reduction Factor: VRF

Covariance structure for $\tilde{\varepsilon}_{T_{ij}}$ and $\tilde{\varepsilon}_{S_{ij}}$:

$$\Sigma_i = \begin{pmatrix} \Sigma_{TTi} & \Sigma_{TSi} \\ \Sigma_{TSi}^T & \Sigma_{SSi} \end{pmatrix}$$

VRF

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

where $\Sigma_{(T|S)i} = \Sigma_{TTi} - \Sigma_{TSi} \Sigma_{SSi}^{-1} \Sigma_{TSi}^T$.

Under Galecki's model: $\Sigma_i = V_i \otimes R_i$,

$$VRF_{\text{ind}} = \sum_i \left(\frac{p_i \sigma_{TTi}}{\sum_i p_i \sigma_{TTi}} \right) \rho_{TSi}^2$$

where: $\rho_{TSi}^2 = \frac{\sigma_{TSi}^2}{\sigma_{SSi} \sigma_{TTi}}$.

Properties of the VRF

1. VRF_{ind} is not symmetric and not invariant by linear transformations.
2. VRF_{ind} ranges between 0 and 1.
3. $VRF_{ind} = 0 \Leftrightarrow \forall i \quad (\tilde{\varepsilon}_{T_i}, \tilde{\varepsilon}_{S_i})$ are independent.
4. $VRF_{ind} = 1 \Leftrightarrow \forall i$ there is a deterministic relationship between $\tilde{\varepsilon}_{T_i}$ and $\tilde{\varepsilon}_{S_i}$.
5. Cross-sectional case $VRF_{ind} = R_{ind}^2$.

b) Individual Level

Parameters	Value	CI
$VRF(T, S)$	0.363	(0.335, 0.391)
$VRF(S, T)$	0.365	(0.336, 0.394)

Canonical Correlation Approach

If at trial i we have p_i time points then

$$\rho_{i1}^2 \geq \rho_{i2}^2 \geq \dots \geq \rho_{ip_i}^2$$

and ρ_{it}^2 are the eigenvalues of

$$MCC_i = \Sigma_{TTi}^{-1/2} \Sigma_{TSi} \Sigma_{SSi}^{-1} \Sigma_{TSi}^T \Sigma_{TTi}^{-1/2}$$

Let $\rho_{vi}^2 = (\rho_{i1}^2, \rho_{i2}^2, \dots, \rho_{ip_i}^2)$ be the vector of the squared canonical correlations at trial i then

- (i) The ρ_{vi}^2 ranges between 0 and 1 for all i in the sense that each of its components does
- (ii) The $\rho_{vi}^2 = 0$ for all i if and only if the error terms are independent within each trial
- (iii) The $\rho_{vi}^2 = 1$ for all i if and only if there exists a deterministic relationship between the error terms
- (iv) The ρ_{vi}^2 are all equal and reduce to R_{ind}^2 when both endpoints are measured only once.

We need a function of the ρ_{vi}^2 , satisfying

1. $\theta : [0, 1]^p \rightarrow [0, 1]$
2. $\theta = g(x_1, x_2, \dots, x_p) = 0 \Leftrightarrow (x_1, x_2, \dots, x_p) = 0$
3. $\theta = g(x_1, x_2, \dots, x_p) = 1 \Leftrightarrow (x_1, x_2, \dots, x_p) = 1$
4. $\theta = g(x, x, \dots, x) = x$

Linear functions $\theta = g(x_1, x_2, \dots, x_p) = \sum a_i x_i$ then (1)–(4) are equivalent to $a_i > 0 \quad \forall i$ and $\sum a_i = 1$.

If we now have data from several trials we can define the following family of parameters

$$\Omega = \left\{ \theta : \theta = \sum_i \sum_k \alpha_{ik} \rho_{ik}^2 : \alpha_{ik} > 0 \quad \forall (i, k), \quad \sum_i \sum_k \alpha_{ik} = 1 \right\}$$

where $i = 1, \dots, N$ denotes the trial and $k = 1, \dots, p_i$ denotes the designed time points.

Relationship between VRF and θ

It is possible to prove that

$$VRF_{\text{ind}} = \sum_i \sum_k \alpha_{ik}^* \rho_{ik}^2,$$

$$\text{where } \alpha_{ik}^* = \frac{\text{diag}(P_i^T \Sigma_{TTi} P_i)_{kk}}{\sum_i \text{tr}(\Sigma_{TTi})}.$$

It is also possible to prove that, under Galecki's model, the Ω family can be rewritten as

$$\Omega_g = \left\{ \theta : \theta = \sum_i \alpha_i \rho_{TSi}^2 : \alpha_i > 0 \quad \forall i, \quad \sum_i \alpha_i = 1 \right\}.$$

Simulation Study

Three different members of Ω_g were studied

$$1. \alpha_i^{\text{vrf}} = \frac{p_i \sigma_{TTi}}{\sum_i p_i \sigma_{TTi}}: \text{VRF}$$

$$2. \alpha_i^{\text{ew}} = \frac{1}{N}, N \text{ is the number of trials: Equally weighted}$$

$$3. \alpha_i^{\text{ssw}} = \frac{n_i}{\sum_i n_i}, n_i \text{ is the number of subjects in trial } i:$$

Sample size weighted

The following settings for the parameters were considered:

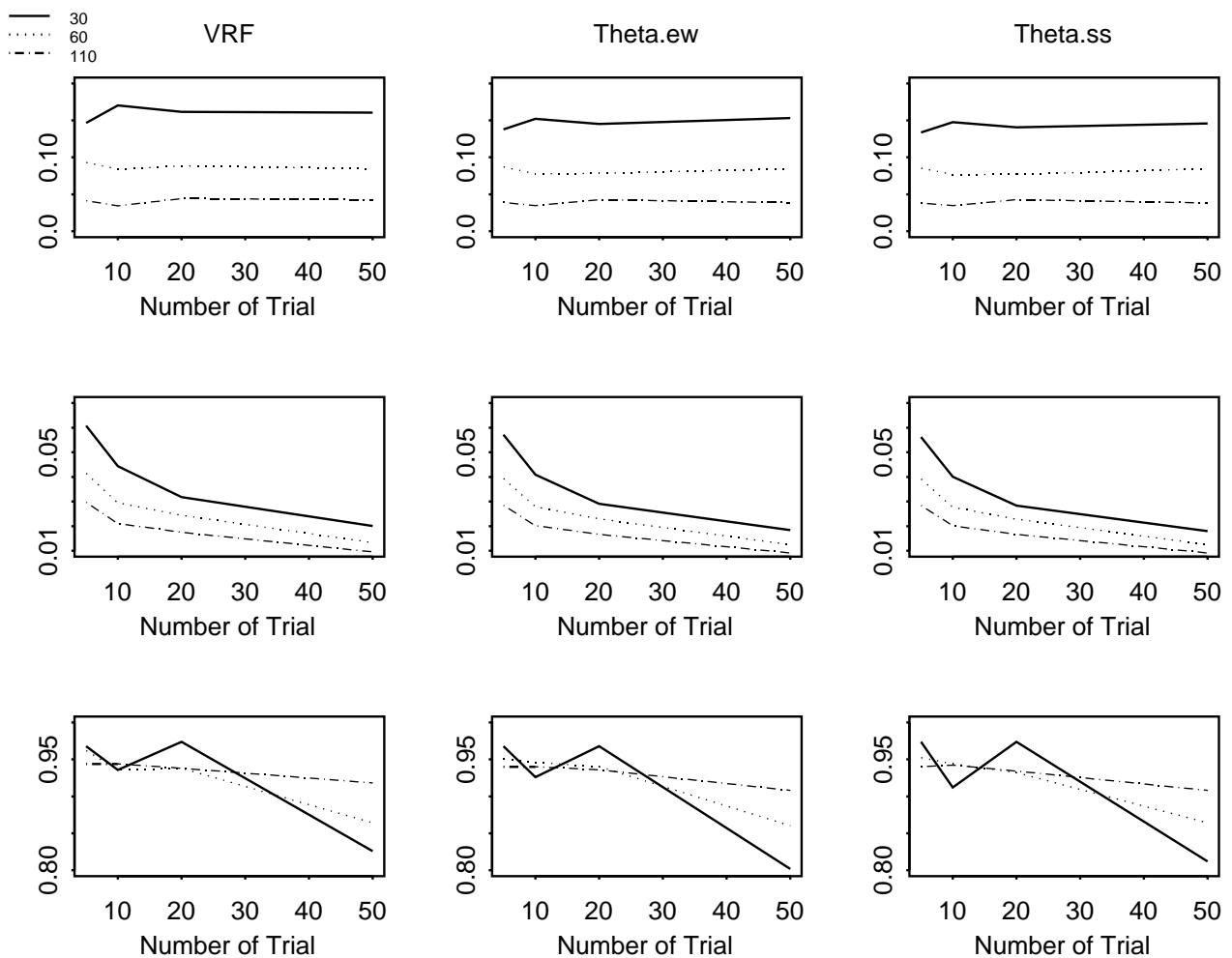
1. Correlation: Low $\rho_{TSi} = 0.20$, middle $\rho_{TSi} = 0.50$, high $\rho_{TSi} = 0.90$.
2. Number of trials: $N = 5, 10, 20, 50$.
3. Patients per trial: n_i sampled with replacement from $\{20, \dots, 40\}$, $\{50, \dots, 70\}$, and $\{100, \dots, 120\}$.

For each setting, five hundred data sets were generated and analyzed.

Simulation Results

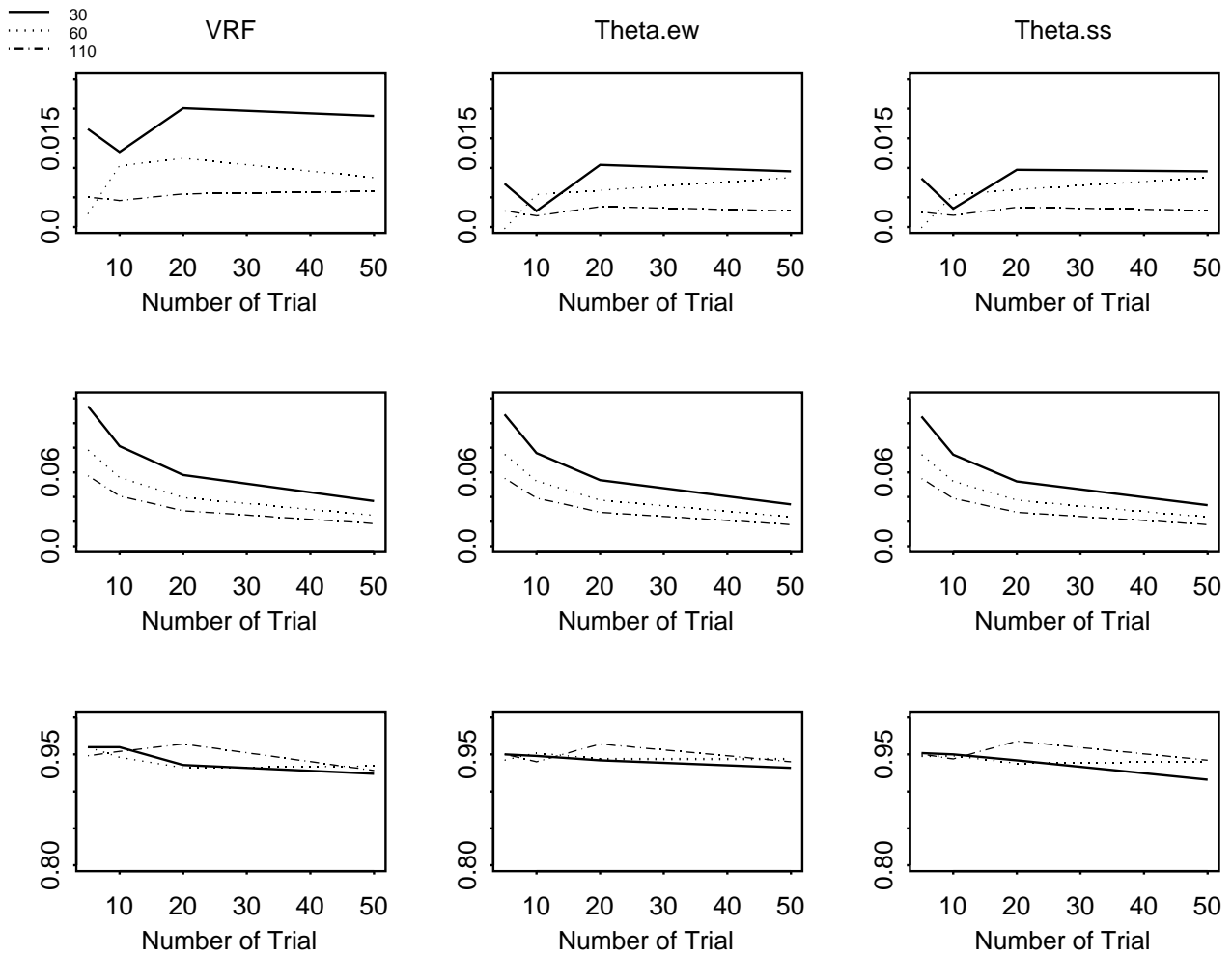
We study the performance with respect to bias, the standard deviation and the percentage of coverage for the confidence intervals.

Low Correlation



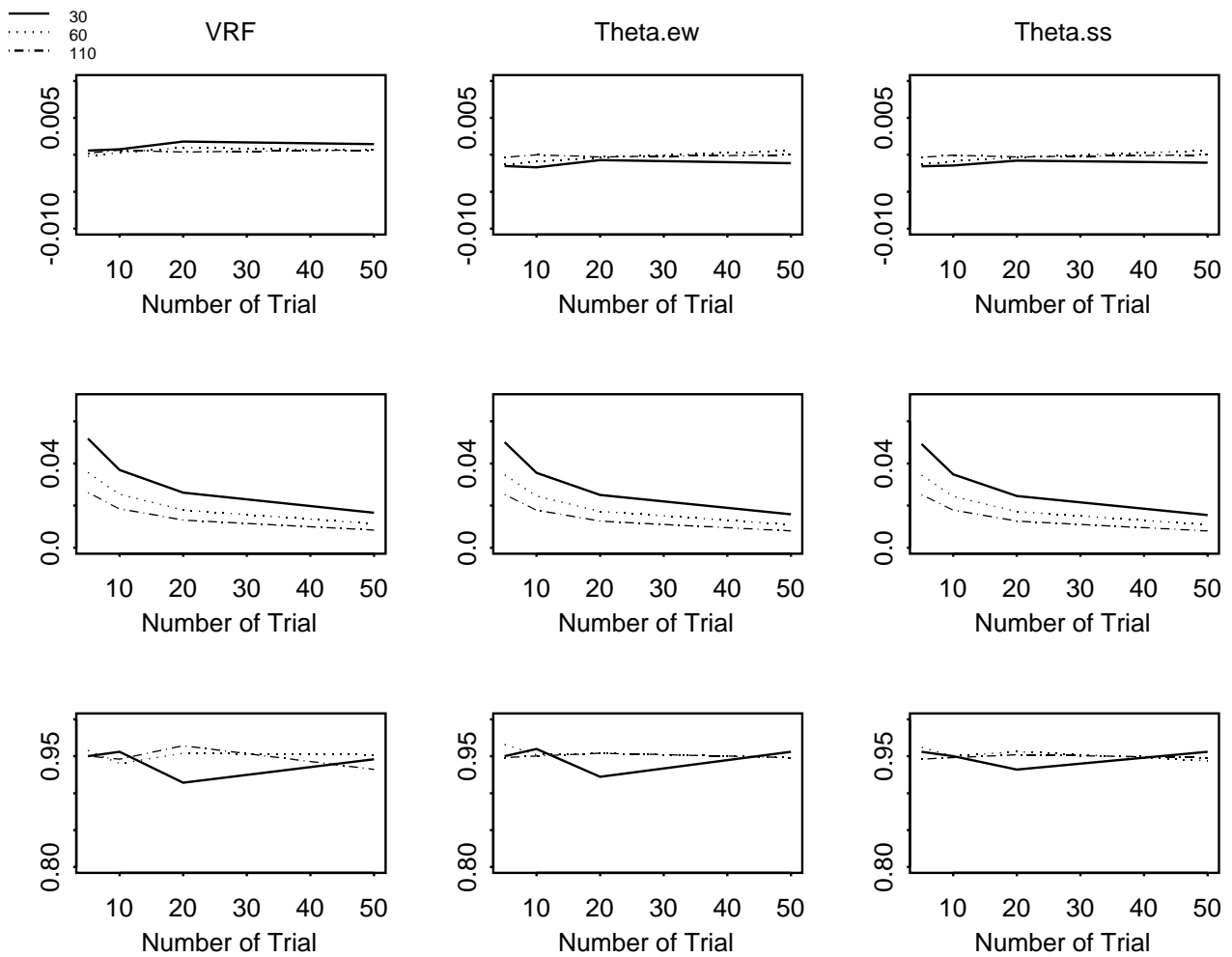
Simulation Results

Middle Correlation



Simulation Results

High Correlation



Simulation Conclusions

- No major differences found, however:

$$\theta_{\text{vrf}} \leq \theta_{\text{ssw}} \approx \theta_{\text{ew}}$$

- Relative bias seems to be unaffected by the number of trials whereas the precision can be improved by increasing the number of trials.
- Using a large number of small units is not an adequate option, mainly when the association between the surrogate and the true endpoint is not that strong.

VRF versus θ_p

In our simulation $\theta_{ew} = \sum_i \frac{1}{N} \rho_{TSi}^2$ had a better performance than the VRF.

Who is θ_{ew} ?

Actually both parameters, VRF and θ_p , are structurally similar

$$\theta_P = \sum_i \frac{1}{N p_i} \text{tr}\{(\Sigma_{TTi} - \Sigma_{(T|S)i})\Sigma_{TTi}^{-1}\}$$
$$VRF_{\text{ind}} = \frac{\sum_i \{\text{tr}(\Sigma_{TTi} - \Sigma_{(T|S)i})\}}{\sum_i \text{tr}(\Sigma_{TTi})}$$

- The VRF is not symmetric and it is not invariant with respect to linear bijective transformations. It is invariant with respect to linear orthogonal transformations.
- θ_p is symmetric as well as invariant with respect to linear bijective transformations.

R_Λ^2 and LRF: Unified approach

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

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

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

1. θ_p is symmetric and invariant by linear transformations.
2. θ_p ranges between zero and one
3. $\theta_p = 0 \Leftrightarrow \forall i \quad (\tilde{\varepsilon}_{T_i}, \tilde{\varepsilon}_{S_i})$ are ind.
4. $\theta_p = 1 \Leftrightarrow \forall i$ deterministic relationship between $\tilde{\varepsilon}_{T_i}$ and $\tilde{\varepsilon}_{S_i}$.
5. Cross-sectional case $\theta_p = R_{\text{ind}}^2$.

1. R_Λ^2 is symmetric and invariant by linear transformations.
2. R_Λ^2 ranges between zero and one
3. $R_\Lambda^2 = 0 \Leftrightarrow \forall i \quad (\tilde{\varepsilon}_{T_i}, \tilde{\varepsilon}_{S_i})$ are ind.
4. $R_\Lambda^2 = 1 \Leftrightarrow \forall i \quad \exists a_i, b_i$ so that $a_i^T \tilde{\varepsilon}_{T_i} = b_i^T \tilde{\varepsilon}_{S_i}$.
5. Cross-sectional case $R_\Lambda^2 = R_{\text{ind}}^2$.

Galecki's Model:

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

$$\theta_p = \sum_i \left(\frac{1}{N}\right) \rho_{TSi}^2$$

p_i is the number of designed time points

Galecki's Model:

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

$$R_\Lambda^2 = 1 - \frac{1}{N} \sum_i (1 - \rho_{TSi}^2)^{p_i}$$

p_i is the number of designed time points

Canonical Correlation Approach:

$$\theta = \sum_i \sum_h \alpha_{ih} \rho_{ih}^2$$

$$\alpha_{ih} > 0 \quad \forall (i, h), \quad \sum_i \sum_h \alpha_{ih} = 1$$

Extension for non-normal settings: ?

Canonical Correlation Approach:

$$\theta_\Lambda = 1 - \sum_i \alpha_i \prod_h (1 - \rho_{ih}^2)$$

$$\alpha_i > 0 \quad \forall i, \quad \sum_i \alpha_i = 1$$

Extension for non-normal settings:

Later

Relationship Between R_{Λ}^2 and θ_p

Let us consider first the special case defined by Galecki's model:

$$\theta_p = \frac{1}{N} \sum_i \rho_{TSi}^2$$
$$R_{\Lambda}^2 = 1 - \frac{1}{N} \sum_i (1 - \rho_{TSi}^2)^{p_i}$$

It is possible to prove that

$$R_{\Lambda}^2 = \theta_p + \frac{1}{N} \sum_i (1 - \rho_{TSi}^2) \{1 - (1 - \rho_{TSi}^2)^{p_i - 1}\}$$

Therefore θ_p can be seen as an approximation for $R_{\Lambda ind}^2$ when the second part of the sum is small. The previous expression also shows that

$$\theta_p \leq R_{\Lambda}^2$$

The equality is obtained for some special interesting cases

1. $p_i = 1 \forall i$, univariate setting
2. $\rho_{TSi}^2 = 0 \forall i \Leftrightarrow (\tilde{\varepsilon}_{T_i}, \tilde{\varepsilon}_{S_i})$ are independent
3. $\rho_{TSi}^2 = 1 \forall i \Leftrightarrow$ there is a deterministic relationship between $\tilde{\varepsilon}_{T_i}$ and $\tilde{\varepsilon}_{S_i}$.

Relationship Between R_Λ^2 and θ_p

In a totally general framework we can define the following two families of parameters

$$\Omega_\Lambda = \left\{ \theta_\Lambda : \theta_\Lambda = 1 - \sum_{i=1}^N \alpha_i \prod_{h=1}^{p_i} (1 - \rho_{ih}^2), \alpha_i > 0 \quad \forall i, \sum_i \alpha_i = 1 \right\}$$

$$\Omega = \left\{ \theta : \theta = \sum_{i=1}^N \sum_{h=1}^{p_i} \alpha_{ih} \rho_{ih}^2, \alpha_{ih} > 0 \quad \forall (i, k), \sum_i \sum_h \alpha_{ih} = 1 \right\}$$

It is easy to see that $R_\Lambda^2 \in \Omega_\Lambda$ and $\theta_p \in \Omega$. Now it is possible to prove that for all $\theta_\Lambda \in \Omega_\Lambda$ there exist $\theta \in \Omega$ so that

$$\theta_\Lambda = \theta + \sum_{i=1}^N \sum_{k=1}^{p_i} \frac{\alpha_i}{p_i} (1 - \rho_{ik}^2) \left(1 - \prod_{h \neq k} (1 - \rho_{ih}^2) \right)$$

Implication: for all $\theta_\Lambda \in \Omega_\Lambda$ there exist $\theta \in \Omega$ so that θ can be considered an approximation of θ_Λ with

$$\theta \leq \theta_\Lambda$$

Non-normal Setting

- Normal-Normal: Bivariate normal regression model. Individual level R_{ind}^2 is defined as the correlation between surrogate and true endpoint.
- Discrete-Continuous (or Continuous-Discrete):
 - ★ Probit Formulation: Probit model. Individual level

$$R_{\text{ind}}^2 = \rho_{TS}^2$$

- ★ Plackett-Dale Formulation: Plackett model. Individual level

$$R_{\text{ind}}^2 = \psi$$

1. Survival-Survival (or Survival-Continuous): Frailty and Copula models. Individual level

$$R_{\text{ind}}^2 = \tau^2$$

Non-normal Setting

- Survival-Ordinal Categorical: Plackett model. Individual level

$$R_{\text{ind}}^2 = \psi$$

defined as the global odds ratio between both endpoints.

- Survival-Longitudinal: Henderson model. Individual level

$$R_{\text{ind}}^2(t) = \text{corr}(W_1(t), W_2(t))^2$$

where $(W_1(t), W_2(t))$ is a latent bivariate Gaussian processes.

- Discrete Longitudinal- Discrete Longitudinal (or mixtures): ?

Likelihood Reduction Factor

Let us consider two generalized linear models for trial i :

$$g_T\{E(T_{ij}|Z_{ij})\} = \mu_{T_i} + \beta_i Z_{ij}, \quad (1)$$

$$g_T\{E(T_{ij}|Z_{ij}, S_{ij})\} = \theta_{0_i} + \theta_{1_i} Z_{ij} + \theta_{2_i} S_{ij}. \quad (2)$$

Longitudinal data are easily incorporated by including functions of time in (1)–(2).

Denote the log-likelihood ratio test statistics to compare (1) with (2) within trial i by G_i^2 .

We then propose to quantify the association using a *likelihood reduction factor* (LRF)

$$\text{LRF} = 1 - \frac{1}{N} \sum_i \exp\left(-\frac{G_i^2}{n_i}\right). \quad (3)$$

Likelihood Reduction Factor

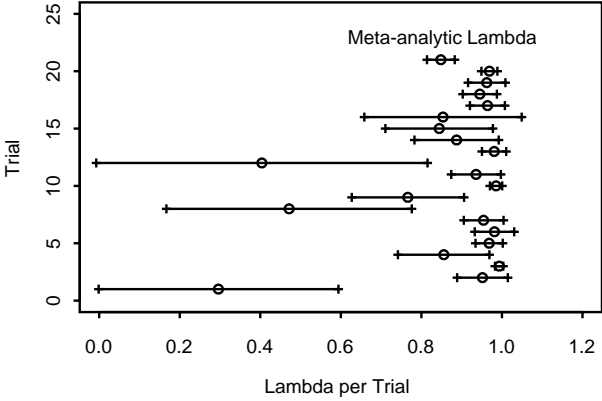
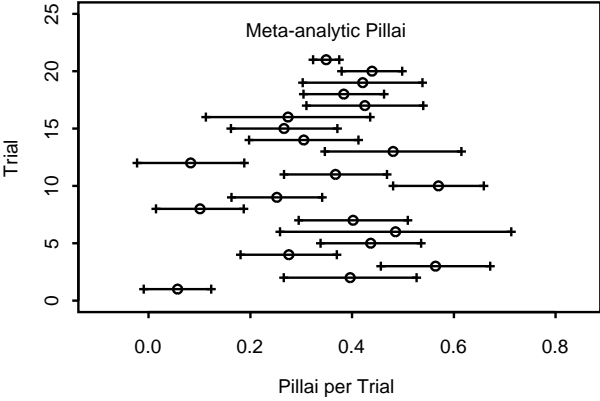
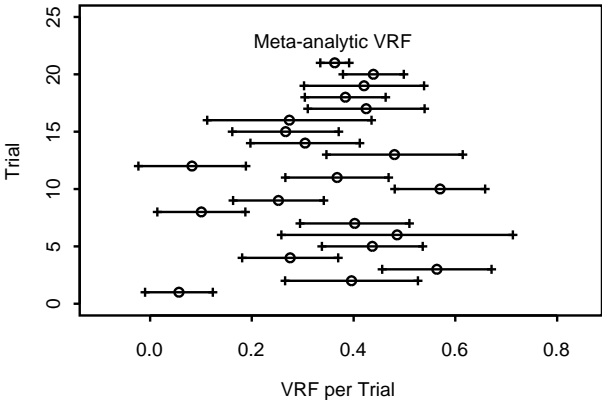
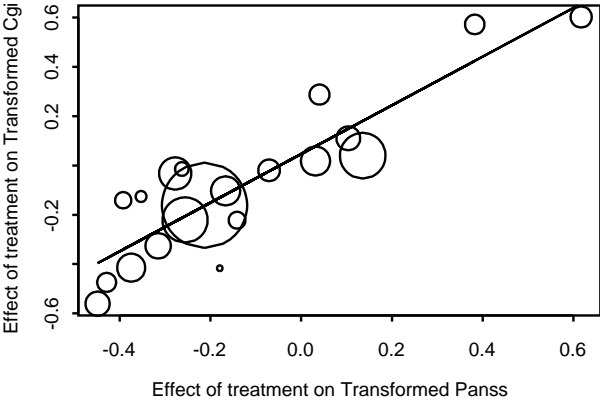
Properties

1. LRF ranges between 0 and 1.
2. $\text{LRF} = 0 \Leftrightarrow \forall i \quad (T_i, S_i)$ are “independent”.
3. $\text{LRF} = 1 \Leftrightarrow \forall i$ there is a “deterministic relationship” between T_i and S_i .
4. Normal-Normal case $\text{LRF} = R_{\text{ind}}^2$.
5. Longitudinal-Longitudinal case $\text{LRF} = R_{\Lambda}^2$.

Some Final Results

Parameter	Estimate	95% C.I.
Trial-level measures		
$R_{\text{trial}}^2(T, S)$	0.866	(0.668,0.942)
$R_{\text{trial}}^2(S, T)$	0.820	(0.611,0.920)
Individual-level measures		
$VRF(T, S)$	0.363	(0.335,0.391)
$VRF(S, T)$	0.365	(0.336,0.394)
θ_p	0.349	(0.324;0.375)
R_{Λ}^2	0.848	(0.814;0.883)

Summary Graph



Conclusions

- A new methodology to evaluate criterion and predictive validity of psychiatric symptom scales was proposed based on surrogate marker validation techniques.
- Two families of parameters were introduced to evaluate surrogacy at individual and trial level based on θ_p , R_{Λ}^2 when repeated measures are present.
- The relationship between these families and previous proposals was shown.
- The LRF offers a unifying approach to the validation problem based on some of Prentice's Criteria.