Efficient Designs for the Estimation of Mixed and Self Carryover Effects

J. Kunert, TU Dortmund
J. Mielke, Novartis

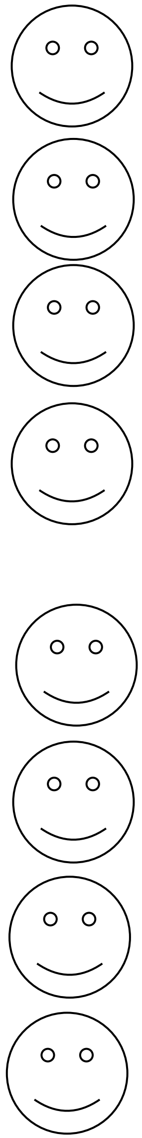
Generica:

Small molecule drugs,
simply rebuild the molecule.

Biosimilars:

Large molecule drugs,
cannot rebuild the Reference exactly.

For admission:
Show in a clinical trial that the
effect of the Test is similar.

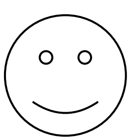


Patient→	treatment→	measurement
	T	$y = \mu + \tau_T + e$
	T	$y = \mu + \tau_T + e$
	T	$y = \mu + \tau_T + e$
	T	$y = \mu + \tau_T + e$
	R	$y = \mu + \tau_R + e$
	R	$y = \mu + \tau_R + e$
	R	$y = \mu + \tau_R + e$
	R	$y = \mu + \tau_R + e$

For admission of T as a biosimilar
make sure that $\tau_T - \tau_R$ is sufficiently near 0.

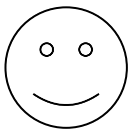
However: chronic diseases.

Patients get treated over a long time



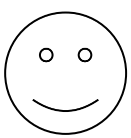
R→R →R →R →R →R →R

Can we switch?



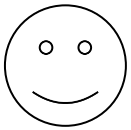
R→R →R →T →T →T →T

Or, even, change from one to the other and back?



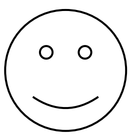
R→R →R →T →T →R →R

Can we switch?



R→R →R →T →T →T →T

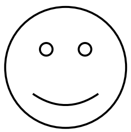
Or, even, change from one to another and back?



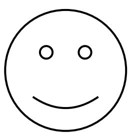
R→R →R →T →T →R →R

This brings in the problem of carryover effects.

Maybe, $\tau_T \approx \tau_R$ does not even imply that the two drugs are truly equivalent.



R→R →R →R →R →R →R



T→ T →T →T → T →T →T

Estimate carryover effects?

Model

$$y = T_d\tau + S_d\chi + M_d\rho + U\alpha + P\beta + e$$

with τ... direct effects

$\chi\ldots$ self carryover effects

$\rho\ldots$ mixed carryover effects

$\alpha\ldots$ units

$\beta\ldots$ periods

For admission, shown already: $\tau_T \approx \tau_R$.

For switchability, show that, additionally,

$\chi_T \approx \chi_R \approx \rho_R \approx \rho_T$.

Information matrix for the estimation of carryover effects

$$C_d = \begin{bmatrix} S_d \\ M_d \end{bmatrix} \omega^{\perp}([U, P, T_d])[S_d, M_d].$$

Try the usual route:

Step 1. Upper bound

$$C_d \leq \tilde{C}_d = B_4 \begin{bmatrix} S_d \\ M_d \end{bmatrix} \omega^{\perp}([U, T_d])[S_d, M_d] B_4$$

Information matrix for the estimation of carryover effects

$$C_d = \begin{bmatrix} S_d \\ M_d \end{bmatrix} \omega^{\perp}([U, P, T_d])[S_d, M_d].$$

Try the usual route:

Step 1. Upper bound

$$C_d \leq \tilde{C}_d = B_4 \begin{bmatrix} S_d \\ M_d \end{bmatrix} \omega^{\perp}([U, T_d])[S_d, M_d]B_4 \checkmark$$

Step 2. Split up into parts

$$\tilde{C}_d = C_{d11} - C_{d12} C_{d22}^{+} C_{d12}^{T},$$

Step 2. Split up into parts

$$\tilde{C}_d = C_{d11} - C_{d12} C_{d22}^{+} C_{d12}^{T}, \checkmark$$

where

$$C_{d11} = B_4 \begin{bmatrix} S_d^T \\ M_d^T \end{bmatrix} \omega^{\perp}(U) [S_d, M_d] B_4,$$

$$C_{d12} = B_4 \begin{bmatrix} S_d \\ M_d \end{bmatrix} \omega^{\perp}(U) T_d,$$

$$C_{d22} = T_d^T \omega^{\perp}(U) T_d.$$

Step 3:

Use Kushner's method:

$$tr\tilde{C}_d \leq trC_{d11} + 2trC_{d12}x + trC_{d22}x^2$$

Step 3:

Use Kushner's method:

$$tr\tilde{C}_d \leq trC_{d11} + 2trC_{d12}x + trC_{d22}x^2$$

????

Step 3:

Use Kushner's method:

$$tr\tilde{C}_d \leq trC_{d11} + 2trC_{d12}x + trC_{d22}x^2$$

The bound is not even defined in our case:

$C_{d12} \in \mathbb{R}^{4\times 2}$ is not a quadratic matrix.

A generalization of Kushner's method:

Theorem:

For any matrix $X \in \mathbb{R}^{2\times 4}$,

$$\tilde{C}_d \leq C_{d11} - C_{d12}X - X^T C_{d12}^T + X^T C_{d22} X$$

in the Loewner-sense.

Equality holds iff

$$X = C_{d22}^{+} C_{d12}^T =: X_d.$$

Then proceed like Kushner:

For fixed X, the right-hand side

$$C_{d11} - C_{d12}X - X^T C_{d12}^T + X^T C_{d22} X$$

can be written as

$$n \sum \pi_s (C_{11}(s) - C_{12}(s)X$$

$$-X^T C_{12}^T(s) + X^T C_{22}(s) X).$$

Sum is over all possible sequences

π_s is the proportion of subjects receiving sequence s.

Some sequences

RTRTRTRTR... provides no information on self carryover,

TTTTTTTTT... provides no information on mixed carryover.

RTTRRTTRR... looks promising

Corollary:

The E-criterion of any design fulfills

$$\lambda_3(d) \le n \max_s \left(k^T C_{11}(s) k - 2k^T C_{12}(s) b_2 x + b_2^T C_{12}(s) b_2^T x^2 \right)$$

where $k \perp 1$ and $x \epsilon \mathbb{R}$
can be arbitrarily chosen.

Corollary:

The E-criterion of any design fulfills

$$\lambda_3(d) \leq n \max_s (k^T C_{11}(s) k - 2k^T C_{12}(s) b_2 x$$
$$+ b_2^T C_{12}(s) b_2^T x^2)$$

where $k \perp 1$ and $x \epsilon \mathbb{R}$
can be arbitrarily chosen.

Using this corollary, we can show for our model that

$$\lambda_3(d) \leq n \frac{p-1}{4p} = a.$$

Note that

$a = n^{\frac{p-1}{4p}}$ hardly increases with p,

$$\lim_{p\to\infty} a = \frac{n}{4}.$$

To get results for more general criteria, we have to find a candidate design.

For p=1 mod 4, chose d^* such that

¼ of the units receive RTTRR...TTRR

¼ of the units receive RRTTR...RTTR

¼ of the units receive TRRTT...RRTT

¼ of the units receive TTRRT...TRRT

Our design d* does not quite attain the bound for the E-criterion:

$$\lambda(d^*) = \frac{n(p-1)}{4(p+1)}$$

while the bound is

$$a = \frac{n(p-1)}{4p}.$$

Second corollary:

If for every sequence s

$$tr(C_f) \geq tr(C_{11}(s) - 2C_{12}(s)X_f + X_f^T C_{22}(s) X_f)$$

then f maximizes the trace of the information matrix.

For our situation, the second corollary shows that

$$trC_d \leq n\frac{(2p+3)(p-1)}{4(p+1)} = L.$$

This bound is the trace of our candidate design d^*.

The A-criterion is

$$\frac{1}{\lambda_1(d)} + \frac{1}{\lambda_2(d)} + \frac{1}{\lambda_3(d)}.$$

We know already that for any design

$\lambda_3(d) \leq a$ and $\lambda_1(d) + \lambda_2(d) + \lambda_3(d) \leq L.$

It therefore is easy to show that

$$\frac{2}{L-a}+\frac{2}{L-a}+\frac{1}{a}$$

is a lower bound of the A-criterion.

Our design d^* does not attain this bound – but it is highly efficient
(the efficiency goes to 1 for $p \to \infty$).