Modelling the impact on the randomized treatment effect of a potent drug introduced post randomization

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The CEOP14 vs CEOP21 Chemotherapy

- First-line treatment of patients with aggressive lymphomas.
- **CEOP** = **C***yclophosphamide*, **E***pirubicin*, **O***ncovin* & **P***rednisone*.
- Two CEOP treatment strategies (every 14 vs 21 days) are compared, with or without Rituximab.
- Six cycles per treatment arm.
- Between February 1999 and March 2005, 238 B-cell lymphoma patients were recruited.
- The two groups are balanced for all relevant factors (sex, age . . . etc).

Rituximab

- Rituximab is a monoclonal antibody of CD20 antigen, introduced as a medicine for lymphoma in 1994

- January 2002: A clinical trial provides evidence that Rituximab offers significant benefit on overall and disease free survival for diffuse large-B-cell lymphoma patients.

- May 2002: Protocol amendment for the addition of Rituximab to both trial arms.

- According to the amendment, Rituximab was administered the day before Chemotherapy (ie every 2 weeks in CEOP14 and every 3 weeks in CEOP21).

Challenges

Aim of trial: Compare CEOP14 against CEOP21.

Issues:

1. Accurate classification of treatment strategies (as randomized or based on mean time interval between successive doses).

2. Half of the patients received Rituximab (those randomized after May 2002).

	No Rituximab	Rituximab	Total
CEOP14	34(41%)	48(59%)	82
CEOP21	83(53%)	73(47%)	156
Total	117(49%)	121(51%)	238

**Classification: As treated*

3. Rituximab was introduced as a very effective drug and there are concerns that actually ”masks” the effect of both CEOP14 and CEOP21

Standard Analysis

Two analyses have been performed.

(A)

Overall Survival							
	β	se	wald	p	exp(b)	lower	upper
Group	-0.191	0.306	0.388	0.533	0.826	0.453	1.506
Rituximab	-0.624	0.302	4.257	0.039	0.536	0.296	0.969

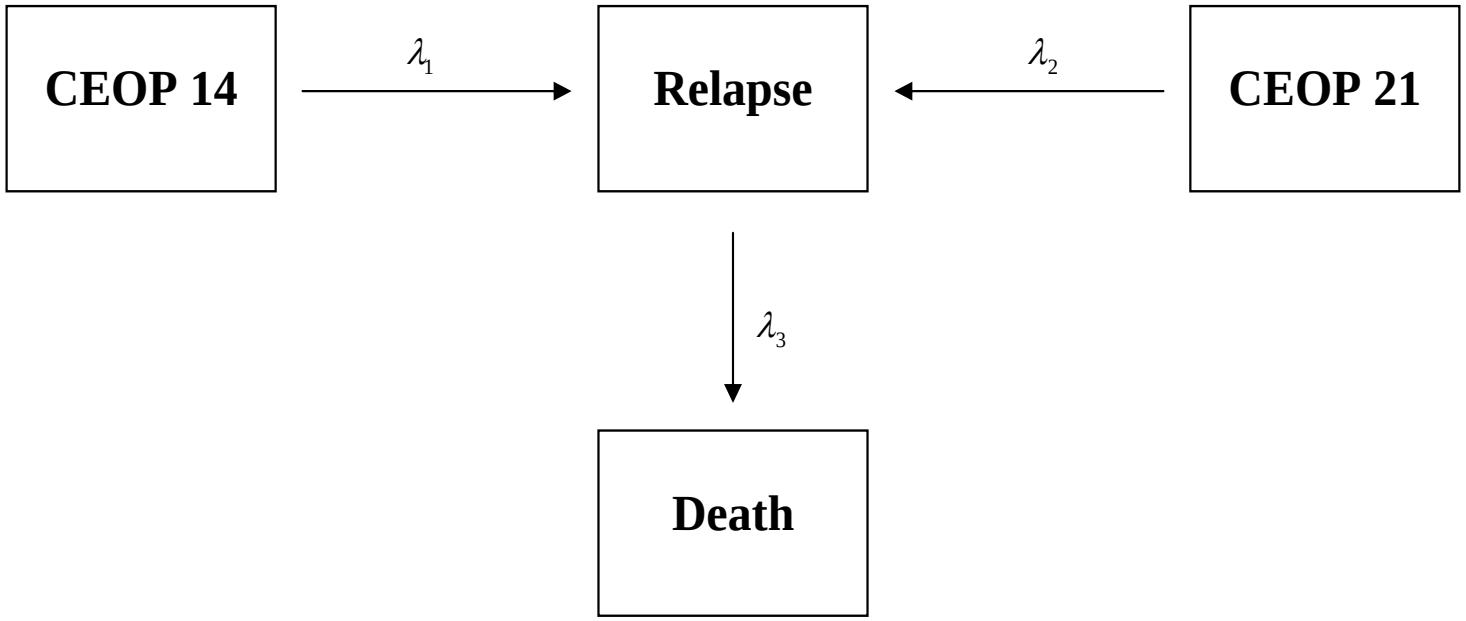
(B)

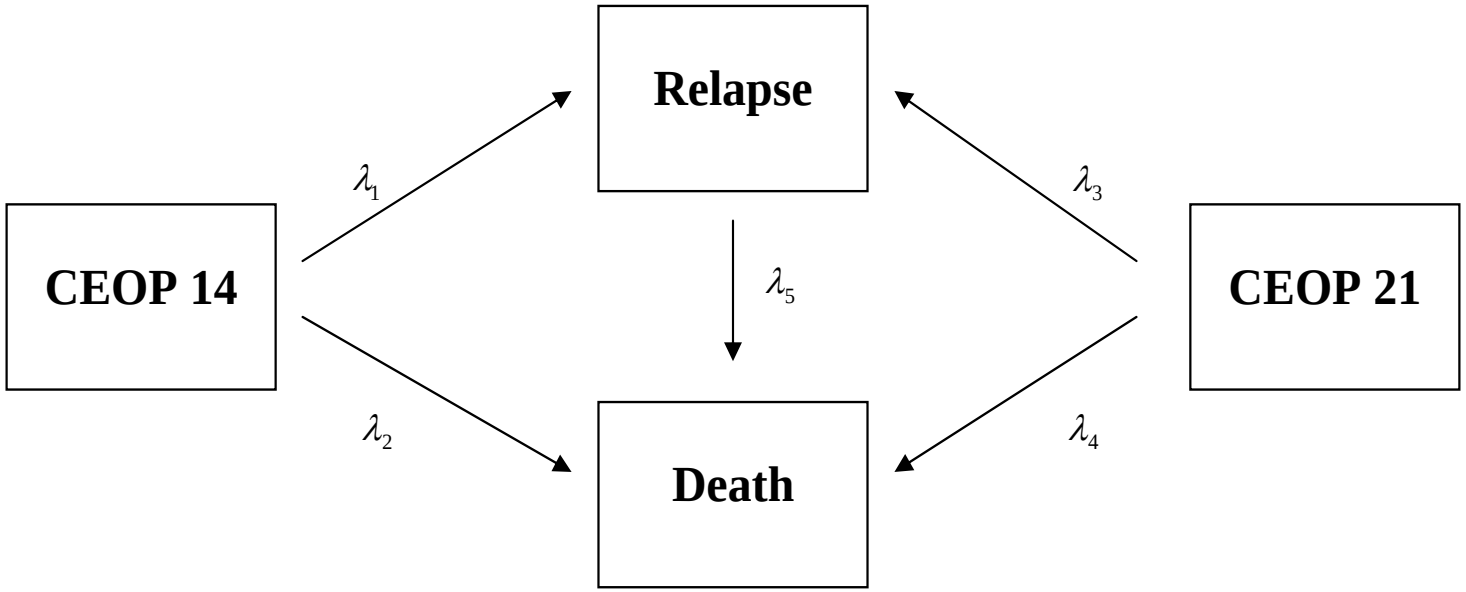
Disease Free Survival							
	β	se	wald	p	exp(b)	lower	upper
Group	-0.308	0.251	1.505	0.220	0.735	0.449	1.202
Rituximab	-0.349	0.238	2.150	0.143	0.705	0.442	1.125

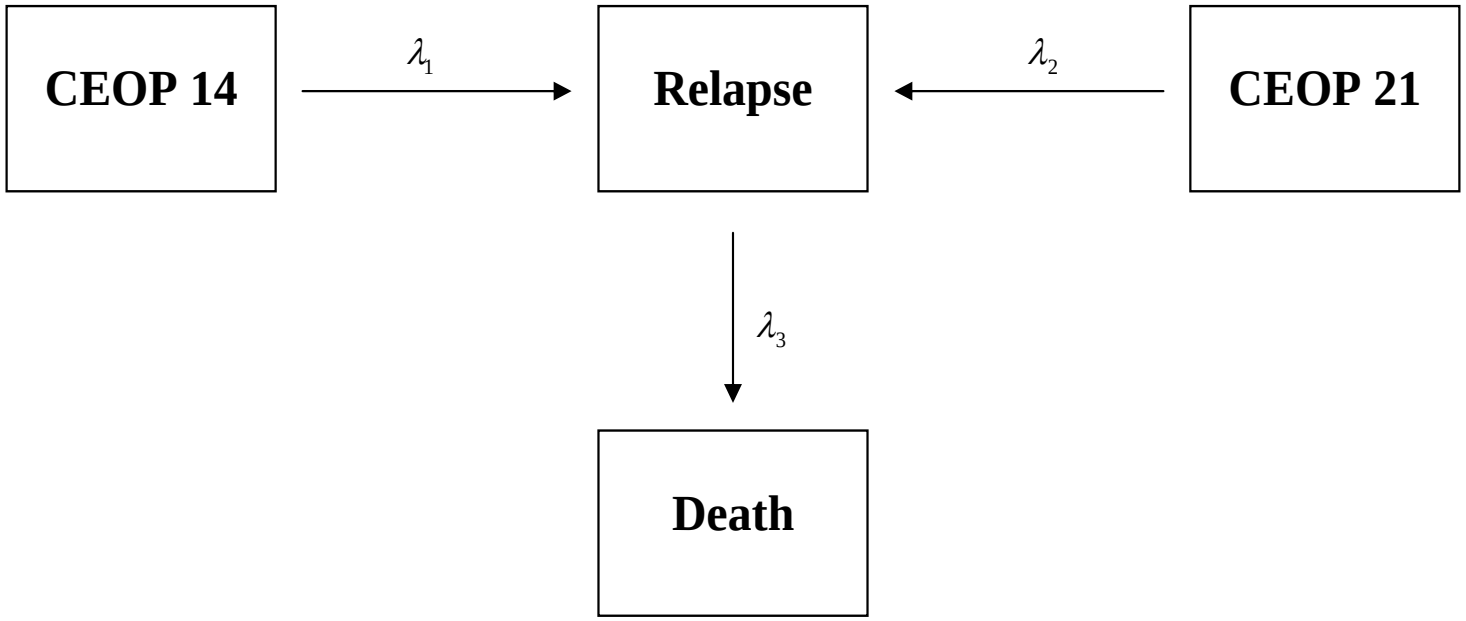
(†) Stratified analysis did not produce any different results with respect to the groups comparison.

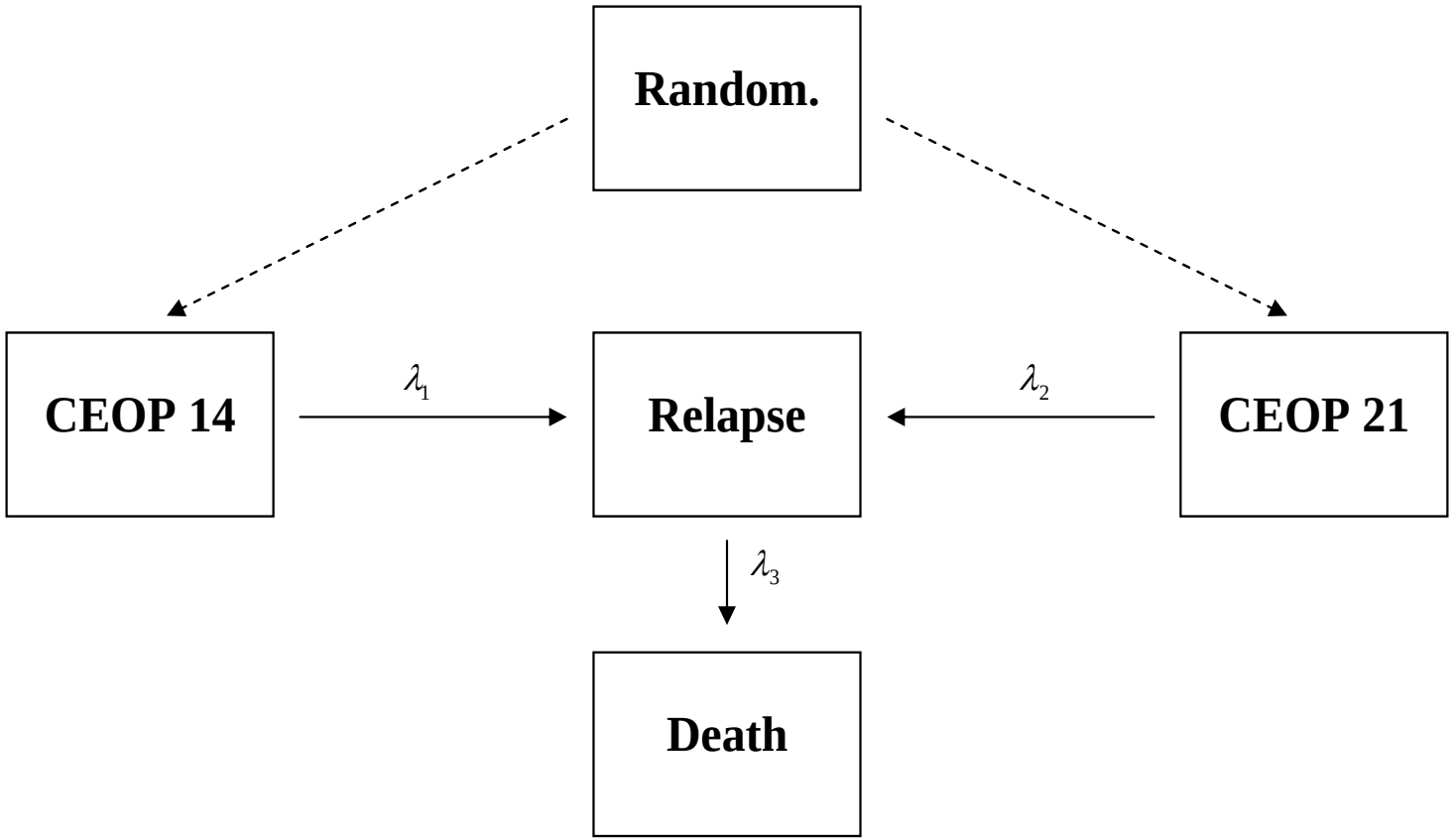
Multi–State Approach

We consider the Multi-State model . . . . . .


CEOP 14
λ_1
Relapse
λ_2
CEOP 21
λ_3
Death


Relapse
CEOP 14
CEOP 21
Death
λ_1
λ_2
λ_3
λ_4
λ_5


CEOP 14
λ_1
Relapse
λ_2
CEOP 21
λ_3
Death


Random.
CEOP 14
λ_1
Relapse
λ_2
CEOP 21
λ_3
Death

We assume:

- Four states (CEOP14, CEOP21, Relapse & Death).
- If patients are observed to die, we assume that they Relapse & then Die.
- The usual Markov like assumption that the transition rates at time t depend only on the state occupied at time t and not on the history up to time t.
- Weibull transition rates between states

$$\lambda_m(t|\mathbf{x}_i) \;=\; e^{\beta'_m \mathbf{x}_i} \alpha_m t^{\alpha_m - 1},$$

  - $\mathbf{x}_i = (1, z_i)$ is a vector of an intercept and an indicator z_i for Rituximab
  - $\beta'_m = (\beta_{m0}, \beta_{m1})'$ is the vector of regression parameters, for $m = 1, 2, 3$ $\big(\beta_{m0}$: CEOP effect – β_{m1} : Rituximab effect $\big)$
  - t is the time since start of study & α_m the scale parameters

Standard Comparison

- Aim: Compare CEOP14 vs CEOP21
- Assume:
  - $\alpha_1 = \alpha_2 = \varphi$
  - $\beta_{11} = \beta_{21} = \psi$
- Then, since

$$\lambda_1(t|z_i) = \exp\{\beta_{10} + \psi z_i\}\varphi t_i^{\varphi-1}; \quad \lambda_2(t|z_i) = \exp\{\beta_{20} + \psi z_i\}\varphi t_i^{\varphi-1},$$

  the comparison between CEOP14 and CEOP21 is down to test for

$$\beta_{10} = \beta_{20}.$$

- Likelihood Ratio Test = 1.45 [not significant for 1 df]

Sensitivity Analysis

Concerns:

- The effect of Rituximab ”masks” the effect of CEOP14 & CEOP21.
- As a result, it is difficult to estimate the actual effect of CEOP14 or CEOP21 in the presence of Rituximab.

Problem:

- The assumption of additive effects is not appropriate.

Assumptions:

- We build the Rituximab "masking" effect into the model by considering

$$\beta_{11} = \beta_{11}^* - k\beta_{10} \qquad \text{and} \qquad \beta_{21} = \beta_{21}^* - k\beta_{20},$$

  where k measures the Rituximab "masking" effect on CEOP14/CEOP21.

- Parameter k is the sensitivity parameter.

- We consider that the Rituximab effect

$$\beta_{11}^* = \beta_{21}^* = \psi^*$$

  is known, and an estimate can be obtained from a number of recent trials*.

- Therefore

$$\lambda_r(t|z_i) = \exp\{\beta_{r0}(1 - kz_i) + \psi^* z_i\}\varphi t_i^{\varphi-1}, \qquad r = 1, 2.$$

- We substitute the intercept with a new one that takes the value 1 for the patients that did not take Rituximab and $1 - k$ for the those who did.

$\Rightarrow$ Parameter k can take any value, however a meaningful set of values are when $k \in (-1, 1)$. Hence,

- if $\underline{k = 0}$ then there is no "masking" effect.
- if $\underline{k = -1}$ then the presence of Rituximab completely removes the effect of CEOP.
- if $\underline{k = 1}$ then the presence of Rituximab doubles the CEOP14 effect.

$\Rightarrow$ Under the new model, we test the hypothesis that $\beta_{10} = \beta_{20}$ for a number of values of k. This results to . . .

Results

- Under the new model, we test the hypothesis that

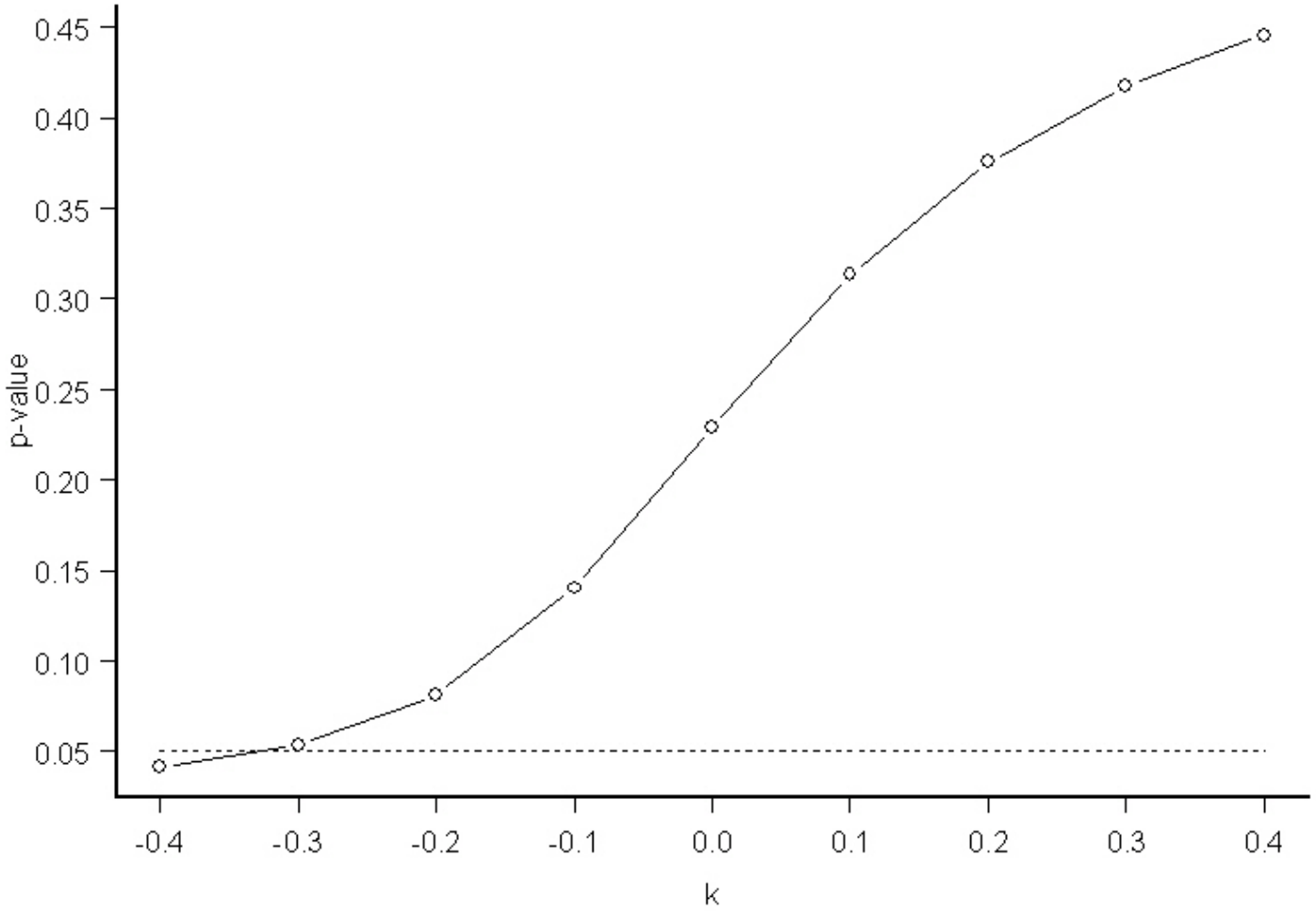
$$\beta_{10} = \beta_{20}$$

  for $k \in [-0.4, 0.4]$.

- Assume $\psi^* = -0.22$, a value that corresponds to a hazard ratio of $0.8^{\dagger}$.

- In these calculations, for simplicity we have assumed that $a_3 = 1$ (i.e. λ_3 follows an exponential).

- The result, for different values of k, are summarized in the graph . . .


0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
p-value
-0.4
-0.3
-0.2
-0.1
0.0
0.1
0.2
0.3
0.4
k

k	R	β_{10}	β_{20}	β_{30}	β_{31}	$\log(\alpha)$	lik	LRT	p-value
-0.4	0	-4.4341	-3.7946	-6.3437	-2.2383	-1.0229	1030.1360		
	1	-3.9357		-6.3442	-2.2390	-1.0385	1032.2250	4.1780	0.0410
-0.3	0	-4.9262	-4.3660	-6.3401	-1.6023	-0.7820	1011.5390		
	1	-4.4894		-6.34068	-1.6028	-0.7944	1013.4110	3.7440	0.0530
-0.2	0	-5.3753	-4.9040	-6.3372	-0.9658	-0.5789	996.2635		
	1	-5.0145		-6.3376	-0.9665	-0.5866	997.7872	3.0474	0.0809
-0.1	0	-5.5507	-5.1750	-6.3360	-0.3298	-0.4606	986.3164		
	1	-5.2826		-6.3363	-0.3302	-0.4618	987.4046	2.1764	0.1401
0	0	-5.3015	-5.0074	-6.3374	0.3060	-0.4533	982.7392		
	1	-5.1047		-6.3377	0.3061	-0.4511	983.4640	1.4496	0.2286
0.1	0	-4.8182	-4.5795	-6.3399	0.9417	-0.5187	984.0015		
	1	-4.6656		-6.3402	0.9420	-0.5147	984.5105	1.0180	0.3130
0.2	0	-4.3233	-4.1191	-6.3429	1.5779	-0.6081	987.8692		
	1	-4.1936		-6.3431	1.5782	-0.6042	988.2620	0.7856	0.3754
0.3	0	-3.8864	-3.7042	-6.3453	2.2138	-0.7011	992.9025		
	1	-3.7695		-6.3453	2.2137	-0.6975	993.2309	0.6568	0.4177
0.4	0	-3.5154	-3.3477	-6.3474	2.8501	-0.7905	998.3613		
	1	-3.4073		-6.3476	2.8502	-0.78682	998.6522	0.5818	0.4456

Conclusion

- For $k < -0.3$, approximately, we can see that the comparison of the two treatments achieves significance ($\alpha = 0.05$).

- This means that if a minimum of 30% ”masking” effect is assumed reasonable, then CEOP14 appears to be a better treatment strategy than CEOP21.

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