Title of your presentation

Your name

Title of the seminar/congress, City
Date

Table of contents

Star wars or not ?

- Dark vador is not my father.
- Are you sure Anakin ?
- Yes, my father said :
  - The yes needs the no to win against the no. [1]

1. Jean-Pierre Raffarin, Archive INA,https ://www.youtube.com/watch ?v=O27mdRvR1GY

Table of contents

The conditions for augmenting Radomized CLinical Trials (RCT) with an external control group [2]

C1. The respect for positivity between the external and RCT controls.

C2. The absence of unmeasured confounders, i.e. determinants of both the outcome and the probability of inclusion in the RCT compared to the external group.

C3. The absence of a direct effect on the outcome of being included in the RCT.

2. Dang et al. A Cross-Validated Targeted Maximum Likelihood Estimator for Data-Adaptive Experiment Selection Applied to the Augmentation of RCT Control Arms with External Data. arXiv :2210.05802v1

How to respect the condition C1 (positivity) ?

1. Use external data but from a recent period.
2. Use external data from the same centers, at least for a large part.
3. Check the inclusion criteria in both the RCT and external study : the targeted population of the RCT must be embedded.
4. Compare the characteristics of two samples of controls to validate the positivity, [3] and restrict the inclusion criteria until no issue is identified.

3. Danelian G, Foucher Y, Léger M, Le Borgne F. and Chatton A. Identification of in-sample positivity violations using regression trees : The PoRT algorithm. Journal of Causal Inference (2023).

How to respect the condition C2 (absence of unmeasured confounders) ?

1. Draw a causal diagram with the inclusion in the RCT versus external study as an element.
2. Propose a complete list of the prognostic factors of the studied outcomes.
3. Propose a complete list of the determinants of the inclusions in the RCT versus external study.
4. Make sure that the variables in the two lists #2 and #3 will be available in both the RCT and the external study with the same methods of collection.

How to respect the condition C3 (no direct effect of being in the RCT) ?

- One can limit/prevent such a direct effect by :
  1. Check the studied treatments are identical in the two studies (doses, administration, etc.).
  2. Use the same definition of the collected outcomes.
  3. Ensure comparable monitoring in the two studies.
- Control patients in the RCT are required for a data-driven check of C3.
- An RCT based on a control arm completely-based with external data or digital twins does not allow for validating C3.

Problem #2 : these checks do not convince on the respect of C3

- **How to validate C3 by using the RCT data ?**

Consider the following usual RCT for superiority with k controls for 1 patient in the experimental arm

- A binary principal outcome Y with π_0 and π_1 the two expected proportions in the control and experimental arms.
- N_{1s} and N_{0s} the required sample sizes for a bilateral test with targeted type-I and type-II errors, α and β respectively.
- $N_{0s} = kN_{1s}$ and $N_{1s} = (\pi_1 - \pi_0)^2(\pi_0(1-\pi_0)/k + \pi_1(1-\pi_1))/(z_{\alpha/2} + z_\beta)^2$

Example

- For $k = 1$, $\alpha = 0.05$, $\beta = 0.20$, $\pi_0 = 0.50$ and $\pi_1 = 0.40$,
- the sample sizes are $N_{0s} = N_{1s} = 385$.

Consider the following method to augment the RCT with external data (one method among others)

- A model M (for instance a logistic regression) is estimated from the external data to predict the outcome $\hat{\pi}_{0i}$ given the characteristics X_i of a patient i with the control treatment.
- There is no direct effect of being in the RCT (condition C3) if M is well-calibrated for the outcome prediction at the inclusion in the control group of the RCT.
- A calibration measure can be O/E :
  - O is the number of observed events : $\sum_i Y_i$ among the control patients.
  - E is the number of expected events : $\sum_i \hat{\pi}_{0i}$ among the control patients.
- The value $O/E = 1$ indicates a perfect calibration.

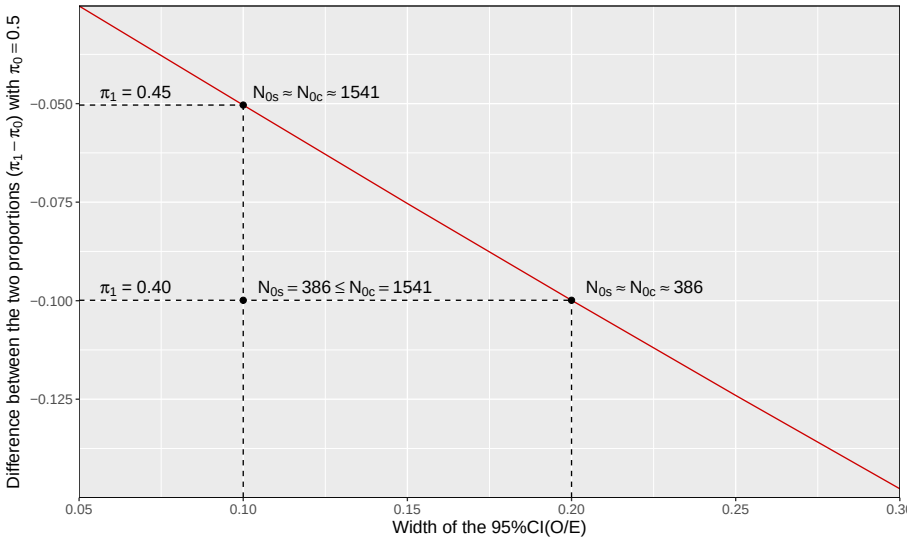
Minimal sample size N_{0c} to evaluate the calibration of the model M

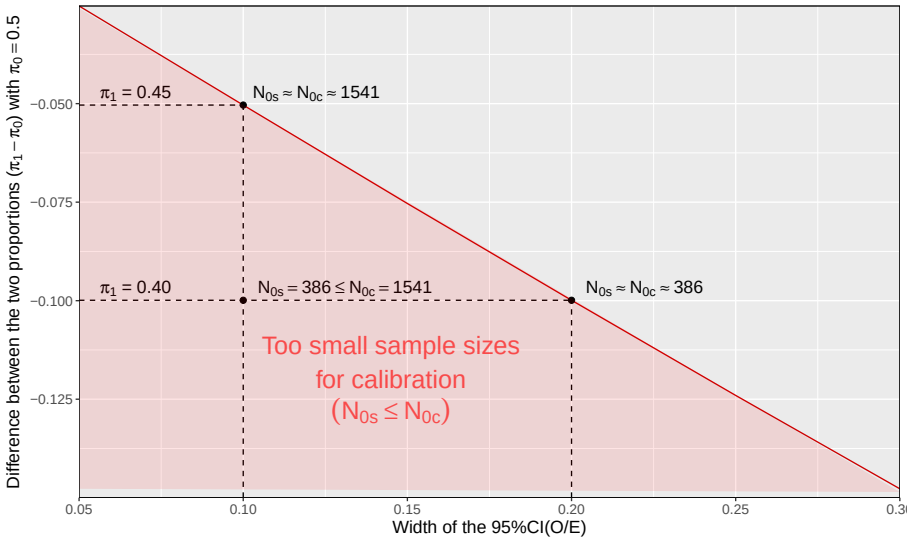
- By using the delta method :[4] $SE(\log(O/E) \approx \sqrt{(1-\pi_0)/(\pi_0 N_{0c})}$.
- Depending on w, the targeted width of confidence interval of the O/E, one can compute $SE_w(\log(O/E)$.
- One can deduce that $N_{0c} = (1-\pi_0)/(\pi_0 SE_w(\log(O/E)^2)$

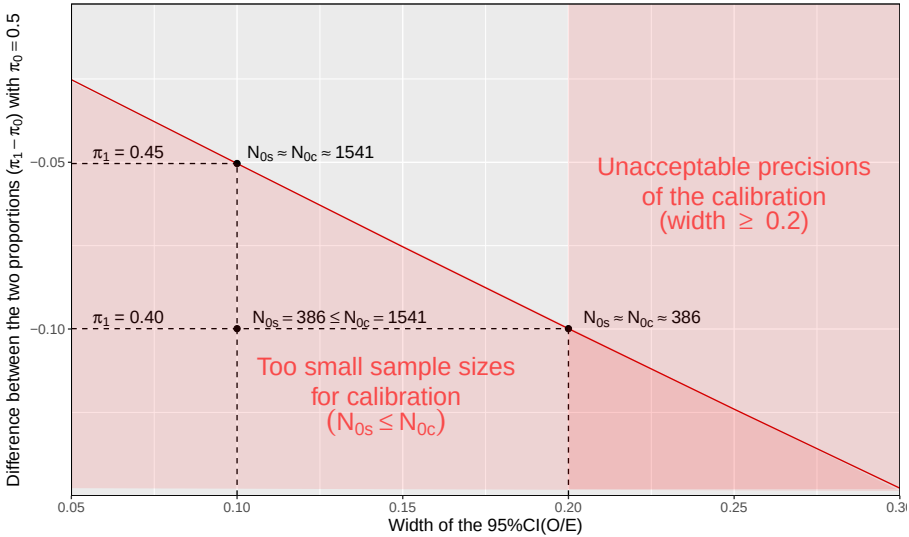
Example (continued, with $k = 1$, $\alpha = 0.05$, $\beta = 0.20$, $\pi_0 = 0.50$ and $\pi_1 = 0.40$)

- For $\alpha = 0.05$ and $w = 0.10$ (i.e., $SE_w(\log(O/E) \approx 0.25$) then $N_{0c} = 1541$.
  - $N_{0c} > 385$: we cannot check the respect of C3.
- For $\alpha = 0.05$ and $w = 0.20$ (i.e., $SE_w(\log(O/E) \approx 0.51$,) then $N_{0c} = 386$.
  - $N_{0c} \approx 385$: we can check the respect of C3.

4. Debray et al. A framework for meta-analysis of prediction model studies with binary and time-to-event outcomes. Stat Methods Med Res. 2019 ;28 :2768-2786.


Difference between the two proportions ($\pi_1 - \pi_0$) with $\pi_0 = 0.5$
−0.050
−0.075
−0.100
−0.125
π_1 = 0.45
$N_{0s} \approx N_{0c} \approx 1541$
π_1 = 0.40
$N_{0s} = 386 \leq N_{0c} = 1541$
$N_{0s} \approx N_{0c} \approx 386$
0.05
0.10
0.15
0.20
0.25
Width of the 95%CI(O/E)


Difference between the two proportions ($\pi_1 - \pi_0$) with $\pi_0 = 0.5$
−0.050
−0.075
−0.100
−0.125
$\pi_1 = 0.45$
$N_{0s} \approx N_{0c} \approx 1541$
$\pi_1 = 0.40$
$N_{0s} = 386 \leq N_{0c} = 1541$
$N_{0s} \approx N_{0c} \approx 386$
Too small sample sizes
for calibration
($N_{0s} \leq N_{0c}$)
0.05
0.10
0.15
0.20
0.25
Width of the 95%CI(O/E)


Difference between the two proportions ($\pi_1 - \pi_0$) with $\pi_0 = 0.5$
−0.05
−0.10
$\pi_1 = 0.45$
$\pi_1 = 0.40$
$N_{0s} \approx N_{0c} \approx 1541$
$N_{0s} = 386 \leq N_{0c} = 1541$
$N_{0s} \approx N_{0c} \approx 386$
Unacceptable precisions
of the calibration
(width $\geq$ 0.2)
Too small sample sizes
for calibration
($N_{0s} \leq N_{0c}$)
0.05
0.10
0.15
0.20
0.25
Width of the 95%CI(O/E)