Boosting the performances of clinical trials from models/algorithms/twins trained on external cohorts: conditions to respect

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Plan

Why augmenting randomized clinical trials (RCTs)?

- RCTs represent the reference protocol for treatment evaluations.
- For large sample size, the comparability of the arms is guaranteed and the power is acceptable.
- But number of trials are based on small sample sizes:
  - Median at 144 patients for RCTs in surgery.[1]
  - Median at 75 patients for RCTs in intensive care units.[2]

[1] Robinson et al. Characteristics of Randomized Clinical Trials in Surgery From 2008 to 2020: A Systematic Review. JAMA Network Open. 2021.

[2] Anthon et al. Overall bias and sample sizes were unchanged in ICU trials over time: a meta epidemiological study. Journal of Clinical Epidemiology. 2019.

Considering data from external controls for increasing the power of RCT

- Context:
  - An RCT with internal patients randomized in an experimental and control arms.
  - We aim to increase the power with external controls from a cohort.
- Methods:
  - Bayesian analysis for borrowing external controls.
  - Matching external controls with internal patients in the experimental arm.
  - Estimating algorithms/models from the external controls for predicting counterfactual outcomes of the internal patients in the experimental arm.
  - Generating digital controls from the external cohort.
  - Etc.
- It introduces bias: selection bias, confounders, etc.
  - **What are the conditions for ensuring unbiased results?**

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Conditions for acceptability of an external control group [3]

A1. The group must have received a precisely defined treatment which must be the same in the RCT.

A2. The group must have been part of a recent study which contained the same requirements for patient eligibility.

A3. The methods of treatment evaluation must be the same.

A4. The distributions of important patient characteristics in the group should be comparable with those in the new trial.

A5. The external must have been collected in the same organization with largely the same clinical investigators.

A6. There must be no other indications leading one to expect differing results between the randomized and external controls.

[3] Pocock. The combination of randomized and historical controls in clinical trials. Journal of Chronic Diseases. 1976.

Conditions for acceptability of an external control group [4]

C1. The respect for positivity between the external and RCT controls.
- It includes A2, A4 and A5.

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.
- It includes A4 and A6.

C3. The absence of a direct effect on the outcome of being included in the RCT.
- It includes A1 and A3.

[4] 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

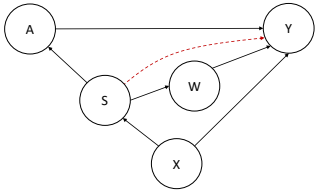
How to respect the condition C1 (positivity)?

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, [5] and restrict the inclusion criteria until no issue is identified.

[5] Danelian G, Foucher Y, Leger 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)?

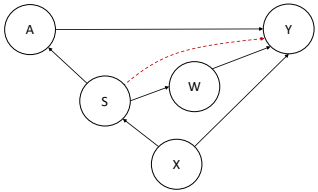
- Draw a causal diagram:
  - Y: the outcome
  - A: the treatment arm
  - S: the data source
  - X: the causes of both Y and S
  - W: the mediators of being included in the RCT



- Make sure that X is available in both the RCT and the external cohort (with the same methods of collection).

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

- Check the studied treatments are identical in the two studies (doses, administration, etc.).
- Use the same definition of the collected outcomes.
- Ensure comparable monitoring in the two studies.



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

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

- A binary 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)

- Consider an algorithm/model 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 it is well-calibrated for the outcome prediction of internal controls.
- 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.

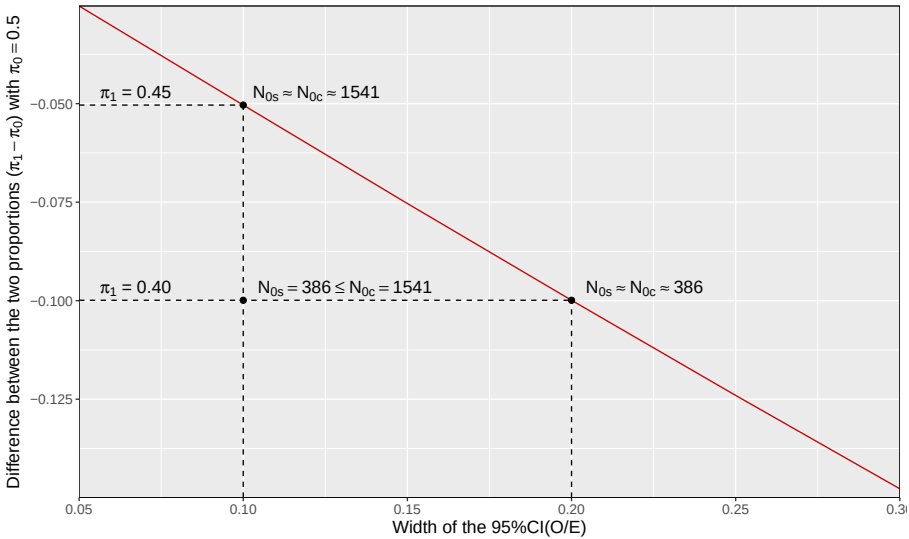
Minimal sample size N_{0c} to evaluate the calibration of the model M

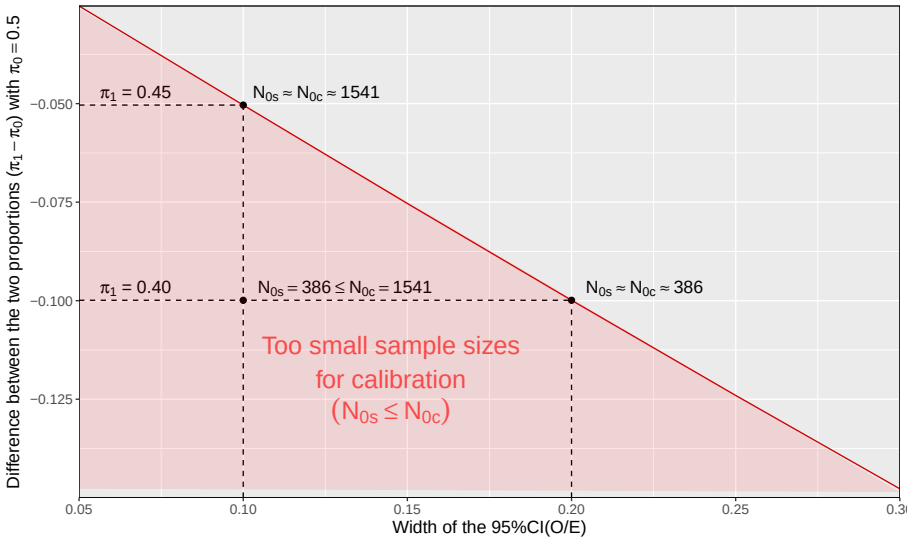
- By using the delta method:[6] $SE(\log(O/E) \approx \sqrt{(1-\pi_0)/(\pi_0 N_{0c})}$.
- Depending on w, the targeted width of confidence interval of the O/E, one can define $SE_w(\log(O/E)$.
- One can deduce that $N_{0c} = (1-\pi_0)/(\pi_0 SE_w(\log(O/E)^2)$

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.

[6] 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)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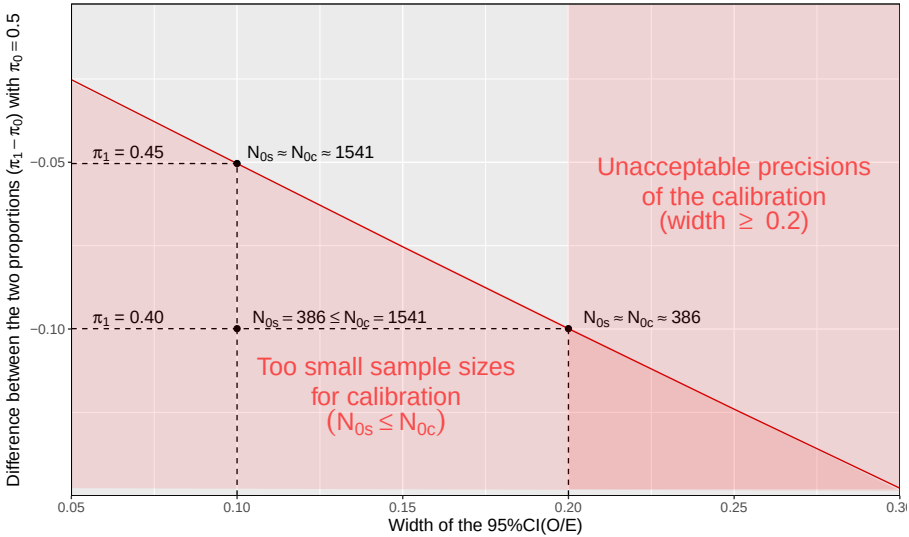
$N_{0s} \approx N_{0c} \approx 386$
Too small sample sizes
for calibration
($N_{0s} \leq N_{0c}$)
0.05
0.10
0.15
0.20
0.25
Width of the 95%CI(O/E)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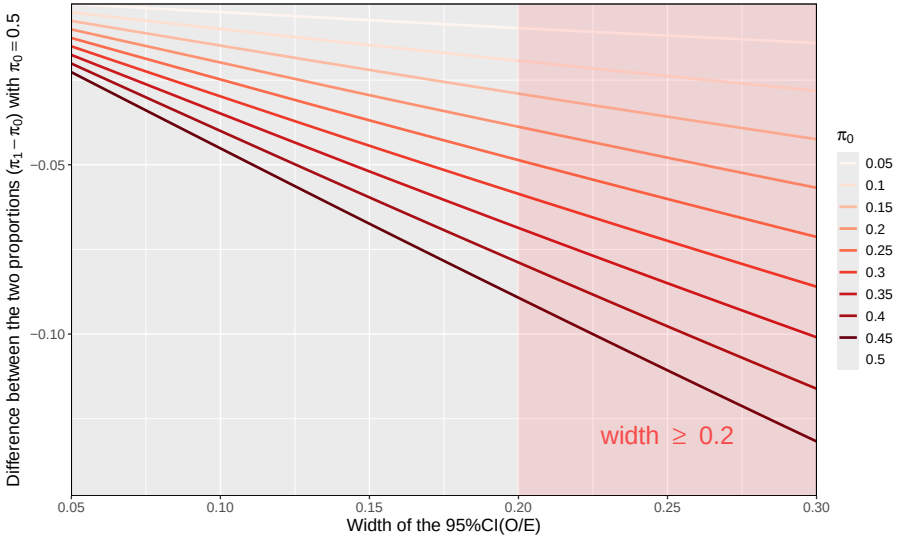
−0.10
$\pi_1 = 0.45$
$N_{0s} \approx N_{0c} \approx 1541$
$\pi_1 = 0.40$
$N_{0s} = 386 \leq N_{0c} = 1541$
$N_{0s} \approx N_{0c} \approx 386$
Unacceptable precisions of the calibration (width $\geq$ 0.2)
Too small sample sizes for calibration ($N_{0s} \leq N_{0c}$)
0.05
0.10
0.15
0.20
0.25
Width of the 95%CI(O/E)


Difference between the two proportions $(\pi_1 - \pi_0)$ with $\pi_0 = 0.5$
−0.05
−0.10
0.05
0.10
0.15
0.20
0.25
0.30
Width of the 95%CI(O/E)
width ≥ 0.2
π_0
0.05
0.1
0.15
0.2
0.25
0.3
0.35
0.4
0.45
0.5

Plan

Summary of the key points

- The augmentation of RCT with models/algorithms or even digital twins is possible under conditions C1 to C3.
- The use of low-quality external data, such as retrospective registries or medico-administrative databases, should be used with caution.
- The use of high-quality cohorts or alternative RCT as external sources with:
  - The collection of confounders X for adjusting.
  - The collection of mediators W for reducing the direct impact of the data sources.
  - The same definition/collection of (A, Y, X, W).
- The same multi-centric consortium should be involved in the collection of external and internal data.
- The RCTs with important sample sizes appear more adapted for C3 validation.