# Leveraging multicohort ALS data for clinical trial improvement

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## INTRODUCTION

### TROPHOS Clinical Trial (CT)

- Population of N=510 ALS patients
- Treatment T = Olesoxime
- Outcome Y: Overall survival according to Kaplan-Meier analysis assessed with a log-rank test → Non-linear !

TROPHOS showed that survival was not significantly different between treatment arms[1]:

| Placebo arm: | Treated arm: | Stratified bulbar/spinal log-rank: |
|---|---|---|
| $69.4\%\ [63.0\%\ ;\ 74.9\%]$ | $67.5\%\ [61.0\%\ ;\ 73.1\%]$ | $P = 0.71$ |

### Objectives

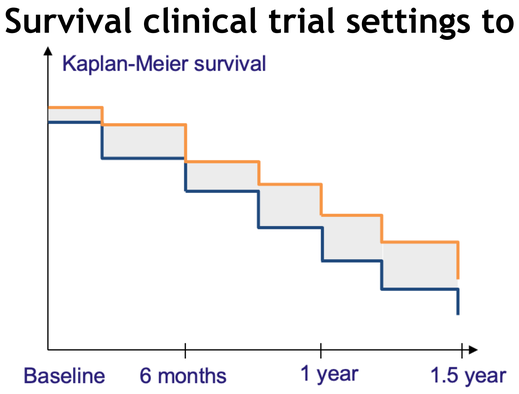
Integrate **machine learning predictions** from **natural history data** to clinical trial analysis.

Narrow **confidence intervals (CI)** on the estimator of the ATE.

- **Reduce sample size** when designing a clinical trial. *A priori*
- Improve **power** of the clinical trial statistical tests[2]. *A posteriori*

## METHODS

### Survival clinical trial settings to stay in a linear framework

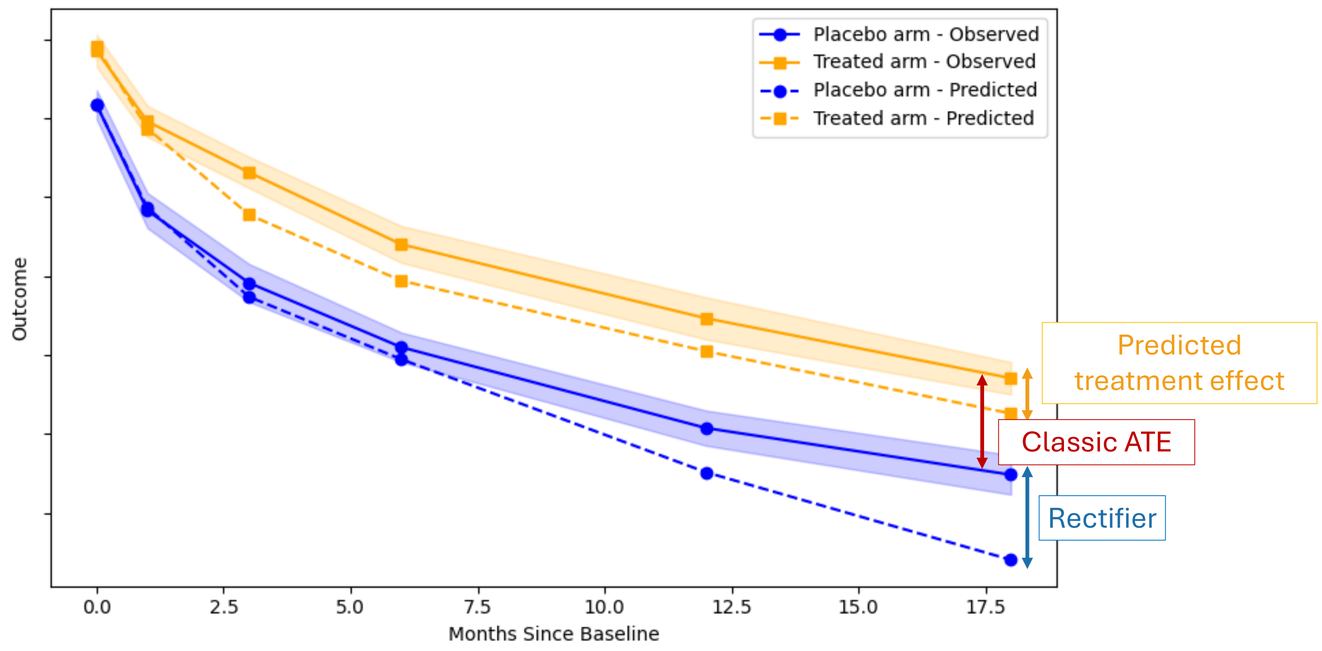



- Outcome Y = Restricted Mean Survival Time (RMST)
- Estimand: the Average Treatment Effect (ATE)

$$\begin{aligned}\widehat{ATE} &= \mathbb{E}(Y_i|T_i=1) - \mathbb{E}(Y_i|T_i=0)\\ &= \widehat{RMST}_{T=1}(t^*) - \widehat{RMST}_{T=0}(t^*)\\ &= \int_0^{t^*} \widehat{S_1}(u)du \ - \int_0^{t^*} \widehat{S_0}(u)du\end{aligned}$$

→ Linear !

### Prediction-powered inference for clinical trials principle (PPCT) in a linear framework




PPCT unbiased estimator of the ATE[2]

$$\widehat{ATE}^{PPCT} = \underbrace{\frac{1}{m}\sum_{i=1}^{m}(Y_{i|T=1} - \lambda f(X_i))}_{\text{Predicted treatment effect}} - \underbrace{\frac{1}{n}\sum_{i=m+1}^{N}(Y_{i|T=0} - \lambda f(X_i))}_{\text{Rectifier}}$$

(1) $Y_{i|T=1}$ (2) $\lambda f(X_i)$

In a simplified case: $\mathbb{V}(ATE^{PPCT}) = (1-R^2)\mathbb{V}(ATE^{Classic})$ → Sample size reduction of **(1-R²)**

### ❶ Leave-one-out pseudo-values necessity

We need values for all individuals $i$, hence the use of pseudo-values, $RMST_i$ :

$$RMST_{i|T_i} = n * RMST_{|T_i} - (n-1) * RMST_{-i|T_i}$$

$RMST_{-i}$ denotes RMST computed on the dataset without individual $i$.
Intuitively, the i-th pseudo-observation $RMST_i$ ) can be viewed as the contribution of individual $i$ to the RMST estimate in the corresponding arm.
This definition ensures that the average of the pseudo-values recovers the original RMST:

$$\frac{1}{n}\sum_{i=1}^{n} RMST_{i|T_i} = RMST_{T_i}$$

### ❷ Predictions

Model trained on PRO-ACT database:

- 2918 ALS patients
- Covariates used:
  - Gender
  - Age at diagnosis
  - Site of onset
  - ALSFRS-r score at inclusion

Cox regression model → Trained to predict age at death based on covariates → We can then compute predicted pseudo-values $RMST^f_{i|T_i}$

Then,

$$\widehat{ATE}^{PPCT} = \frac{1}{m}\sum_{i=1}^{m}(RMST_{i|T=1} - \lambda RMST^f_{i|T=1}) - \frac{1}{n}\sum_{i=m+1}^{N}(RMST_{i|T=0} - \lambda RMST^f_{i|T=0})$$

## RESULTS

### Simulations

Exponential survival with discrete visit times:

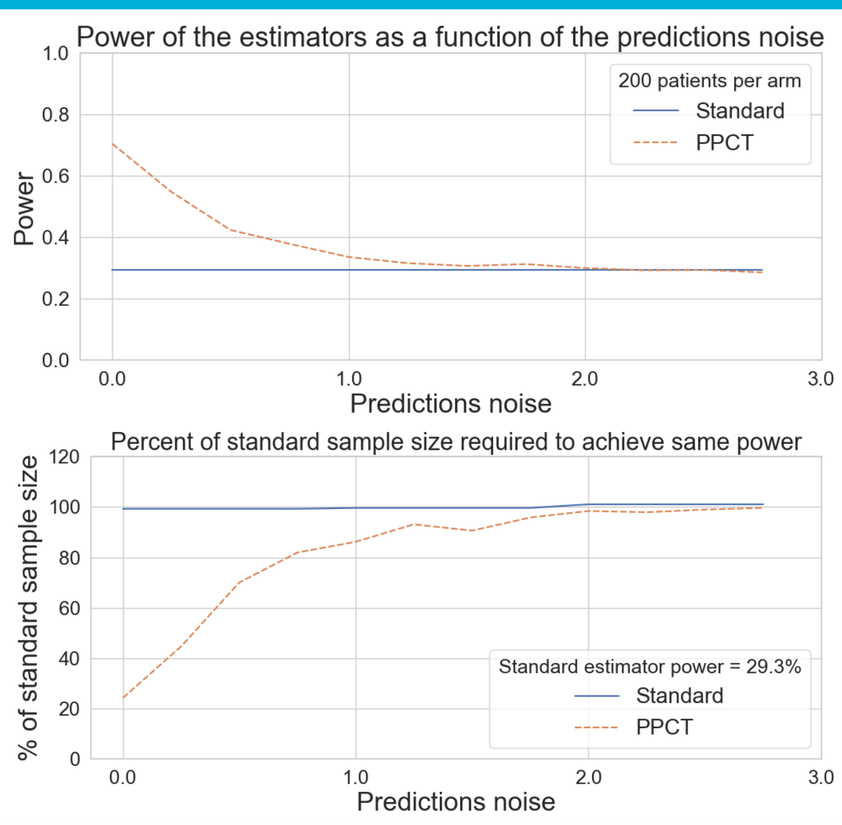
- Failure probability in the control group: $p = 40\%$
- Follow-up duration: $\tau = 1.5$ years
- Treatment effect percentage: $TE$ = 30%

→ 60% of placebo patients and 72% of treated patients are censored.

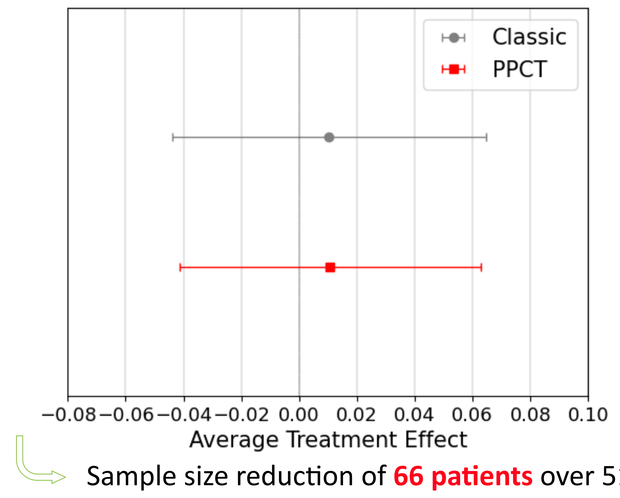
Over 1000 simulations, we compute:

- the power (for n=200 patients)
- the % of reduction of the sample size (for power = 30%)

with different prediction noise levels.




### Application on TROPHOS data




Sample size reduction of **66 patients** over 510.

**References**

1. *Lenglet T, Lacomblez L, Abitbol JL, Ludolph A, Mora JS, Robberecht W, Shaw PJ, Pruss RM, Cuvier V, Meininger V; Mitotarget study group. A phase II-III trial of olesoxime in subjects with amyotrophic lateral sclerosis. Eur J Neurol. 2014 Mar;21(3):529-36.*
2. *Poulet, PE., Tran, M., Tezenas du Montcel, S. et al. Prediction-powered inference for clinical trials: application to linear covariate adjustment. BMC Med Res Methodol 25, 204 (2025).*