

## Mission

**Subject:** Estimating a difference in restricted mean survival time in cluster randomized trials using pseudo-values regression with covariate adjustment

**Context:** Cluster randomized trials (CRTs) are trials in which intact social units, such as medical practices, hospitals, or communities, are randomised to intervention or control conditions while outcomes are assessed on individuals within such clusters. This study design is a natural choice to evaluate the impact of public health or health system interventions delivered at the cluster level and their use is rapidly increasing. In CRTs, outcomes assessed on individuals from a given cluster tend to be more similar than outcomes of individuals from different clusters. This clustering must be accounted for in statistical analysis, to avoid an increased risk of Type I error.

In randomized clinical trials with a time-to-event outcome, the intervention effect is usually quantified by a hazard ratio, relying on the proportional hazards assumption. Alternative measures could be more relevant, such as the difference in restricted mean survival time ( $\Delta\text{RMST}$ ) between the intervention and control groups up to time  $t^*$ . The intervention effect measured by the  $\Delta\text{RMST}$  is not relying on the proportional hazards assumption and is easily interpretable as the expected survival duration gain due to intervention over  $t^*$ .

Pseudo-values regression has been proposed for the  $\Delta\text{RMST}$  estimation in CRTs. It consists in computing pseudo-values for each individual and considering them as the dependent variable of a linear regression model fitted by generalized estimating equations, to take into account the clustering. Pseudo-values regression has shown good performances in terms of estimation of the intervention effect and its variance in a simulation study. However, only one covariate, the intervention group, was considered in this simulation study whereas covariate adjustment is not uncommon in CRTs. Adjustment on covariates is useful in CRTs because the randomization of a smaller number of units, compared to individually randomized trial, does not always allow for balance in cluster and individual-level covariates.

**Objective:** The objective will be to conduct a simulation study to assess the performance of the pseudo-values regression in estimating a  $\Delta\text{RMST}$  in CRTs when adjusting on covariates. In addition, this method will be applied on data from a real cluster randomized trial.

## Profile

**Level:** Bac +5 in statistics (ENSAI, ISUP, Master 2 University, ...)

**Required skills:**

- Knowledge in survival models and in methods for correlated data (e.g. mixed-effect models, etc)
- Knowledge in clinical trials and simulation study would be appreciated
- Proficient in programming (preferably with R)
- Writing and communication skills

**Working environment:** [Inserm Unit SPHERE 1246](#) in Tours (37), France.

**Duration:** 4 to 6 months (beginning between February and April 2024)

**The internship will be paid according to the applicable rate.**

**If you are interested, please apply directly to the following tutor by mail:**

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*Reference: Vilain-Abraham F, Tavernier E, Dantan E, Desmée S, Caille A. Restricted mean survival time to estimate an intervention effect in a cluster randomized trial. Stat Methods Med Res. 2023 Oct;32(10):2016-2032.*