Evaluating the effect of lung transplantation: a case study in sequential emulated trials with time-varying sources of bias

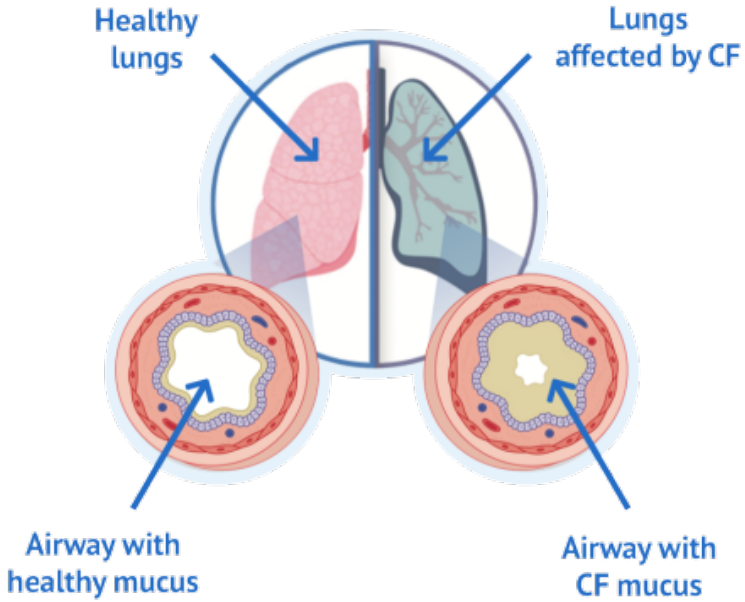
Iqraa Meah

CRESS, METHODS Team

Séminaire hebdomadaire, MIA, Paris-Saclay

Clinical context

(Q) How lung transplantation (TX) affects patients diagnosed with cystic fibrosis (CF) ?

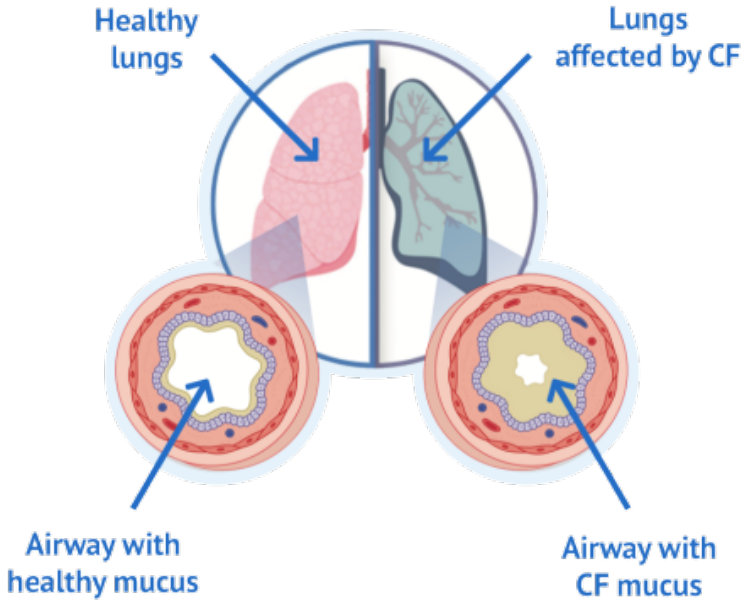


Disclaimer TX no longer practiced for CF

Source: www.pulmozyme.com/patient/about/what-is-cystic-fibrosis.html

Clinical context

(Q) How lung transplantation (TX) affects patients diagnosed with cystic fibrosis (CF) ?



Disclaimer TX no longer practiced for CF

Source: www.pulmozyme.com/patient/about/what-is-cystic-fibrosis.html

Presentation outline

(Q) How lung TX affects patients diagnosed with CF ?

Stake : clear methodology for practical case $\rightarrow$ build generic theoretical model of emulated trial

- Randomized Control Trials (RCTs) vs observational studies
- Confounding and selection bias
- Sources of confounding and selection bias in our case

- Proposed methodology

Presentation outline

(Q) How lung TX affects patients diagnosed with CF ?

Stake : clear methodology for practical case $\rightarrow$ build generic theoretical model of emulated trial

- Randomized Control Trials (RCTs) vs observational studies
- Confounding and selection bias
- Sources of confounding and selection bias in our case

- Proposed methodology

How to understand TX effect in practice ?

Randomized Control Trials (RCTs)

Random treatment assignment to individuals in population of interest
Gold standard : protocol study allows to discard sources of bias

Limits : costly/challenging or ethically/practically infeasible in some contexts

Analysis from observational data

Data collected without epidemiological purpose
$\hookrightarrow$ Observational data $\neq$ experimental data
Difficulty : decipher causation effects from correlation effect

Causal inference formalism

Potential outcomes and average treatment effect

For $i \in \{1 \dots n\}$ individuals

- $A_i \in \{0, 1\}$: binary r.v for intervention/treatment
- $Y_i \in \mathbb{R}$: r.v for outcome of interest
- $\{Y_i(A_i = 0), Y_i(A_i = 1)\}$: couple of potential outcomes

Individual treatment effect : $Y_i(A_i = 1) - Y_i(A_i = 0)$

$\hookrightarrow$ only one quantity available !

Average Treatment Effect (ATE)

$$\text{ATE} := \text{E}[Y(A = 1)] - \text{E}[Y(A = 0)]$$

Still causal quantity but can be estimated under certain conditions

Causal inference formalism

Potential outcomes and average treatment effect

For $i \in \{1 \dots n\}$ individuals

- $A_i \in \{0, 1\}$: binary r.v for intervention/treatment
- $Y_i \in \mathbb{R}$: r.v for outcome of interest
- $\{Y_i(A_i = 0), Y_i(A_i = 1)\}$: couple of potential outcomes

Individual treatment effect : $Y_i(A_i = 1) - Y_i(A_i = 0)$

$\hookrightarrow$ only one quantity available !

Average Treatment Effect (ATE)

$$\text{ATE} := \text{E}[Y(A = 1)] - \text{E}[Y(A = 0)]$$

Still causal quantity but can be estimated under certain conditions

Causal inference formalism

Potential outcomes and average treatment effect

For $i \in \{1 \dots n\}$ individuals

- $A_i \in \{0, 1\}$: binary r.v for intervention/treatment
- $Y_i \in \mathbb{R}$: r.v for outcome of interest
- $\{Y_i(A_i = 0), Y_i(A_i = 1)\}$: couple of potential outcomes

Individual treatment effect : $Y_i(A_i = 1) - Y_i(A_i = 0)$

$\hookrightarrow$ only one quantity available !

Average Treatment Effect (ATE)

$$\text{ATE} := \text{E}[Y(A = 1)] - \text{E}[Y(A = 0)]$$

Still causal quantity but can be estimated under certain conditions

Identifiability assumptions

Stable Unit Treatment Value Assumption (SUTVA)

$$Y_i = Y_i(1)A_i + Y_i(0)(1 - A_i) \text{ for all } i \in \{1, \ldots, n\}$$

$\hookrightarrow$ consistency + no interference

Ceteris Paribus

$$A_i \perp \{Y_i(0), Y_i(1)\} \text{ for all } i \in \{1, \ldots, n\}$$

$\hookrightarrow$ treatment assignment indep of POTENTIAL outcomes

$$\begin{aligned} &\mathrm{E}[Y \mid A = 1] - \mathrm{E}[Y \mid A = 0] \\ &= \mathrm{E}[Y(1) \mid A = 1] - \mathrm{E}[Y(0) \mid A = 0] \\ &= \mathrm{E}[Y(1)] - \mathrm{E}[Y(0)] := \mathrm{ATE} \end{aligned}$$

Identifiability assumptions

Stable Unit Treatment Value Assumption (SUTVA)

$$Y_i = Y_i(1)A_i + Y_i(0)(1 - A_i) \text{ for all } i \in \{1, \ldots, n\}$$

$\hookrightarrow$ consistency + no interference

Ceteris Paribus

$$A_i \perp \{Y_i(0), Y_i(1)\} \text{ for all } i \in \{1, \ldots, n\}$$

$\hookrightarrow$ treatment assignment indep of POTENTIAL outcomes

$$\begin{aligned}
&\mathrm{E}[Y \mid A = 1] - \mathrm{E}[Y \mid A = 0] \\
&= \mathrm{E}[Y(1) \mid A = 1] - \mathrm{E}[Y(0) \mid A = 0] \\
&= \mathrm{E}[Y(1)] - \mathrm{E}[Y(0)] := \mathrm{ATE}
\end{aligned}$$

How to understand TX effect in practice ?

Key differences between RCTs and observational data

Randomized Control Trials (RCTs)

Random treatment assignment to individuals in population of interest

SUTVA ✓ Ceteris Paribus ✓

Analysis from observational data

Observational data $\neq$ experimental data

SUTVA ? Ceteris Paribus ?

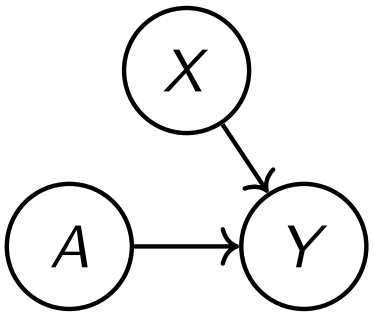
$\hookrightarrow$ Difficulty : decipher causation effect from correlation effects

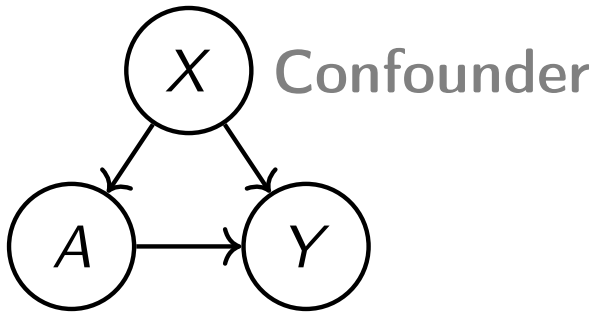
$\hookrightarrow$ Leads to biased conclusion

Sources of bias

Confounding bias

Confounder affect outcome **and** treatment assignment !



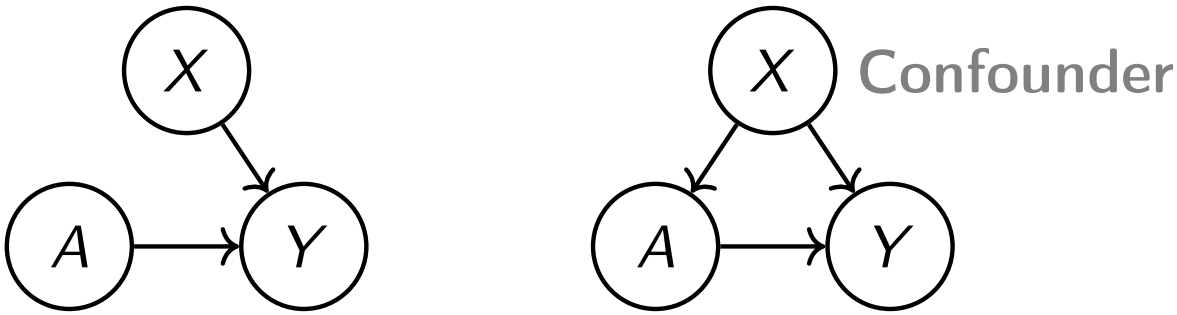


$$
\begin{aligned}
&\mathrm{E}[Y(1) \mid A=1] - \mathrm{E}[Y(0) \mid A=0] \\
&= \mathrm{E}[Y(1) \mid A=1] - \mathrm{E}[Y(0) \mid A=0] \\
&+ \underbrace{\mathrm{E}[Y(0) \mid A=1] - \mathrm{E}[Y(0) \mid A=1]}_{=0} \\
&= \underbrace{\mathrm{E}[Y(1) - Y(0) \mid A=1]}_{\text{ATE on treated}} + \underbrace{\mathrm{E}[Y(0) \mid A=1] - \mathrm{E}[Y(0) \mid A=0]}_{\text{Bias}}
\end{aligned}
$$

Sources of bias

Confounding bias

Confounder affect outcome **and** treatment assignment !

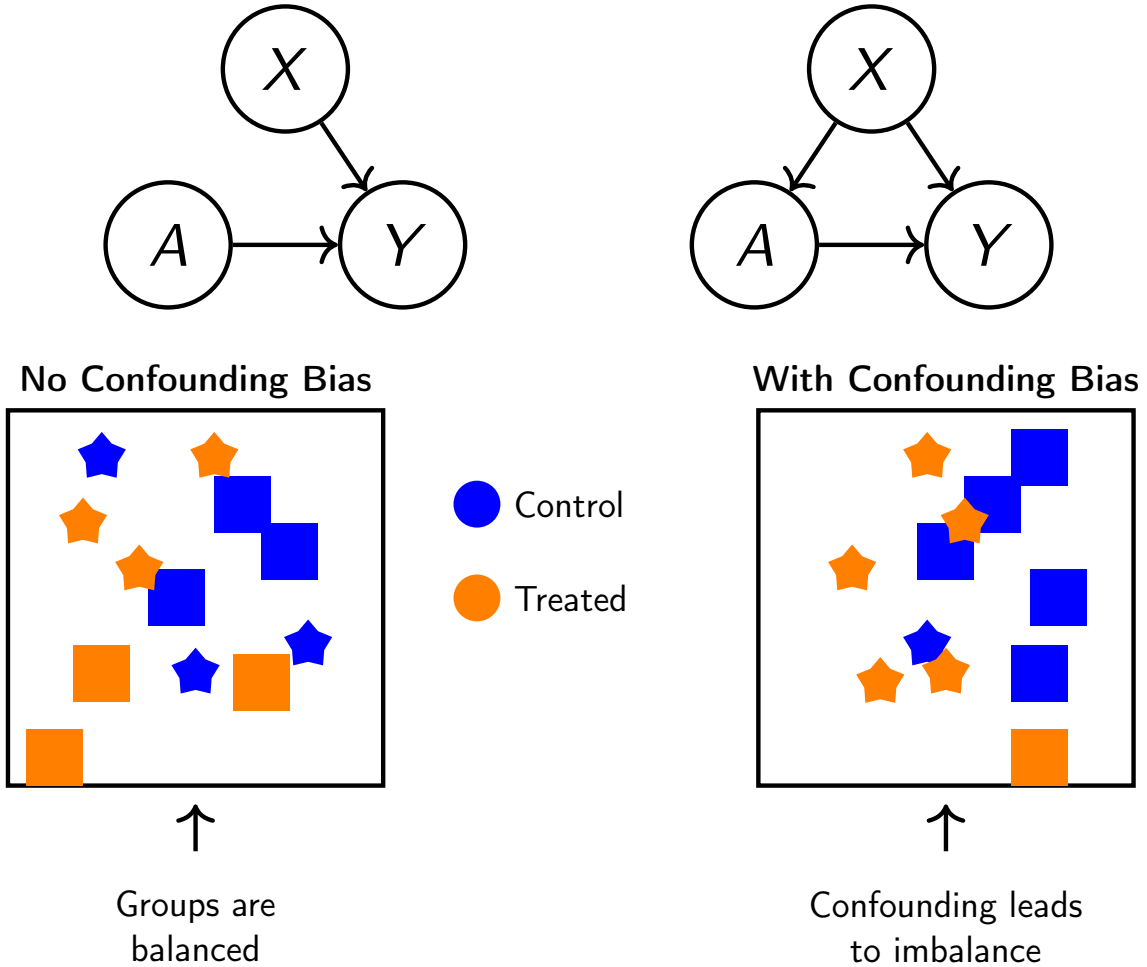


$$
\begin{aligned}
&\mathrm{E}[Y(1) \mid A=1] - \mathrm{E}[Y(0) \mid A=0] \\
&= \mathrm{E}[Y(1) \mid A=1] - \mathrm{E}[Y(0) \mid A=0] \\
&+ \underbrace{\mathrm{E}[Y(0) \mid A=1] - \mathrm{E}[Y(0) \mid A=1]}_{=0} \\
&= \underbrace{\mathrm{E}[Y(1) - Y(0) \mid A=1]}_{\text{ATE on treated}} + \underbrace{\mathrm{E}[Y(0) \mid A=1] - \mathrm{E}[Y(0) \mid A=0]}_{\text{Bias}}
\end{aligned}
$$

Sources of bias

Confounding bias

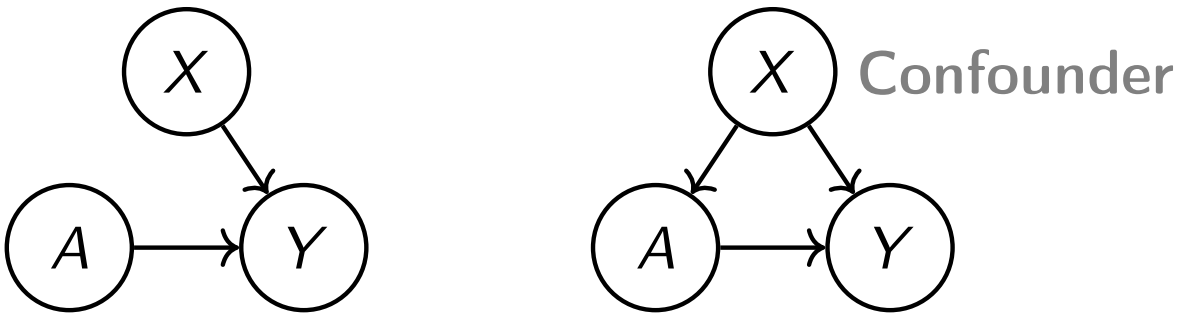
Confounder affect outcome **and** treatment assignment !



Sources of bias

Confounding bias

Confounder affect outcome **and** treatment assignment !



Ceteris Paribus: $A_i \perp \{Y_i(0), Y_i(1)\}$ for all $i \in \{1, \ldots, n\}$

$\hookrightarrow$ guarantees both groups are comparable

$\hookrightarrow$ hardly verified in observational data

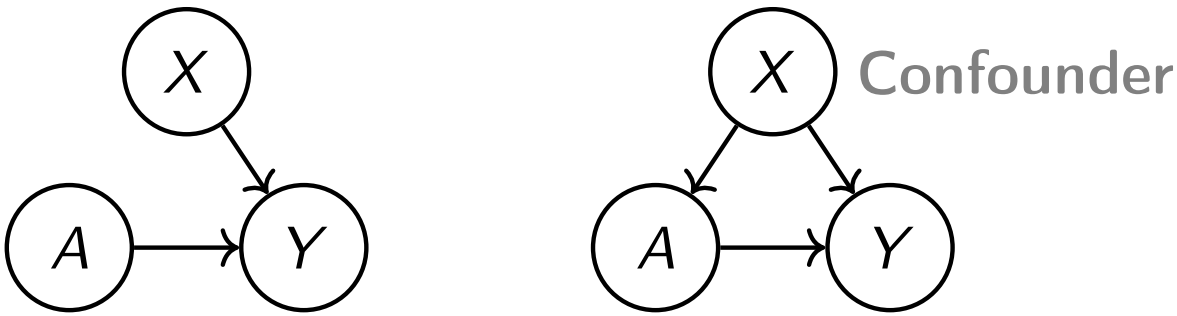
Rather

Unconfoundedness : $A_i \perp \{Y_i(0), Y_i(1)\} \mid X_i$ for all $i \in \{1, \ldots, n\}$

Sources of bias

Confounding bias

Confounder affect outcome **and** treatment assignment !



Ceteris Paribus: $A_i \perp \{Y_i(0), Y_i(1)\}$ for all $i \in \{1, \ldots, n\}$

$\hookrightarrow$ guarantees both groups are comparable

$\hookrightarrow$ hardly verified in observational data

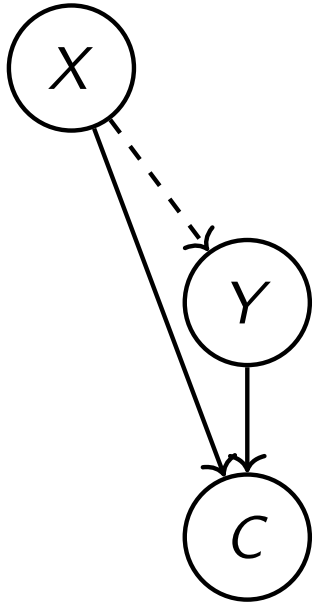
Rather

Unconfoundedness : $A_i \perp \{Y_i(0), Y_i(1)\} \mid X_i$ for all $i \in \{1, \ldots, n\}$

Sources of bias

Selection bias

Selection bias affect sample used for analysis $\rightarrow$ not representative of target population



Collider

Example : time spent on waiting list

Types of bias in our observational study

Natural bias in data

- Confounding bias due to lung allocation process

Bias due to the analysis process

- Selection bias due to immortal time and informative censoring

Confounding bias

Lung Allocation Score (LAS) [?]

LAS goal : reduce waitlist deaths and futile TX

- Cox model to measures survival gain:
  LAS $\sim$ post-TX survival - waitlist survival
- Graft attribution :
  "large" LAS + distance perimeter to graft

LAS = main source of confounding bias
LAS varies in time $\rightarrow$ time-varying confounding

Emulated Target Trial (ETT)

Study procedure from observational data [Hernán and Robins, 2016]

Protocol Element	Target Trial	Emulated Trial
Eligibility criteria for patients	Defined eligibility	Observed data
Therapeutic strategies	Randomized treatments	Observed treatments
Treatment assignment	Randomization	Data-driven assignment
Outcome	Predefined	Observed
Causal contrast	Defined a priori	Derived from data
Follow-up	Specified duration	Defined follow-up period
Statistical analysis plan	Pre-specified	Retrospective analysis

ETT $\rightarrow$ specification retrospective to data collection

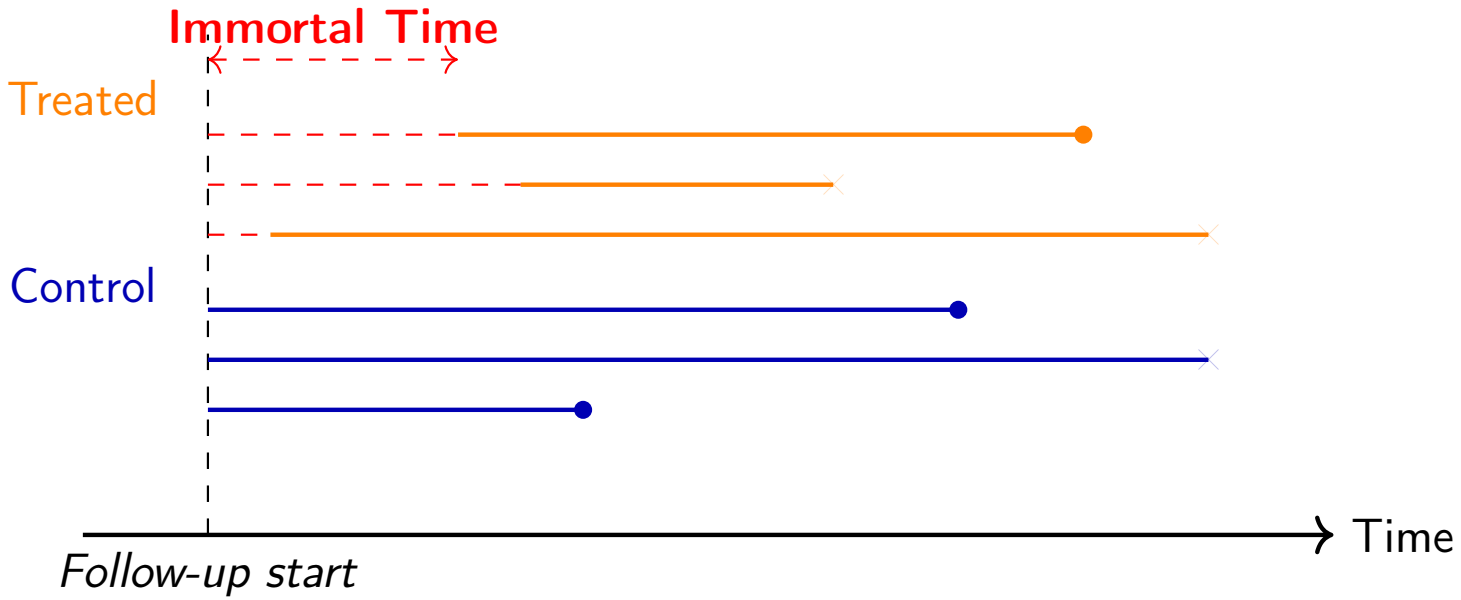
- Specifying some elements requires subjective choices or assumptions
- Design errors can introduce bias

Selection bias

Immortal time

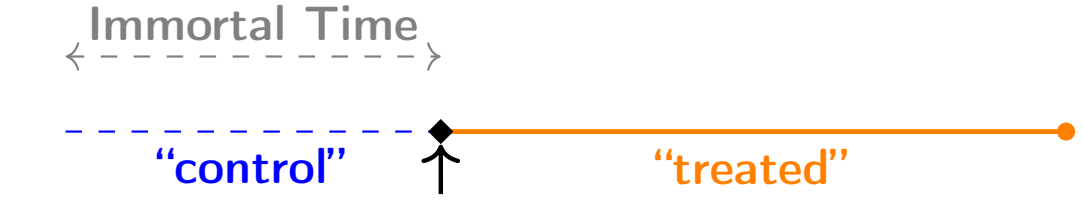
Immortal time : period during which outcome cannot occur

↪ period between follow-up start and TX



Selection bias

Informative censoring



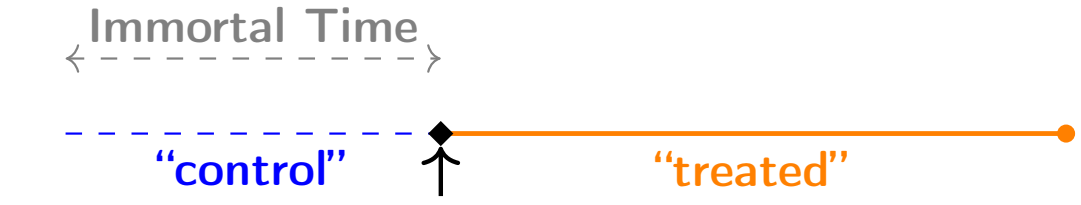
TX : patient censored from control arm

Selection bias :

- information removal at different times between controls and treated
- to be TX you need to survive long enough on waiting list

Selection bias

Informative censoring



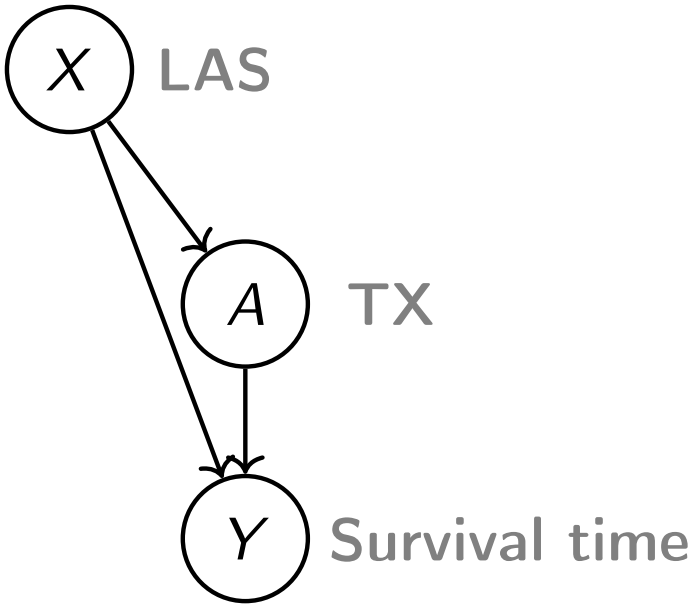
TX : patient censored from control arm

Selection bias :

- information removal at different times between controls and treated
- to be TX you need to survive long enough on waiting list

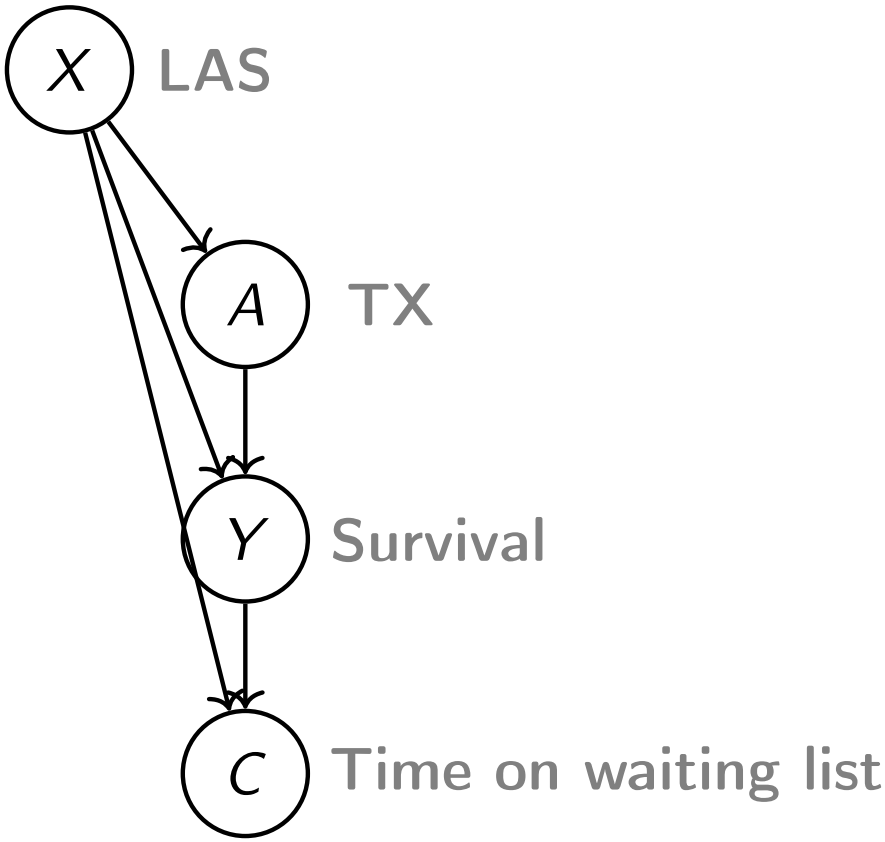
Final causal graph

Confounding bias



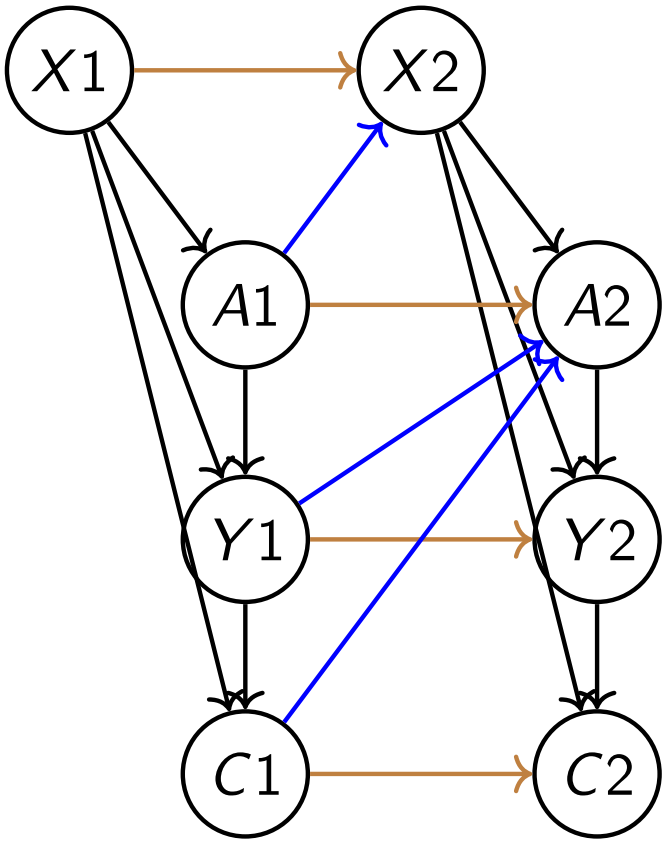
Final causal graph

Confounding bias and selection bias



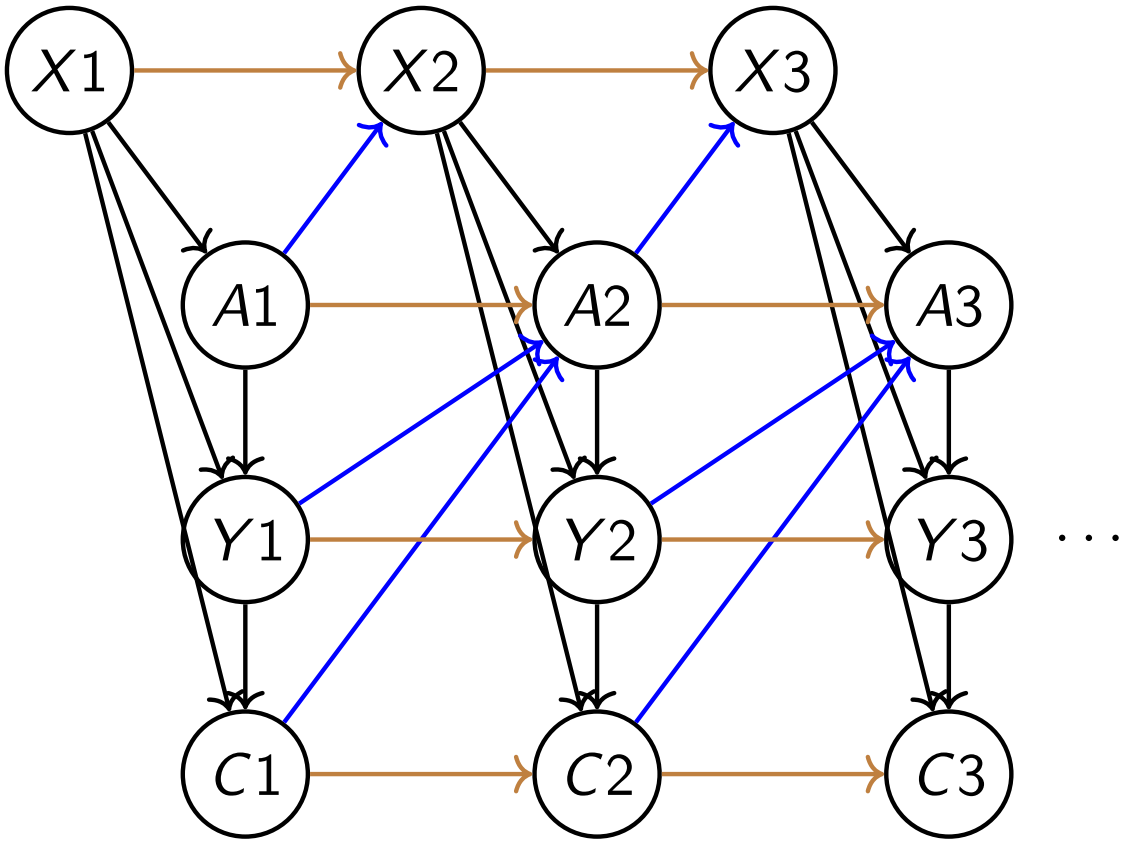
Final causal graph

Confounding bias and selection bias **throughout time**



Final causal graph

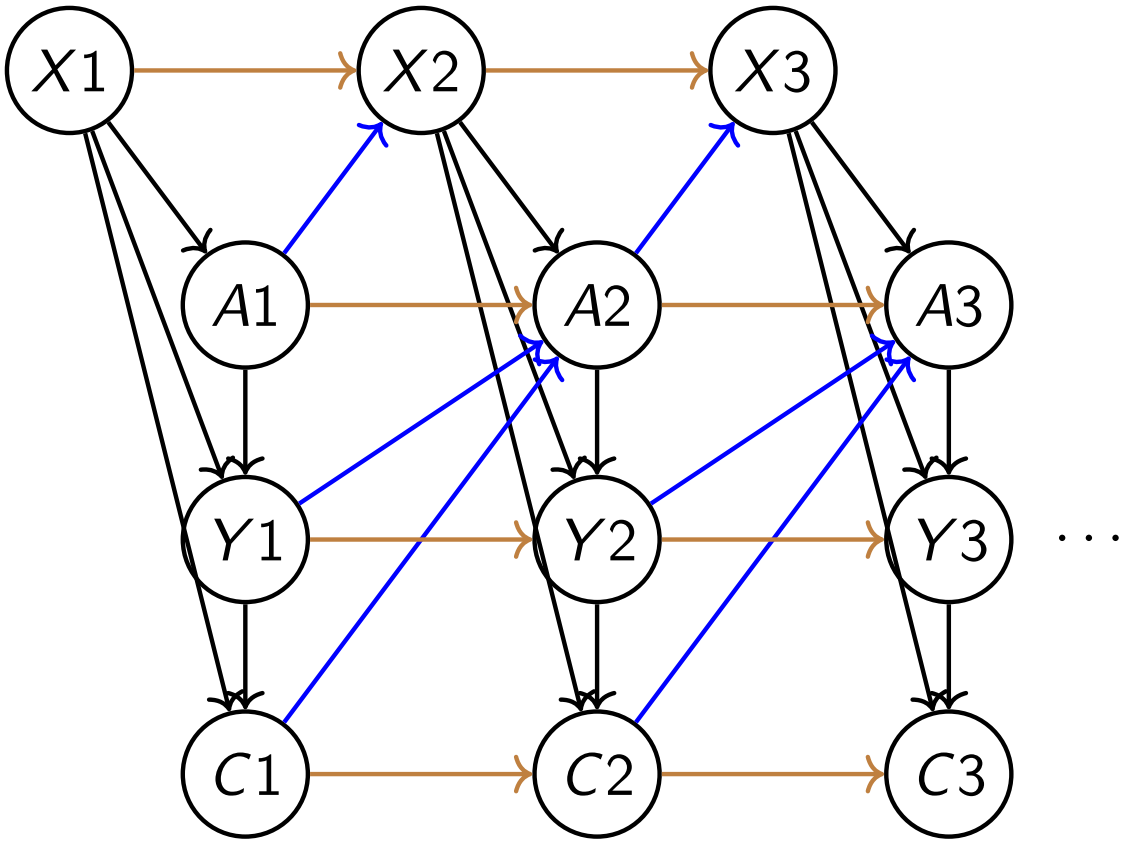
Confounding bias and selection bias **throughout time**



Existing methods : Marginal Structural Models (MSM)

Final causal graph

Confounding bias and selection bias **throughout time**



Existing methods : Marginal Structural Models (MSM)

Final assumptions we need to make

Stable Unit Treatment Value Assumption (SUTVA)

$Y_i = Y_i(1)A_i + Y_i(0)(1 - A_i)$ for all $i \in \{1, \ldots, n\}$

Unconfoundedness

$A_i \perp \{Y_i(0), Y_i(1)\} \mid X_i$ for all $i \in \{1, \ldots, n\}$

Conditionally independent censoring

$C_i \perp \{Y_i(0), Y_i(1)\} \mid X_i, A_i$ for all $i \in \{1, \ldots, n\}$

Positivity assumptions

$0 < \mathrm{P}(A_i = a_i \mid X_i = x_i) < 1$

$0 < \mathrm{P}(C_i > t \mid X_i = x_i, A_i = a_i) < 1$

Methodology

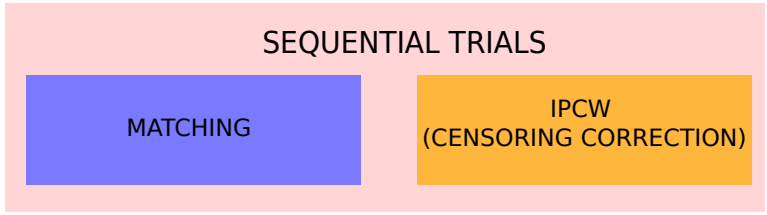
Emulated Target Trial (ETT)

Protocol element specification

- **Eligibility criteria:** Individuals $\geq$ 18 years, listed for lung TX only, diagnosed with CF.
- **Treatment :** Lung TX.
- **Treatment assignment:** Based on LAS.
- **Start and end of follow-up:** Starts at lung TX and ends at event or (natural) censoring.
- **Outcome :** Survival time up to 2 years.
- **Causal contrast:** ATE, defined by difference between areas under both survival curves (RMST).
- **Statistical analysis:** Survival estimator.

Methodology components

Sequential trials

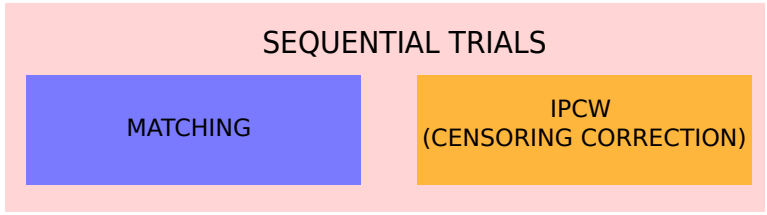


Sequential trials

- Sequence of trials with different follow-up starts
- Account as treated only patient TX at the follow-up start

Methodology components

Sequential trials

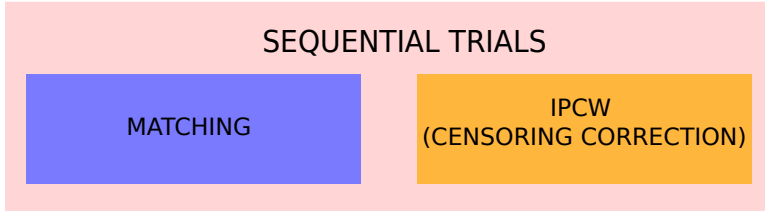


Sequential trials

- Sequence of trials with different follow-up starts
- Account as treated only patient TX at the follow-up start

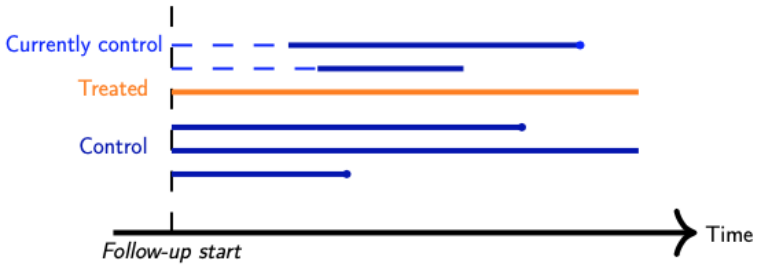
Methodology components

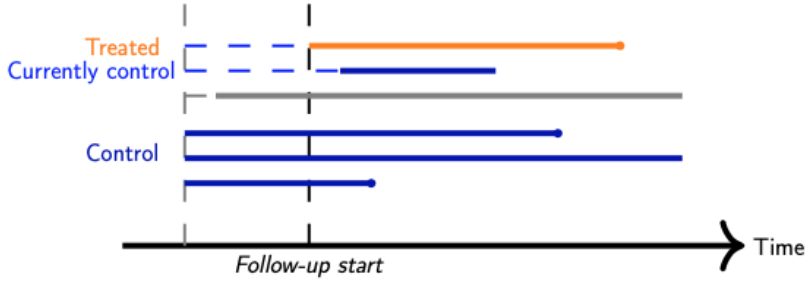
Sequential trials



Sequential trials

- Sequence of trials with different follow-up starts
- Account as treated only patient TX at the follow-up start

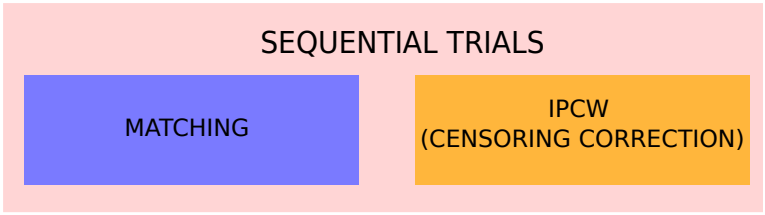




↪ simulates a no foreshadowing → reduces immortal time

Methodology components

Correction for censoring



Transition "currently control" $\rightarrow$ "control" through censoring

$\hookrightarrow$ artificial-informative censoring

IPCW for artificial-informative censoring

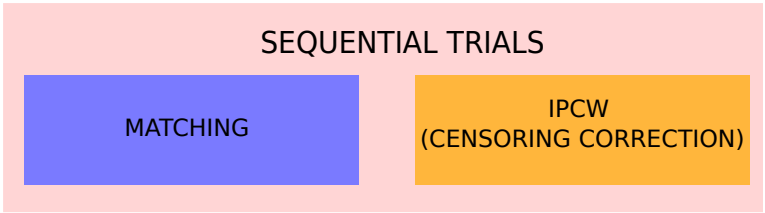
Weight uncensored individuals by $\frac{1}{P(\mathrm{C_i} > \mathrm{t} | X_i)}$

$\hookrightarrow$ Rebalances contributions : makes high censoring risk individual account for censored individuals

$\rightarrow$ Estimated using a Cox model

Methodology components

Correction for censoring



Transition "currently control" $\rightarrow$ "control" through censoring

$\hookrightarrow$ artificial-informative censoring

IPCW for artificial-informative censoring

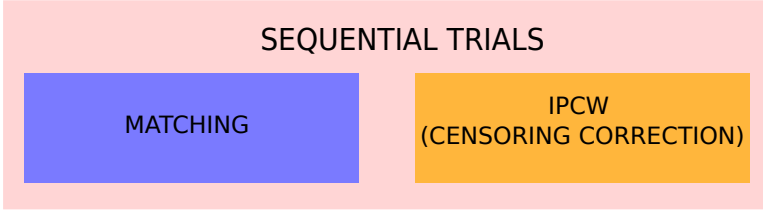
Weight uncensored individuals by $\frac{1}{P(\mathrm{C_i}>\mathrm{t}|X_i)}$

$\hookrightarrow$ Rebalances contributions : makes high censoring risk individual account for censored individuals

$\rightarrow$ Estimated using a Cox model

Methodology components

Correction for censoring



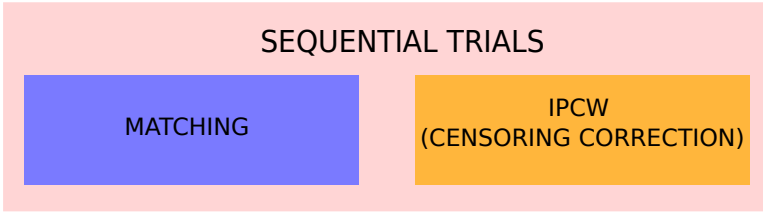
Population for small trial : how to choose the control ? i.e. those who are not TX at the current follow-up start

Matching on LAS

Match a control to a treated w.r.t to LAS value
$\rightarrow$ get comparable groups
$\hookrightarrow$ conditioning on confounding variable

Methodology components

Correction for censoring



Population for small trial : how to choose the control ? i.e. those who are not TX at the current follow-up start

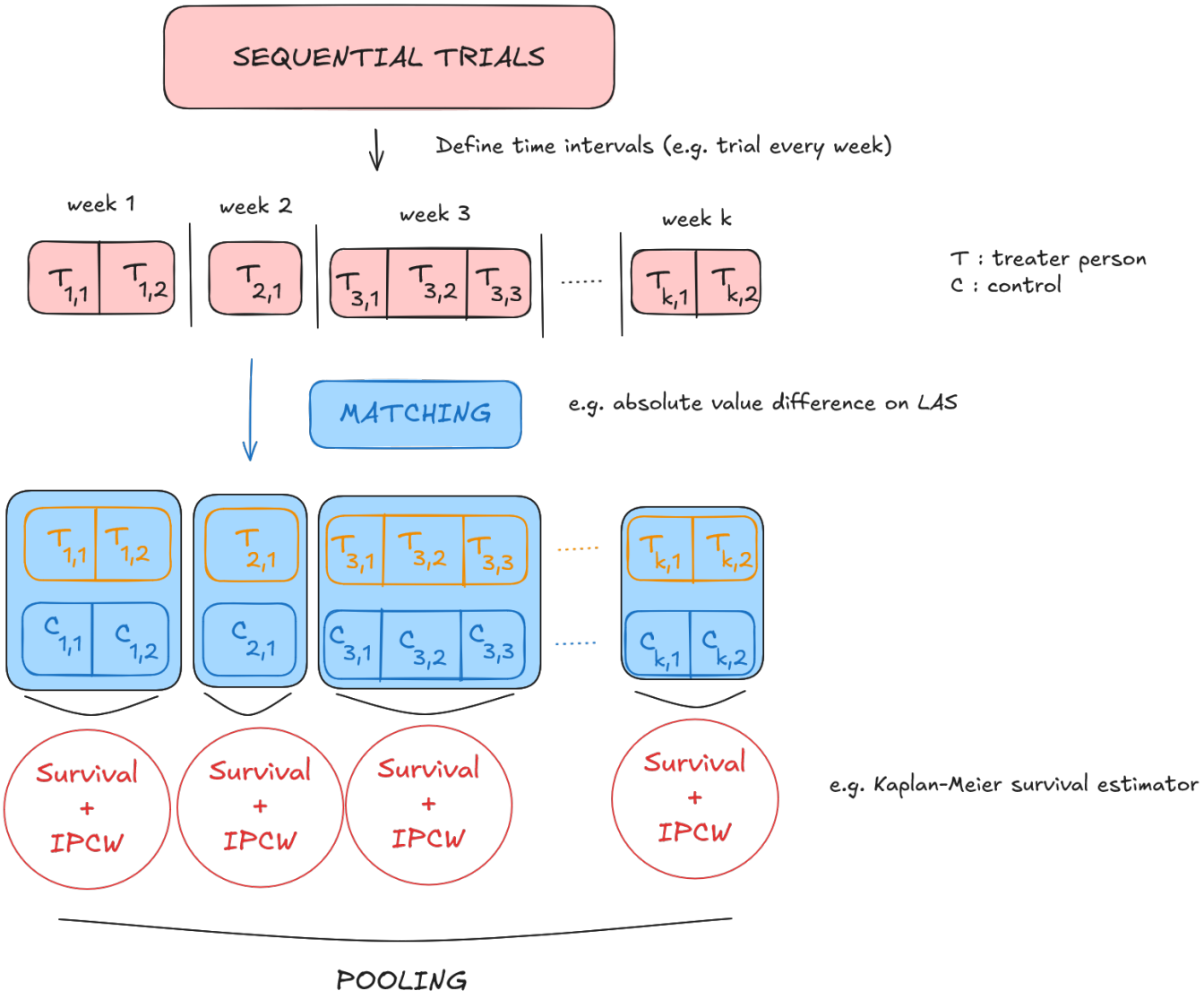
Matching on LAS

Match a control to a treated w.r.t to LAS value

$\rightarrow$ get comparable groups

$\hookrightarrow$ conditioning on confounding variable

Methodology



Database

United Network for Organ Sharing (UNOS)

Listing dataset:

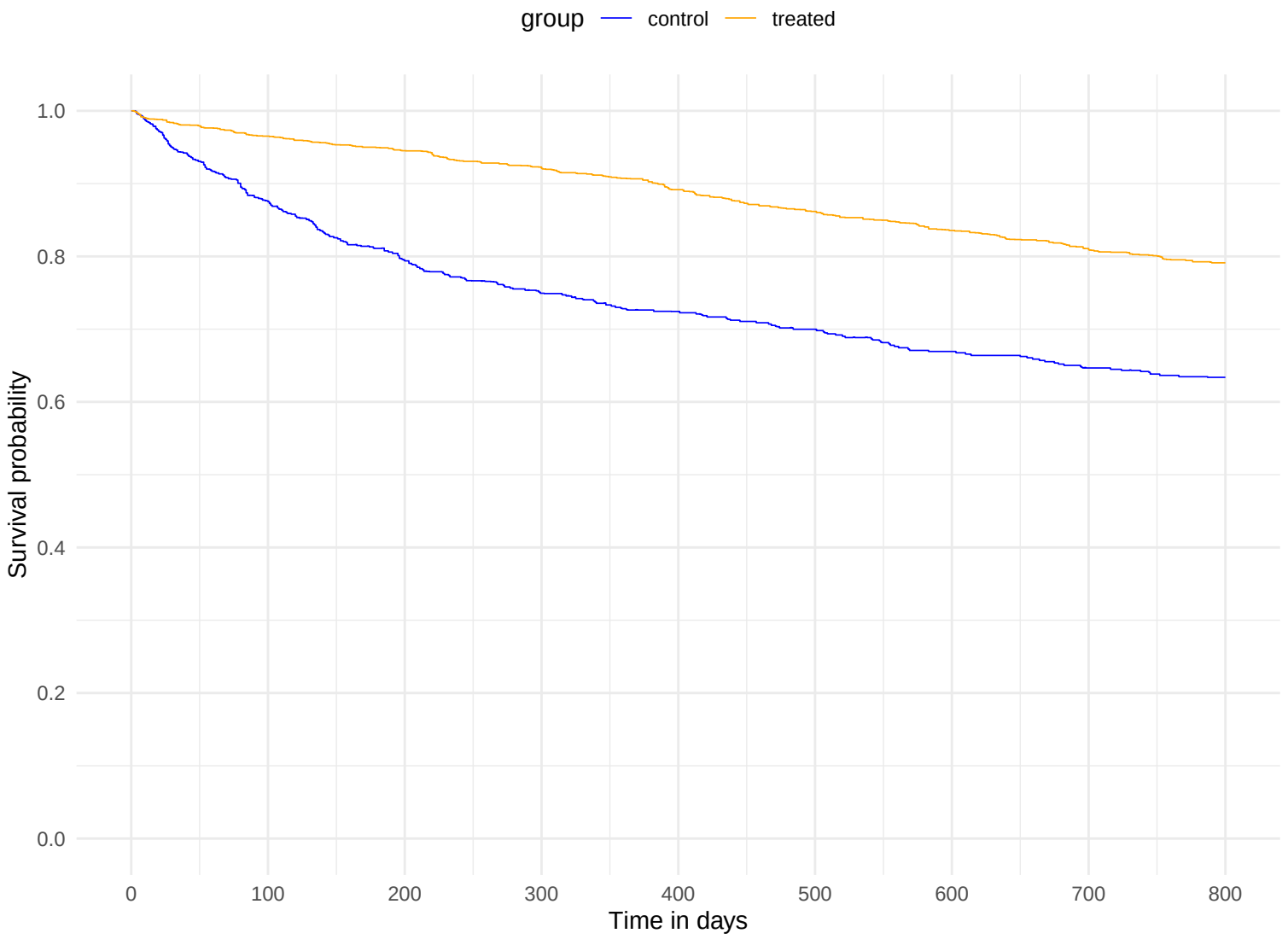
- 2411 individuals diagnosed with CF from the US, 494 variables
- Data recorded over $\sim$ 10 years
- Contains key variables for survival analysis

LAS dataset:

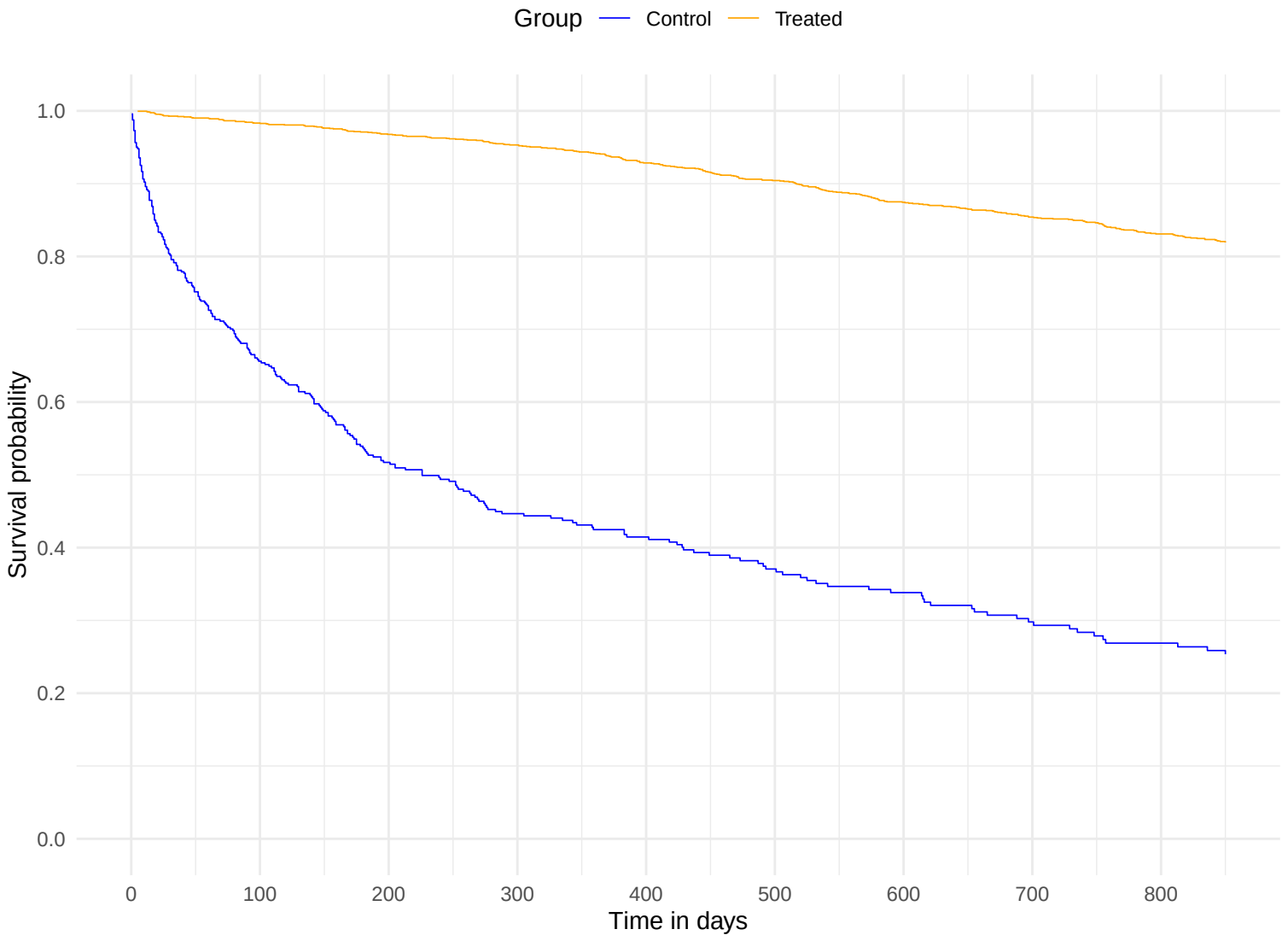
- Longitudinal LAS records of varying lengths per individual
- Tracks patient health trajectories over time

$\rightarrow$ Missing data filled using LME

Results on UNOS database



Biased results on UNOS database



Conclusion

Limits

- No-interference in SUTVA not verified
  How to take treatment availability into account ?
- LAS not only confounding factor :
  e.g. socio-economic background $\Rightarrow$ better healthcare
  but not geographic information available
- No account for surgical advances
  Break down analysis in time ?

Survival ATE

Survival ATE : RMST difference between both groups

$$ATE := \mathbb{E}[\min(Y(1), \tau)] - \mathbb{E}[\min(Y(0), \tau)]$$

$\hookrightarrow$ Area between both curves

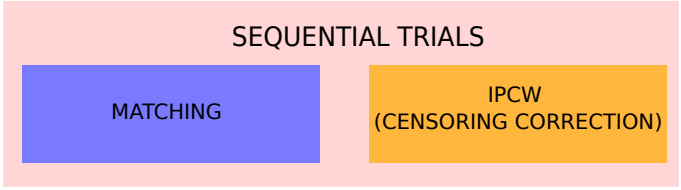
Expected survival time restricted to predefined time τ

$$\text{RMST}(\tau) = \mathbb{E}[\min(Y, \tau)] = \int_0^\tau S(t)\, dt$$

Y : the time-to-event
$S(t)$: survival function, $S(t) = P(Y > t)$

Next

Limit of sequence of trials ?

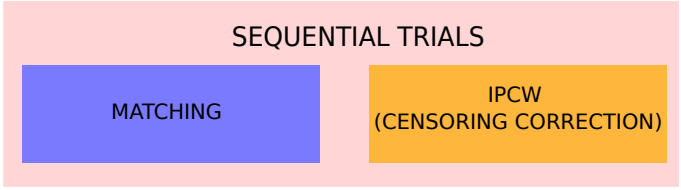


What's the limit object of such sequential design ? Do we correctly estimate the ATE ?

- Confounding bias $\rightarrow$ LAS
  Solution : matching
  OK [Rubin, 1997] : LAS $\sim$ propensity score $\rightarrow$ unconfoundedness
- Selection bias $\leftrightarrow$ immortal time and informative censoring
  Solutions : sequential trials and IPCW correction
  Dependencies between each trial ...
  $\hookrightarrow$ a control can match a treated again at another time
  $\hookrightarrow$ a control can change group

Next

Limit of sequence of trials ?



What's the limit object of such sequential design ? Do we correctly estimate the ATE ?

- Confounding bias $\rightarrow$ LAS
  Solution : matching
  OK [Rubin, 1997] : LAS $\sim$ propensity score $\rightarrow$ unconfoundedness
- Selection bias $\leftrightarrow$ immortal time and informative censoring
  Solutions : sequential trials and IPCW correction
  Dependencies between each trial ...
  $\hookrightarrow$ a control can match a treated again at another time
  $\hookrightarrow$ a control can change group

Hernán, M. A. and Robins, J. M. (2016).

Using big data to emulate a target trial when a randomized trial is not available: Table 1.

American Journal of Epidemiology, 183(8):758–764.

Keogh, R. H., Gran, J. M., Seaman, S. R., Davies, G., and Vansteelandt, S. (2023).

Causal inference in survival analysis using longitudinal observational data: Sequential trials and marginal structural models.

Statistics in medicine, 42(13):2191–2225.

Robins, J. M. et al. (1993).

Information recovery and bias adjustment in proportional hazards regression analysis of randomized trials using surrogate markers.

In *Proceedings of the biopharmaceutical section, American statistical association*, volume 24, page 3. San Francisco CA.

Rubin, D. B. (1997).

Estimating causal effects from large data sets using propensity scores.

Annals of internal medicine, 127(8_Part_2):757–763.

Thomas, L. E., Yang, S., Wojdyla, D., and Schaubel, D. E. (2020).

Matching with time-dependent treatments: a review and look forward.

Statistics in medicine, 39(17):2350–2370.