The hypothetical estimand and its potential estimators in clinical trials impacted by COVID-19

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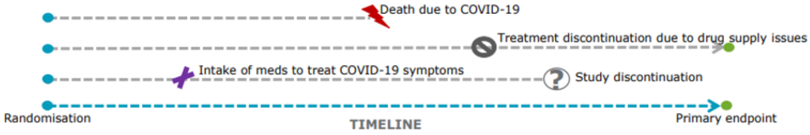
Complications due to pandemic

1. Due to **administrative/operational challenges**:
   e.g., treatment discontinuation due to drug supply issues, missed visits due to lockdown, . . .

2. Directly related to impact of COVID-19 on **health status**:
   e.g., death due to COVID-19, treatment discontinuation due to COVID-19 symptoms, . . .



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- Protocol deviations inevitable result in:
  - **Increased missing data** and different types of missing data
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- Protocol deviations inevitable result in:
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  - Affected interpretation or existence of the measurements associated with the clinical question of interest (**intercurrent events**)
- Unforeseen intercurrent events due to COVID-19
  - **Introduce ambiguity** to the original trial questions
  - Teams need to discuss how to account for them

Example: treatment discontinuation

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- **Hypothetical strategy**: "had patients not discontinued treatment"
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- **Treatment policy strategy**: "intercurrent event as part of the treatment"
  - No adaptation of the original estimand

Hypothetical Estimands

- A world where **COVID-19 does not exist**

- A world where **COVID-19 exists but is under control**:
  - individuals can suffer from COVID-19 infections
  - administrative/operational challenges caused by the pandemic assumed absent

Motivating Example

- Double-blind randomized trial in a neuroscience indication
- Comparing a new treatment ($A = 1$) with placebo ($A = 0$) wrt an outcome on a continuous diseases rating scale at 24 months
    - Y_t: outcome measured at time t ($t \in \{0, \ldots, 8\}$)
- X_t: time-varying covariates measured at time t ($t \in \{0, \ldots, 8\}$)
- $\bar{X}_t$ and $\bar{Y}_t$: history until (and including) timepoint t

Motivating Example

- Following intercurrent events were added to address impact of pandemic:
  - Infections with the COVID-19 virus, COVID-19 vaccinations or treatments: **treatment-policy strategy**
  - Withdrawal from or interruption of medication due to pandemic-related reasons: **hypothetical strategy**

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Hypothetical treatment effect estimand

$$\theta = E\left(Y_8^{a=1,\bar{E}_8=\bar{0}}\right) - E\left(Y_8^{a=0,\bar{E}_8=\bar{0}}\right)$$

Potential estimators

1. Estimators from **missing data literature**

[1] Sergey Tarima, and Zhanna Zenkova. IEEE, 2020.

Potential estimators

1. Estimators from **missing data literature**
2. Estimators that **combine unbiased and possibly biased estimators**[1]
   - Unbiased estimator: based on data observed before COVID-19 outbreak (not impacted by COVID-19)
   - Possibly biased estimator: based on data observed after COVID-19 outbreak

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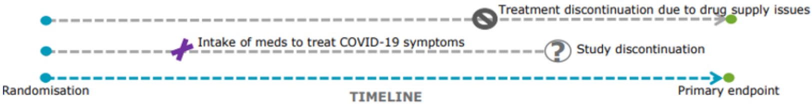
Missing data estimation

- **Monotone missingness**: data after relevant intercurrent event
  - may be physically missingness, or
  - if observed can be initially set missing



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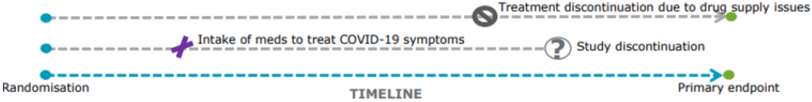
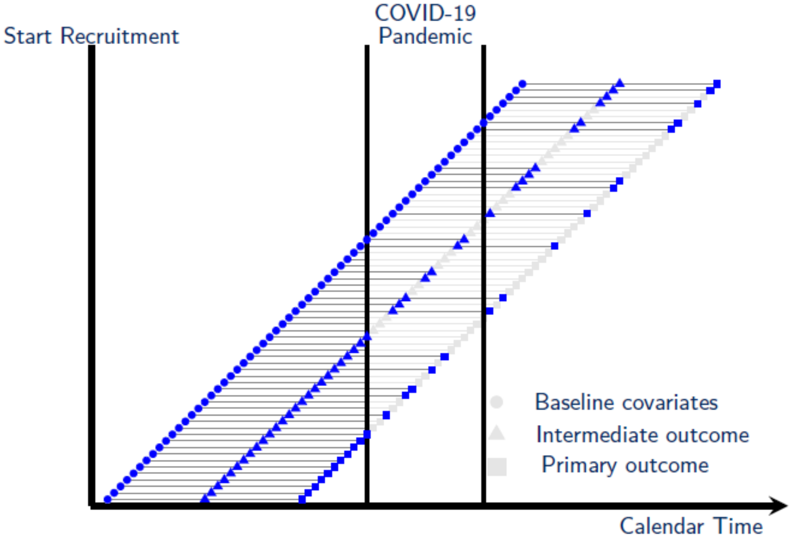


- **Missing at random (MAR)** assumption: at each time in study, we have access to all prognostic factors (possibly time-varying) of outcome that are associated with having an intercurrent event

Missing data estimation: observed data



Likelihood based analyses and multiple imputation

- A **linear mixed model for repeated measures**, including treatment and baseline covariates, can be fitted to all observed data unaffected by relevant intercurrent events
  - Different endpoints: Cox model or generalized linear mixed model

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  - Different endpoints: Cox model or generalized linear mixed model

- Alternatively, **multiple imputation** samples missing data from the conditional distribution of the missing outcomes given treatment indicator, baseline covariates and observed outcomes

Advantages and limitations

- **Consistent and asymptotically efficient** when
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  - Higher risk of model misspecification
- When people with and without missing data are very different, these methods rely on **extrapolation**

Inverse Probability Weighting

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  3. Obtain estimate for θ:

$$\hat{\theta} = n_1^{-1} \sum_{i=1}^{n} I(A_i = 1, \bar{E}_{8,i} = \bar{0}) W_i Y_{8,i} - n_0^{-1} \sum_{i=1}^{n} I(A_i = 0, \bar{E}_{8,i} = \bar{0}) W_i Y_{8,i}$$

Inverse Probability Weighting

- **Consistent** estimator provided that
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- Easily **allows for time-varying prognostic factors** of missingness
- **Less efficient** than likelihood based/imputation approaches

Improving upon previous estimators

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Possible solution:
Augmented inverse probability weighting

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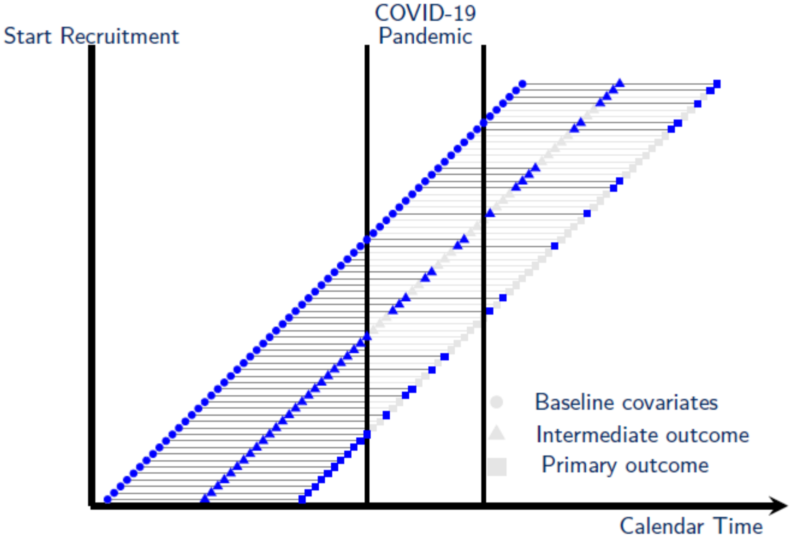
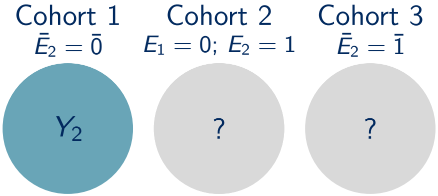


Augmented Inverse Probability Weighting

Cohort 1	Cohort 2	Cohort 3
$\bar{E}_2 = \bar{0}$	$E_1 = 0;\ E_2 = 1$	$\bar{E}_2 = \bar{1}$

Augmented Inverse Probability Weighting



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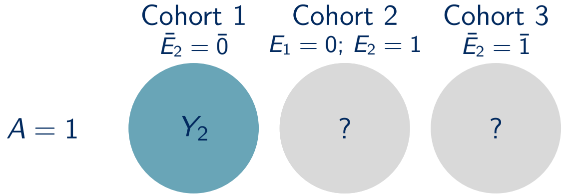
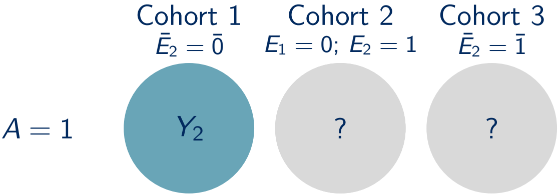


Estimator for $E\left(Y_2^{a=1,\bar{E}_2=\bar{0}}\right)$ is obtained by

Augmented Inverse Probability Weighting



Estimator for $E\left(Y_2^{a=1,\bar{E}_2=\bar{0}}\right)$ is obtained by

1. Fitting a (weighted) linear model for Y_2 among the treated ($A = 1$) patients in cohort 1 ($\bar{E}_2 = \bar{0}$) given $\bar{X}_1$ and $\bar{Y}_1$

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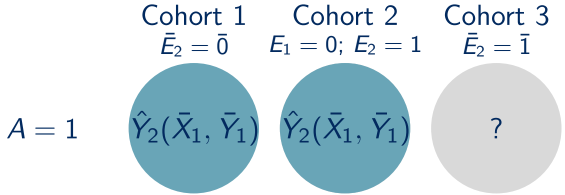

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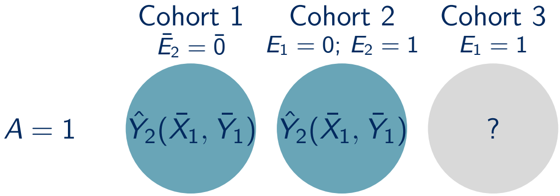
1. Fitting a (weighted) linear model for Y_2 among the treated ($A = 1$) patients in cohort 1 ($\bar{E}_2 = \bar{0}$) given $\bar{X}_1$ and $\bar{Y}_1$
2. Using this model to impute Y_2 for the treated patients in cohort 1 and 2

Augmented Inverse Probability Weighting

	Cohort 1 $\bar{E}_2 = \bar{0}$	Cohort 2 $E_1 = 0;\ E_2 = 1$	Cohort 3 $E_1 = 1$
$A = 1$	$\hat{Y}_2(\bar{X}_1, \bar{Y}_1)$	$\hat{Y}_2(\bar{X}_1, \bar{Y}_1)$	?

Augmented Inverse Probability Weighting



3. Fitting a (weighted) linear model for the prediction $\hat{Y}_2(\bar{X}_1, \bar{Y}_1)$ among the treated $(A = 1)$ patients in the imputed dataset (cohort 1 and 2; $E_1 = 0$) given X_0 and Y_0

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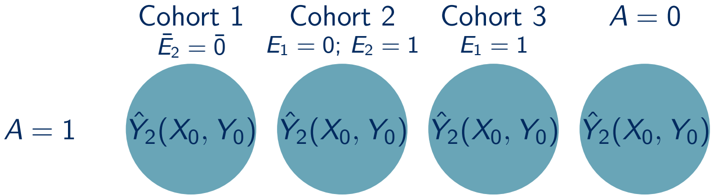

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4. Using this model to impute Y_2 for all patients

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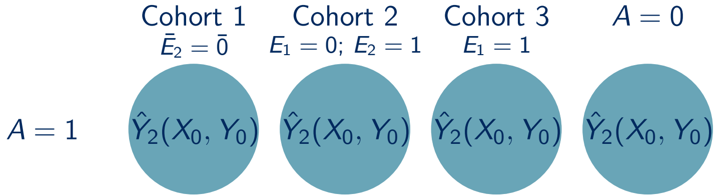

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5. Take the sample average of the fitted values $\hat{Y}_2(X_0, Y_0)$ for **all** patients

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- **Consistent and asymptotically more efficient** than IPW estimators provided that
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- (Augmented) inverse probability weighting works for different kind of endpoints
- How can we obtain more robustness against model misspecification?

Augmented Inverse Probability Weighting

- **Robustness against model misspecification** can be obtained by using weights:
  - $\prod_{t=1}^{2} \frac{1}{P(E_t=0|A,E_{t-1}=0,\bar{X}_{t-1},\bar{Y}_{t-1})}$ in Step 1
  - $\frac{1}{P(E_1=0|A,\bar{X}_0,\bar{Y}_0)}$ in Step 3

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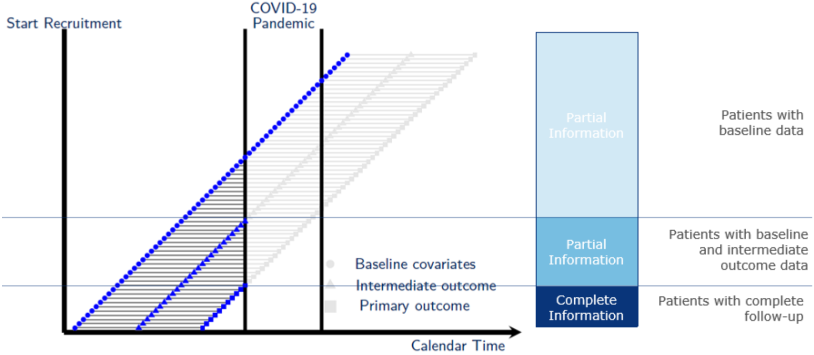
- **Double robust**: Consistent if either outcome models or models for not having a relevant intercurrent event (no missingness) are correctly specified

Assumption "free" estimator

Previous estimator (without weights) naturally leads to an "**assumption free**" estimator[2] for treatment effect in a COVID-19 free world



[2] Kelly Van Lancker, et al. Pharmaceutical statistics (2020): 583-601.

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- “Assumption free” estimator because
  - **Asymptotically unbiased** estimator, even if outcome models are misspecified
    - No statistical modeling assumptions
  - No MAR assumption for post-baseline data observed after the COVID-19 outbreak
  - Overcomes misclassification of COVID-19-related intercurrent events

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  - No MAR assumption for post-baseline data observed after the COVID-19 outbreak
  - Overcomes misclassification of COVID-19-related intercurrent events
- Different extensions possible: pandemic free world, allowing for population shift, . . .

Thank you for your attention!

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