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

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on behalf of the NISS working group
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, . . .
Additional Intercurrent Events

- Protocol deviations inevitable result in:
  - Increased missing data and different types of missing data
  - Affected interpretation or existence of the measurements associated with the clinical question of interest (intercurrent events)
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- 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

- Hypothetical strategy: “had patients not discontinued treatment”
  - Need to predict the hypothetical outcome
Example: treatment discontinuation

- **Hypothetical strategy**: “had patients not discontinued treatment”
  - Need to predict the hypothetical outcome

- **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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- **\( E_t \):** indicator for occurrence of (second) intercurrent event at time \( t \) \( (t \in \{1, \ldots, 8\}) \)
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- Following intercurrent events were added to address impact of pandemic:
  - Infections with the COVID-19 virus, COVID-19 vaccinations or treatments: **treatment-policy strategy**
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- $E_t$: indicator for occurrence of (second) intercurrent event at time $t$ ($t \in \{1, \ldots, 8\}$)

### Hypothetical treatment effect estimand

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

1 Estimators from **missing data literature**

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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

Missing data estimation

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

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  - may be physically missingness, or
  - if observed can be initially set missing

- **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
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.
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

- 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
  - MAR holds (assuming no time-varying covariates are relevant, except outcome)
  - Analysis (and imputation) models are correctly specified

In theory, time-varying prognostic factors can be accommodated. However, this complicates implementation as these factors need to be (jointly) modeled/imputed. Higher risk of model misspecification when people with and without missing data are very different.
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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

- Weight observed data in an appropriate manner that corrects for the patients with missing data:

1. At each timepoint $t$: estimate $P(E_t = 0 | A, \bar{E}_{t-1}, \bar{X}_{t-1}, \bar{Y}_{t-1})$

2. Calculate the weights: $W_i = \prod_{t=1}^{8} \frac{1}{P(E_t, i = 0 | A_i, \bar{E}_t, i, \bar{X}_{t-1}, i, \bar{Y}_{t-1})}$

3. Obtain estimate for $\theta$: $\hat{\theta} = \frac{n-1}{n} \sum_{i=1}^{n} I(A_i = 1, \bar{E}_8, i = \bar{0}) W_i Y_8, i - \frac{n-1}{n} \sum_{i=1}^{n} I(A_i = 0, \bar{E}_8, i = \bar{0}) W_i Y_8, i$
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3. Obtain estimate for \( \theta \):

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

- **Consistent** estimator provided that
  - MAR holds (allowing for time-varying covariates)
  - Model for not having a relevant intercurrent event (no missingness) is correctly specified
  - Positivity assumption holds: probability of not having an intercurrent event given observed history is always positive
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- Easily **allows for time-varying prognostic factors** of missingness

- **Less efficient** than likelihood based/imputation approaches
Improving upon previous estimators

- Can we improve upon the efficiency of the IPW estimator?
- Can we obtain methods that are more robust against model misspecification than previous estimators?
Improving upon previous estimators

- Can we **improve upon the efficiency** of the IPW estimator?
- Can we obtain methods that are **more robust against model misspecification** than previous estimators?

**Possible solution:**

Augmented inverse probability weighting
Missing data estimation: observed data
Augmented Inverse Probability Weighting

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

Estimator for
\[ E(\bar{Y}_a = 1, \bar{E}_2 = \bar{0}) \]
is obtained by

1. Fitting a (weighted) linear model for \( \bar{Y}_2 \) 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 \( \bar{Y}_2 \) for the treated patients in cohort 1 and cohort 2.
Augmented Inverse Probability Weighting

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

- $Y_2$
- ?
- ?

Estimator for $E(Y_{a=1}, \bar{E}_2 = \bar{0})$ is obtained by:

1. Fitting a (weighted) linear model for $Y_2$ among the treated $(A = 1)$ patients in cohort 1 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

Estimator for $E \left( Y_2^{a=1, E_2=0} \right)$ is obtained by

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 $\bar{Y}_1$.

Using this model to impute $Y_2$ for the treated patients in cohort 1 and 2.

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

$A = 1$

$Y_2$
Augmented Inverse Probability Weighting

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
<th>Cohort 3</th>
</tr>
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<tbody>
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Augmented Inverse Probability Weighting

\[ \bar{E}_2 = 0; \quad E_1 = 0; \quad E_2 = 1 \]

Cohort 1

Cohort 2

Cohort 3

\[ \hat{Y}_2(\bar{X}_1, \bar{Y}_1) \]

\[ \hat{Y}_2(\bar{X}_1, \bar{Y}_1) \]

?
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 $Y_0$
Augmented Inverse Probability Weighting

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

Using this model to impute \( Y_2 \) for all patients.
Augmented Inverse Probability Weighting

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

\[ \hat{Y}_2(X_0, Y_0) \]

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 $Y_0$

4. Using this model to impute $Y_2$ for all patients

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

- Becomes more complicated for more timepoints
Augmented Inverse Probability Weighting

- Becomes **more complicated** for more timepoints

- **Consistent and asymptotically more efficient** than IPW estimators provided that
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Augmented Inverse Probability Weighting

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- (Augmented) inverse probability weighting works for different kind of endpoints
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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:
  
  \[ \prod_{t=1}^{2} \frac{1}{P(E_t=0|A, E_{t-1}=0, \bar{X}_{t-1}, \bar{Y}_{t-1})} \text{ in Step 1} \]

  \[ \frac{1}{P(E_1=0|A, X_0, Y_0)} \text{ in Step 3} \]
Augmented Inverse Probability Weighting

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  \[ \prod_{t=1}^{2} \frac{1}{P(E_t=0|A,E_{t-1}=0,X_{t-1},Y_{t-1})} \text{ in Step 1} \]

  \[ \frac{1}{P(E_1=0|A,X_0,Y_0)} \text{ in Step 3} \]

- **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

Assumption “free” estimator

- “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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Different extensions possible: pandemic free world, allowing for population shift, ...
Thank you for your attention!

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