Addressing Administrative Withdrawals in Clinical Trials in Estimation under the Treatment Policy Strategy

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PSI
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This is a joint work with Rong Liu (Eli Lilly and Company) and Feng Li (FDA)

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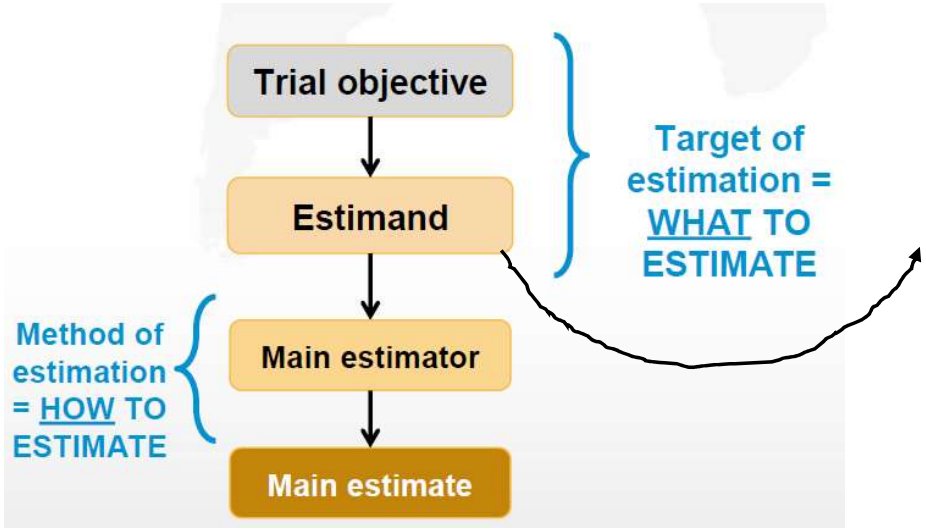
Estimand framework [ICH E9 (R1)]



- Treatment(s) of interest
- Population of interest
- Outcome variable (endpoint) at patient level
- Population-level summary
- Handling of relevant ICEs

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- Treatment policy
- Hypothetical
- Composite variable
- While on treatment (WOT)
- Principal stratum (PS)

ICEs, intercurrent events

Use a mix of strategies to handle ICEs in a study (Darken et al., 2020; Qu et al., 2020)

- One common drawback in most current clinical studies is that only ONE strategy is used to handle all ICEs
- Strategies for handling ICEs should be based on the underlying reasons
  - ICEs due to AE
  - ICEs due to lack of efficacy (LoE)
  - ICEs due to administrative reasons (relocation, family situation changed, COVID-19 control measures, geographical conflict, sanctions, etc.)
  - ICEs due to sufficient efficacy or disease curation

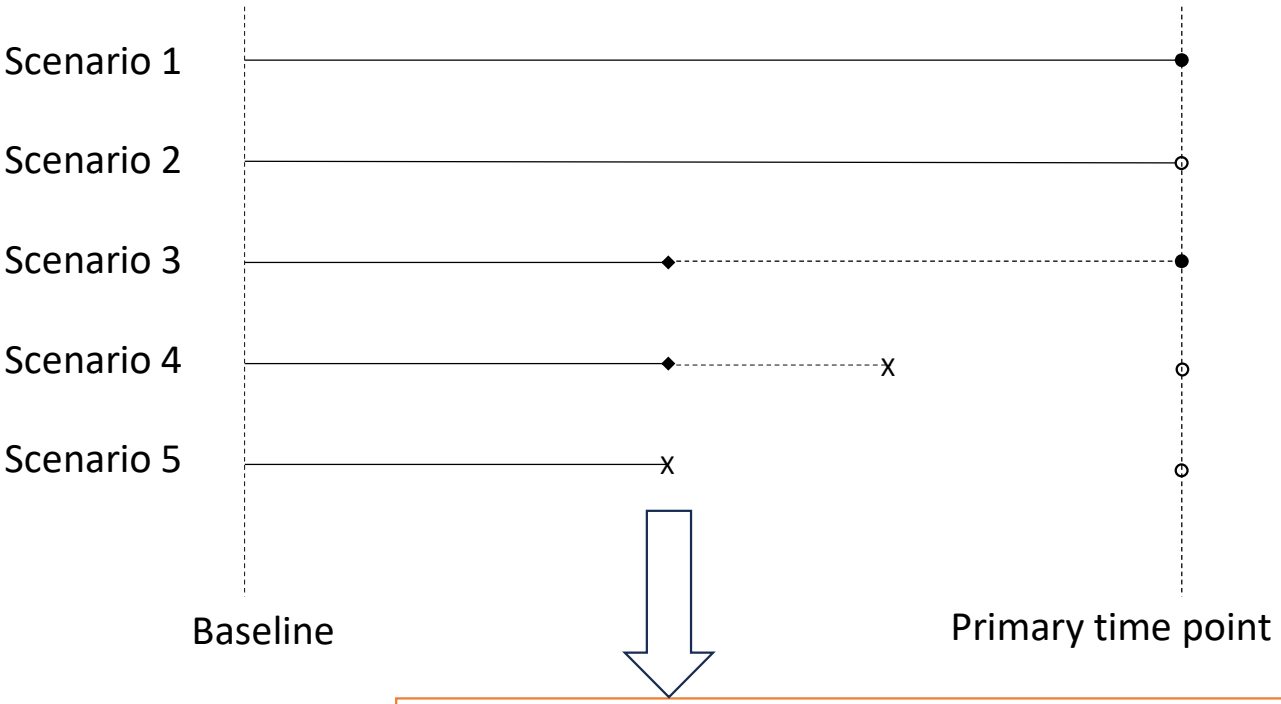
ICEs, intercurrent events

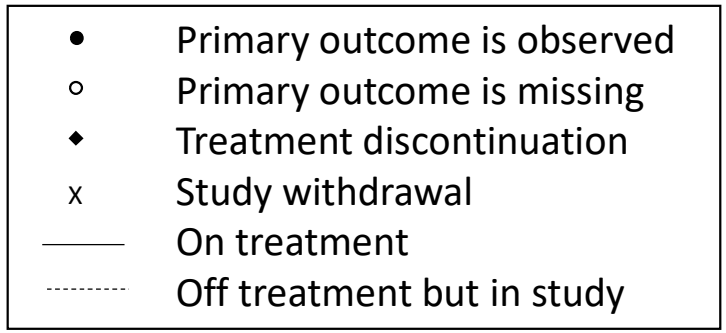
Treating administrative study withdrawals as censoring treatment discontinuations

- In real world, those administrative study withdrawals will not impact patients' adherence status
  - For example, scheduling conflict may prevent a patient participating in the clinical trials due to frequent clinical visits, but it should not prevent patients taking marketed medications in real life
- It automatically handles the unusual circumstances (pandemic, geographical conflicts, natural disasters, etc.)
  - E.g., during the COVID pandemic, many protocols or statistical analysis plans were amended to handle the COVID related study/treatment discontinuation differently

Different ICEs and study withdrawals are competing events!

Illustration of intercurrent events, study withdrawal, and missing data





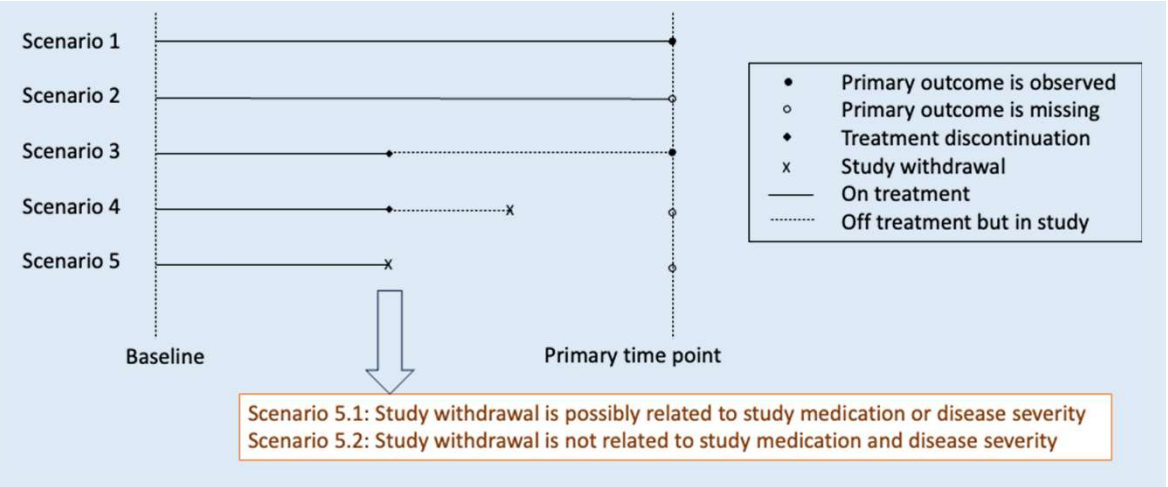
Scenario 5.1: Study withdrawal is possibly related to study medication or disease severity
Scenario 5.2: Study withdrawal is not related to study medication and disease severity

Notation

- Y: the outcome
- X: baseline covariates
- U: time to treatment discontinuation
- V: time to study withdrawal (V censors U!)
- D: type of study withdrawal (D = 0 for study withdrawal being possible related to study medication or disease severity; D = 1 otherwise)
- R: missingness indicator (R = 1 for being missing; R = 0 for being observed)
- U(i): the potential outcome for U if assigned to treatment *i*, *i* = 0 for control treatment, *i* = 1 for the experimental treatment

Assumptions

- For Scenarios 3 and 4, assume the outcome and the study discontinuation are independent: $Y(i) \perp\!\!\!\perp V(i) | V(i) > U(i)$
- For Scenario 5.1, assume the treatment discontinuation occurs at the same time as study withdrawal : $\Pr\{U(i) = V(i) \,| V(i) > U(i), D(i) = 0\} = 1$
- For Scenario 5.2, assume the treatment discontinuation censored by study withdrawal: $V(i) \perp\!\!\!\perp \{U(i), Y(i)\} | D(i) = 1$



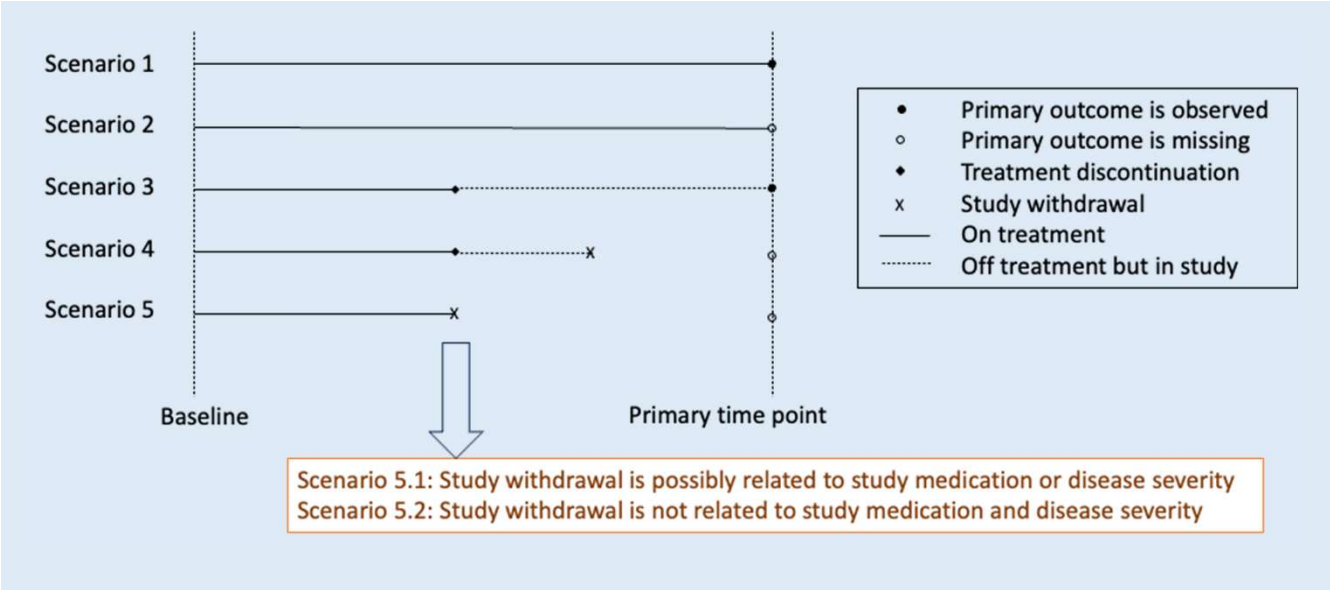
Missing data imputation

- Method A: Using the ***non-missing values for those who are adherent to the assigned treatment*** to impute the missing values due to study withdrawal.
- Method B: Using the ***retrieved dropouts*** to impute the missing values due to study withdrawal

Missing data imputation – Method C

Imputation Steps:

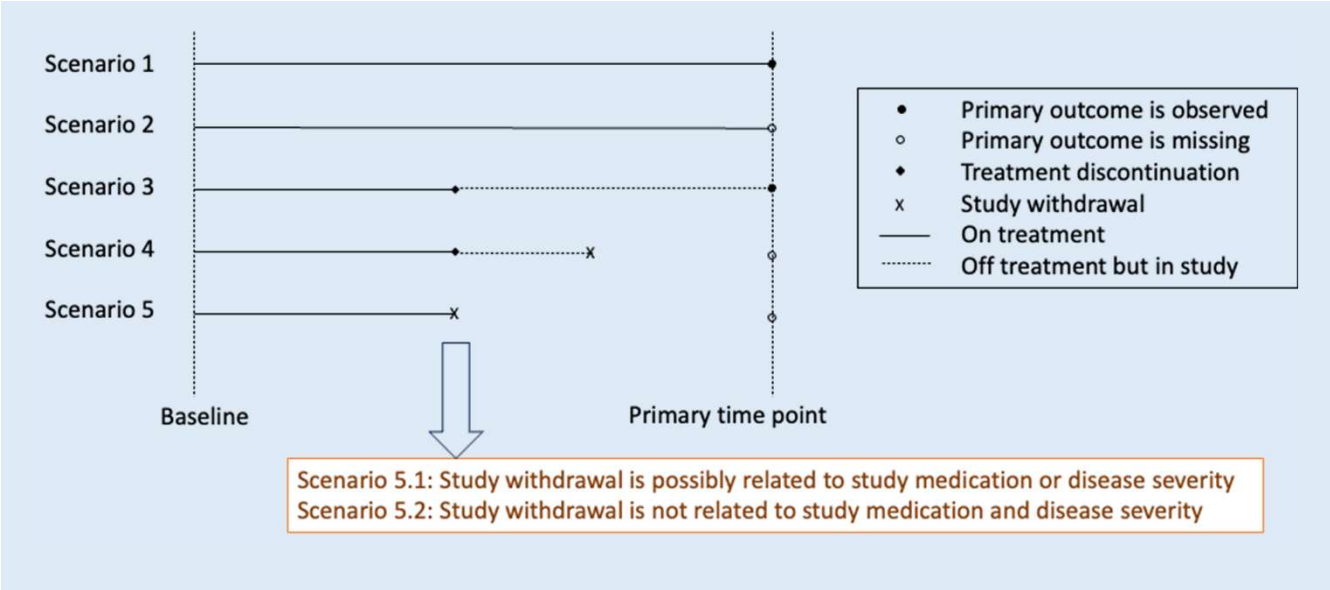
- Missing data in Scenario 2 is imputed by data from Scenario 1 assuming missing at random (MAR)
- Missing data in Scenarios 4 and 5.1 may be imputed by the “retrieved dropouts” in Scenario 3
- For Scenario 5.2
  - Using Kaplan-Meier estimator to estimate the survival function for V and calculate the conditional probability of treatment discontinuation at study end, say p
  - Generate a Bernoulli random variable ξ with probability of p. If $\xi = 1$, we use retrieved dropouts to impute; otherwise, use adherers to impute



Missing data imputation – Method D

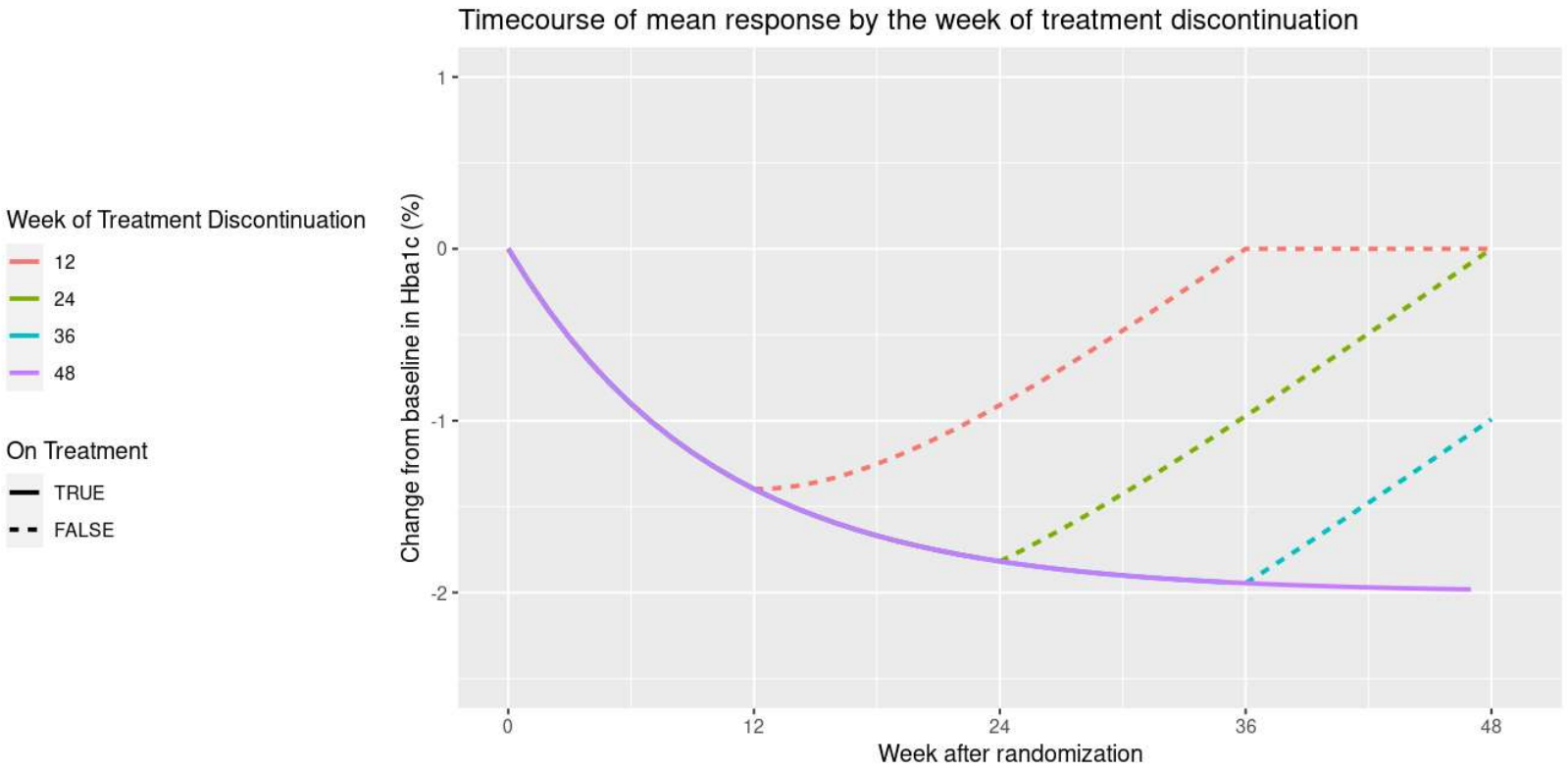
Imputation Steps:

- Missing data in Scenario 2 is imputed by data from Scenario 1 assuming missing at random (MAR)
- Missing data in Scenarios 4 and 5.1 may be imputed by the “retrieved dropouts” in Scenario 3
- Missing data in Scenario 5 may be imputed by all data (observed and imputed) in Scenarios 1, 2, 3, 4, and 5.1.



Simulation

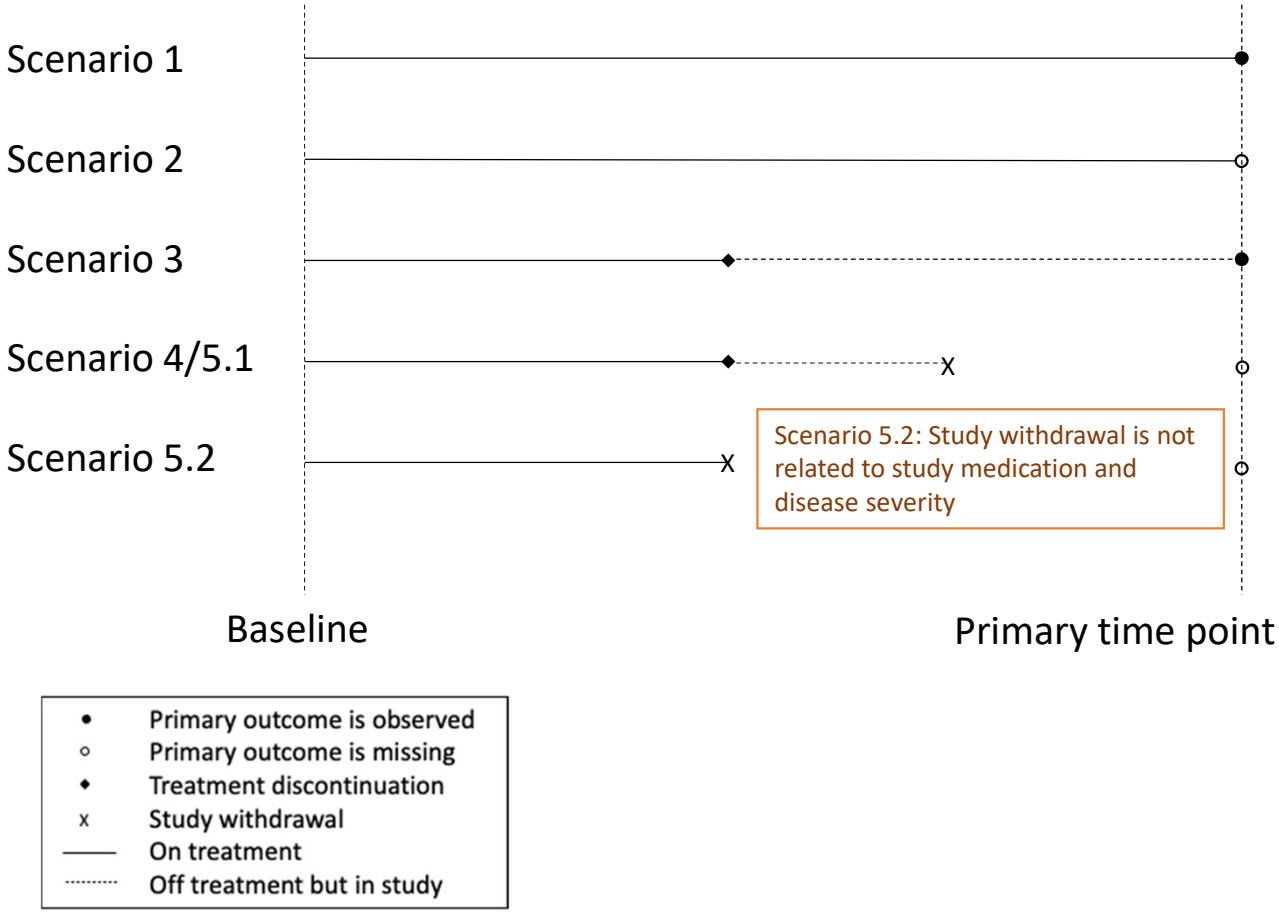
Generating the response under the treatment policy strategy



$$Y_{jk}(Z_j) = [\theta_{Z_j} - (\theta_{Z_j} - \theta_0) \cdot \min\{\max(t_k - t_{a,j}, 0), 24\}/24 + (\beta_0 + \beta_1 Z_j)(X_j - \mu_x) + s_j](1 - e^{-\kappa t_k}) + \epsilon_{jk}$$

$X \sim 7 + 3 * Beta(1.5,2)$
$(\beta_0, \beta_1) = (-0.1,0.2)$
$\theta_0 = 0, \theta_1 = -2.0$
$\kappa = 0.1$
$s_j \sim N(0,1)$
$\epsilon_{jk} \sim N(0,0.5^2)$

Simulating treatment discontinuations and missing values



Missing values not due to study withdrawal: Bernoulli distribution with mean of 0.05

Treatment discontinuation:

$$\Pr(A_{ijk} = 0|Y_{j,k-1}) = \frac{\exp(\alpha_0 + \alpha_1 Y_{j,k-1})}{1 + \exp(\alpha_0 + \alpha_1 Y_{j,k-1})} + c_k(i)$$

$\alpha_0 = -3.5; \alpha_0 = 1.5$
$c_k(0) = 0.2$ for $k = 1,2,3,4;$
$c_k(1) = 0.06, 0.06, 0.03, 0.02$ for $k = 1,2,3,4$

Missingness for those with treatment discontinuation was generated using a Bernoulli distribution with mean of 0.8

Study withdrawal due to administrative reasons is generated from an exponential distribution with hazard rate of 0.002

RL0

Average Percentage of Subjects in Each Scenario out of 5000 Simulations

	Control (N = 200)	Treatment (N = 200)
Scenario 1: no treatment discontinuation and no missing primary outcome	65.9%	68%
Scenario 2: no treatment discontinuation but missing primary outcome	3.46%	3.57%
Scenario 3: treatment discontinuation but no study withdrawal with non-missing primary outcome	4.38%	3.97%
Scenario 4 and 5.1: treatment discontinuation with missing primary outcome	17.8%	16.2%
Scenario 5.2: Administrative study withdrawal	8.48%	8.34%

Mean Response on HbA1c reduction across 5000 simulations	Control (N = 200)	Treatment (N = 200)
Adherers	- 0.187	-2.01
Retrieved dropout	0.6	-0.04

Slide 14

RL0 [@Yongming Qu] I added the % of pts in each scenario. I do not know how you want to present the mean value across the simulations. I just pasted them in another table below. See if you like it.
Rong Liu, 2024-05-30T23:37:07.970

Simulation results (10000 simulated samples, 10 multiple imputations for each simulated data)

Arm	Method	BIAS	ESE	ASE	CP
Control	A	-0.007	0.126	0.140	0.957
	B	0.058	0.160	0.181	0.943
	C	0.002	0.132	0.147	0.959
	D	0.003	0.134	0.151	0.956
Treatment	A	-0.017	0.139	0.141	0.931
	B	0.147	0.176	0.189	0.854
	C	-0.009	0.146	0.152	0.938
	D	0.017	0.149	0.153	0.930
Treatment Difference	A	-0.010	0.186	0.190	0.941
	B	0.089	0.239	0.244	0.931
	C	-0.011	0.196	0.202	0.944
	D	0.015	0.199	0.204	0.941

Notations and abbreviations: BIAS, empirical bias; CP, 95% empirical coverage probability; ASE, mean standard error estimates of the mean; ESE: standard deviation of the estimates;

ASE and CP were based on Rubin's rule to combine the between and within imputation variabilities

Bootstrap inference was not provided due to insufficient numbers of retrieved dropouts in some bootstrap samples

Method A: using adherers to impute all missing values under MAR assumption

Method B: using retrieved dropouts to impute all missing values

Method C: estimating the proportion of adherers by Kaplan-Meier estimator and impute the adherence status

Method D: using both adherers and retrieved dropouts to impute missing due to administrative study withdrawal

- **This simulation setting shows the performance was similar between Methods A, C, and D. More simulation studies are needed to better understand the performance of these estimators**
- **In Method C, the time to treatment discontinuation was estimated using Kaplan-Meier estimator, which does not adjust for baseline covariates. This method needs further improvement (adjusting for baseline covariates).**

Handling missing values considering study withdrawal without imputation

- For Scenarios 3 and 4, assume the outcome and the study discontinuation are independent: $Y \perp\!\!\!\perp V(i) | V(i) > U(i)$
- For Scenario 5.1, assume the treatment discontinuation occurs at the same time as study withdrawal : $\Pr\{U(i) = V(i) \,|V(i) > U(i), D(i) = 0\} = 1$
- For Scenario 5.2, assume the treatment discontinuation censored by study withdrawal: $V(i) \perp\!\!\!\perp \{U(i), Y(i)\} | D(i) = 1$

$$\hat{\mu}_{ik}^{\text{MAR-RD}} = \hat{\phi}_{ik}\hat{\mu}_{ik}^{\text{MAR},A=1} + (1-\hat{\phi}_{ik})(\hat{\beta}_{0k,0}^{-} + (\hat{\boldsymbol{\nu}}_{ik}^{A=0})'\hat{\boldsymbol{\beta}}_{0k,1}^{-})$$

Proportion of subjects being adherers

Estimator based on MAR assumption for adherers

Mean baseline covariates for non-adherers

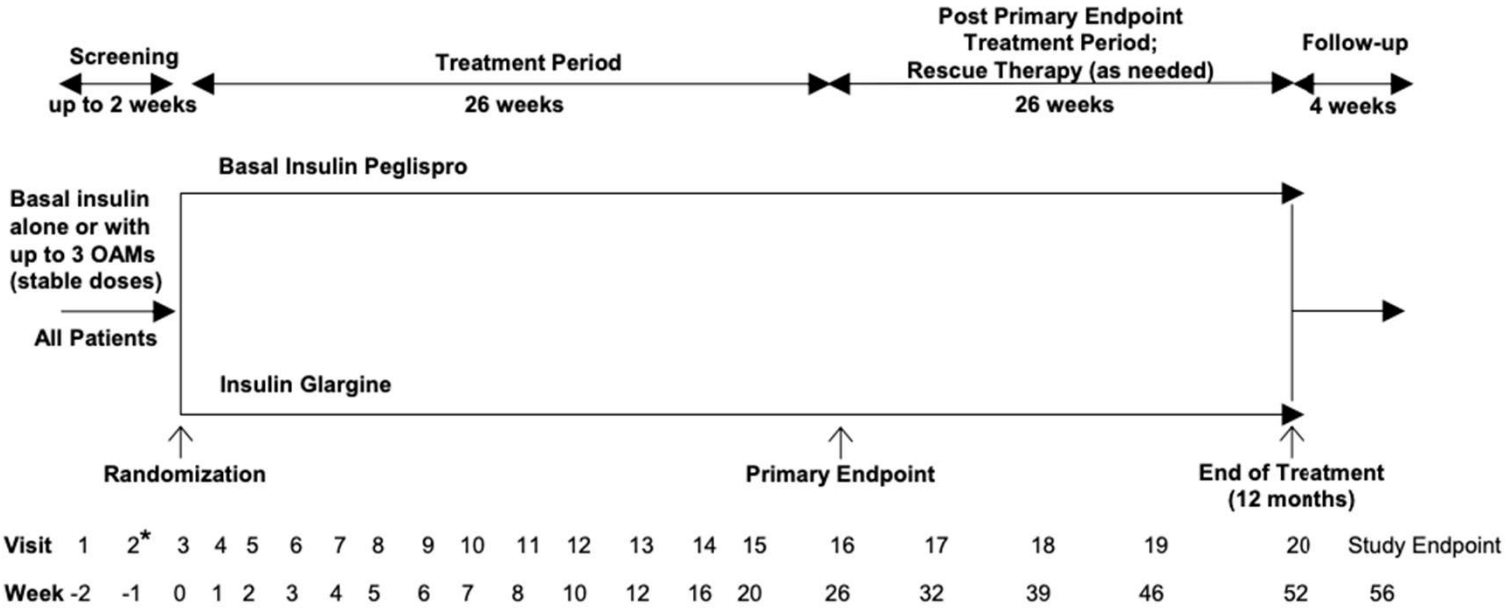
Regression coefficients of retrieved dropouts on baseline covariates

This analytic method is under further development and will be shared in the future

Application

IMAGEIN-5 Study (Buse et al., 2016)

- 52-week Phase 3 study comparing insulin peglisro with insulin glargine
- Primary analysis variable: change in HbA1c from baseline to 52 weeks



Reasons for study discontinuations

- We consider “Lost to Follow-Up” and “Withdrawal by Subject” as administrative study withdrawals that are not related to efficacy and safety

	Insulin Glargine (N = 159)	Insulin Peglispro (N = 307)
Adverse Event	3 (1.9%)	1 (0.3%)
Death	3 (1.9%)	3 (1.0%)
Protocol Violation	3 (1.9%)	11 (3.6%)
Physician Decision	0 (0.0%)	3 (1.0%)
Sponsor Decision	0 (0.0%)	1 (0.3%)
Withdrawal by Subject	9 (5.7%)	13 (4.2%)
Lost to Follow-Up	2 (1.3%)	0 (0.0%)

RL0

Administrative study withdrawals

N = number of randomized subjects

RL1

Slide 19

RL0 [@Yongming Qu] I have changed your number from 466 to 307 here.
Rong Liu, 2024-05-30T19:52:26.338

RL1 [@Yongming Qu] added this footnote.
Rong Liu, 2024-05-30T20:01:53.890

RL0

Treatment discontinuation and missing values

	Insulin Glargine (N = 159)	Insulin Peglispro (N = 307)
Scenario 1: no treatment discontinuation and no missing primary outcome	130	257
Scenario 2: no treatment discontinuation but missing primary outcome	1	0
Scenario 3: treatment discontinuation but no study withdrawal with non-missing primary outcome	5	13
Scenario 4 and 5.1: treatment discontinuation with missing primary outcome	7	19
Scenario 5.2: Administrative study withdrawal	9	13

Slide 20

RL0 [@Yongming Qu] I summarized based upon pts who have baseline value. So it does not add up to total N.
Rong Liu, 2024-05-30T20:03:00.776

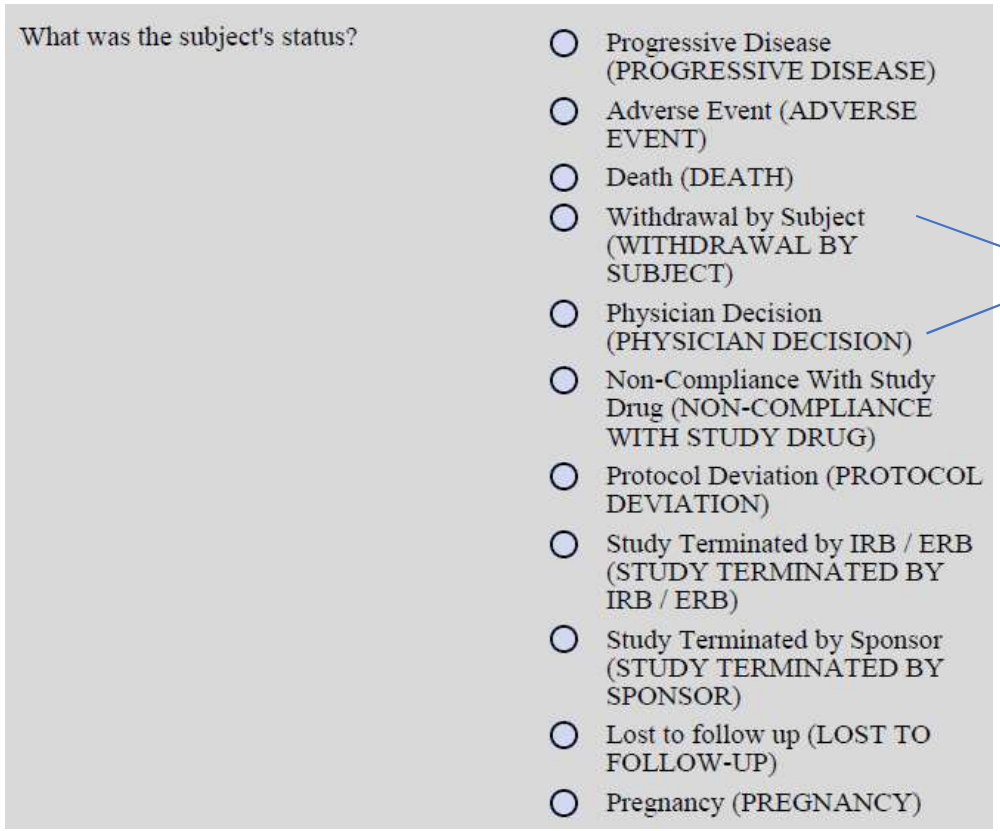
Results

Method	Insulin Glargine [estimate (se)] (N = 159)	Insulin Peglispro [estimate (se)] (N = 307)	Treatment Difference (95% CI) (Peplispro vs. Glargine)
A. Assuming MAR to impute all missing values	-0.230 (0.061)	-0.602 (0.045)	-0.372 (-0.519,-0.224)
B. Using retrieved dropouts to impute for all missing values	-0.218 (0.061)	-0.594 (0.045)	-0.376 (-0.524, -0.228)
C. estimating the proportion of adherers by Kaplan-Meier estimator and impute the adherence status	-0.232 (0.061)	-0.603 (0.045)	-0.371 (-0.520,-0.222)
D. using both adherers and retrieved dropouts to impute missing due to administrative study withdrawal	-0.224 (0.061)	-0.606 (0.045)	-0.382 (-0.531,0.233)

Observed mean change in HbA1c for adherers (Scenario 1): -0.236 for insulin glargine and -0.672 for insulin peglispro
Observed mean change in HbA1c for retrieved dropouts (Scenario 3): -0.060 for insulin glargine and -0.031 for insulin peglispro

Better collection of treatment discontinuation and study withdrawal

Current widely used case report form (CRF) for treatment discontinuation



Who makes the decision to discontinue the treatment?

The CRF mixed the answers for 2 questions:

- **What is the underlying reason for treatment discontinuation?**
- **Who makes the decision to discontinue the treatment?**

Treatment discontinuation

Suggested CRF for Treatment Discontinuation

Document the subject's status for trial period. If the subject discontinued treatment prematurely, record the primary reason for discontinuation.	What was the subject's status? DS.DSDECOD DS.DSTERM	○ DEATH ○ ADVERSE EVENT. List the adverse event ID: _____ ○ PREGNANCY ○ LACK OF EFFICACY ○ SUFFICIENT EFFICACY PROTOCOL DEVIATIONS ○ DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT ○ TOOK PROTOCOL PROHIBITED CONCOMITANT MEDS ○ NONCOMPLIANCE TO STUDY PROCEDURES ○ NON-COMPLIANCE WITH STUDY DRUG LOGISTICAL PROBLEM ○ RELOCATION ○ SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE ○ PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE ○ UNSATISFIED WITH STUDY PROCEDURES ○ UNSATISFIED WITH STUDY DRUG DELIVERY DEVICES/METHODS ○ FEAR OF NEW OR RECURRENT ADVERSE EVENTS ○ STUDY TERMINATION OR SITE CLOSURE ○ CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE ○ GEOPOLITICAL LOGISTICAL RESTRICTIONS ○ OPERATIONAL ERROR ○ BLIND BROKEN ○ LOST TO FOLLOW-UP

Study withdrawal

Document the subject's status for the study. If the subject discontinued study prematurely, record the primary reason for discontinuation.	What was the subject's status? **DS.DSDECOD** **DS.DSTERM**	○ **COMPLETED** ○ **ADVERSE EVENT.** LINK TO ADVERSE EVENT: _____ ○ **DEATH** ○ **PREGNANCY** ○ **PROTOCOL DEVIATIONS** • DID NOT MEET STUDY ELIGIBILITY CRITERIA AT ENROLLMENT • NONCOMPLIANCE TO STUDY PROCEDURES ○ **LOGISTICAL PROBLEM** • RELOCATION • SCHEDULE CONFLICTS OR DIFFICULTY TRAVELING TO SITE • PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE • UNSATISFIED WITH STUDY PROCEDURES • STUDY TERMINATION OR SITE CLOSURE • CLINICAL TRIAL MATERIAL QUALITY ISSUE OR SHORTAGE • GEOPOLITICAL LOGISTICAL RESTRICTIONS • OPERATIONAL ERROR • BLIND BROKEN ○ **LOST TO FOLLOW-UP**

Summary

- Handling treatment discontinuations due to administrative study withdrawal differently from other intercurrent events has two major benefits
  - Better reflects the real clinical practice
  - Automatically handles unusual situations
- We used multiple imputation to impute the missing values due to study withdrawal differentially by considering the competing risks between study withdrawal and treatment discontinuations
  - There were little difference in the estimates in the simulation without and with considering the competing risk for administrative censoring (Methods A and D)
  - Further simulation studies are needed to understand the difference between Methods A and D
- The current data collection standards for treatment and study discontinuations need to be improved
  - PHUSE working group “Optimizing the Use of Data Standards” is tackling this problem

References

- Buse, J. B., Rodbard, H. W., Trescoli Serrano, C., Luo, J., Ivanyi, T., Bue-Valleskey, J., ... & Chang, A. M. (2016). Randomized clinical trial comparing basal insulin peglispro and insulin glargine in patients with type 2 diabetes previously treated with basal insulin: IMAGINE 5. *Diabetes Care*, *39*(1), 92-100.
- Darken, P., Nyberg, J., Ballal, S., & Wright, D. (2020). The attributable estimand: a new approach to account for intercurrent events. *Pharmaceutical Statistics*, *19*(5), 626-635.
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