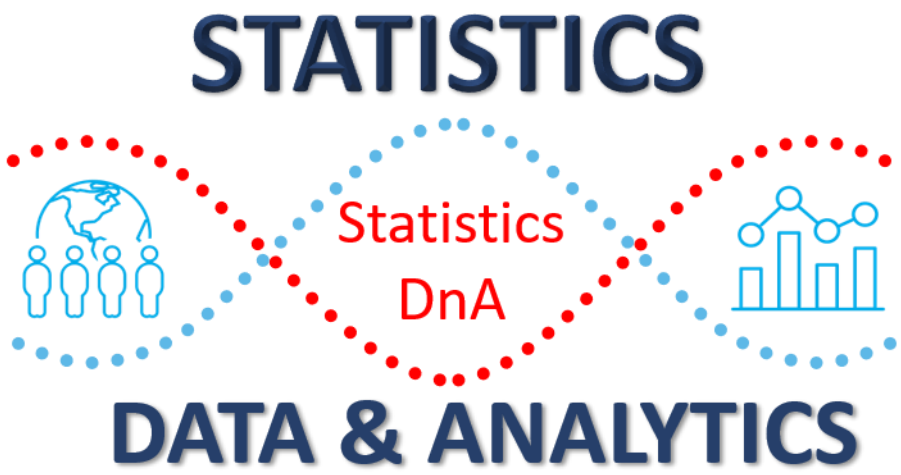


# Causal Inference in Drug Development

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Eli Lilly and Company

CAUSAL MACHINE LEARNING FOR NOVEL SETTINGS BOOT CAMP

August 20, 2022

Lilly | Statistics DnA
Statistics, Data and Analytics

Acknowledgement: Steve Ruberg, Junxiang Luo, Haoda Fu, Ying Zhang, Ilya Lipkovich, Run Zhang, Jiaxun Chen, Arman Sabbaghi

# Causal inference in drug development



| | |
|---|---|
| Target identification | Mostly based on biology and observational data |
| Target validation | Vitro and vivo experiments, animal studies |
| Transferability from vitro/vivo/animal to human | Mostly observational data |
| Clinical validation (ph1-3 clinical studies) | Mostly randomized trials with some unavoidable confounding factors (adherence) |
| Real world evidence | Mostly observational data |

# Clinical questions – example 1



- REWIND study is a cardiovascular outcome study comparing dulaglutide (a drug treating diabetes) and placebo
- A well-known endocrinologist asks what is the risk reduction for cardiovascular events if the HbA1c reduction was greater than 1.5%

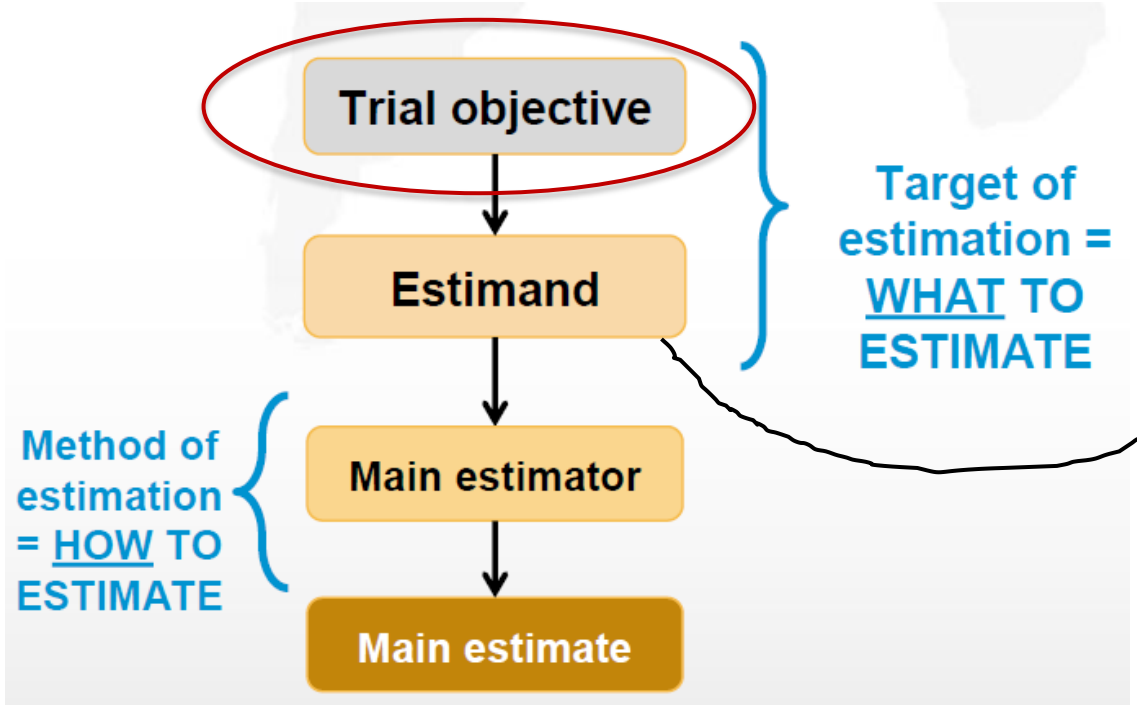
# Clinical questions – example 2



- Physicians: What is the treatment effect for adherers? (a very vague question)
- Traditionally, the so-called per-protocol analysis
  - Using the regulator statistical models (e.g., linear models) by only including those patients who adhere to the study medication during the study
  - It is not “causal”
- What is the new analysis to replace the non-causal per-protocol analysis?

# Estimand framework [ICH E9 (R1)]






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

ICEs, intercurrent events

# All randomized patients vs. adherers

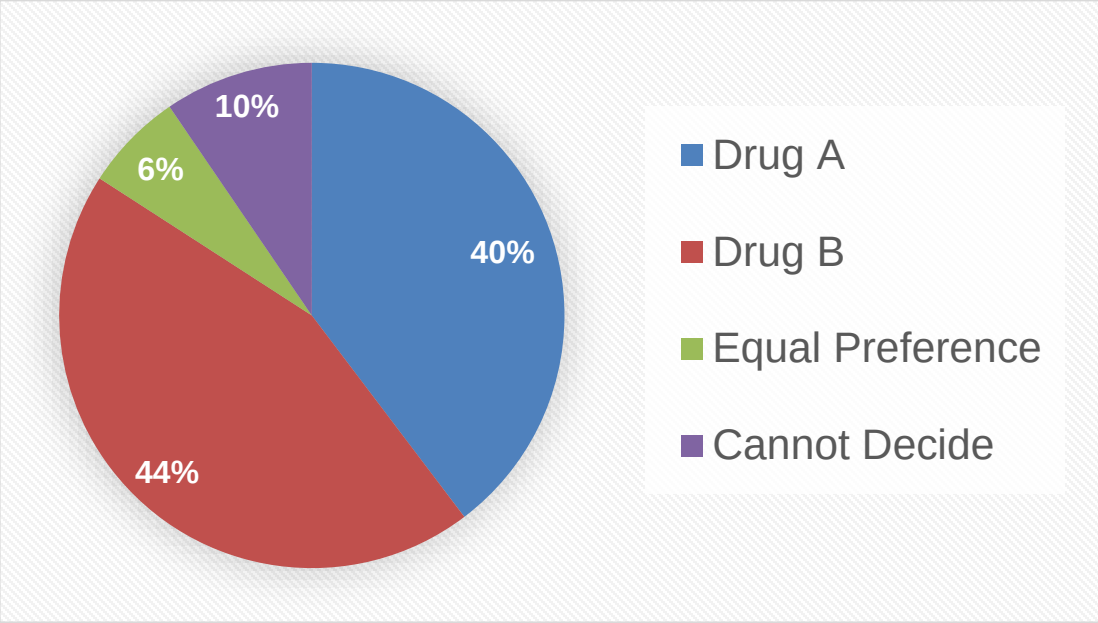


***Adherers:*** Patients who complete the randomized treatment without intercurrent events

- Suppose we have 2 anti-diabetes drugs
  - Drug A: Only 50% of patients can tolerate the drug(adherers), and on average it can reduce HbA1c by 2% for adherers
  - Drug B: Every patient can tolerate the drug, and on average it can reduce HbA1c by 1%
- If you were to treat a diabetes patient, which drug do you prefer to try first?

# A simple survey for researchers in diabetes






N = 63

## Some Comments

- "It depends on patients' baseline information. If a patient had high HbA1c, I would start Drug A; Otherwise, I would start Drug B"
- "What type of tolerability? It is important for my decision"

**Estimands for adherers (based on principal strata) are equally important as estimands for all randomized patients**

# Principal strata based on sdherence



***A*(*T*) is the indicator of adherence on treatment *T* (*T* = 0, 1)**

| Adherence to Control Treatment | Adherence to Experimental Treatment | | |
|---|---|---|---|
| | $A(1) = 0$ | $A(1) = 1$ | $A(1) \in \{0,1\}$ |
| $A(0) = 0$ | | | |
| $A(0) = 1$ | | **Principal Strata** | |
| $A(0) \in \{0,1\}$ | | | |

Frangakis, C. E., & Rubin, D. B. (2002). Principal stratification in causal inference. *Biometrics*, *58*(1), 21-29.

# Principal strata based on adherence



**A(T) is the indicator of adherence on treatment *T* (*T* = 0, 1)**

| Adherence to Control Treatment | Adherence to Experimental Treatment | | |
|---|---|---|---|
| | $A(1) = 0$ | $A(1) = 1$ | $A(1) \in \{0,1\}$ |
| $A(0) = 0$ | | | |
| $A(0) = 1$ | | $S_{++}$ | $S_{+*}$ |
| $A(0) \in \{0,1\}$ | | $S_{*+}$ | $S_{**}$ |

Patients that would adhere to both treatments

Patients that would adhere to experimental treatment

All randomized patients

# Estimands based on adherer status



**Y(T) is the potential outcome on treatment T (T=0,1)**

| Adherence to Control Treatment | Adherence to Experimental Treatment | | |
|---|---|---|---|
| | $A(1) = 0$ | $A(1) = 1$ | $A(1) \in \{0,1\}$ |
| $A(0) = 0$ | | | |
| $A(0) = 1$ | | $E[Y(1) - Y(0)\|S_{++}]$ | $E[Y(1) - Y(0)\|S_{+*}]$ |
| $A(0) \in \{0,1\}$ | | $E[Y(1) - Y(0)\|S_{*+}]$ | $E[Y(1) - Y(0)\|S_{**}]$ |

Patients that would adhere to both treatments

Patients that would adhere to experimental treatment

All randomized patients

# Existing methods

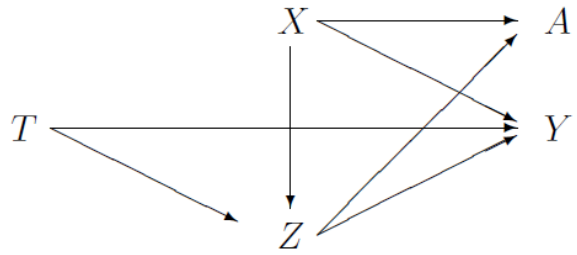


- Estimators using the monotonicity assumption
  - For any patient, A(0) = 0 ⇒ A(1) = 0 or A(1) = 1 ⇒ A(0) = 1
  - Drawback: a simplistic deterministic relationship on random variables of A(0) and A(1)
- Estimators based on principal scores
  - Model the probability of principal stratum membership through baseline covariates: $\Pr(A(1) = 1|X) = g(X)$
  - Drawback: assuming the principal stratum membership can be modeled through only baseline covariates

# Assumptions



***X* is the baseline covariates**
***Z*(*T*) is the potential intermediate outcome on treatment T**
***A*, *Y*, *Z* are the outcomes under the actual assigned treatment**




A1: $Y = Y(1)T + Y(0)(1-T)$

A2: $Z = Z(1)T + Z(0)(1-T)$

A3: $A = A(1)T + A(0)(1-T)$

⟹ Stable unit treatment value assumption (SUTVA)

A4: $T \perp \{Y(1), A(1), Z(1), Y(0), A(0), Z(0)\}|X$ ⟹ Ignorable treatment assignment assumption

A5: $A(i) \perp \{Y(1), Y(0), Z(1-i)\}|\{X, Z(i)\}, \quad \forall i = 0, 1$ ⟹ Ignorable adherence assumption

A6: $Y(i) \perp Z(1-i)|\{X, Z(i)\}, \quad \forall i = 0, 1$

A7: $Z(0) \perp Z(1)|X$

⟹ Conditional potential outcome cross-world independence assumption

# Notation



| Notation | Description |
|---|---|
| $g(X,Z) \coloneqq \Pr(A=1\|X,Z)$ | The probability of being adherent given $X$ and $Z$ |
| $h_i(X) \coloneqq E\{(g(X,Z(i))\|X\}$ | The conditional probability of being adherent only conditional on baseline covariate $X$, for treatment $i$ |
| $F_{Z(i)\|X}$ | CDF of $Z(i)$ given $X$ |
| $\psi_i\big(X,Z(i)\big) = E\{Y(i)\|X,Z(i)\}$ | The conditional expectation of the outcome given baseline covariate $X$ and the intermediate outcome $Z(i)$ |
| $\phi_i(X) = E\big\{\psi_i\big(X,Z(i)\big)\big\|X\big\}$ | The conditional expectation of the outcome given the covariate $X$ |
| $\varphi_i(X) = E\big\{g(X,Z(i))\psi_i\big(X,Z(i)\big)\big\|X\big\}$ | The conditional expectation for the potential outcome under treatment i for patients who are adherent to treatment $i$ |

# Adherence causal estimators (ACEs)



| Population | Method A: Estimator Based on Distribution of $(X, Z, Y)$ |
|---|---|
| $S_{**}$ | $\frac{1}{n_1}\sum_{j\in\{j:T_j=1\}}\hat{\psi}_1(X_j,Z_j)-\frac{1}{n_0}\sum_{j\in\{j:T_j=0\}}\hat{\psi}_1(X_j,Z_j).$ |
| $S_{*+}$ | $\frac{1}{n_{11}}\sum_{j\in\{j:T_j=1,A_j=1\}}Y_j-\frac{1}{n_{11}}\sum_{j\in\{j:T_j=1,A_j=1\}}\hat{\phi}_0(X_j)$ |
| $S_{+*}$ | $\frac{1}{n_{01}}\sum_{j\in\{j:T_j=0,A_j=1\}}\hat{\phi}_1(X_j)-\frac{1}{n_{01}}\sum_{j\in\{j:T_j=0,A_j=1\}}Y_j$ |
| $S_{++}$ | $\frac{\sum_{j\in\{j:T_j=0,A_j=1\}}\hat{\varphi}_1(X_j)}{\sum_{j\in\{j:T_j=0,A_j=1\}}\hat{h}_1(X_j)}-\frac{\sum_{j\in\{j:T_j=1,A_j=1\}}\hat{\varphi}_0(X_j)}{\sum_{j\in\{j:T_j=1,A_j=1\}}\hat{h}_0(X_j)}$ |

Mixed Model Repeated Measures (MMRM)

| Population | Method B: Estimator Based on Distribution of $(X, Z, A)$ |
|---|---|
| $S_{**}$ | $\frac{1}{n_1}\sum_{j\in\{j:T_j=1,A_j=1\}}\frac{Y_j}{\hat{g}(X_j,Z_j)}-\frac{1}{n_2}\sum_{j\in\{j:T_j=0,A_j=1\}}\frac{Y_j}{\hat{g}(X_j,Z_j)}$ |
| $S_{*+}$ | $\frac{1}{n_{11}}\sum_{j\in\{j:T_j=1,A_j=1\}}Y_j-\frac{n_1}{n_{11}n_0}\sum_{j\in\{j:T_j=0,A_j=1\}}\frac{\hat{h}_1(X_j)Y_j}{\hat{g}(X_j,Z_j)}$ |
| $S_{+*}$ | $\frac{n_0}{n_1n_{01}}\sum_{j\in\{j:T_j=1,A_j=1\}}\frac{\hat{h}_0(X_j)Y_j}{\hat{g}(X_j,Z_j)}-\frac{1}{n_{01}}\sum_{j\in\{j:T_j=0,A_j=1\}}Y_j$ |
| $S_{++}$ | $\frac{\sum_{j\in\{j:T_j=1,A_j=1\}}\hat{h}_0(X_j)Y_j}{\sum_{j\in\{j:T_j=1,A_j=1\}}\hat{h}_0(X_j)}-\frac{\sum_{j\in\{j:T_j=0,A_j=1\}}\hat{h}_1(X_j)Y_j}{\sum_{j\in\{j:T_j=0,A_j=1\}}\hat{h}_1(X_j)A_j}$ |

Marginal Structural Model (MSM)

# Estimator for $E[Y(1) - Y(0)|S_{*+}]$ based on Method A



$$\frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} Y_j - \frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} \hat{\phi}_0(X_j)$$

| Step | Data Used | Estimator for Parameter or Model |
|---|---|---|
| 1 | *X* and *Z* from the **control** group | $\hat{F}_{Z(0)\|X}$: Conditional distribution of $Z(0)$ given $X$ |
| 2 | *X*, *Z* and *Y* from the **control** group | $\hat{\psi}_0\big(X, Z(0)\big) = E\{Y(0)\|X, Z(0)\}$ |
| 3 | $\hat{F}_{Z(0)\|X}$ (Step 1) and $\hat{\psi}_0\big(X, Z(0)\big)$ (Step 2) | $\hat{\phi}_0(X) = E\{\hat{\psi}_0\big(X, Z(0)\big)\|X\}$ |
| 4 | *X* from the **treatment** group | $\hat{\phi}_0(X_j)$ for $T_j = 1$ |

# Estimator for $E[Y(1) - Y(0)|S_{*+}]$ based on Method B



$$\frac{1}{n_{11}} \sum_{j \in \{j:T_j=1, A_j=1\}} Y_j - \frac{n_1}{n_{11} n_0} \sum_{j \in \{j:T_j=0, A_j=1\}} \frac{\hat{h}_1(X_j) Y_j}{\hat{g}(X_j, Z_j)}$$

| Step | Data Used | Estimator for Parameter or Model |
|---|---|---|
| 1 | *X* and *Z* from the **experimental** treatment group | $\hat{F}_{Z(1)\|X}$: Conditional distribution of $Z(1)$ given $X$ |
| 2 | *X*, *Z* and *Y* from the **BOTH** treatment groups | $\hat{g}(X,Z) \coloneqq \widehat{\Pr}(A = 1\|X,Z)$ |
| 3 | $\hat{F}_{Z(1)\|X}$ (Step 1) and $\hat{g}(X,Z)$ (Step 2) | $\hat{h}_1(X) \coloneqq E\left\{\hat{g}\left(X, \hat{Z}(1)\right)\middle\|X\right\}$ |
| 4 | *X* from the **control** group | $\hat{h}_1(X_j)$ for $T_j = 0$<br>$\hat{g}(X_j, Z_j)$ for $T_j = 0$ |

# Estimator for $E[Y(1) - Y(0)|S_{++}]$ based on Method B



$$\frac{\sum_{j\in\{j:T_j=1,A_j=1\}} \hat{h}_0(X_j)Y_j}{\sum_{j\in\{j:T_j=1,A_j=1\}} \hat{h}_0(X_j)} - \frac{\sum_{j\in\{j:T_j=0,A_j=1\}} \hat{h}_1(X_j)Y_j}{\sum_{j\in\{j:T_j=0,A_j=1\}} \hat{h}_1(X_j)}$$

Probability of being adherent to the control treatment

$$h_i(X) := E\{(g(X, Z(i))|X\}$$

# Longitudinal repeated intermediate outcomes



$A = \prod_{k=0}^{K-1} A^{(k)}$ , and $A^{(k)}$ satisfies the Markov Property,

$$\Pr(A^{(k)} = 1 | A^{(k-1)} = 1, X, Z^{(1)}, Z^{(2)}, \cdots, Z^{(k)}) = \Pr(A^{(k)} = 1 | A^{(k-1)} = 1, X, Z^{(k)})$$

$$\Pr(A = 1) = g(X, Z, \beta) = \prod_{k=0}^{k-1} \Pr\left(A^{(k)} = 1 \middle| A^{(k-1)} = 1, X, Z^{(k)}\right)$$

$$= \prod_{k=0}^{K-1} g_k(X, Z^{(k)}, \beta^{(k)})$$

# Simulation Setting

**Mimic the Change in HbA1c in Clinical Trials for Anti-Diabetes Treatments**



Baseline $X_j \sim NID(\mu_x, \sigma_x^2)$

3 Intermediate Outcomes $Z_j^{(k)}(T) = \alpha_{0k} + \alpha_{1k} X_j + \alpha_{2k} T + \eta_j^{(k)}(T), \quad 1 \le k \le 3 \qquad \eta_j^{(k)}(T) \sim NID(0, \sigma_\eta^2)$

Endpoint $Y_j(T) = \beta_0 + \beta_1 X_j + \beta_2 T + \sum_{k=1}^{3} \beta_{3k} Z_j^{(k)}(T) + \epsilon_j(T) \qquad \epsilon_j(T) \sim NID(0, \sigma_\epsilon^2)$

Treatment Indicator $T_j \sim \text{Bernoulli}(0.5)$

Adherence indicators $\text{logit}\{\Pr(A_j^{(k)} = 1 | A_j^{(k-1)} = 1, X_j, Z_j^{(k)})\} = \gamma_0 + \gamma_1 X_j + \gamma_{3k} Z_j^{(k)}$

$\mu_x = 8.0,\ \sigma_x = 1.0,\ \alpha_{01} = \alpha_{02} = \alpha_{03} = 2.3,\ \alpha_{11} = \alpha_{12} = \alpha_{13} = -0.3,$

$\alpha_{21} = -0.4,\ \alpha_{22} = -0.9,\ \alpha_{23} = -1.2,\ \beta_0 = 0.2,\ \beta_1 = -0.02,\ \beta_2 = -0.2,\ \beta_{31} = 0.2,\ \beta_{32} = 0.4,$

$\beta_{33} = 0.7,\ \sigma_\eta = 0.4,\ \sigma_\epsilon = 0.3,\ \gamma_0 = 3,$ and $\gamma_1 = -0.1$ (Setting 1) or -0.25 (Setting 2),

$\gamma_{31} = -1,\ \gamma_{32} = -2,\ \gamma_{33} = -2.5,$ and $j$=1 to 300 (overall sample size of 300).

72% and 91% adherers for T=0 and 1, respectively

45% and 77% adherers for T=0 and 1, respectively

# True values for various estimands



| Estimand Stratum | Setting 1 | | | Setting 2 | | |
|---|---|---|---|---|---|---|
| | $T=0$ | $T=1$ | Trt. Diff. | $T=0$ | $T=1$ | Trt. Diff. |
| $S_{*+}$ | -0.102 | -1.588 | -1.487 | -0.107 | -1.606 | -1.499 |
| $S_{++}$ | -0.192 | -1.637 | -1.446 | -0.272 | -1.679 | -1.406 |
| $S_{**}$ | -0.090 | -1.570 | -1.480 | -0.090 | -1.570 | -1.480 |
| Naive Completers | -0.185 | -1.588 | -1.403 | -0.263 | -1.606 | -1.342 |

Abbreviations: Trt. Diff., difference between the experimental and control treatments

**Very complex numerical integration to calculate the estimands except for $S_{**}$!**

# Simulation results (Setting 1)



| Parameter | True Value | Estimates by Method A | | | Estimates by Method B | | |
|---|---|---|---|---|---|---|---|
| | | Mean | Bias | SD | Mean | Bias | SD |
| $\mu_{0,*+}$ | -0.102 | -0.103 | -0.002 | 0.049 | -0.102 | -0.001 | 0.055 |
| $\mu_{1,*+}$ | -1.588 | -1.590 | -0.002 | 0.047 | -1.590 | -0.002 | 0.047 |
| $\mu_{d,*+}$ | -1.487 | -1.487 | 0.000 | 0.057 | -1.488 | -0.001 | 0.064 |
| $\mu_{0,++}$ | -0.192 | -0.200 | -0.009 | 0.053 | -0.200 | -0.008 | 0.054 |
| $\mu_{1,++}$ | -1.637 | -1.643 | -0.005 | 0.056 | -1.642 | -0.004 | 0.051 |
| $\mu_{d,++}$ | -1.446 | -1.442 | 0.004 | 0.064 | -1.442 | 0.004 | 0.061 |

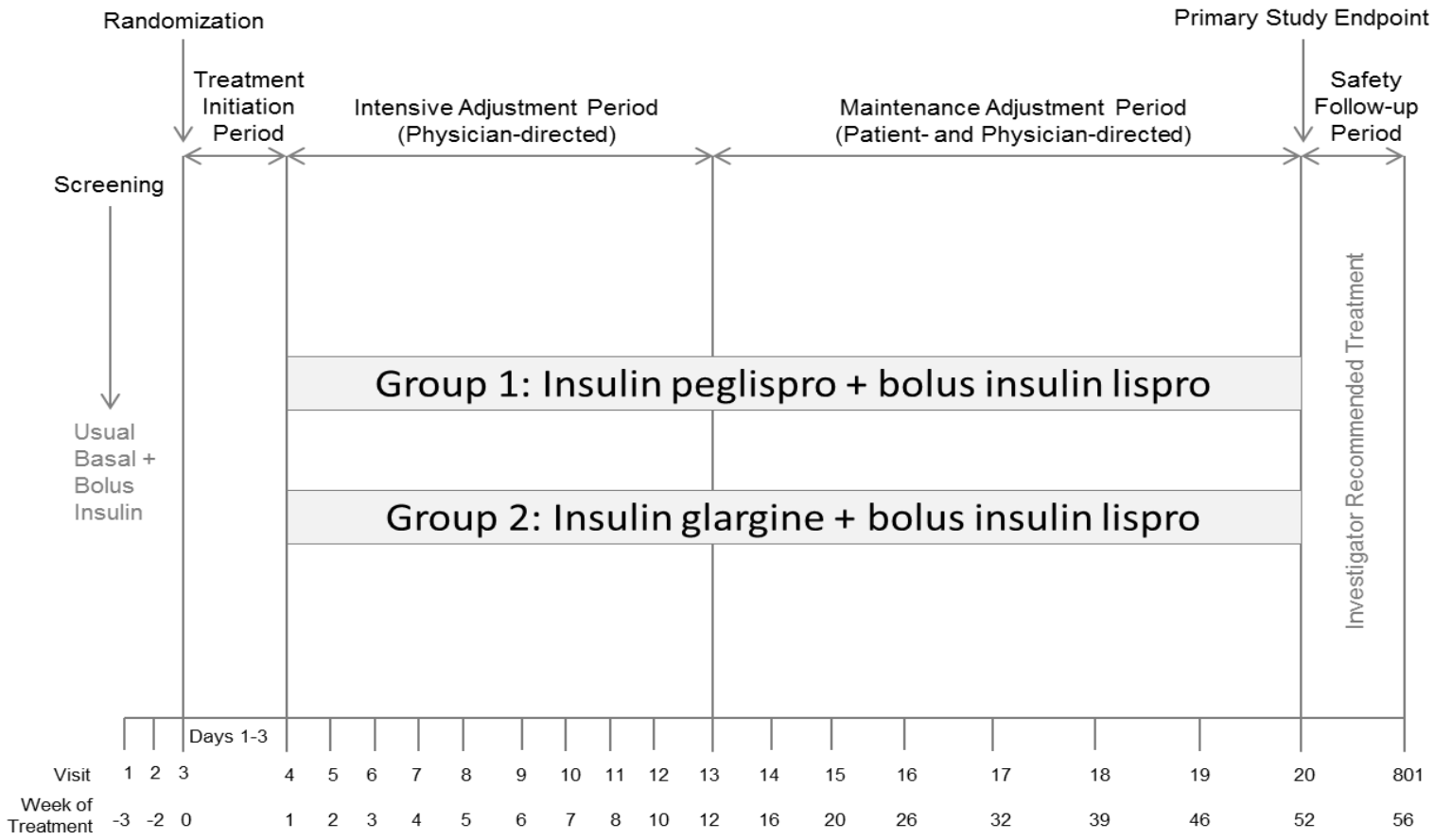
# Simulation results (Setting 2)



| Parameter | True Value | Estimates by Method A | | | Estimates by Method B | | |
|---|---|---|---|---|---|---|---|
| | | Mean | Bias | SD | Mean | Bias | SD |
| $\mu_{0,*+}$ | -0.107 | -0.105 | 0.001 | 0.063 | -0.106 | 0.000 | 0.086 |
| $\mu_{1,*+}$ | -1.606 | -1.608 | -0.003 | 0.052 | -1.608 | -0.003 | 0.052 |
| $\mu_{d,*+}$ | -1.499 | -1.503 | -0.004 | 0.068 | -1.502 | -0.003 | 0.095 |
| $\mu_{0,++}$ | -0.272 | -0.282 | -0.010 | 0.072 | -0.281 | -0.008 | 0.075 |
| $\mu_{1,++}$ | -1.679 | -1.685 | -0.007 | 0.072 | -1.685 | -0.006 | 0.066 |
| $\mu_{d,++}$ | -1.406 | -1.403 | 0.003 | 0.080 | -1.404 | 0.002 | 0.078 |

# IMAGINE-3 Study





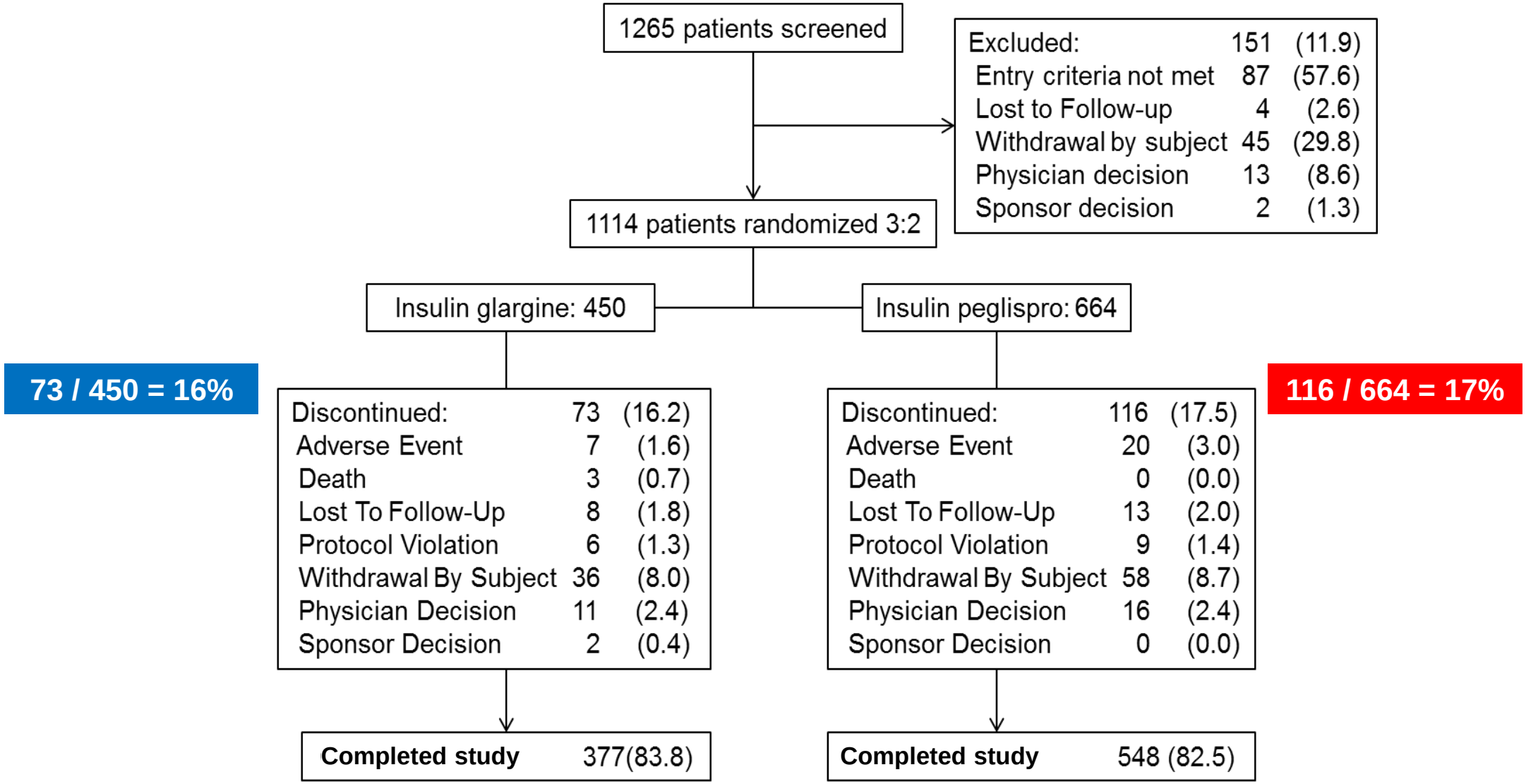

**Primary Endpoint**
HbA1c at 52 weeks

**Primary Analysis**
Non-Inferiority
Margin = 0.4%

**Bergenstal RM, Lunt H, Franek E, etc, Diabetes Obes Metab. 2016 Nov;18(11):1081-1088**

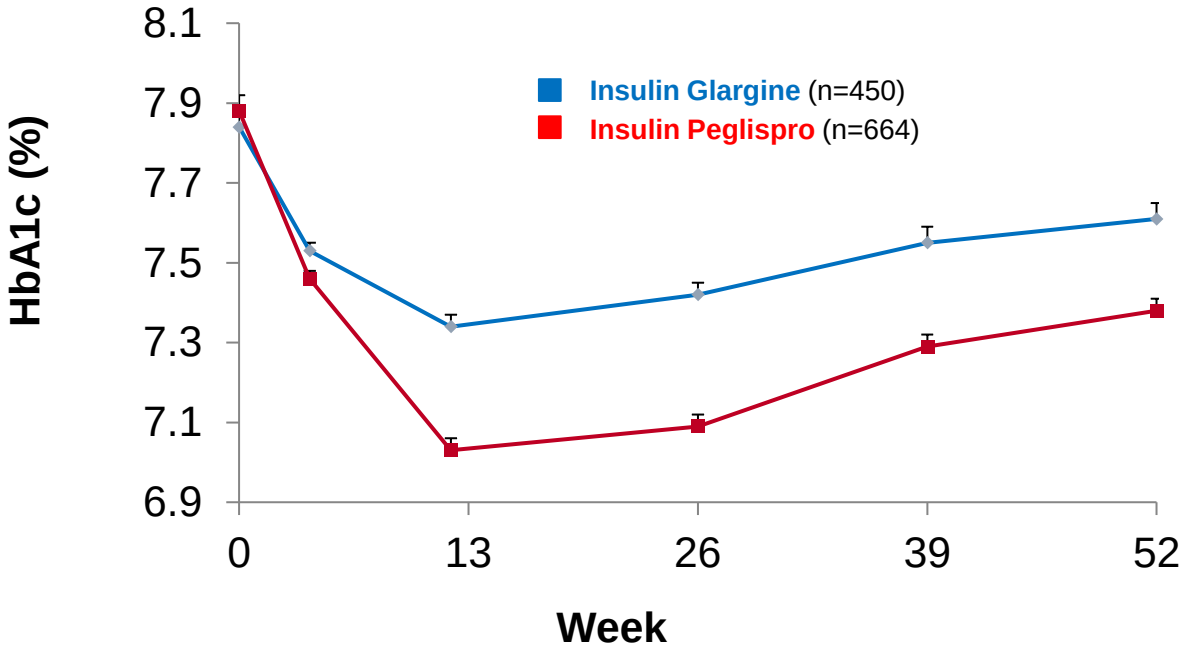
# Patient disposition

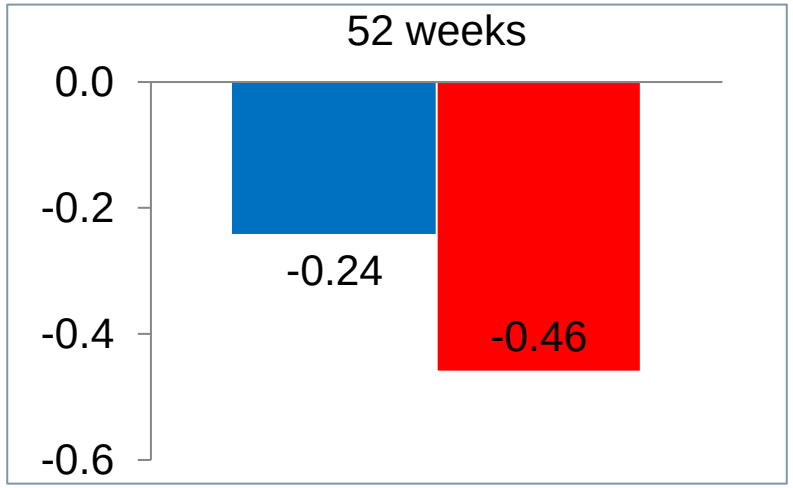




# Primary result: HbA1c at 52 weeks






**MMRM Analysis**

LSM Diff = -0.22%, CI = (-0.32, -0.12)

Primary endpoint was met since the upper limit of CI is <0.4%

Superiority was also met

# Classify the reasons for ICEs



| Reason for Treatment Discontinuation | | Category of ICE | Classification Criteria |
|---|---|---|---|
| • Adverse Event<br>• Death | → | Category I (Potentially Related to Safety) | With obvious AE or abnormal lab which could lead to discontinuation |
| • Lost To Follow-Up<br>• Protocol Violation<br>• Withdrawal By Subject<br>• Physician Decision<br>• Sponsor Decision | → | Category 2 (Potentially Due to LoE) | No obvious improvement in HbA1c or glucose at discontinuation as compared to baseline values |
| | → | Category 3 (Administrative) | No obvious safety or lack of efficacy reason leading to discontinuation |

# Patients disposition after reclassification

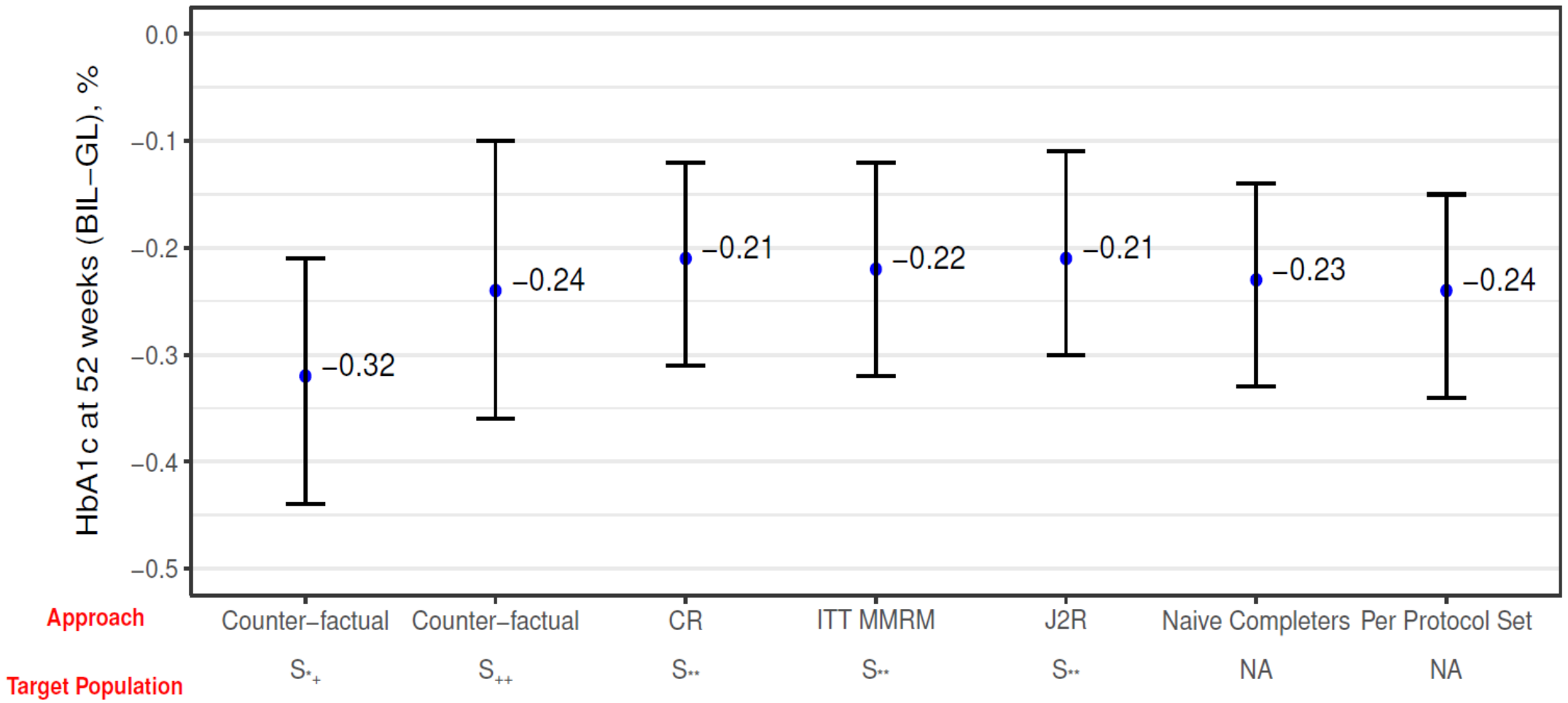


| Adherence and ICE Status | Insulin Peglispro (N=663) n (%) | Insulin Glargine (N=449) n (%) |
|---|---|---|
| ICEs | 154 (23.2) | 81 (18.0) |
| Category 1 ICEs (Potentially Related to Safety) | 70 (10.6) | 24 (5.3) |
| Category 2 ICEs (Potentially Related to Efficacy) | 18 (2.7) | 11 (2.4) |
| Category 3 ICEs (Administrative Reasons) | 70 (10.6) | 50 (11.1) |
| Adherers | 509 (76.8) | 368 (82.0) |

**Abbreviations: ICE = Intercurrent Event**

# Results on adherers … and more






Bootstrap method was used to construct the 95% confidence interval

# Implementing AdACE – “adace” R Package



- https://cran.r-project.org/web/packages/adace/index.html
- est_S_Star_Plus_MethodA(X, A, Z, Y, TRT)

  est_S_Plus_Plus_MethodA(X, A, Z, Y, TRT)
  - X: a matrix, each row is a vector for baseline covariates for a subject
  - A: adherence status (A = 1 for adherence)
  - Z: a list of matrices, each list is the value for a set of intermediate outcome at each intermediate time point
  - Y: a vector for the value of the response variable
  - TRT: a vector for treatment indicator (1 for the experimental treatment and 0 for control)

# Implementing AdACE – multiple imputation

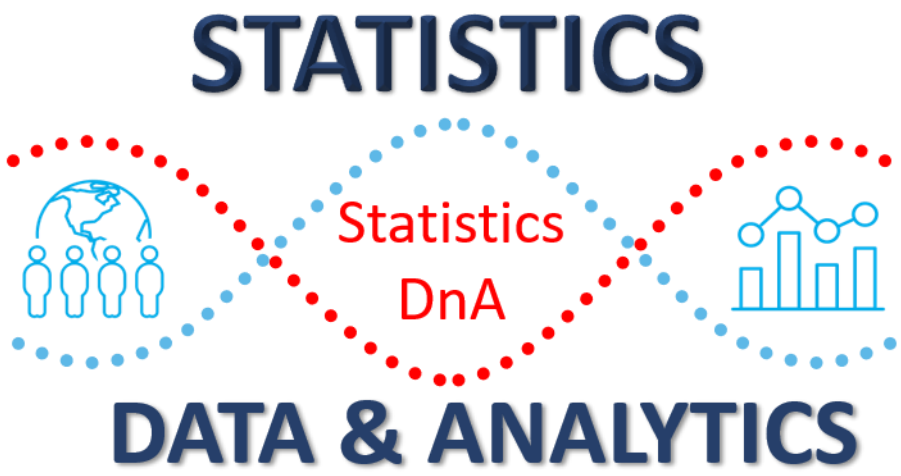


**TABLE 1** Illustration of MI to impute the potential outcome under treatment $T = t$ for patients assigned to treatment $T = 1 - t$

| Subject | Randomized treatment | $X$ | $Z^{(1)}$ | $Z^{(2)}$ | $Z^{(3)}$ | $I^{(1)}$ | $I^{(2)}$ | $I^{(3)}$ | $Y$ |
|---|---|---|---|---|---|---|---|---|---|
| 001 | $t$ | √ | √ | √ | √ | 1 | 1 | 1 | √ |
| 002 | $t$ | √ | √ | √ | √ | 1 | 1 | 0 | · |
| 003 | $t$ | √ | √ | √ | · | 1 | 0 | 0 | · |
| … | | | | | | | | | |
| 101 | $1 - t$ | √ | · | · | · | · | · | · | · |
| 102 | $1 - t$ | √ | · | · | · | · | · | · | · |
| 103 | $1 - t$ | √ | · | · | · | · | · | · | · |

Abbreviations: MI, multiple imputation; "√", observed data; "·", unobserved data.

Luo, J., Ruberg, S. J., & Qu, Y. (2022). Estimating the treatment effect for adherers using multiple imputation. *Pharmaceutical Statistics*, *21*(3), 525-534.




# Handling intercurrent events

Lilly | Statistics DnA
Statistics, Data and Analytics

# Strategies for handling ICEs – an example



ICH E9 (R1): “The question of what the values for the variable of interest would have been if rescue medication had not been available may be an important one. In contrast, the question of what the values for the variable of interest would have been under the hypothetical condition that subjects who discontinued treatment because of adverse drug reaction had in fact continued with treatment, might not be justifiable as being of clinical or regulatory interest.”

“The additional granularity, identifying different intercurrent events, is necessary if different strategies are to be used. If the intercurrent event for which a strategy should be selected depends not only on, for example, failure to continue with treatment, but also on the reason, magnitude, or timing associated with that failure, this additional information should be defined and recorded accurately in the clinical trial.”

# CHMP guideline on diabetes treatments (draft)



- "… Specifically, since patients are not expected to benefit once treatment is discontinued (e.g. due to adverse events) the treatment effect should be estimated based on observed or modelled data reflecting adherence to treatment as observed in the clinical trial."
- "… Therefore, the treatment effect can be estimated under the assumption that rescue medication, or use of other medications that will influence HbA1c values, was not introduced (hypothetical scenario), provided that a reliable estimate of that effect can be obtained."

# Use a mix of strategies to handle ICEs in a study



- 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.)
- Similarly, assumptions for missing data imputation should be based on the underlying reason of missingness including the intercurrent events that cause missingness

ICEs, intercurrent events

Darken et al., 2020; Qu et al., 2021; Qu and Lipkovich, 2021

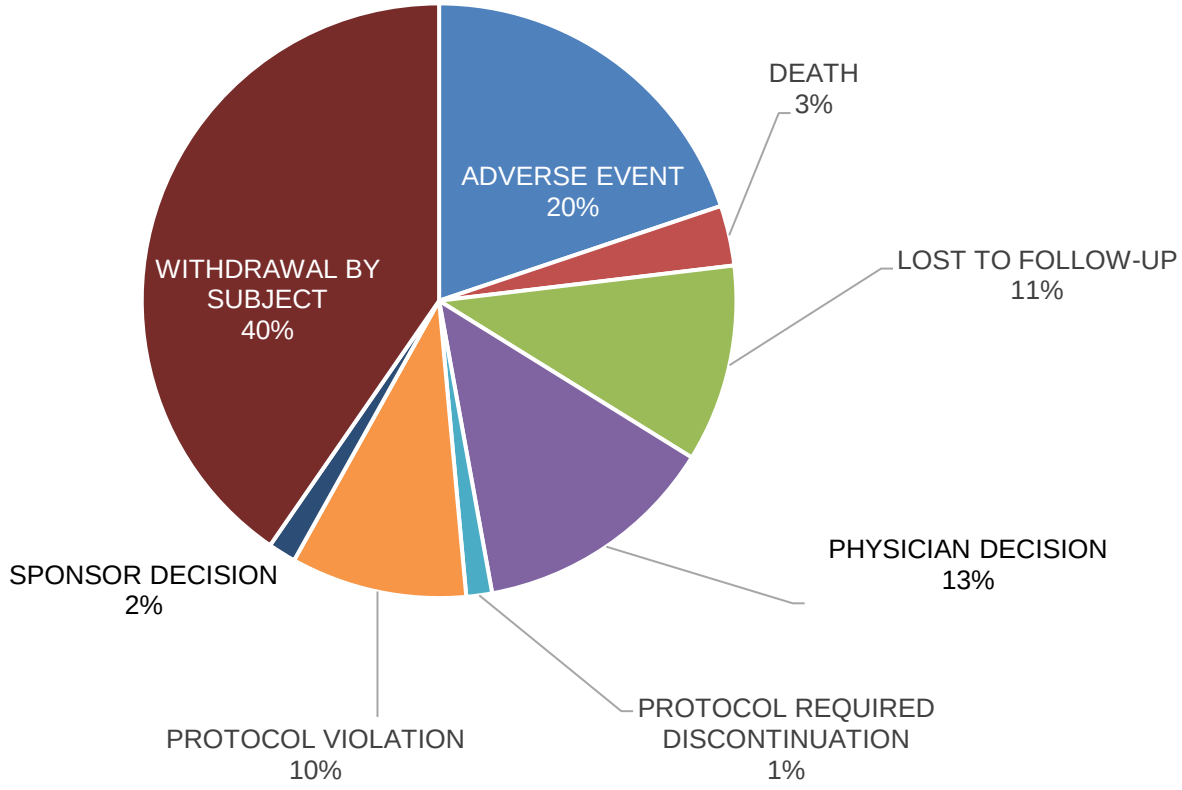
# A systematic review of treatment discontinuations



- We intended to use historical data to understand the misclassification of disposition as well as propose a new set of categories for disposition case report form (CRF)
- Data
  - 9 phase 2/3 basal insulin peglispro (BIL) studies were included
  - A total of 6215  patients were assigned treatments in these studies
  - A total of 857 patients who discontinued study medication or from the study
- Methods
  - Summarized the reason for treatment discontinuation based on the categories in the original CRF
  - Manually reviewed the discontinuation comments to attempt to reclassify the reasons

# Treatment disposition based on the CRF





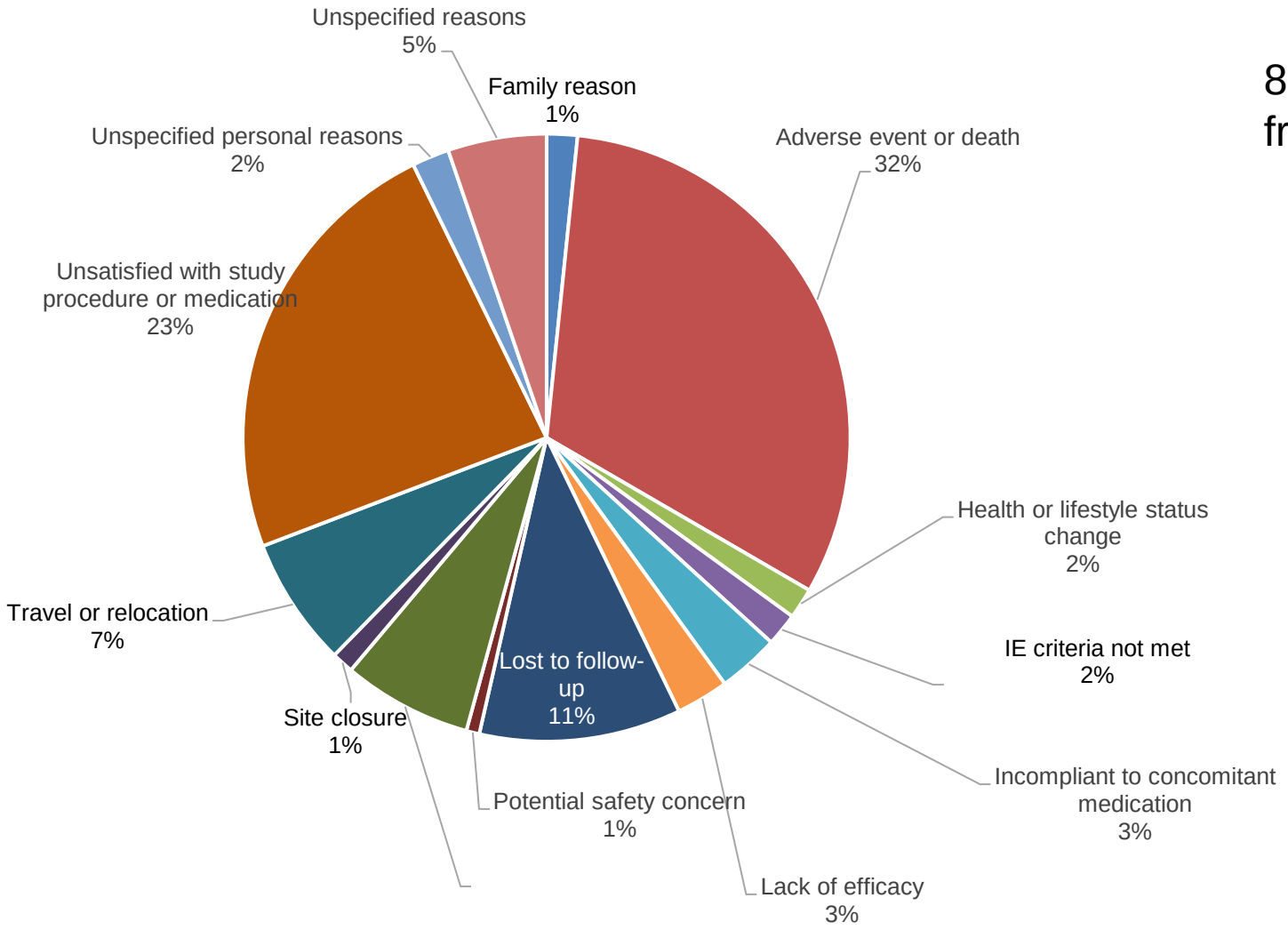

857 treatment discontinuations from BIL phase 2-3 studies

Lack of efficacy was not included as one category in CRF

CRF, case report form

# Regrouped reasons for treatment discontinuations

Lilly | Statistics DnA




857 treatment discontinuations from BIL phase 2-3 studies

# Temporary solution



What was the subject's status?

- ○ Progressive Disease (PROGRESSIVE DISEASE)
- ○ Adverse Event (ADVERSE EVENT)
- ○ Death (DEATH)
- ○ Withdrawal by Subject (WITHDRAWAL BY SUBJECT)
- ○ Physician Decision (PHYSICIAN DECISION)
- ○ Non-Compliance With Study Drug (NON-COMPLIANCE WITH STUDY DRUG)
- ○ Protocol Deviation (PROTOCOL DEVIATION)
- ○ Study Terminated by IRB / ERB (STUDY TERMINATED BY IRB / ERB)
- ○ Study Terminated by Sponsor (STUDY TERMINATED BY SPONSOR)
- ○ Lost to follow up (LOST TO FOLLOW-UP)
- ○ Pregnancy (PREGNANCY)

| Disposition Reason | Associated sub-categories |
|---|---|
| WITHDRAWAL BY SUBJECT | CONCERN ABOUT STUDY PROCEDURES/PERCEIVED RISKS |
| | HEALTH INSURANCE CHANGES |
| | SCHEDULING CONFLICTS |
| | SUBJECT IS MOVING OR HAS MOVED |
| | OTHER (option to include a specify field) |
| | PERSONAL ISSUE UNRELATED TO TRIAL |
| | DUE TO EPIDEMIC/PANDEMIC |
| PHYSICIAN DECISION | CONCERN ABOUT STUDY PROCEDURES/PERCEIVED RISKS |
| | HEALTH INSURANCE CHANGES |
| | SCHEDULING CONFLICTS |
| | SUBJECT IS MOVING OR HAS MOVED |
| | DUE TO EPIDEMIC/PANDEMIC |
| | OTHER (option to include a specify field) |

**An intermediate solution**

**The multiple choices mix the true reason and who made the decision for discontinuation**

# Potential future CRF for treatment discontinuation



- DEATH
- ADVERSE EVENT. List the adverse event ID: _____
- PREGNANCY
- LACK OF EFFICACY
- SUFFICIENT/EXCESSIVE EFFICACY (if appropriate for the disease state under study)
- ADMINISTRATIVE (not related to safety and efficacy of study medication and

Protocol Related

- DID NOT MEET INCLUSION/EXCLUSION CRITERIA AT BASELINE
- NONCOMPLIANCE TO STUDY MEDICATION
- NONCOMPLIANCE TO STUDY PROCEDURE
- NONCOMPLIANCE TO STUDY DRUG DELIVERY DEVICE/METHOD
- UNSATISFIED WITH THE STUDY PROCEDURE
- UNSATISFIED WITH THE STUDY DRUG DELIVERY DEVICE/METHOD
- NEED TO TAKE PROTOCOL EXCLUDED CONCOMITANT MEDS

Personal Circumstances

- TRAVEL OR RELOCATION
- SCHEDULE CONFLICT OR DIFFICULT TO TRAVEL TO SITES
- UNSPECIFIED PERSONAL/FAMILY REASONS NOT RELATED TO EFFICACY OR SAFETY OF THE STUDY DRUG/DEVICE
- UNEXPECTED EVENTS (NATURAL DISASTER, GEOGRAPHICAL CONFLICTS, OR PANDEMIC/EPIDEMIC)

Study Logistics

- STUDY TERMINATION, SITE CLOSURE, OR SITE PROCEDURE/SCHEDULE ERROR
- DRUG SUPPLY CHAIN DISRUPTION

- LOST TO FOLLOW-UP

Note:

1. Other categories may be added to this list
2. These categories may not be consistent with CDISC standard, but we are working to influence the changes

# Summary



- Understand and draw causal inference are important even in randomized clinical trials
- We provide a general framework for AdACEs
- Theory and simulation show the estimators consistently estimate the corresponding estimands
- Methods were applied to a clinical trial in diabetes
- "adace" R package (analytic formulas) and SAS programs (multiple imputation) are available for easy implementation of the methods
- Reason for intercurrent events, especially treatment discontinuations, should be collected accurately
  - A PHUSE working group is tackling this problem

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