# Combining Covariate Adjustment with Information Adaptive Designs

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# Planning

# Outline

# Covariate Adjustment

- **Covariate adjustment** is a statistical analysis method with high potential to **improve precision** for many trials.
  - **Pre-planned** adjustment for baseline variables when estimating **average treatment effect**.
  - Estimand is same as when using unadjusted estimator (e.g., difference in means).
  - **Goal**: avoid making any model assumptions beyond what's assumed for unadjusted estimator (**robustness to model misspecification**).

(e.g., Koch et al., 1998; Yang and Tsiatis, 2001; Rubin and van der Laan, 2008; Tsiatis et al., 2008; Moore and van der Laan, 2009b,a; Zhang, 2015; Jiang et al., 2018; Benkeser et al., 2020)

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- Estimator: G-computation/Standardization

1. Fit logistic regression model for

$$P(Y=1|A,B) = logit^{-1}(\gamma_0 + \gamma_1 A + \gamma_2 B).$$

2. Compute standardized estimators for treatment specific means
   - $\hat{E}(Y|A=1) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_1 + \hat{\gamma}_2 B_i)$
   - $\hat{E}(Y|A=0) = \frac{1}{n}\sum_{i=1}^{n} logit^{-1}(\hat{\gamma}_0 + \hat{\gamma}_2 B_i)$
3. Calculate $\hat{\theta} = \hat{E}(Y|A=1) - \hat{E}(Y|A=0)$

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  - **Approach 2**: consider how much precision can be gained based on external (trial) data when calculating the sample size. (Li et al., 2023)
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        - An incorrect projection of a covariate's prognostic value, may still lead to an over- or underpowered future trial.
    - **Potential solution**: combine covariate adjustment with **information-adaptive designs** (also known as information monitoring).

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- We **compute the maximum/total information** needed to preserve these operational characteristics

$$\left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0}\right)^2,$$

for a fixed design (no interim analyses), and

$$\left(\frac{z_{\alpha/2} + z_{\beta}}{\theta_A - \theta_0}\right)^2 IF$$

when data is sequentially monitored with the possibility of early stopping.

(Mehta and Tsiatis, 2001)

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  - We conduct the final analysis at time $t_2$ when

$$(\widehat{se}(\hat{\theta}_{t_2}))^{-2} \geq \left(\frac{z_{\alpha/2} + z_\beta}{\theta_A - \theta_0}\right)^2 IF.$$

(Mehta and Tsiatis, 2001; Zhang, 2009)

# Algorithm for Analysis Timing: (Dis)advantages

- The **information-adaptive design** is well suited for being adopted for covariate adjusted estimators:
  - We do **not have to prespecify the prognostic value of the covariates** nor other nuisance parameters.
  - When the estimator is more efficient than unadjusted estimator, covariate adjustment can lead to a **shorter trial** due to faster information accrual.

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  - When the estimator is more efficient than unadjusted estimator, covariate adjustment can lead to a **shorter trial** due to faster information accrual.
- **Administrative inconvenience**: it does not give an idea to the investigators about the necessary resources (i.e., length of study, sample size, . . . ).

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- However, **miscalculations can occur** at the design stage.
- We should use the **emerging data to evaluate** whether the maximum information will be reached with the planned sample size.
- If not, we should **update the maximum sample size** at time $t$ as

$$n_{max} = n(t) \frac{\left(\frac{z_{\alpha/2}+z_{\beta}}{\theta_A-\theta_0}\right)^2 IF}{(\widehat{se}(\hat{\theta}_t))^{-2}},$$

where $n(t)$ is the number of patients used in the analysis at time $t$.

(Mehta and Tsiatis, 2001)

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- We proposed an **information-adaptive trial design**, where the analysis timing is based on **accruing information** and is **data-adaptive**.
- By **automatically adapting to amount of precision gain** due to covariate adjustment, it results in **correctly powered** trials.
- Information will accrue faster as covariate adjusted estimators typically have smaller variance, leading to **faster trials at no additional cost**.
- Since adaptations to the analysis timing are **pre-planned** based on nuisance parameters only, they are generally **acceptable to regulators**.

# Outline

# MISTIE III trial (Stroke)

- Functional outcome: proportion of patients who achieved a modified Rankin Scale score of 0-3 at 365 days (**binary**).

- Estimand of interest: **risk difference**.

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  - Success rate: 25% in standard medical care group versus 38% in MISTIE group

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- We will focus on information instead of sample size!

# Simulation Study: $K = 1$

- **Information-adaptive design** with maximum information equal to 582
- **Maximum sample size design** with $n_{max} = 498$

| | | $\theta = 0.13$ (Alternative) | | | |
|---|---|---|---|---|---|
| | | Power | **ASN** | AAT | AI |
| Information-adaptive design | Unadjusted | 88.4% | **571** | 1876 | 582 |
| | Standardization | 87.3% | **433** | 1509 | 567 |
| Maximum sample size design | Unadjusted | 83.1% | - | 1682 | 508 |
| | Standardization | 91.1% | - | 1682 | 652 |

ASN: average sample number; AAT: average analysis time (days); AI: average information.

**Conclusion under alternative:**

**24% reduction of sample size due to covariate adjustment**

# Simulation Study

- **Information-adaptive design** with maximum information equal to 582
- **Maximum sample size design** with $n_{max} = 498$

| | | $\theta = 0$ (Null) | | | |
|---|---|---|---|---|---|
| | | Type I | **ASN** | AAT | AI |
| Information-adaptive design | Unadjusted | 5.28% | **569** | 1871 | 582 |
| | Standardization | 5.28% | **402** | 1427 | 568 |
| Maximum sample size design | Unadjusted | 5.14% | - | 1682 | 509 |
| | Standardization | 5.14% | - | 1682 | 705 |

ASN: average sample number; AAT: average analysis time (days); AI: average information.

**Conclusion under null:**

**29% reduction of sample size due to covariate adjustment**

Thank you for your attention!

Interested? https://doi.org/10.48550/arXiv.2201.12921

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