Conditional and Unconditional treatment effects in randomized clinical trials: Estimands, Estimation, and Interpretation

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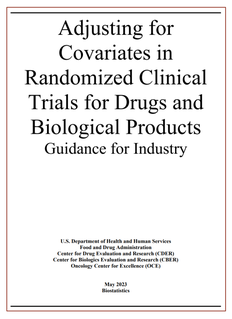
Executive summary

- For nonlinear models (e.g., logistic regression and Cox regression), including baseline covariates can change the treatment effect (estimand) from unconditional to conditional due to non-collapsibility.
- The conditional treatment effect intends to provide more relevant information to individual patients, the unconditional treatment effect answers how well the drug works in a well-defined patient population.
- Standardization method (G-computation) is a robust and efficient method that can be applied to estimate unconditional estimands for binary and time-to-event endpoints with covariate adjustment.

Background

FDA released final guideline on covariate adjustment in May 2023. Two key points:

- Estimand: Marginal or conditional treatment effect?
- Estimation: Adjusting for covariates for precision gain



Causal Estimands: Conditional vs. Unconditional

Both conditional and unconditional effects are causal effects but different estimands!.

Unconditional treatment effect

- $E[Y(1)]$ vs. $E[Y(0)]$
- Treatment effect had all patients in the population taken test treatment (Z=1) vs. had all patients taken control (Z=0)

Conditional treatment effect

- $E[Y(1)|\boldsymbol{X}=\boldsymbol{x}]$ vs. $E[Y(0)|\boldsymbol{X}=\boldsymbol{x}]$
- Treatment effect had the subset of patients with $\boldsymbol{X}=\boldsymbol{x}$ taken test treatment vs. had they taken control

Table 1: Population-level summaries commonly used in clinical trials

Type of Endpoint	Population-level summary	Collapsible	Examples of analysis methods
Continuous	Mean difference	Yes	Linear regression, Analysis of Covariance Analysis of Variance (ANOVA)
Binary	Odds ratio	No	Logistic regression, Cochran-Mantel-Haenszel method
	Risk difference	Yes	Logistic regression
	Risk ratio	Yes	Logistic regression
Time-to-event	Hazard ratio	No	Cox regression
	Restricted mean survival time difference	Yes	Kaplan-Meier estimators, parametric regression, *Cox regression
	Milestone survival probabilities	Yes	Kaplan-Meier estimators, parametric regression, *Cox regression

Marginal HR with Covariate Adjustment ⚠

Estimation of marginal HR from a conditional model not straightforward. Various issues:

- Selection bias: By definition, hazard conditions on prior survival. Leads to imbalanced / non-comparable populations post-baseline between treatment groups.
- Non-proportional hazards: Usually assume PH in conditional model. This does not simultaneously hold marginally which leads to time-varying HR. Therefore. marginal HR is some weighted average of HR
- Interpretability: Due to above, no longer holds causal interepretation

OAK Study

OAK trial is a randomized phase III trial comparing atezolizumab with docetaxel (standard of care) for patients with the second or third line of treatment for locally advanced or metastatic non-small-cell lung cancer (NSCLC). Co-primary endpoints of the study were overall survival (OS) in the overall intention-to-treat (ITT) population and PD-L1 sub-population. OAK trial demonstrated a significant improvement in OS with atezolizumab in the overall population and PD-L1 sub-population. bTMB is considered as a prognostic predictive of the treatment effect, and PD-L1 is a key stratification factor in the primary analysis.

Estimands of the OAK Study – Binary endpoint as an example

Population-level summary of unconditional treatment effect

- Unconditional odds ratio

Population-level summary of conditional treatment effect

- Conditional odds ratio adjusting for baseline PD-L1 and bTMB

Estimation methods of unconditional effects with covariate adjustment

Binary endpoint - Standardization approach on odds ratio

1. Fit a logistic regression model for the outcome with treatment and prespecified baseline covariates.
2. Use the fitted logistic regression model to predict the probability of response for every subject in the study as if they had received the experimental treatment or the control.
3. Estimate the average response under each arm by averaging (across all subjects in the trial) the probabilities of response, and then use the average response of two arms to estimate an unconditional treatment effect, such as the risk difference, relative risk, or odds ratio.

Time-to-event endpoint - Standardization approach on restricted mean survival time (RMST)

Due to issues with marginal HR, prefer alternative more appropriate measures such as RMST.

1. Fit a stratified Cox model with treatment as stratification variable and adjust for covariates. Baseline hazard function for each treatment is left unspecified.
2. Estimate the baseline cumulative hazard function for each treatment group using the Breslow estimators.
3. Predict the survival function for each subject under the experimental treatment and control with the given value of covariates.
4. For each treatment arm, estimate the average survival function by averaging the survival estimated in Step 3 across all subjects in the trial.
5. Integrate the average survival functions for two arms to estimate the unconditional RMSTs and the difference or ratio between the two treatment groups.

Application to OAK study

Table 2: Estimated treatment effect on objective response

Estimand	Analysis Method	Estimated effect (logOR)	SE	95% CI
Conditional	Adjusted	0.28	0.25	(-0.21, 0.77)
Unconditional	Unadjusted	0.32	0.25	(-0.16, 0.8)
	Adjusted	0.28	0.25	(-0.21, 0.77)

Table 3: Estimated treatment effect on overall survival

Estimand	Analysis Method	Estimated effect (RMST difference)	SE	95% CI
Conditional	Adjusted	2.94	0.97	(1.03, 4.84)
Unconditional	Unadjusted	3.26	0.74	(1.82, 4.71)
	Adjusted	3.27	0.66	(1.98, 4.55)

Conclusions

- Marginal and conditional effects can target different estimands (i.e., when non-linear non-collapsible scales are applied), but they both can provide valuable summaries of treatment effects in a randomized control trial.
- While estimation of conditional estimands is more established, estimation of marginal estimands with covariate adjustment are gaining attention.
- Good solutions for binary and count outcomes suggested in the FDA guideline.
- Solutions also exist for time to event data, but these are less established.
- Both approaches have advantages and disadvantages, and the choice should be driven by the question of interest (i.e., the estimand).

References

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