**Average Treatment Effect**

randomized controlled trials estimate the average treatment effect, which has a causal interpretation due to randomization

= counterfactual outcome mean if every patient had been assigned

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can be easily calculated unless have to adjust for baseline covariates

**Baseline Covariates**

quantitative variables expected to influence the outcome

must be measured before the start of the intervention

e.g. demographics, disease characteristics, prognostic factors, centers, baseline values of primary outcome

Table 1 in all randomized controlled trials describe the population enrolled in the study

examine if groups are comparable and control for confounding through adjusted analysis

**Post-Randomization Variables**

variables collected after randomization

never adjust for post-randomization covariates

crucial for per-protocol effect estimation and trials with adaptive design

**Baseline Imbalance**

randomization usually produces balance between groups with respect to all measured and unmeasured factors that may influence the outcome

randomization doesn’t guarantee balance in any specific trial for any specific variable

e.g. a prognostic characteristics might by more common in one treatment group

Rule of Thumb: likelihood of baseline imbalance is small if

statistical testing to assess imbalance not recommended because multiple testing needed and hard to reject null hypothesis in small trials

Randomization Stratification Factors

analysis should always be adjusted for randomization stratification factors to improve the variance

e.g. sex, race, age group, study center

adjusted analysis should include covariates found between imbalanced between groups and stratified variables during randomization

**Conditional Methods for Baseline Adjustment**

ANCOVA for Continuous Outcomes

H0:

HA:

baseline covariates are known to be correlated with the primary outcome

e.g. baseline DNA level, initial depression scores

correlation coefficient > 0.3 indicated moderate to high correlation

analysis of covariance tests adjusts for baseline covariates to give more precise treatment effect estimates

adjusting for variables not correlated with the outcome will decrease the precision

Binary Outcomes

H0:

HA:

e.g. whether there was a decrease in depression scores at end of trial

baseline adjustment tries to deal with imbalance and stratification factors

adjusting for covariates that are moderately or strongly correlated with the outcome will give a less precise treatment effect estimate

Disadvantages of Conditional Approaches

regression models rely on assumptions made about the relationship between baseline covariates and the outcome

treatment effect is defined in strata of individuals with the same baseline characteristics

no direct causal interpretation

**Conditional Methods for Baseline Adjustment**

Inverse Probability Weighting

adjust for baseline covariates through weighting

Step 1: assign each subject a weight that’s the inverse of being assigned to the treatment they received conditional on their baseline covariates

Step 2: fit an unadjusted model in the weighted population that’s not conditional on

denominator is the probability of having the assigned treatment giving value

denominator not same for everyone with the same value because it also depends on value

each subject represents themselves and someone else who received the other treatment assignment but with the same baseline covariates

creates a population twice the size of the actual population where everyone appears once as treated and once as untreated

and are statistically independent in the pseudo-population