New Investigator Clinical Trial Section 6: Database analysis and interpretation

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Outline

- Types of Analysis in Clinical Trials
- Analysis Population
- Statistical Analysis
- Interim Analysis: Futility
- Issues in Clinical Trials Data Analysis
  - Exclusions and withdraws
  - Covariate adjustment
  - Sub-group analysis

1. Types of Analysis in RCT

- By time line of clinical trials
  - Interim Analysis
  - Final Analysis
  - Follow-up Analysis
- By the nature of the endpoints
  - Efficacy analysis
  - Safety analysis
- By the objectives
  - Confirmatory analysis
  - Exploratory analysis and /or hypothesis generations

Analysis – II

- By the type of endpoints
  - Analysis of the primary endpoints
  - Analysis of the secondary endpoints
- Others analyses related to clinical trials
  - Quality of life analysis
  - Economical analysis
  - Correlative science analysis

Analysis – III

- Clearly specify the primary method of analysis
  - Reduce Type I error rate
  - Reduce bias
- Define the population for the analysis of each endpoint
  - Intent to treat analysis:
    - All the patients would be included in the analysis based on treatment arm they were randomized
  - Per protocol analysis:
    - Includes only patients complying with the protocol, e.g. eligibility, treatment compliance, complete and good quality data
    - May introduce bias

2. Analysis Population

- Efficacy analysis
  - Intent to treat as the primary population of analysis
  - Analysis based on per protocol population as sensitivity analysis
    - Bias the analysis results (e.g. withdraw related to treatment)
    - Reduce credibility of the trials results
- Safety analysis
  - All patients who have receive at least one dose of treatment are analyzed based on treatment they actually received.

3. Analysis Methods

- Measures of continuous outcomes
  - Usually expressed as difference between means
    - $D = X_T - X_C$
  - Sometimes "standardized" as effect size
- Statistical methods
  - Two sample t-test, Wlicoxon rank-sum test
  - Generalized linear regression models
- e.g. QoL, Economical

Analysis Methods – II

- Measures of binary outcomes
  - Relative Risks (RR)
    - $RR = P_T / P_c$
  - Relative Risk reduction (1 – RR)
  - Odds Ratios (OR)
    - $OR = [P_T (1 - P_T)]/[P_C (1 - P_C)]$ clinical interpretation: difficult
  - Absolute measures
    - $D = P_T - P_c$ (Actual percentage reduction)
- Statistical methods
  - Chi-square test, Fisher's exact test
  - logistic regression models
- e.g. Response Rate, Pain Incidence, adverse event rate

Analysis Methods – III

- Measures of survival outcomes
  - Relative difference
    - Ratio of median survivals (e.g. Double ~)
    - Relative risk (or Hazard ratio, e.g. HR = 0.5)
    - Relative risk reduction (1 – HR)
  - Absolute difference
    - Prolongation of median survival (e.g. ~ prolonged by 6 months)
    - Proportion surviving at specific point in time (e.g. 5 year event free survival increased by 10%)

Analysis Methods – IV

- Hazards
  - Hazard function
    - h(t) = probability of death just after time t conditional on patient alive at time t
  - Hazard ratio
    - HR = $h_T(t)/h_C(t)$

Analysis Methods – V

- Define survival outcomes
  - Time origin (e.g. time of randomization)
  - Time scale (year, month, week, day)
  - Event time (clinical definition of events)
    - Overall survival: Death
    - Progression free survival: Progression
    - Event free survival: Event
    - e.g. STEEP System (Hudis C et al, JCO, 2007)
  - Censoring time
    - Patients who do not develop a defined event at the time of the analysis, or have been lost to follow-up, will be censored at the time of last contact with them

Analysis Methods – VI

- Statistical methods for survival outcomes
  - Log-rank test or Wilcoxon test
  - Product-limit (Kaplan-Meier) estimate and plot of survival function S(t)
  - Cox proportional hazards regression models
    - Hazard ratio is a constant
  - Other nonparametric methods
    - Hazard ratio depends on time

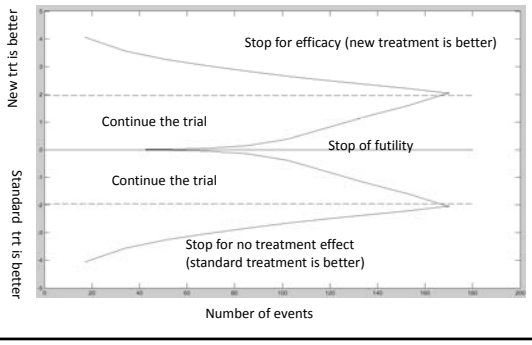
4. Futility Analysis

- Stop the trial when cumulative data suggest the difference the trial is design to detect is unlikely to be statistically significant
  - NCIC CTG is now routinely incorporate futility analysis into the statistical analysis plan of its Phase III trials
- Stopping for futility may decrease the power of the study (increase type II error)
  - Increase sample size to maintain the power

Futility Analysis – II

- The trial may fail to detect a smaller difference if it is stopped for futile
  - This smaller difference may be clinically significant
- Difference rules are available for futility analysis (*Freidlin and Korn, JCO 2009*)
  - Aggressive early stopping
  - Moderate aggressive early stopping
  - Aggressive late stopping
  - Conservative late stopping
- Futility ≠ Non-inferiority (or Equivalence)

Futility Analysis – III -Group Sequential Tests



Futility Analysis – IV

- Example: NCIC CTG MA.32
  - Event: IDFS, 5-yrs IDFS in placebo = 85%
  - H1: HR = 0.76 (Metformin V.S. Placebo)
  - Required 417 events,
  - Adjust for two IA: increases to 431 events
  - N = 3582 (3 yrs accrual, 3 yrs follow-up)

Futility Analysis – V

	First IA (144 events)		Second IA (288 events)	
	Superiority	Futility	Superiority	Futility
P-values	0.00185	0.971	0.138	0.468
Observed HR	HR < 0.60 or HR > 1.68	0.994<HR<1.006	HR < 0.84 or HR > 1.19	0.92 < HR < 1.09
	Final analysis (431 events)			
P-value	0.0463			
Observed HR	HR < 0.825			

5. Issues in Data Analysis

- Improper analysis leads to biased results of unknown magnitude or direction
  - Excluding randomized patients
  - Excluding based observed outcomes
  - Adjustment for response variables
  - Sub-grouping based on outcomes

Issues in Data Analysis – II

- Which patients should be analyzed?
  - ***Exclusions:*** Patients who do not meet all of the entry criteria (no randomized).
    - Exclusions does not bias the results
  - ***Withdraws:*** Patients who have been randomized but are deliberately not included in the analysis
    - Ineligibility
    - non-compliance
    - poor quality data or missing data
    - competing events

Issues in Data Analysis – III

- Covariate adjustment
  - Goal of RCT: groups are comparable except the intervention being studied
  - Adjust for imbalanced prognostic factors
    - Reduce variance
    - Produce more sensitive analysis
  - Stratified analysis for discrete covariates
  - Analysis of covariance for continuous variable

Issues in Data Analysis – IV

- Covariate adjustment
  - Covariates should be measured at baseline
  - Variables evaluated after randomization are considered as response variables
  - Adjust for other response variables may introduce bias
  - Pre-specify baseline variables to be adjusted

Issues in Data Analysis – V

- Subset Analysis
  - Intervention-control comparison within one or more particular subgroups
    - Among which group of patients is the intervention most beneficial or harmful
  - Only baseline variable can be used to define subgroup
    - Categorization by any outcome variable (e.g. compliance rate) can lead to bias conclusion
  - No data-dredging or data fishing
    - Subgroups should be pre-specified in protocol or statistical analysis plan

Summary

- Population for efficacy analysis and safety analysis
- Continuous, binary and survival outcomes
- Futility ≠ Non-inferiority
- All randomized patients shall be analyzed
- Adjust for covariates after randomization may introduce bias
- Subset analysis shall be well planned: No data-dredging or data fishing

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