Statistical Issues in Trial Design

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Time	Section
02:28	**Clinical Trials** • Statistical challenges that are commonly faced when designing/reporting a clinical trial • Why? Statistics play a crucial role in clinical • Going to focus on randomized parallel group trials
03:22	**Objectives** • Randomization schemes • Baseline significance testing • To adjust or not to adjust • Choice of primary outcomes • Good reporting practices

03:55	**Clinical Trials**
	• Pyramid infographic
	• Participants are assigned to an experimental treatment and followed for event of interest
	• The randomized, double-blind, placebo-controlled, parallel design is considered to be the best to determine efficacy
	• Often provides the strongest evidence in support of cause-effect relationships
	  o Basis for clinical and public health policy
	  o Minimize/eliminate bias and confounding

05:33	**Randomization**
	• Purpose (balance groups regarding characteristics, avoid selection bias and confounding)
	• Difference in outcome between groups:
	  o The intervention exhibits a real effect;
	  o The outcome difference is solely due to chance
	  o There is a systematic difference (or bias) between the groups due to factors other than the intervention
	• Theory versus practice
	• Randomization schemes:
	  o Simple randomization
	  ▪ Like tossing a coin for each participant
	  ▪ Easy to implement
	  o Permuted-block designs
	  ▪ Randomize patients in blocks of size X
	  ▪ With a block size of 4 for two groups (A,B), there are 6 possible permutations and they are: AABB, ABAB, ABBA, BAAB, BABA, BBAA
	  ▪ Perfect assignment balance after every 4 patients in this example (differs from simple randomization)
	  o Stratification
	  ▪ Blocked randomization is performed within each strata
	  ▪ Ensures that treatment and control groups are balanced on prognostic factors associated with the outcome

14:03	**Baseline Significance Testing** • "Significance testing of baseline differences in randomized controlled trials (RCTs) should NOT be performed, because it is superfluous and can mislead investigators and their readers" • Why do people believe testing of baseline differences should be done and why is this a misconception? o Whether randomization was successful

	▪ If randomization was done properly, it can be expected that any baseline difference between treatment groups is solely due to chance ▪ With any statistical test, there is a 5% chance that you will observe a false positive o Whether randomization was performed properly ▪ There isn't a test in statistics to evaluate this ▪ But how can we be sure that randomization was correct? • The methods section of a paper • Meticulous description of trial conduct • Description of allocation concealment • Quantitative assessments of differences o To adjust for these significant variables in the model ▪ Very important to specify primary analysis in the a priori specified Statistical Analysis Plan ▪ Adjusted—greater power and precision in estimates ▪ There are several RCTs that choose unadjusted as their primary analysis and some that choose adjusted as their primary analysis ▪ Large degree of inconsistency in whether trials choose adjusted or unadjusted as their primary analysis
22:45	**<u>To adjust or not to adjust</u>** • Results from the MIND-USA Trial, with and without covariate adjustment • Well-defined appropriate covariate-adjusted analysis is worth doing—offers a slight gain in statistical power at no extra cost and with minimal statistical effort • The following principles should be followed: o Choose variables known (or thought) to have a substantial bearing on patient prognosis on the basis of prior knowledge—they should be limited in number and accurately recorded at baseline o Document using a pre-specified SAP: Model details, variable type. Make choices in advance o Stay away from post-hoc variable selection o Present both unadjusted and adjusted analyses, with pre-specification as to which is the primary analysis
25:50	**<u>Choice of primary outcomes</u>** • Table with a couple of trials that explain designs and outcomes • Daily-level outcomes (daily occurrence of delirium) • Composite outcomes (delirium/coma-free days) o To combine evidence across 2 or more outcomes into a single primary endpoint- ventilator free days, delirium/coma-free days o DCFD in 14 days: number of days during 14-day study period that the patient was alive and free of delirium and coma o Pros: competing risk of death o Oversimplifying evidence by putting too much emphasis on the composite, without adequate inspection of the contribution from each separate component ▪ Treatment associated with 60% reduction in DCFDs o Con: Can be misleading in their definition (infographic highlighting this point) • Summary outcomes (delirium duration) • Choice depends on: o Important of the outcome to patients and health care professionals o Feasibility of measuring the outcome o Efficient of executing trial • Statistical Power

	○ Goal: making the trial large enough so that it is adequately powered to detect (or refute) any treatment differences of clinical importance ○ Consider multiple measurements—units of information ○ Power to detect a 10-point absolute reduction in daily incidence of delirium. Control group incidence of delirium= 40% (graph) ○ Amount of information does not equal number of subjects ○ Effective sample size= True amount of information in the data= n or n*t? ○ Effective sample size (equation)
38:26	**Good Reporting Practices** • Statistical Analysis Plan – Gamble et al. (https://jamanetwork.com/journals/jama/fullarticle/2666509) ○ www.clinicaltrials.gov ○ The Open Science Framework (OSF): https://osf.io/gkb6u/ MIND-USA SAP ○ Peer-reviewed Journal (e.g. Trials, Critical Care Resuscitation) • Complete analysis report and code • Good practice—transparency, rigor
41:43	**Questions and Answers**