CHAMP STUDY SIMULATIONS: PICK THE WINNER

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CT/DMC
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Outline

- Introduction
- Design
- Endpoints
- “Pick the Winner” Simulation
- Results

CHAMP Study: Introduction

- CHAMP = Childhood and Adolescent Migraine Prevention Study
  - PI's: Dr. Andrew Hershey and Dr. Scott Powers
- Global objective: to determine the optimal treatment for the prevention of migraines in children and adolescents
- First trial of it's kind in this study population

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CHAMP Study: Design

- Phase III intent-to-treat, 3-arm, multi-center, randomized, double-blind, placebo controlled safety and efficacy study
- 675 subjects, 8 to 17 years old
- 2:2:1 Randomization
  - Stratified by age and headache frequency
- 2 drugs: Amitriptyline and Topiramate
- 3 trials in 1
  - Amitriptyline vs. placebo
  - Topiramate vs. placebo
  - Amitriptyline vs. Topiramate

CHAMP Study: Endpoints

- Primary endpoint: 50% reduction in migraine frequency per month
  - Powered to detect 20% improvement for each treatment vs. placebo
  - 15% difference in comparative effectiveness portion
- Secondary endpoint: migraine-related disability (PedMIDAS)
- Tertiary endpoint: tolerability
  - Treatment groups differ on occurrence of SAEs
  - Have a drop-out rate greater than 35% or worse than other therapy

CHAMP Study: Endpoints Cont.

- Primary endpoint assessed using logistic regression model
  - Estimate log-odds of primary endpoint success for each treatment group
  - Adjusted for stratification variables
    - Age and headache frequency at baseline
- Three pair-wise treatment comparisons:
  - AMI vs. PBO
  - AMI vs. TPM
  - TPM vs. PBO
- Bonferroni corrected significance level of 0.017 = (0.05/3)

“Pick the Winner”

- 3 Tiered approach
- 4 Possible practice recommendations:
  - AMI because it is superior to PBO and TPM on primary outcome
  - TPM because it is superior to PBO and AMI on primary outcome
  - Both are possible first choice and ‘tie-breaker’ is secondary outcome
    - If no difference in secondary outcome, go to tertiary outcome
  - Neither as first choice if neither are superior to placebo

Simulation Study

- Designed to assess the likelihood of picking the “correct” winning treatment
- Actual “power” can be thought of as making a correct decision using decision algorithm
- Uses 1st tier of decision algorithm

Simulation Study

- Steps:
  - Determine plausible range of values for true response rate for each treatment
    - PBO + Response Rates: 40%, 45%, 50%, 55%
    - AMI + Response Rates: 50%, 60%, 70%, 80%
    - TPM + Response Rates: 50%, 70%, 85%, 95%
  - 4*4*4 = 64 conditions
  - For each condition, one of the 4 possible decisions was reached
  - 10,000 replications for each condition

Simulation Results

Probability of picking “correct” winner	>80%	50%-80%	<50%
Number of conditions	57	4	3

Notable Results

- Condition 33: 50% PBO, 50% AMI, 50% TPM
  - Provides assurance that decision algorithm maintains type 1 error level at or below 0.05

Individual Trials				Decision					"Power"
Power: AMI vs. PBO	Power: TPM vs. PBO	Power: AMI vs. TPM	"Correct" Winner	AMI Better	TPM Better	Both	None	Prob. of Picking Winner	Prob. of Picking "Correct" Winner
0.7%	0.9%	1.7%	None	1.4%	1.4%	0.2%	97%	3%	97%

Notable Results

- Condition 43: 50% PBO, 70% AMI, 85% TPM
  - Used to choose sample size for each primary hypothesis
  - Study would have ~100% “power” to correctly select TPM

Individual Trials				Decision					“Power”
Power: AMI vs. PBO	Power: TPM vs. PBO	Power: AMI vs. TPM	“Correct” Winner	AMI Better	TPM Better	Both	None	Prob. of Picking Winner	Prob. of Picking “Correct” Winner
89%	>99%	94%	TPM	0%	93.6%	6.4%	0%	100%	100%

Notable Results

- Condition 38 : 50% PBO, 60% AMI, 70% TPM
  - Demonstrates ~ 91% “power” to select TPM when difference between response rates is 10%, compared to 44% power in head to head comparison

Individual Trials				Decision					“Power”
Power: AMI vs. PBO	Power: TPM vs. PBO	Power: AMI vs. TPM	“Correct” Winner	AMI Better	TPM Better	Both	None	Prob. of Picking Winner	Prob. of Picking “Correct” Winner
26%	89%	44%	TPM	0.1%	70.5%	20.4%	9%	91%	91%

Results Cont.

- 4 Conditions with 50-80% “power”
  - Condition 21: 45% PBO, 60% AMI, 50% TPM
    - Correctly selects AMI 70% of the time
  - Condition 27: 50% PBO, 60% AMI, 50% TPM
    - Correctly selects AMI 51% of the time
  - Condition 54: 55% PBO, 60% AMI, 70% TPM
    - Correctly selects TPM 74% of the time
  - Condition 58: 55% PBO, 70% AMI, 70% TPM
    - Correctly selects both 76% of the time
- All show improvement over individual comparisons
  - Power for individual comparisons between 0.8% and 64%

Results Cont.

- 3 Conditions with <50% “power”
  - Condition 1: 40% PBO, 50% AMI, 50% TPM
    - 37% probability of selecting a winner
  - Condition 17: 45% PBO, 50% AMI, 50% TPM
    - 11% probability of selecting any winner
  - Condition 53: 55% PBO, 60% AMI, 50% TPM
    - Probability of correctly selecting AMI is 43%
- Small treatment differences
- Benefits in these situation over individual trials
  - Power for individual comparisons between 1.5% and 41%

Conclusion

- Combined 3 in 1 approach provides benefits above and beyond what can be achieved with separate hypotheses
- Clear ‘winner’ in over 90% of conditions
- Power to determine ‘ winner’ was greater when results examined together as opposed to separate trials
- Confidence in using this *a priori* decision algorithm to inform clinicians
- Only considers tier 1 in decision algorithm

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Questions?

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