CHAMP STUDY
SIMULATIONS: PICK THE WINNER

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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
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%
  • $4 \times 4 \times 4 = 64$ conditions
  • For each condition, one of the 4 possible decisions was reached
  • 10,000 replications for each condition
# Simulation Results

<table>
<thead>
<tr>
<th>Probability of picking “correct” winner</th>
<th>&gt;80%</th>
<th>50%-80%</th>
<th>&lt;50%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of conditions</td>
<td>57</td>
<td>4</td>
<td>3</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Individual Trials</th>
<th>Decision</th>
<th>“Power”</th>
</tr>
</thead>
<tbody>
<tr>
<td>Power: AMI vs. PBO</td>
<td>Power: TPM vs. PBO</td>
<td>Power: AMI vs. TPM</td>
</tr>
<tr>
<td>0.7%</td>
<td>0.9%</td>
<td>1.7%</td>
</tr>
</tbody>
</table>
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

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</thead>
<tbody>
<tr>
<td>Power: AMI vs. PBO</td>
<td>Probability of Picking Winner</td>
<td><strong>Power</strong></td>
</tr>
<tr>
<td>Power: TPM vs. PBO</td>
<td>AMI Better</td>
<td>TPM Better</td>
</tr>
<tr>
<td>Power: AMI vs. TPM</td>
<td>“Correct” Winner</td>
<td>AMI Better</td>
</tr>
<tr>
<td>Power: AMI vs. TPM</td>
<td>89%</td>
<td>&gt;99%</td>
</tr>
</tbody>
</table>
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

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<tr>
<td>Power: AMI vs. PBO</td>
<td>Power: TPM vs. PBO</td>
<td>Power: AMI vs. TPM</td>
</tr>
<tr>
<td>26%</td>
<td>89%</td>
<td>44%</td>
</tr>
</tbody>
</table>
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
Acknowledgements

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  • Jon Yankey
Questions?
References

• CHAMP Study Protocol and DSMB Materials