ASCPT 2016 Workshop: Lessons Learned from Failed Pediatric Trials
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Guanfacine for ADHD in Adolescents: Utility of Clinical Trial Simulation

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Acknowledgements and Support

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- Contributors

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  MetrumRG: Bill Knebel, Marc Gastonguay, Jim Rogers and Dan Polhamus
Learning Objectives

- Present an example of how clinical trial simulation can be used to optimize key design features of a new pediatric study

- Discuss application of clinical trial simulation to inform pediatric trials including accounting for potential differences in adult and pediatric disease manifestations
Simulation Based Decision-Making Process Flow

1. Understand Key Questions and Constraints
   - Quantitative Translation

2. Define Prior Knowledge/Data Sources
   - Model Building/Checking
   - Construct Simulation Model
   - Simulate Outcomes of Each Path/Option

3. Summarize Simulation Results
   - Check Sensitivity to Assumptions/Uncertainties

4. Identify Potential Decision Paths/Options
   - Choose highest value path given the current state of knowledge
Simulation Based Decision-Making Process Flow

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Identify Potential Decision Paths/Options

Choose highest value path given the current state of knowledge
- Will the proposed trial design lead to a successful study?

- Is the placebo response consistent across populations?

- What’s the impact of dropout on data analysis methods and conclusions?
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Quantitative Translation
- Under a dose-optimization/titration trial design, what is the probability that guanfacine extended release (GXR) will beat placebo (p < 0.05) on the ADHD RS-IV score at week 13?

- Are conclusions dependent on analysis methods (LOCF/ANCOVA vs. MMRM) data analysis methods, given missing data due to expected dropout rate?
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Summarize Simulation Results

Check Sensitivity to Assumptions/Uncertainties

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- Placebo data from nine studies using GXR or other ADHD compounds

- Dropout information from nine studies with GXR or other ADHD compounds

- Exposure-response data from five studies with GXR.
ADHD RS-IV score vs time in weeks for placebo patients. Median (dotted lines) with 5th and 95th percentiles (grey polygon)
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Distribution of simulated dropout times within each individual are compared to the actual observed dropout times from the model building dataset. Simulations were performed using the final time to event dropout model. Kaplan-Meir survival curves (thick black line) for each study demonstrate the observed distribution of dropout times.
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## Simulation Results

<table>
<thead>
<tr>
<th>Method</th>
<th>Probability of Success</th>
<th>Treatment Effect&lt;sup&gt;a&lt;/sup&gt;</th>
<th>SD of Change from Baseline</th>
<th>Effect Size&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRM</td>
<td>98%</td>
<td>-7.9 [-12, -3.4]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>10.4 [0.14, 11.8]</td>
<td>-0.76 [-1.2, -0.31]</td>
</tr>
<tr>
<td>ANCOVA</td>
<td>97%</td>
<td>-7.6 [-11, -3.2]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.8 [10.0, 13.5]</td>
<td>-0.64 [-1.0, -0.26]</td>
</tr>
</tbody>
</table>

<sup>a</sup> = difference between placebo and active at Visit 13  
<sup>b</sup> = median [95% CI]  
<sup>c</sup> = calculated as Treatment Effect/SD of Change from Baseline

- Treatment effect was consistent with historical data  
- Both analysis methods provided similar results
Simulation Based Decision-Making Process Flow

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   - Identify Potential Decision Paths/Options
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Sensitivity Analysis

- Conclusions independent of uncertainties in simulation model parameters
Successful Trial and Approval

Mean reductions in ADHD-RS-IV total scores at endpoint were statistically significantly greater for INTUNIV® compared to placebo in both AM and PM dosing groups of INTUNIV® (see Table 6).

Table 6: Flexible-Dose studies

<table>
<thead>
<tr>
<th>Study (Age Range)</th>
<th>Treatment Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>AM</td>
</tr>
<tr>
<td>Mean Baseline (SD)</td>
<td>37.7 (7.75)</td>
</tr>
<tr>
<td>3&lt;sup&gt;a&lt;/sup&gt; (6 – 17 years)</td>
<td>-15.9 (0.96)</td>
</tr>
<tr>
<td>LS Mean Change from Baseline (SE)</td>
<td>--</td>
</tr>
<tr>
<td>LS Mean Difference from Placebo (95% CI)</td>
<td>--</td>
</tr>
<tr>
<td>Mean Baseline (SD)</td>
<td>42.9 (6.21)</td>
</tr>
<tr>
<td>4 (6 – 12 years)</td>
<td>-10.6 (1.20)</td>
</tr>
<tr>
<td>LS Mean Change from Baseline (SE)</td>
<td>--</td>
</tr>
</tbody>
</table>

UNTUNIV Prescribing Information: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022037s009lbl.pdf
Thank You

Modeling and simulation of the exposure-response and dropout pattern of guanfacine extended-release in pediatric patients with ADHD

William Knebel, Jim Rogers, Dan Polhamus, James Ermer & Marc R. Gastonguay

Journal of Pharmacokinetics and Pharmacodynamics

ISSN 1567-567X

J Pharmacokinet Pharmacodyn
DOI 10.1007/s10928-014-9397-6
The time course of ADHD RS-IV total scores were best described by an inverse Bateman function (placebo data) and an Emax model (GXR exposure-response data).

\[
EFF_{plcb} = \theta_{scale} \cdot \frac{k_{forp}}{k_{elp} - k_{forp}} \cdot (e^{-k_{forp} \cdot TIME} - e^{-k_{elp} \cdot TIME})
\]

\[
E_{max} = E_{max,ss} \cdot (1 - e^{-0.693 \cdot \frac{TIME}{T_{ss}}})
\]

\[
EFF_{guan} = \frac{E_{max} \cdot DKG}{EE_{50} + DKG}
\]

\[
ADHD \text{ RS-IV} = S_0 \cdot (1 - EFF_{plcb}) \cdot (1 - EFF_{guan})
\]
Models

- The distribution of dropout times was best described using a "cure" model where the maximum percentage of non-dropout patients was an estimated parameter.

\[ S_1(t) = \pi + (1 - \pi)S(t) \]
\[ t_{ij} \sim \text{Weibull}(r, \mu_i) \]
\[ \mu_i = e^{(\nu_0 + \nu_i^{\text{study}})} \] (2)

- \( S(t) \) denotes the survival function in the patients and \( \pi \) is the fraction of patients that will not experience dropout.

- Weibull distribution for subject \( j \) in study \( i \) was described by a shape parameter \( (r) \), a scale parameter \( (\mu_i) \), and a random study effect \( (\nu_i^{\text{study}} \sim N(\nu_0, \sigma^2)) \) on the scale parameter.
Distributions of variance in change from baseline to endpoint in ADHD RS-IV score in simulated individuals are compared to the actual observed variance in change from baseline to endpoint for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for dropouts.
Distributions of simulated ADHD RS-IV score at endpoint within each individual are compared to the actual observed distribution of baseline values for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for dropouts.
Distributions of simulated ADHD RS-IV score at baseline within each individual are compared to the actual observed distribution of baseline values for adolescents from the model building datasets. Simulations were performed using the final placebo model and exposure-response models with correction for dropouts.
Summary

- This analysis is the first to describe the placebo response time course of ADHD RS-IV total scores, exposure-response of GXR, and dropout pattern in this group of ADHD patients.
- Structured, organized, approach to modeling/simulation process facilitates implementation and generation of useful results.
- Days, weeks, and sometimes months of work can often be summarized in one table or figure.