Application of a Novel Model for Analyzing Data from Randomized Pretest, Posttest, Follow-up Designs:

Results from a Pediatric Randomized Behavioral Clinical Trial

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Outline

• Quick overview of RPPF designs

• Description of the STAR trial

• Analysis options for RPPF designs

• Analysis of the STAR trial data using a novel Latent Change Model
Randomized pretest, post-test, follow-up designs (RPPF)

• A common longitudinal design in intervention research

• Participants are randomly assigned to treatment and control conditions, where only participants in the treatment group receive the active intervention.

• All participants are measured prior to the intervention (pretest or baseline), immediately following (or shortly after) the intervention (post-test or post-intervention or post-treatment), and at some time following the termination of the intervention (one or more follow-ups).
Randomized pretest, posttest, follow-up designs

• Researchers are usually interested in:

  – whether the intervention is more effective than the control condition at the primary endpoint (usually post-treatment)

  – whether the treatment effects (if there are any) are sustained (or even accentuated) over time (in the follow-up period).
Baseline Scores in RPPF Designs

• When participants are randomly assigned to groups, comparing the groups on the outcome post-intervention (or follow-up) after covarying for baseline scores will provide a more powerful test
  – E.g., ANCOVA more powerful than ANOVA on change scores (aka difference scores; posttest – pretest)

• Covarying for baseline scores adjusts for chance variations in outcome scores between the groups
  – i.e., participants are randomly assigned to groups and therefore any differences observed at baseline between the groups can be attributed to chance
The STAR trial – a pediatric randomized behavioral clinical trial

• STAR: **Supporting Treatment Adherence Regimes**

• PI: Avani Modi, PhD, Cincinnati Children’s Hospital
• NIH funded grant: R01HD073115-01A1
• 2013-2019
The STAR Trial

• Approximately 60% of youth with epilepsy are nonadherent to ASMs, with devastating consequences:
  – increased risk of seizures
  – suboptimal health-related quality of life (HRQOL)
  – inaccurate clinical decision-making
  – higher health care utilization and costs

• Thus, improving ASM adherence is critical to the health and well-being of youth with epilepsy
The primary aim:
- examine the efficacy of a family-tailored adherence intervention (STAR) on adherence in children with new onset epilepsy compared to an education only (EO) intervention.

Primary hypotheses:
- Participants in the STAR intervention were would demonstrate a statistically significant increase in adherence at postintervention and 3-, 6-, and 12-month follow-up visits compared to participants receiving EO.
The STAR Trial

• Methods:
  – Children between the ages of 2-12 within 7 months of diagnosis and their caregivers were recruited during routine epilepsy clinic visits (N = 200)
  – Baseline questionnaires completed, and electronic adherence monitoring devices provided
  – Enrichment design – Only participants with less than 95% adherence during the screening period were randomized
The STAR Trial
The STAR intervention

• STAR intervention group = 8 sessions (6 face-to-face; 2 check-in telephone calls)

• Used a problem-solving approach to address the family’s individualized adherence barriers:
  
  – 1) Identification of adherence barrier experienced by the family
  – 2) Generation of 8-10 creative solutions by family members involved
  – 3) Evaluation of the solutions by family members
  – 4) Choice of 1 or 2 solutions to implement
  – 5) Information on how the solution will be implemented
    • who, what, when, where, and how

• Check-in sessions to troubleshoot.
Education Only (EO) Group – attention control

• The education only group (attention control group) = 8 sessions (6 face-to-face; 2 check-in telephone calls).

• Sessions covered the following topics:
  – seizure safety
  – sleep hygiene
  – communication and psychosocial comorbidities
  – school-based issues

• Check in sessions to follow-up and answer questions
The STAR Trial

• Primary Outcome:
  – electronically monitored adherence
    • # of doses taken / # of doses prescribed in a 30 day period.
      – E.g., post-intervention = adherence during their 5th month in the study
    • Reported in percentages (0-100%)

• Secondary Outcomes:
  – Health-related quality of life (HRQOL)
  – Seizure severity

• Simulated dataset (n = 75 per group) based on the original STAR trial data.
Some Analysis Options

• Typical Approaches:
  – ANCOVA
  – Longitudinal Mixed/Multilevel Models
  – Latent Growth Curve Models
  – GEEs
  – Etc..
Analytic Approaches: Longitudinal Mixed Effect Model (LMM)

Do the groups differ in their outcome trajectories over time?

• Uses all longitudinal data in one model

• No estimation of amount of change across each of the time points
  – Change is averaged across all timepoints
  – The LMM (or even a latent growth curve model) approach is typically not appropriate for RPPF designs because researchers are interested in isolating the specific changes that occur across each of the time points

• Baseline scores typically incorporated into the overall trajectory
Analytic Approaches: ANCOVA

Do the groups differ in their outcome scores at a specific timepoint, adjusting for chance variation in baseline scores?

- Can estimate the difference between treatment groups across each of the time points discretely
  - Conveys important clinical information about treatment effects and their sustainability over time.

- Covaries the baseline scores in each model, improving power over other approaches

- Each timepoint analyzed in separate models.
  - Not taking advantage of the longitudinal data
Analytic Approaches: Latent Change Models (LCM)

Do the groups differ in the amount of change from baseline to post-treatment, and from post-treatment to follow-up(s)?

- LCMs have been proposed as a method for estimating discrete changes over time in longitudinal designs.

- These models incorporate a latent difference score approach
  - change between timepoints is estimated using multiple difference score estimates of the amount of change across each of the timepoints

- Willoughby, et al. (2007) proposed an LCM to accommodate RPPF designs, followed by Mun at al. (2009) who addressed some limitations of the Willoughby et al. RPPF specific LCMs.

- One limitation remained to these LCMs, as applied to RPPF designs:
  - they use a difference score based approach to controlling for the pretest.
Analytic Approaches: Latent Change Models (LCM)

• Solution?
  – a more powerful test of the group differences in change from pretest to posttest (or post-test to follow-up) would be obtained if the model covaried for the pretest score since the participants are randomly assigned to groups.
Analysis basics

• Analyses assumed intent-to-treat and retained all participants within their randomized intervention arm

• Analyses conducted in Mplus version 8.9 (via runmplus in Stata version 18)
Proposed LCM model for the STAR data
Proposed LCM model for the STAR data

MODEL:

s1 | adh5@1 adh7@1 adh10@1 adh16@1;
s2 | adh7@1 adh10@1 adh16@1;
s3 | adh10@1 adh16@1;
s4 | adh16@1;

adh5 adh7 adh10 adh16 on adh0 ;

s1 s2 s3 s4 on group ;
Latent Change Model Fit

MODEL FIT INFORMATION

RMSEA (Root Mean Square Error Of Approximation)

<table>
<thead>
<tr>
<th>Estimate</th>
<th>0.014</th>
</tr>
</thead>
<tbody>
<tr>
<td>90 Percent C.I.</td>
<td>0.000  0.217</td>
</tr>
<tr>
<td>Probability RMSEA &lt;= .05</td>
<td>0.395</td>
</tr>
</tbody>
</table>

CFI/TLI

<table>
<thead>
<tr>
<th>CFI</th>
<th>1.000</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLI</td>
<td>0.998</td>
</tr>
</tbody>
</table>

SRMR (Standardized Root Mean Square Residual)

| Value | 0.019 |
## Latent Change Model Results

<table>
<thead>
<tr>
<th></th>
<th>Estimate</th>
<th>S.E.</th>
<th>Est./S.E.</th>
<th>Two-Tailed P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>ON GROUP</td>
<td>3.994</td>
<td>3.632</td>
<td>1.100</td>
</tr>
<tr>
<td>S2</td>
<td>ON GROUP</td>
<td>-2.092</td>
<td>3.353</td>
<td>-0.624</td>
</tr>
<tr>
<td>S3</td>
<td>ON GROUP</td>
<td>6.824</td>
<td>5.536</td>
<td>1.233</td>
</tr>
<tr>
<td>S4</td>
<td>ON GROUP</td>
<td>7.040</td>
<td>2.997</td>
<td>2.349</td>
</tr>
</tbody>
</table>
STAR Trial Results
### Descriptive Summary of Primary Outcome by Group and Timepoint

<table>
<thead>
<tr>
<th>Monthly Adherence %</th>
<th>% adherence</th>
<th>Cohen’s d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline</strong></td>
<td>3.35%</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>Post-treatment</strong></td>
<td>5.5%</td>
<td>0.26</td>
</tr>
<tr>
<td><strong>3-mth follow-up</strong></td>
<td>5.95%</td>
<td>0.23</td>
</tr>
<tr>
<td><strong>6-mth follow-up</strong></td>
<td>9.18%</td>
<td>0.34</td>
</tr>
<tr>
<td><strong>12-mth follow-up</strong></td>
<td>15.89%</td>
<td>0.65</td>
</tr>
</tbody>
</table>
Conclusions

• Families who received STAR demonstrated sustained adherence, compared to a progressive adherence decline for EO.

• Although there are numerous strategies for analyzing the data from RPPF designs, the proposed variation of a LCM offers several advantages over more traditional approaches.
Questions?

Comments?

Suggestions?


• Acknowledgement and thanks to my graduate mentors at York University (Rob Cribbie and Dave Flora) as well as my fellow grad students who co-authored the original paper presenting this model in 2012

• Many thanks to Avani Modi for her mentorship, advocacy, and granting me permission to use the STAR trial as my example in this presentation