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

Results from a Pediatric Randomized Behavioral Clinical Trial

Constance A. Mara, PhD
Associate Professor, Quantitative Psychology
Behavioral Medicine & Clinical Psychology
Cincinnati Children's Hospital Medical Center
Department of Pediatrics
University of Cincinnati, College of Medicine

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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, post-test, 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: **S**upporting **T**reatment **A**dherence **R**egimes

- PI: Avani Modi, PhD, Cincinnati Children's Hospital
- NIH funded grant: R01HD073115-01A1
- 2013-2019

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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 STAR Trial

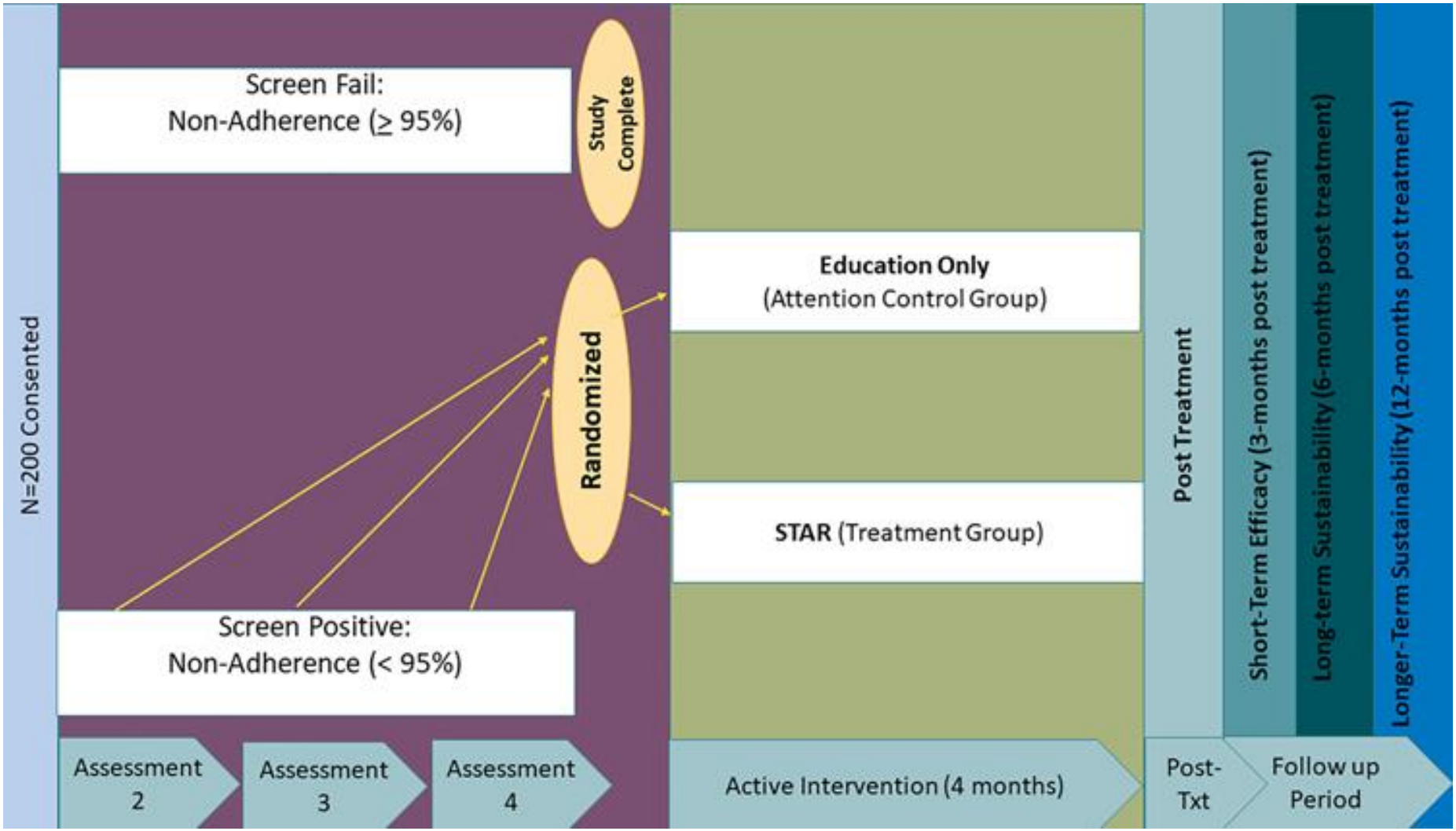
- The primary aim:
  - examine the efficacy of a family-tailored adherence intervention (STAR) on adherence in children with new onset epilepsy compared to an education only (EO) intervention.

- 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)

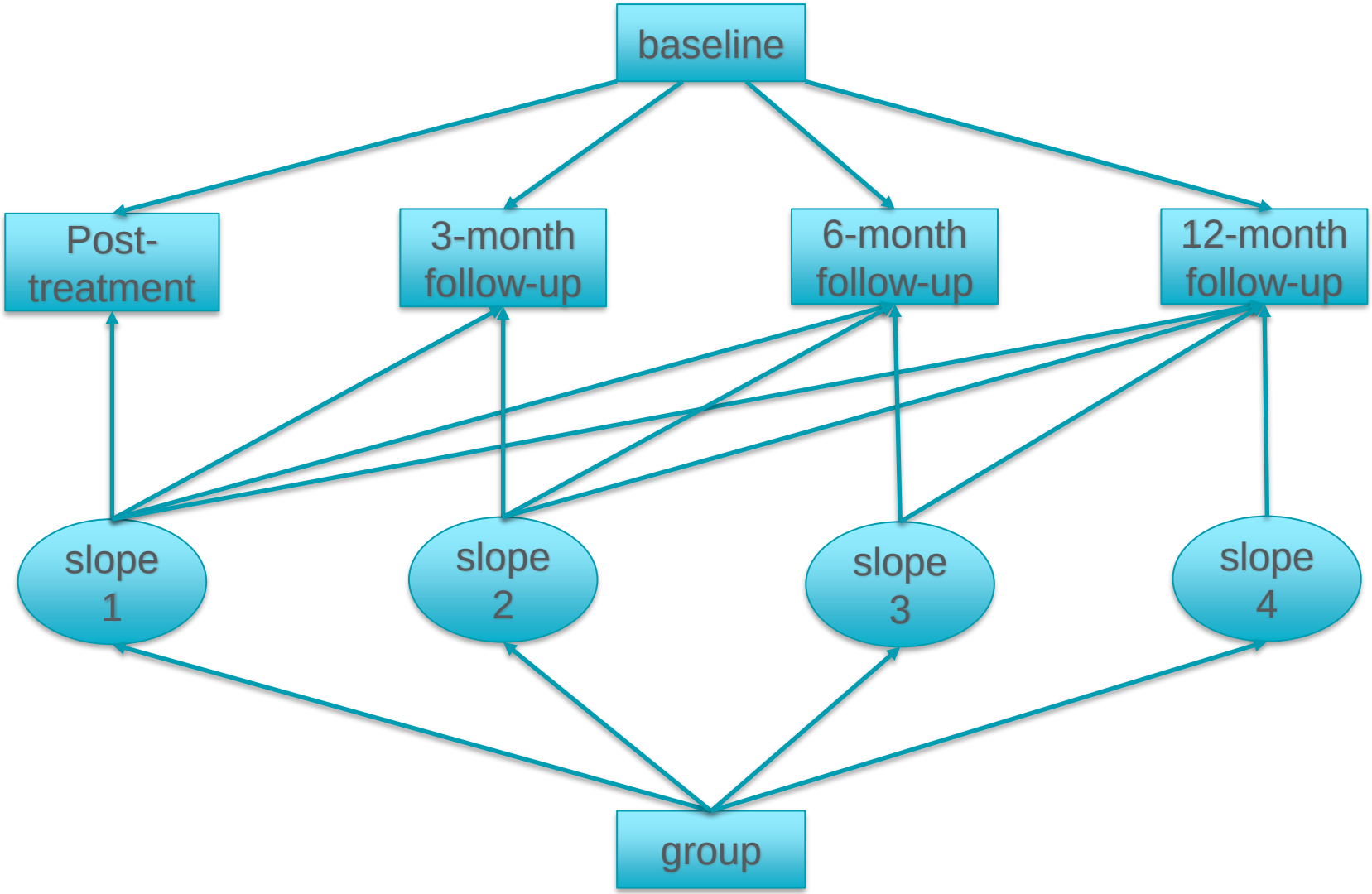
- Solution?
  - a more powerful test of the group differences in change from pretest to posttest (or post-test to follow-up) would be obtained if the model covaried for the pretest score since the participants are randomly assigned to groups.

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)

Estimate	0.014	
90 Percent C.I.	0.000	0.217
Probability RMSEA <= .05	0.395	

CFI/TLI

CFI	1.000
TLI	0.998

SRMR (Standardized Root Mean Square Residual)

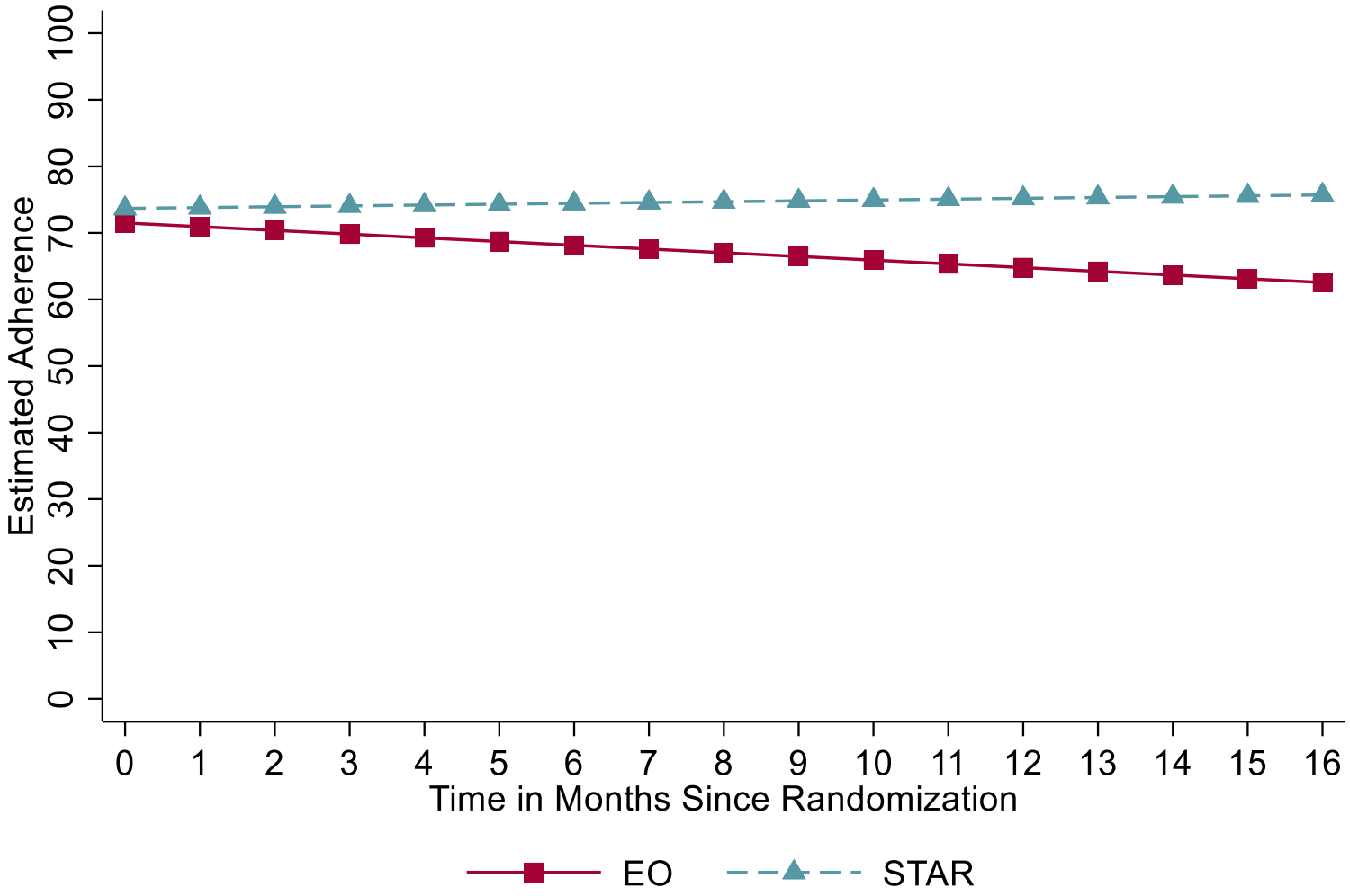
Value	0.019

Latent Change Model Results

MODEL RESULTS

		Estimate	S.E.	Est./S.E.	Two-Tailed P-Value
S1	ON				
	GROUP	3.994	3.632	1.100	0.271
S2	ON				
	GROUP	-2.092	3.353	-0.624	0.533
S3	ON				
	GROUP	6.824	5.536	1.233	0.218
S4	ON				
	GROUP	7.040	2.997	2.349	0.01

STAR Trial Results



Descriptive Summary of Primary Outcome by Group and Timepoint

	Effect Sizes for the Group Difference	
Monthly Adherence %	% adherence	Cohen's d
Baseline	3.35%	0.17
Post-treatment	5.5%	0.26
3-mth follow-up	5.95%	0.23
6-mth follow-up	9.18%	0.34
12-mth follow-up	15.89%	0.65

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?

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