Idiographic Clinical Trials: What are They, When are They Useful, and Recent Developments

Ty A. Ridenour & Stephen J. Tueller

Funded by NCATS (R21 TR002402) and RTI IR&D Innovation Grants

PersonAlytics™ Team and Website: https://personalytics.rti.org/

Outline

* Motivations for Idiographic Clinical Trials (ICTs)
* What are ICTs?
* When are ICTs (not) useful?
* Strengths and limitations
* Recent developments

Motivations for Idiographic Clinical Trials

Small population or sample

In-the-field research required

Active ingredients / processes

Precision treatment

What works for whom (mechanisms)

Rapid program evaluation

Heterogeneous outcomes

What are Idiographic Clinical Trials?

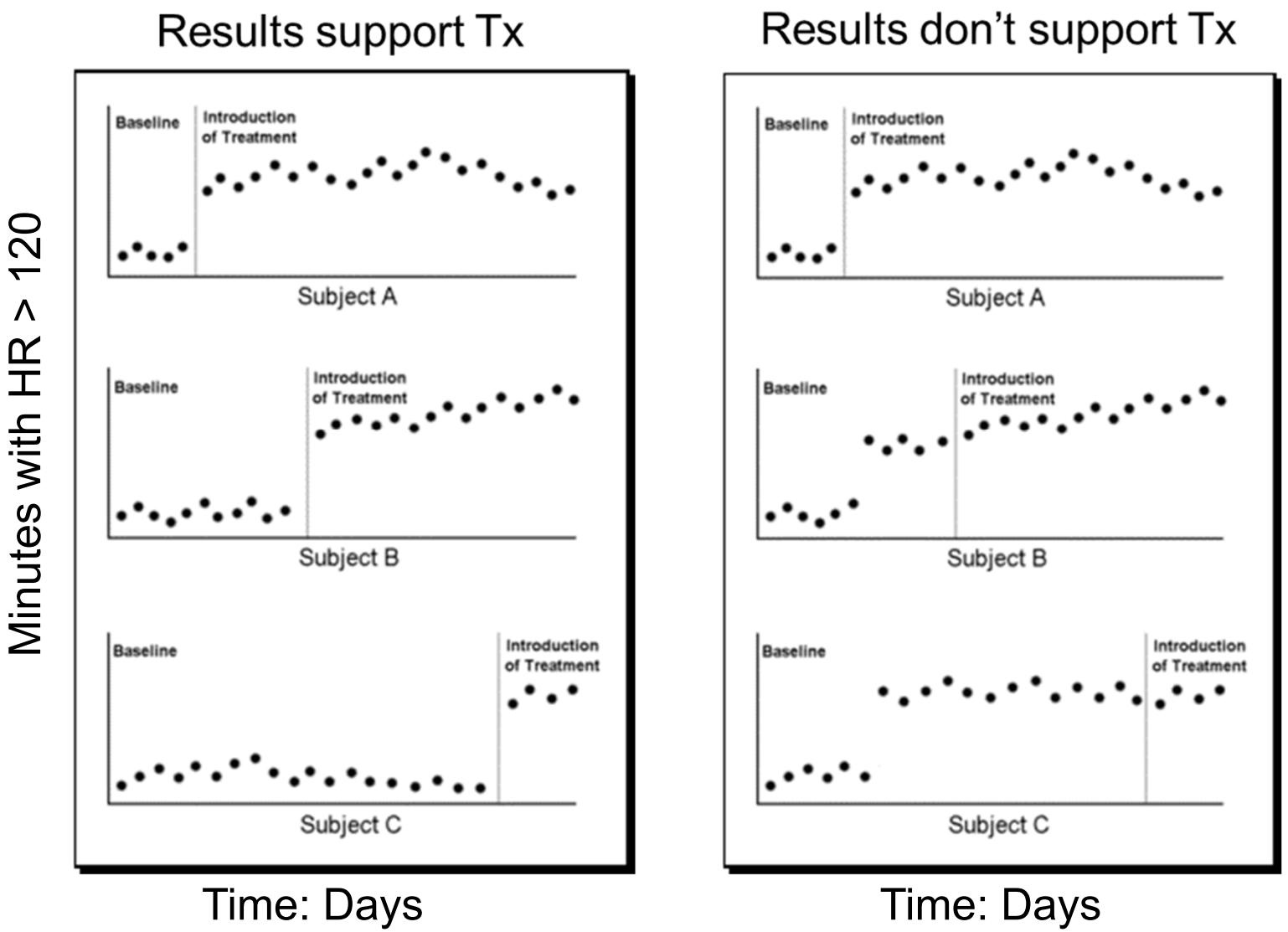
Within-subject Experimental Designs + **Stochastic Analysis for Small Samples and N=1** = **Idiographic Clinical Trials**

- Each participant get 2+ conditions
- Time series data
- Logical, flexible, causal designs
- Few participants required
- Detailed data per participant
- Can be overlaid on usual care

- Models “shifts” and gradual changes
- Focus on individuals
- Yields aggregates
- Intuitive results
- Tailorable for small samples
- Efficacy-like output
- Resolves historical sources of bias in WSEDs

Within-subject Experimental Designs

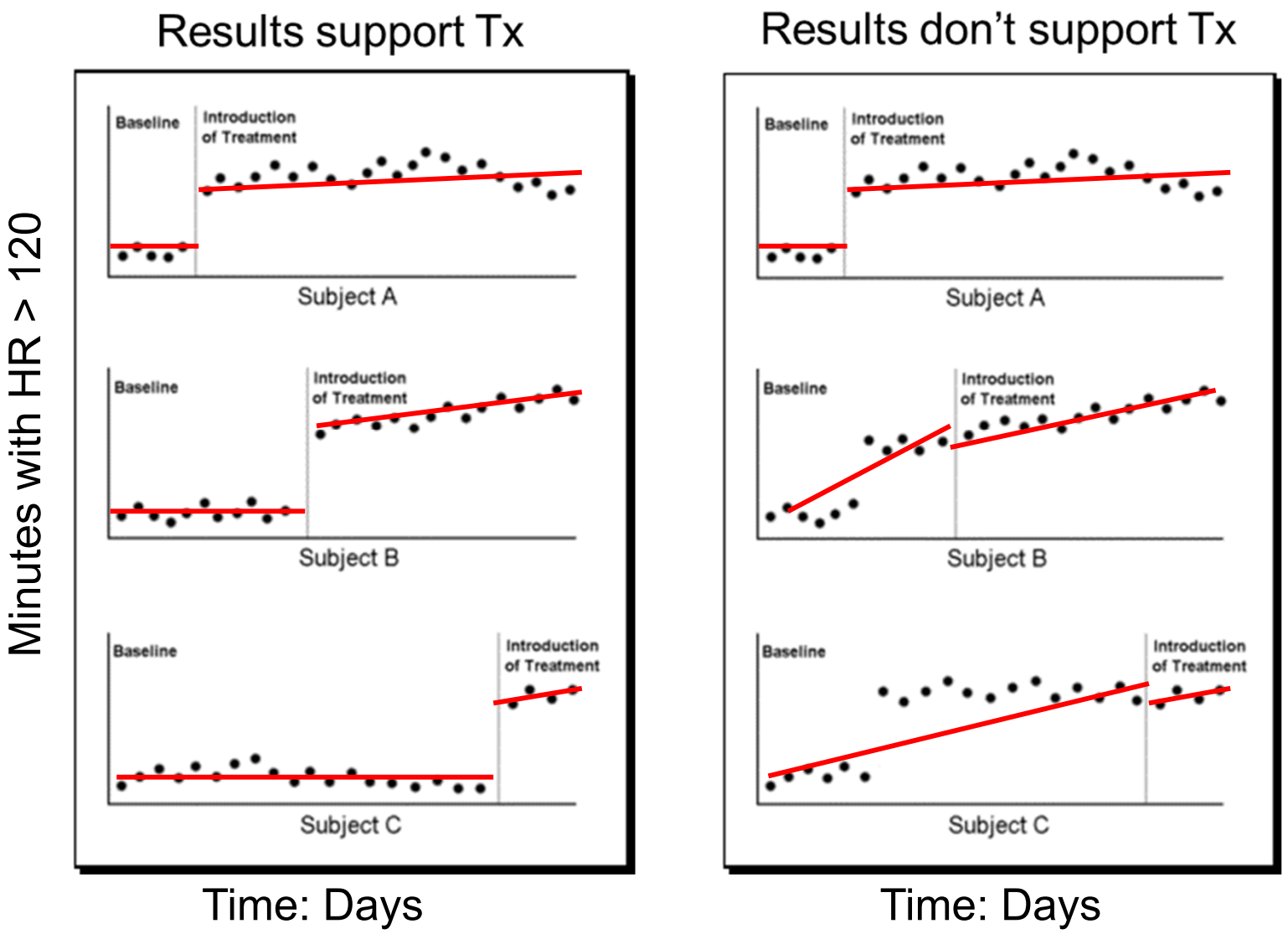
Most Common: Multiple Baseline Design



From: AllPsych; //allpsych.com/researchmethods/multiplebaselines/#.Vd30PvlVhBe

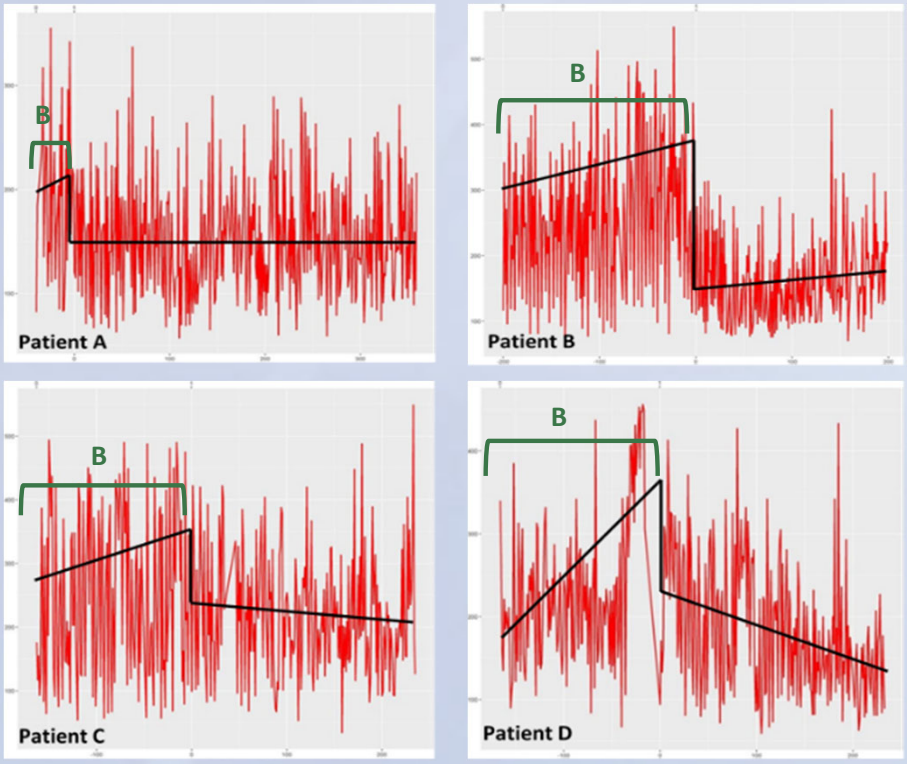
Within-subject Experimental Designs

Most Common: Multiple Baseline Design

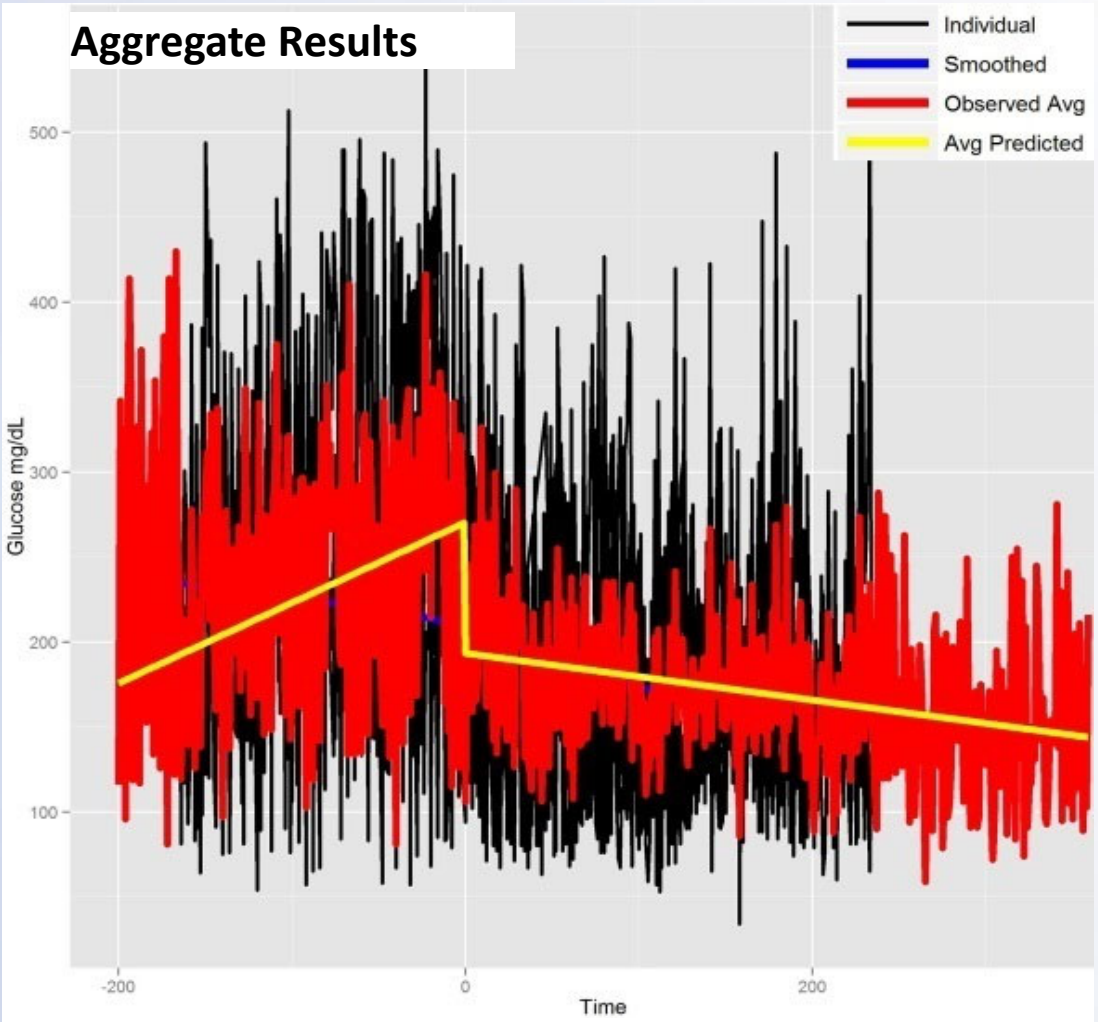


From: AllPsych; //allpsych.com/researchmethods/multiplebaselines/#.Vd30PvlVhBe

Illustration 1: Rigorous Pilot Study



Note: Y-axis is blood glucose in mg/dL. **B** = baseline phases. The treatment instant impact (without slope) in mg/dL is -49.0 for A, -152.9 for B, -45.0 for C, and -73.0 for D.



Note: Average decrease in glucose immediately following Manual Pancreas = 77.13 mg/dL ($p < .001$). Smoothed model not shown.

From: Ridenour et al., 2013

Wide Applicability

Field	Outcomes	Intervention
Addiction Treatment	Smoking cessation	Pharmacist-aided use of patch
Behavior Medicine	Blood-glucose test usage	MI, CM, internet-aided adherence
Clinical Psychology	Psychopathy	Contingency management
Family Therapy	Satisfaction, Depression	Emotion Focused Therapy
Geriatric Medicine	Blood sugar level	"Manual Pancreas"
Neurology	Migraine headache severity	Track triggers and lifestyle change
Organ Transplantation	Transplanted liver/kidney function	Prograf vs generic transplant drug
Pharmacy	Pain, Patient satisfaction	ICU Sedatives
Policing	Electrodermal activity	Etiology: stressful confrontations
Rehabilitation	Pain, Adherence	Virtual Coach Power Seat
	Cardiac arrest recovery	Exercise outside physical therapy
Speech Therapy	Verbal- & e-communication	Speech therapist laptop facilitator
FDA Clinical Trial	Pediatric Hemodialysis	(confidential)

When to Generally (not) Use ICTs

ICTs Generally Strong For:

- N = 1 results ("impact")
- Outcomes heterogeneity
- All participants get novel treatment
- Engagement / attrition
- Intrapersonal processes / mechanisms
- Real world effectiveness
- "Active ingredients" research
- Small population efficacy

ICTs Generally Limited For:

- Large population efficacy
- Acute illnesses
- Few "waves"
- Phase III drug trials
- Surveys / prevalence
- Long interviews / questionnaires
- Change in traits / personality
- Note: Stigma among methodologists

Analytic Strategy: Intensive Hierarchical Regression

$$y_{ij} = \pi_{0i} + \pi_{1i} Time_j + \pi_2 \left(Time_j \times Phase_j \right) + \pi_3 Phase_j + \varepsilon_{ij}$$

Where:

y_{ij} represents outcomes for patient i at time j

π_{0i} represents random intercepts

$\pi_{1i}\ Time_j$ represents random slopes

$Phase_j$ is dummy coded to estimate the effect of time separately by phase

$\pi_2 \left(Time_j \times Phase_j \right)$ is a fixed effect of time

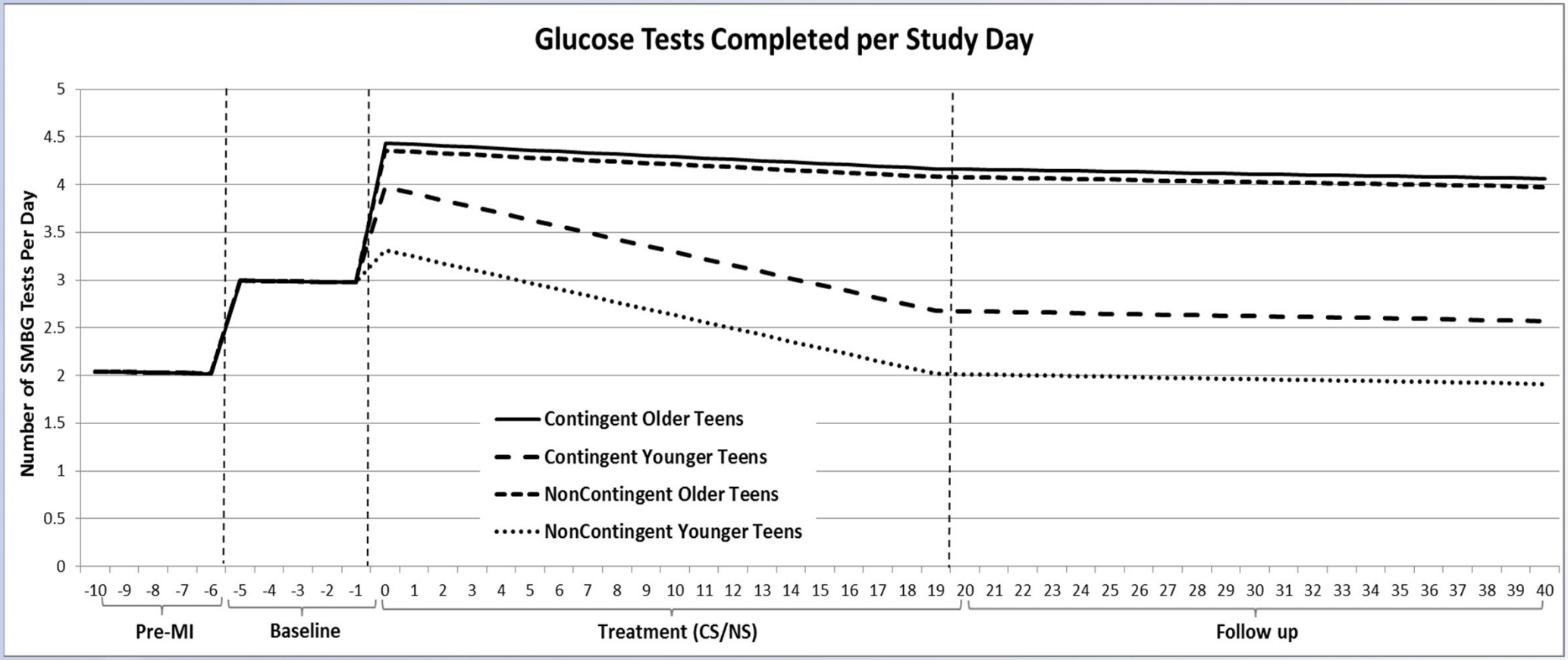
$\pi_3 Phase_j$ a fixed effect of difference in intercepts among phases

ε_{ij} is residual variance term

Model assumes that during baseline the mean intercept = 0 and mean slope = 0 and that autoregression in data has been parsed out using the appropriate error covariance structure.

Can add term(s) to test subgroup differences and analyze covariates.

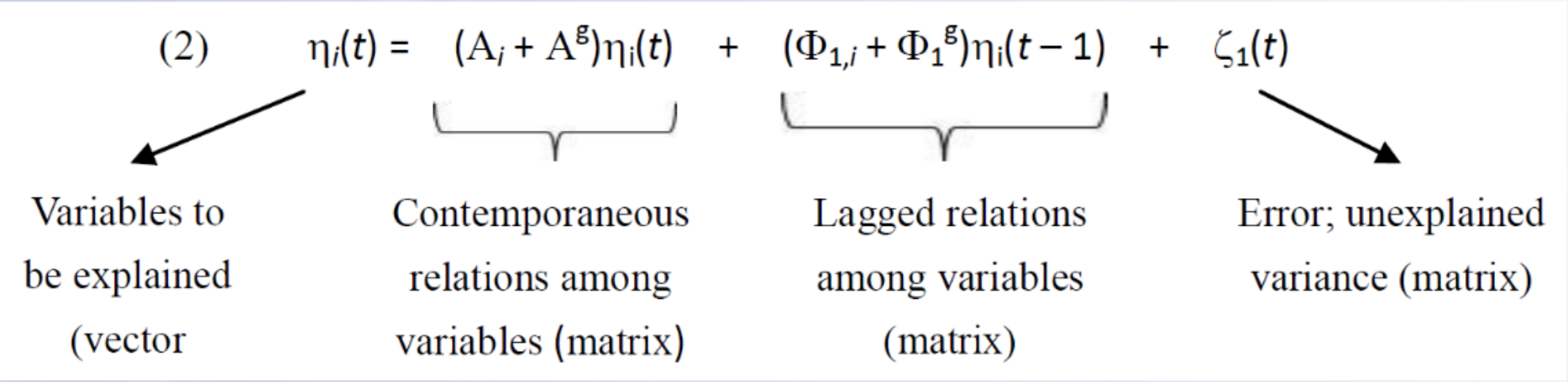
Illustration 2: Comparative Effectiveness Research



Daily Tests = 1.9885 - 0.00501 (per day) + 0.9805 (effect of MI) + 1.3240 (change in intercept at Treatment phase) - 0.06317 (per day of Treatment phase) + 1.0430 (additional intercept change for older teens during Treatment phase) + 0.6598 (additional intercept for CS) – 0.05378 (per day of Treatment phase for younger teens)

From: Raiff et al., 2016

Analytic Strategy: Unified SEM



Where:

$\eta_i(t)$ are the variables to be "explained" for individual *i*

$(A_i + A^g)\eta_i(t)$ is a matrix of contemporaneous covariations among variables

$(\Phi_{1,i} + \Phi_1^g)\ \eta_i(t\text{-}1)$ is a matrix of lagged covariations among variables

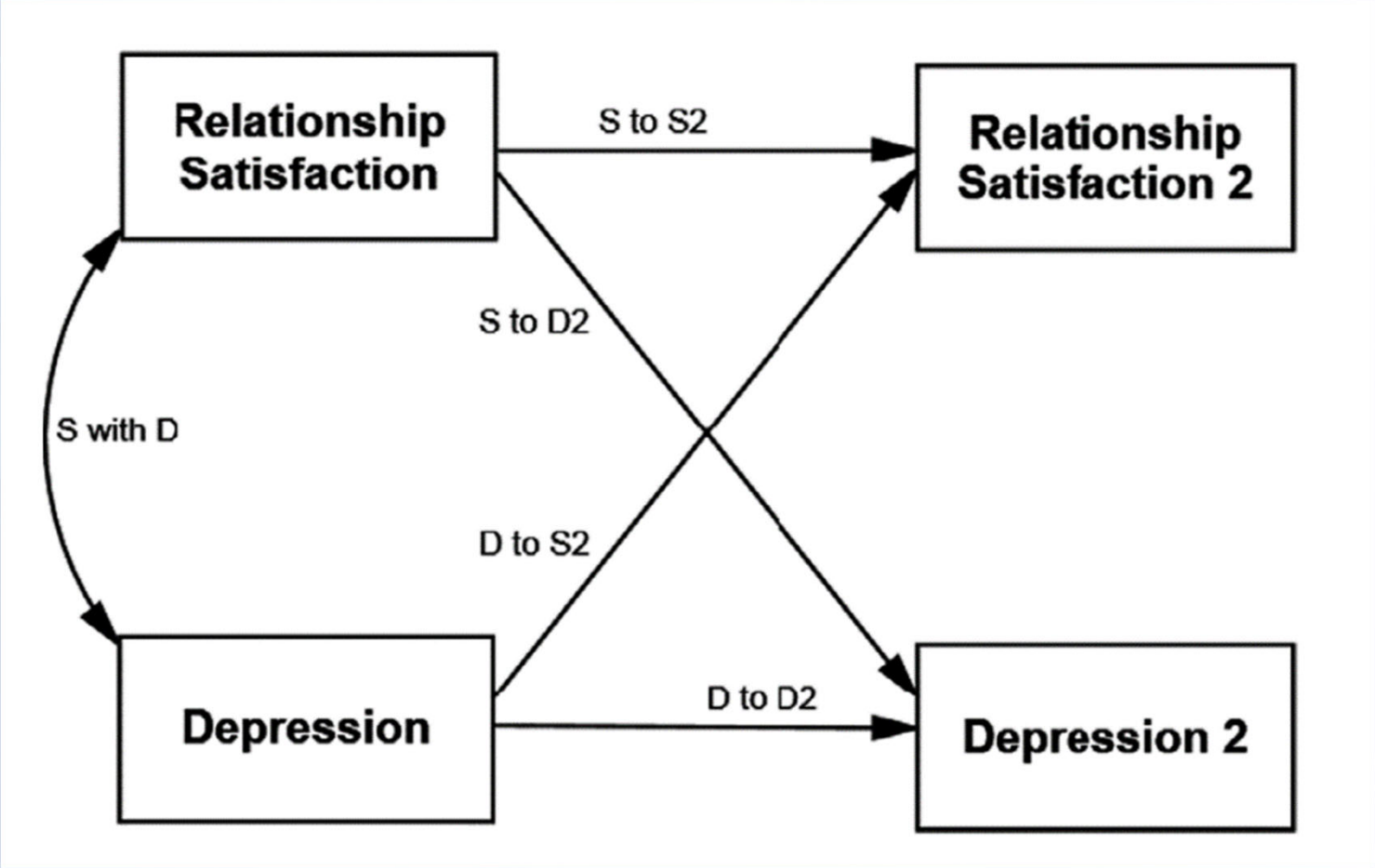
$\zeta_1(t)$ is an error matrix

Notation, assumptions, and modelling strategy are based on the Group Iterative Multiple Model Estimation (GIMME) programs.

From: Beltz et al., 2016; Gates et al., 2012

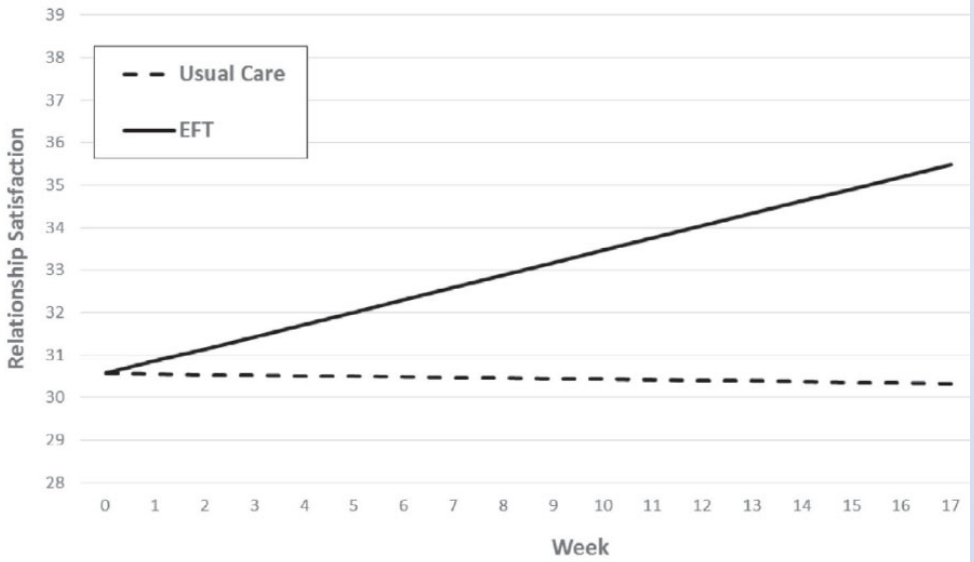
Illustration 3: Testing Mechanisms of Action

Hypothesized model of Emotion Focused Therapy outcomes



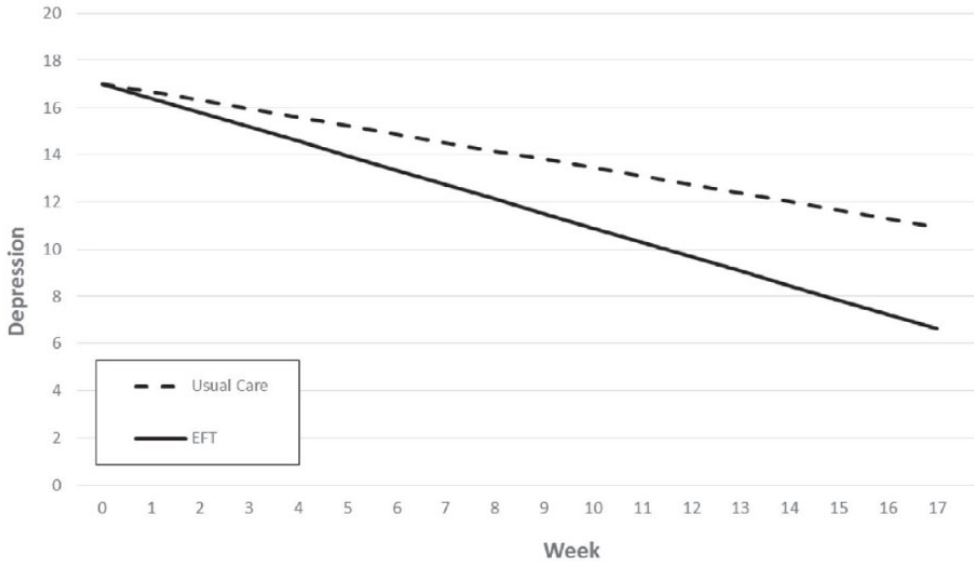
From: Wittenborn et al., 2019; Ridenour et al., 2016

Illustration 3: Outcomes for the Men



Satisfaction = 30.57 + 0.29 (Week) – 0.30 (Week*Treatment)

Figure 3. Mixed model trajectory analysis of relationship satisfaction.



Depression = 17.01 - 0.61 (Week) + 0.25 (Week*Treatment)

Figure 4. Mixed model trajectory analysis of depression.

From: Wittenborn et al., 2019

USEM: Testing of Fit to the Data

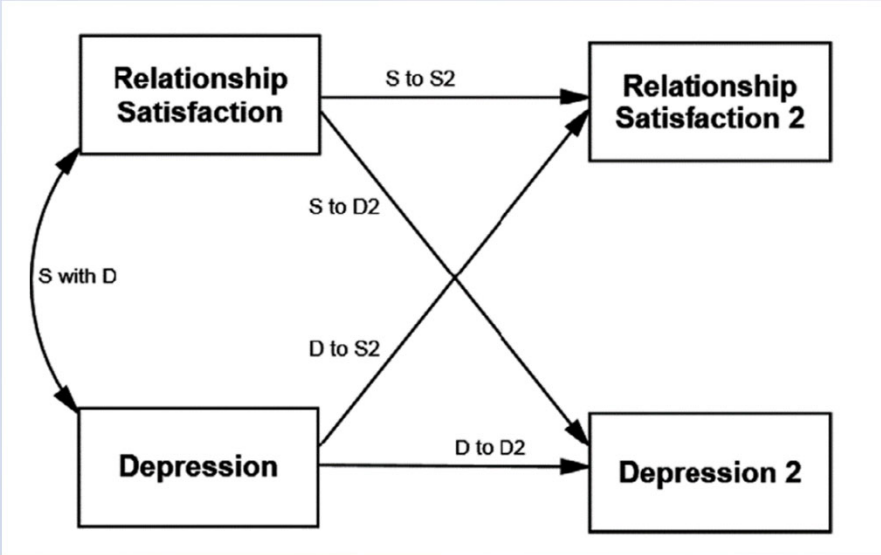


Table 3
Fit Statistics of Three Competing Subgroupings of Men

Path parameters fixed equal. . .	χ^2, *df*	AIC	BCC	LR χ^2, *df* vs. model 1
1. . . . across all participants	1199.09, 171	1277.1	1305.0	–, –
2. . . . within treatment arms	1183.18, 166	1271.2	1302.6	15.9, 5
3. . . .within each of 4 clusters	1124.27, 151*	1242.3*	1284.4*	58.9, 20*

Note. *df* = degrees of freedom; RMSEA = root mean square error of approximation; AIC = Akakie's Information Criterion; BCC = Brown-Cudeck Criterion; LR = likelihood ratio. Models 2 and 3 are not nested and thus were not compared using LR χ^2.
*The best fitting model indicated by the fit statistic.

USEM: Testing of Fit to the Data

Table 4
Standardized Path Coefficients of the Four-cluster Solution for Men

Aggregate estimates	ID	Autocorrelation		Cross-lag paths		Cluster path characteristics	Study arm
		$S \rightarrow S_2$	$D \rightarrow D_2$	$S \rightarrow D_2$	$D \rightarrow S_2$		
Cluster 1:	20	−0.02	0.64	−0.30	−0.96	Autocorrelation in depression only; Granger	UC
$S \rightarrow S_2 = 0.03$;	25	−0.05	0.71	−0.13	−0.56	causality from depression to satisfaction	UC
$D \rightarrow D_2 = 0.26$;	27	−0.08	0.71	0.04	−0.54		EFT
$S \rightarrow D_2 = -0.37$;							
$D \rightarrow S_2 = -0.35$							
Cluster 2:	11	1.09	0.01	−0.69	0.26	Autocorrelation in satisfaction only;	EFT
$S \rightarrow S_2 = 0.77$;	21	0.50	−0.09	−0.83	−0.40	Granger causality from satisfaction to	EFT
$D \rightarrow D_2 = 0.02$;	26	0.47	0.05	−0.39	−0.28	depression; lesser sequence from	UC
$S \rightarrow D_2 = -0.71$;						depression to satisfaction	
$D \rightarrow S_2 = -0.05$							
Cluster 3:	8	0.16	0.50	0.31	−0.24	Moderate autocorrelation for depression;	UC
$S \rightarrow S_2 = 0.43$;	15	0.16	0.50	0.00	−0.20	small-to-nil cross-lagged correlations	EFT
$D \rightarrow D_2 = 0.31$;	22	−0.33	0.33	0.11	−0.23		EFT
$S \rightarrow D_2 = -0.17$;							
$D \rightarrow S_2 = -0.14$							
Cluster 4:	2	0.65	0.64	−0.32	−0.20	Large autocorrelations for depression and	EFT
$S \rightarrow S_2 = 0.40$;	3	0.86	0.76	−0.19	0.01	satisfaction; moderate-to-nil cross-lagged	EFT
$D \rightarrow D_2 = 0.50$;	16	0.54	0.90	−0.04	−0.45	correlations	UC
$S \rightarrow D_2 = -0.17$;	23	0.63	0.91	−0.02	0.19		UC
$D \rightarrow S_2 = -0.14$	28	0.55	0.76	0.12	0.05		EFT

Note. S = relationship satisfaction; D = depression. Model parameters of one participant (ID 24) did not fit into any of the clusters; they were −0.71, 0.07, 2.23, and −0.09, respectively.

From: Wittenborn et al., 2019

(Some) Recent Advances

Understanding ICT outcomes as “factuals” & “counterfactuals”

Daza et al., 2018

Simulation studies to inform study design

Blackson et al., 2019; Duan et al., 2013; Ferron et al., 2009; Percha et al., 2019

Understanding patient preferences for study designs (by illness)

Cheung et al., 2020; Sarcristan et al., 2021

Alternative designs and analytic strategies

Howe et al., 2010; Liao et al., 2021; Nahum-Shani et al., 2015;

Some Resources

Stats-of-1: Inference for the Individual

References, links to useful tools

https://statsof1.org/resources/#sample-size--statistical-power

International Collaborative Network

https://www.nof1sced.org/

Single Case Design Masked Visual Analysis

Data visualization and sharing apps

https://singlecasemva.app/

Ksana Health data visualization apps

https://ksanahealth.com/ears/

Evolving Resource: *PersonAlytics*™

Statistical and power analysis programs to support ICTs

Automate certain analytic processes

Support simulation research

Provide GUI interface for users that don't code in R

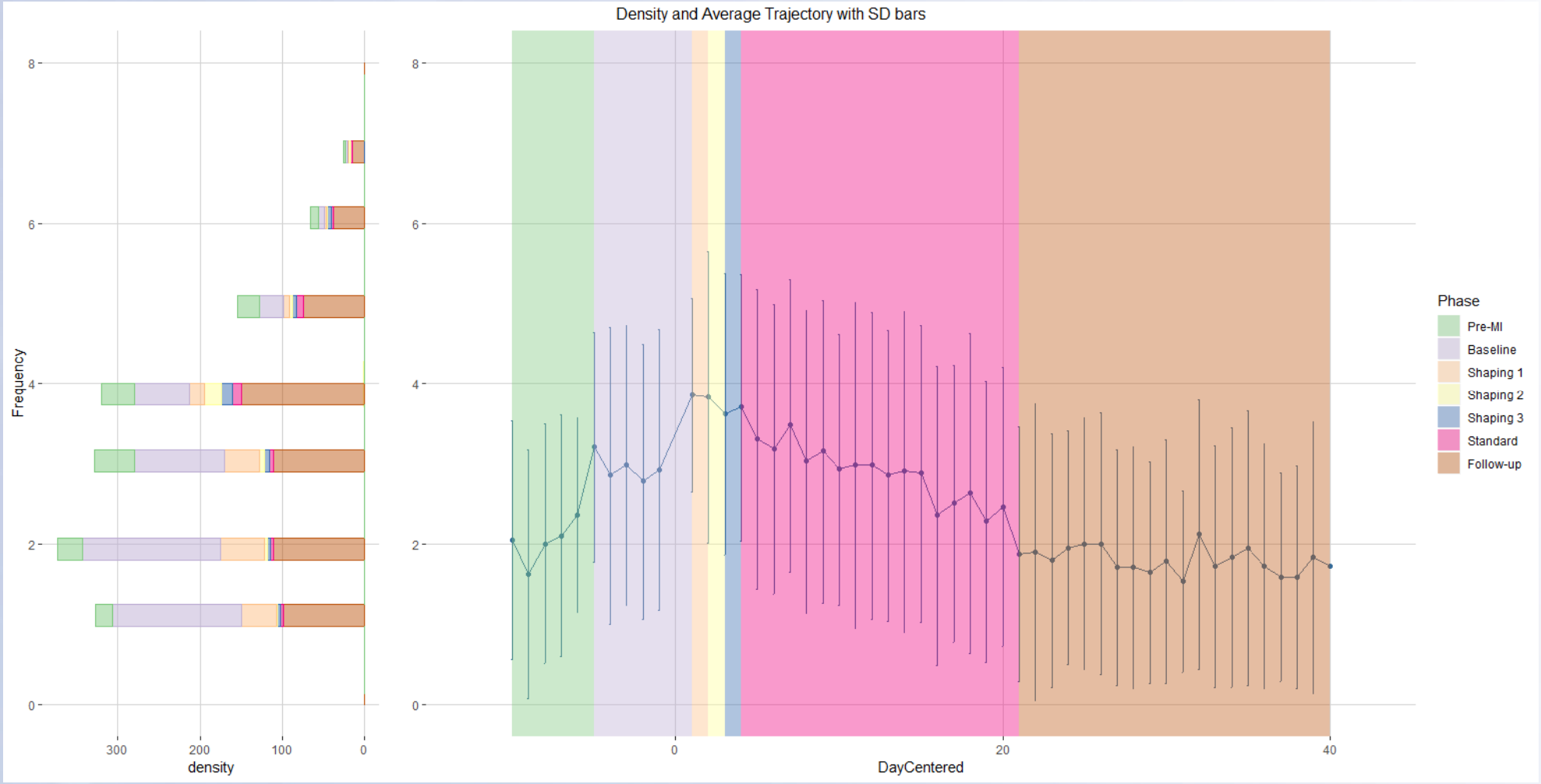
Evolve with methodological developments

Website: https://personalytics.rti.org/

PersonAlytics R Package

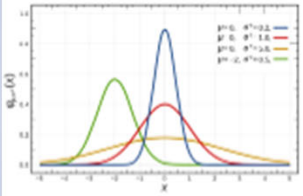
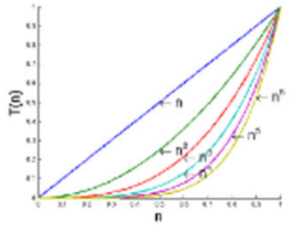
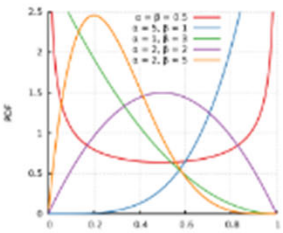
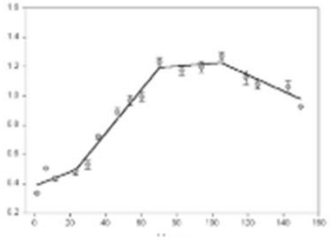
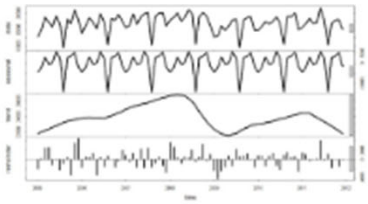
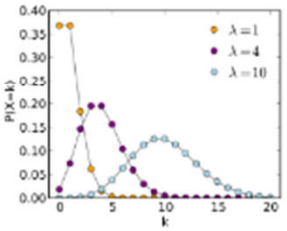
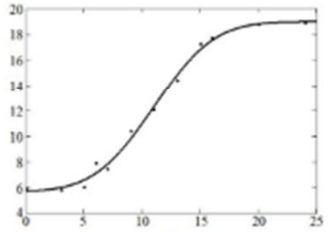
- Analytics for N-of-1 and small N intensive longitudinal designs, idiographic clinical trials (ICT), and interrupted time series
- Single subject data: Linear `ARMA` models
- Small N data: Mixed effects models (MLM/HLM/GCM)
  - Linear mixed effects model
  - Generalized additive models for location, scale and shape (70+ distributions)
- Mixed effects modeling options
  - Standard MLM/HLM with polynomial orders of time (`time`, `time`^{2}, `time`^{3}, etc.)
  - Piecewise growth model
  - Simultaneous estimate of phase and group specific MLM/HLM/GCM
- Data visualization
- Finite population correction (FPC)
- https://github.com/ICTatRTI/PersonAlytics

Visualizing ICT Data



Mixed Effects and Time Series Modeling for N=1, small N, and ICT

If N > 1

Outcome	=	Fixed Effects	+	Random Effects/Trajectory Shape	+	Error
	Normal	Experimental Condition (Phase)			Polynomial	Time Series Models, e.g., ARMA(p, q)
	Beta	Static factors (if n>1), e.g., demographics			Piecewise	
	Poisson	Dynamic factors/ time varying covariates, e.g., weather			Logarithmic	Other Correlation Structures: (Compound) Symmetry, Spherical, Unstructured

Generalized Additive Models for Location, Scale and Shape (GAMLSS) distributions

Modeling Process Automation Features

- Model selection using AIC or BIC
- All model selection uses ML, final model is fit with REML
- Automated tasks
  - Residual correlation structure selection
    - `ARMA(p,q)` for all possible combinations of `p` & `q`
    - User specified `p` & `q`
  - Time structure selection
    - Polynomial (`time`, `time`^{2}, `time`^{3}, etc.)
    - Pending feature: estimating polynomial time structure within each phase
  - Standardization of outcomes, predictors, or both
  - Centering of the time variable
  - Outcome distribution selection

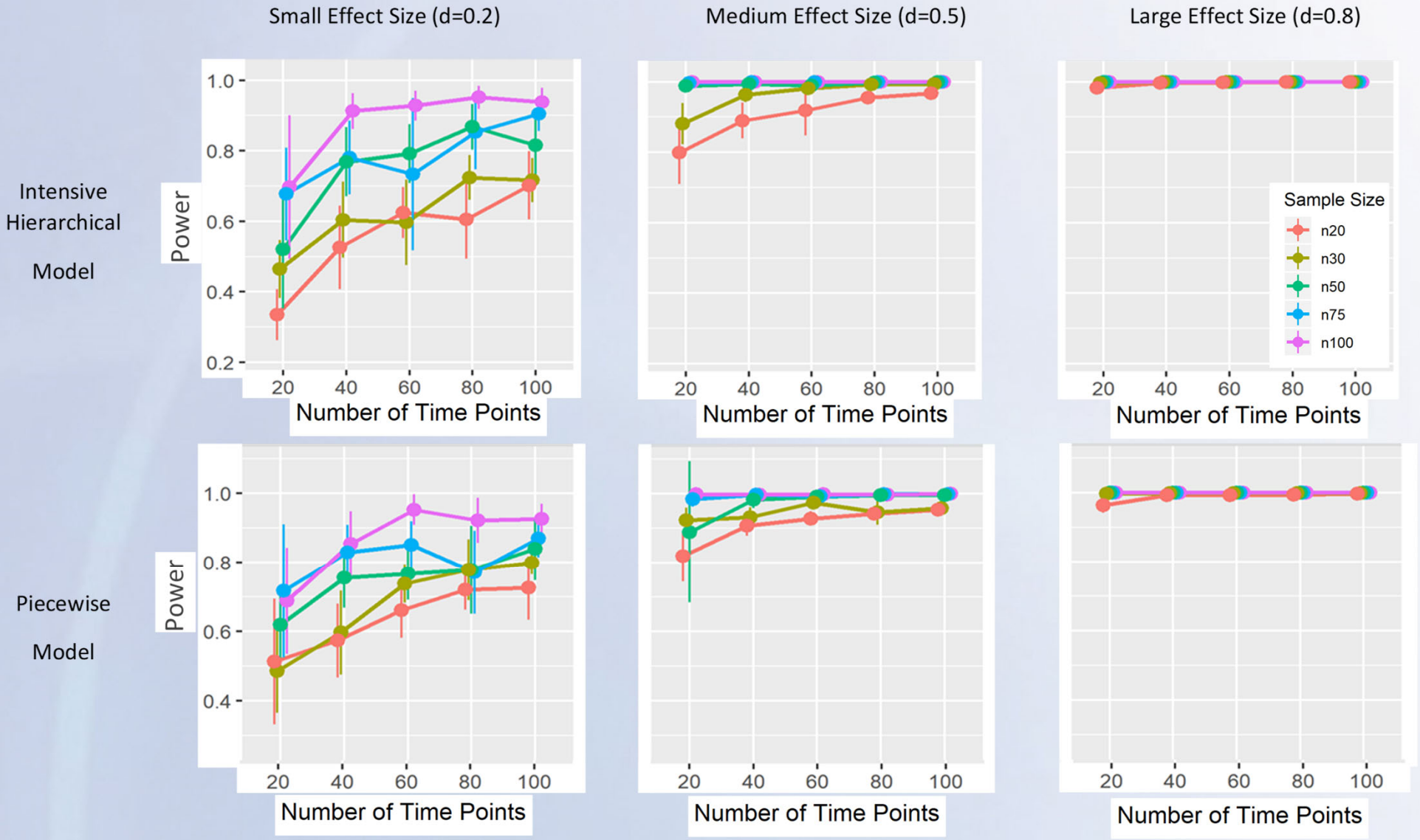
PersonAyltics High Throughput

- Personalized medicine: N-of-1 models for multiple patients
  - 776 patients recorded information on 71 potential migraine and non-migraine headache triggers (food, alcohol, weather, exercise, etc.)
  - Outcomes: severity of headache for migraine and non-migraine headaches
  - Research aim: find patient specific migraine triggers with the largest effect sizes to target interventions
  - 776 patients X 71 triggers X 2 headache types = 110,192 analyses
- Metabolomics: search for potential THC impairment detection metabolite
  - N=17 participants, with 20 observations over 6 hours in an ABA design
  - Multiple treatment orders and controlling for batch effects
  - Outcomes: sleepiness, reaction time, attention, memory, behavior
  - Research aim: find metabolites with the largest effect sizes on outcomes
  - 8 outcomes X 18,023 blood metabolites = 144,184 analyses
- Type I error correction or False Discovery Rate corrections

PersonAlyticsPower R Package

- Power Analysis for N-of-1 and small N intensive longitudinal designs, idiographic clinical trials (ICT), and interrupted time series
- Simulation based power analysis for any number of phases or groups
- Binary and normal outcomes (other distributions in development)
- User inputs are average intercepts and slopes in each phase and each group with standardized effect size differences
- Web based GUI in development
- https://github.com/ICTatRTI/PersonAlyticsPower

PersonAlytics Power Analysis



Debrief

* Introduction to ICTs
* Strengths and limitations
* Examples from the literature
* Recent and ongoing developments
* Areas of application

Idiographic Clinical Trials: What are They, When are They Useful, and Recent Developments

Ty A. Ridenour, Ph.D., M.P.E.
Developmental Behavioral Epidemiologist, RTI International
TRidenour@rti.org

Stephen J. Tueller, Ph.D.
Senior Research Statistician, RTI International
STueller@rti.org

Funded by NCATS (R21 TR002402), NIDA (P50-005605),
and RTI Game-changing Innovation Grants

PersonAlytics™ Team and Website: https://personalytics.rti.org/