Hierarchical models for combining N-of-1 trials

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Grants Funding this Work

- **N-of-1 Trials Using mHealth in Chronic Pain**
  National Institute of Nursing Research R01 NR13938
- **Using Single Subject (N-of-1) Designs to Answer Patient-Identified Research Questions**
  PCORI ME-16
- **Combining N-of-1 Trials to Assess Fibromyalgia Therapies**
  National Institute of Arthritis and Musculoskelatal and Skin Diseases R01 AR45416

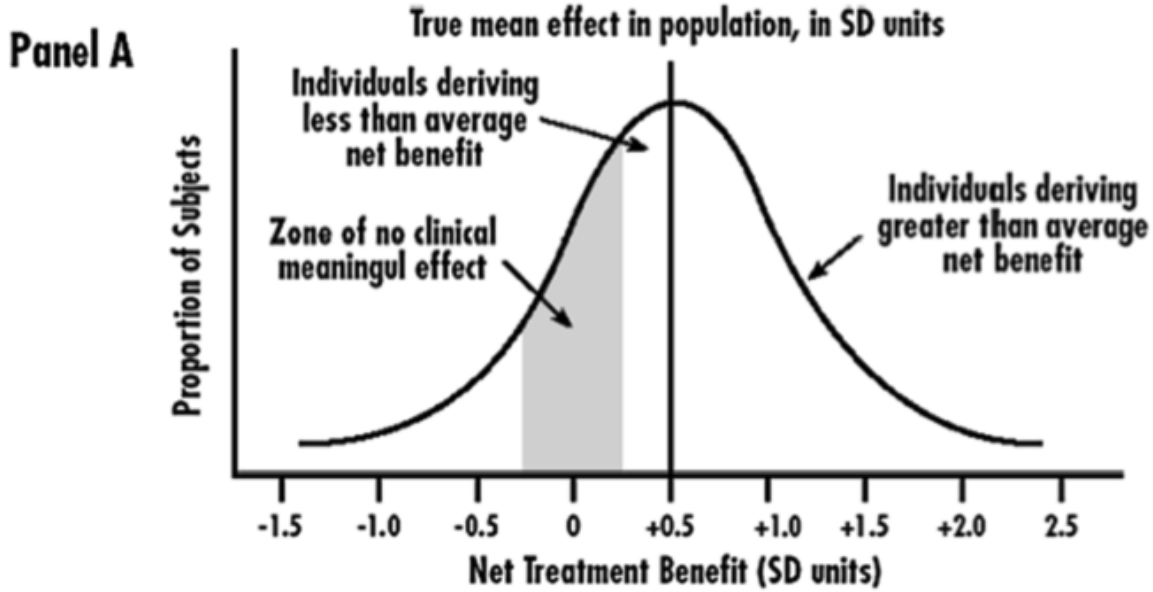
Joint work with Youdan Wang and members of the PREEMPT study

Outline

- Motivation for N-of-1 trials
- Design
- Analysis
- Combining N-of-1 trials
- Networks of N-of-1 Trials
- Example
- Ongoing Work

Heterogeneity of Treatment Effects

- Center based RCTs give average effects but
- Average effects may not (and in some cases, demonstrably do not) apply to the individual patient



Heterogeneity from a Crossover Trial

- Crossover trial with 19 patients treated for fibromyalgia (Goldenberg, 1996)
- Patients treated with combination of AM + FL did better than on either treatment alone
- But not all patients responded
- Improvement of $> 25\%$ compared to baseline in:
  - 5% Placebo
  - 24% AM
  - 32% FL
  - 62% AM+FL

N-of-1 Trials

- Single patient multiple period blocked crossover trials to estimate individual treatment effects
- Personalized protocol (personalized medicine)
  - Clinician and patient can design own study
  - Can select own (multiple) outcomes
  - Patients have more control over study design

- Multiple measurements per period
- Potential missing data
- Compare measurements in A periods with those in B periods

Indications

- Substantial therapeutic uncertainty about treatment
- Measureable, easily collected outcomes
- Heterogeneous treatment effects
- Stable chronic condition
- Short-acting treatments with rapid ramp-up
- Negligible persistence of treatment effect (no carryover)
- Outcome expected to return to baseline after each period

Kravitz and Duan (2014), AHRQ

Key Design Elements

- Pairing within patient
- Randomization or systematic counterbalanced design (AB/BA)
  - Usually each treatment once in each block
- Blinding
- Replication to assess within and between period variability
  - Number of study periods, number of measurements per period
  - Patients may not finish their protocol
- Washout period to control for carryover effects
  - May not be practical or ethical and may compromise design
  - Carryover hard to estimate unless many crossovers
  - Can downweight first measurements after each crossover

Schmid and Duan (2014), AHRQ

Examples of N of 1 Studies

Condition	**Sponsor**	**Outcome**	**Comparison**
Fibromyalgia	NIH	Impact scale	AM vs. AM + FL
ADHD	Australia	Sleep (kids)	Melatonin vs. None
Chronic Pain	NIH	Various	Various
IBD	PCORI	Various	Strict vs. relaxed diet
Atrial Fibrillation	PCORI	Episodes	Trigger vs. no trigger
Behavioral	WNYC	Various	Various

PREEMPT Study: Design

- Compares N-of-1 trials versus usual care for treating adults with chronic musculoskeletal pain
- 215 patients equally randomized
- Outcomes: Pain, Quality of life, Participatory decision making, Satisfaction, Trust, Adherence

Barr *et al* 2015, Trials

PREEMPT N-of-1 Study Arm Protocol

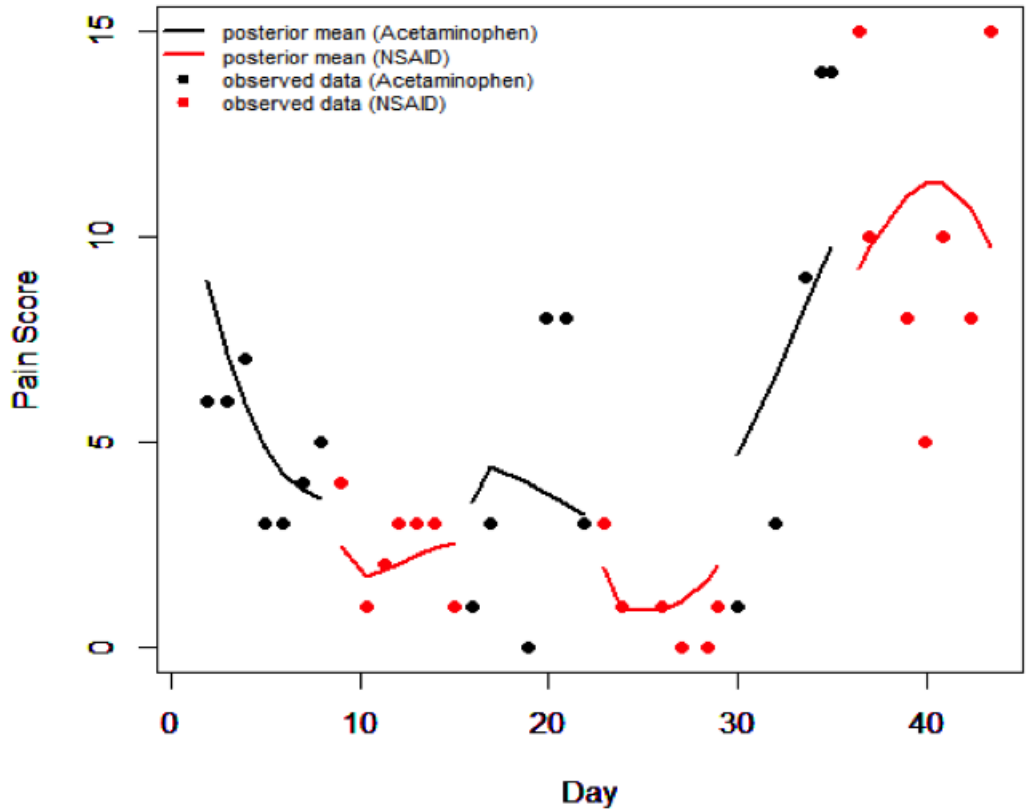
- Develop mobile application to conduct N-of-1 trials (108 patients)
- Compare 2 interventions within each patient
  - 1-2 week treatment periods
  - Cycle of 2 periods (2 to 4 weeks long, AB or BA)
  - Study of 2-4 cycles (4-16 weeks)
- Outcomes examined: pain, fatigue, drowsiness, sleep problems, cognitive function, constipation
- Choice of treatments by patient/clinician
- Measured daily by self-report
- Most are categorical, but pain treated as continuous

PREEMPT Treatments

- No treatment
- Tylenol (acetaminophen)
- NSAID (e.g., ibuprofen, naproxen, sulindac)
- Opiates
  - Codeine, tramadol, hydrocodone, oxycodone
  - Often in combination pill form with NSAID
- Non-pharmaceutical (self and professionally administered)
  - Complementary and alternative (e.g., yoga, massage)
  - Physical therapy
  - Exercise

Many patients also already on treatments that continue

N-of-1 Data Structure



- Structured time series with treatment factor
- Time trends and time-varying treatment effects
- Carryover
- Correlation

Basic N-of-1 Models

Treatment Effect Model

$$y_j = \mu + \delta z_j + \epsilon_j; j = 1, 2, \ldots, J$$

$$\epsilon_j \sim N(0, \sigma^2)$$

y_j: measurement j for outcome y
z_j: treatment indicator; $z_j = 1$ if tx B and 0 if tx A

Basic N-of-1 Models

Treatment Effect Model

$$y_j = \mu + \delta z_j + \epsilon_j; j = 1, 2, \ldots, J$$

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Treatment and Linear Time Trend Model

$$y_j = \mu + \delta z_j + \beta t_j + \epsilon_j; j = 1, 2, \ldots, J$$

$$\epsilon_j \sim N(0, \sigma^2)$$

t_j: time of jth measurement

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Treatment and Linear Time Trend and Correlated Error Model

$$y_j = \mu + \delta z_j + \beta t_j + \epsilon_j; j = 1, 2, \ldots, J$$

$$\epsilon_j = \rho \epsilon_{j-1} + u_j$$

$$u_j \sim N(0, \sigma^2)$$

Model for Single N-of-1 Trial

$$y_j = \mu + \delta z_j + F(t_j) + \epsilon_j; j = 1, 2, \ldots, J$$

$$\epsilon_j = \epsilon_{j-1} + u_j$$

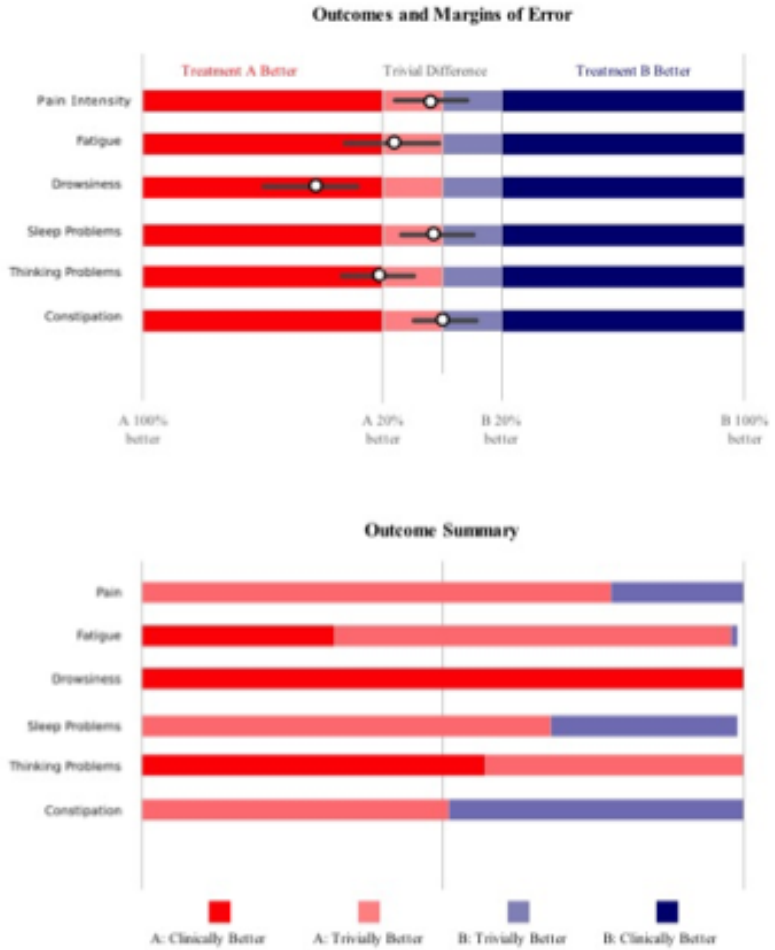
$$u_j \sim N(0, \sigma^2)$$

$F(t_j)$: Time trend e.g. $F(t_j) = \boldsymbol{B}(t_j)\boldsymbol{\gamma} = \sum_{m=1}^{M} \gamma_m B_m(t_j)$ is spline

Rationale for Using Bayesian Models

- Personalized nature of decision
- Need to incorporate external information (patient, clinician)
- Interpretation of probability that one treatment better than other
- Lack of sufficient data for standard methods to return 'significant' result
- Joint posterior distribution for composite statements about multiple outcomes
- Can also combine multiple N-of-1 studies together to get both average treatment effect and better individual treatment effects through borrowing of strength

Graphs


Outcomes and Margins of Error
Treatment A Better
Trivial Difference
Treatment B Better
Pain Intensity
Fatigue
Drowsiness
Sleep Problems
Thinking Problems
Constipation
A 100% better
A 20% better
B 20% better
B 100% better
Outcome Summary
Pain
Fatigue
Drowsiness
Sleep Problems
Thinking Problems
Constipation
A: Clinically Better
A: Trivially Better
B: Trivially Better
B: Clinically Better

Extension to Multiple N-of-1 Trials

$$y_{ij} = \mu_i + \delta_i z_{ij} + F(t_{ij}) + \pi_{z_{i(j-u)}, z_{ij}} + \epsilon_{ij}$$

$$\epsilon_{ij} = \rho \epsilon_{i(j-1)} + u_{ij}$$

$$u_{ij} \sim N(0, \sigma^2)$$

$$i = 1, \ldots, N; j = 1, 2, \ldots, J_i$$

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π_{z_{j-U}, z_j}: Carryover lasts for U time units after changing treatment
$F(t_j)$: Time trend e.g. $F(t_j) = \boldsymbol{B}(t_j)\boldsymbol{\gamma} = \sum_{m=1}^{M} \gamma_m B_m(t_j)$ is spline

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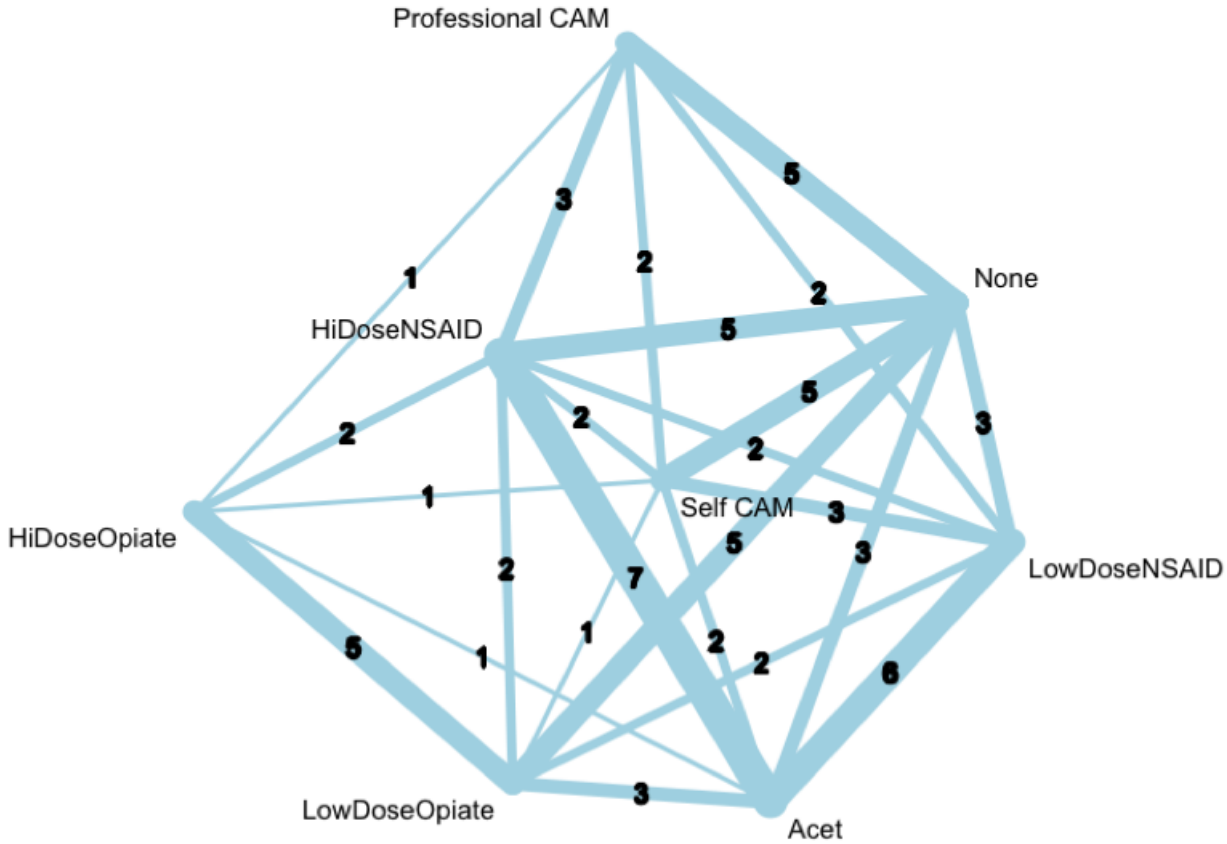
- Random effect for δ_i, e.g., $\delta_i \sim N(d, \sigma_\delta^2)$
- Fixed or random effect for μ_i
- $\pi_{z_{i(j-u)},z_{ij}}$, ρ constant across patients
- Can estimate carryover effect across patients
- May want to use common within-patient variance $\sigma_i^2 = \sigma^2$

Multilevel Model Combining N-of-1 Studies

- Consider each N-of-1 trial as a study and combine via meta-analysis
- Population estimate of treatment efficacy, d
- Improved estimates for individuals by borrowing strength δ_i
- Including covariates enables subgroup estimates
- Compromise between population estimate (complete pooling) and individual's observed results (no pooling)
  - Weighted to observed if low variation or many crossovers
  - Weighted to pooled (or subgroup) if little information for individual
- Helps make treatment decision if individual outcomes equivocal
- May also permit more complex modeling of short series

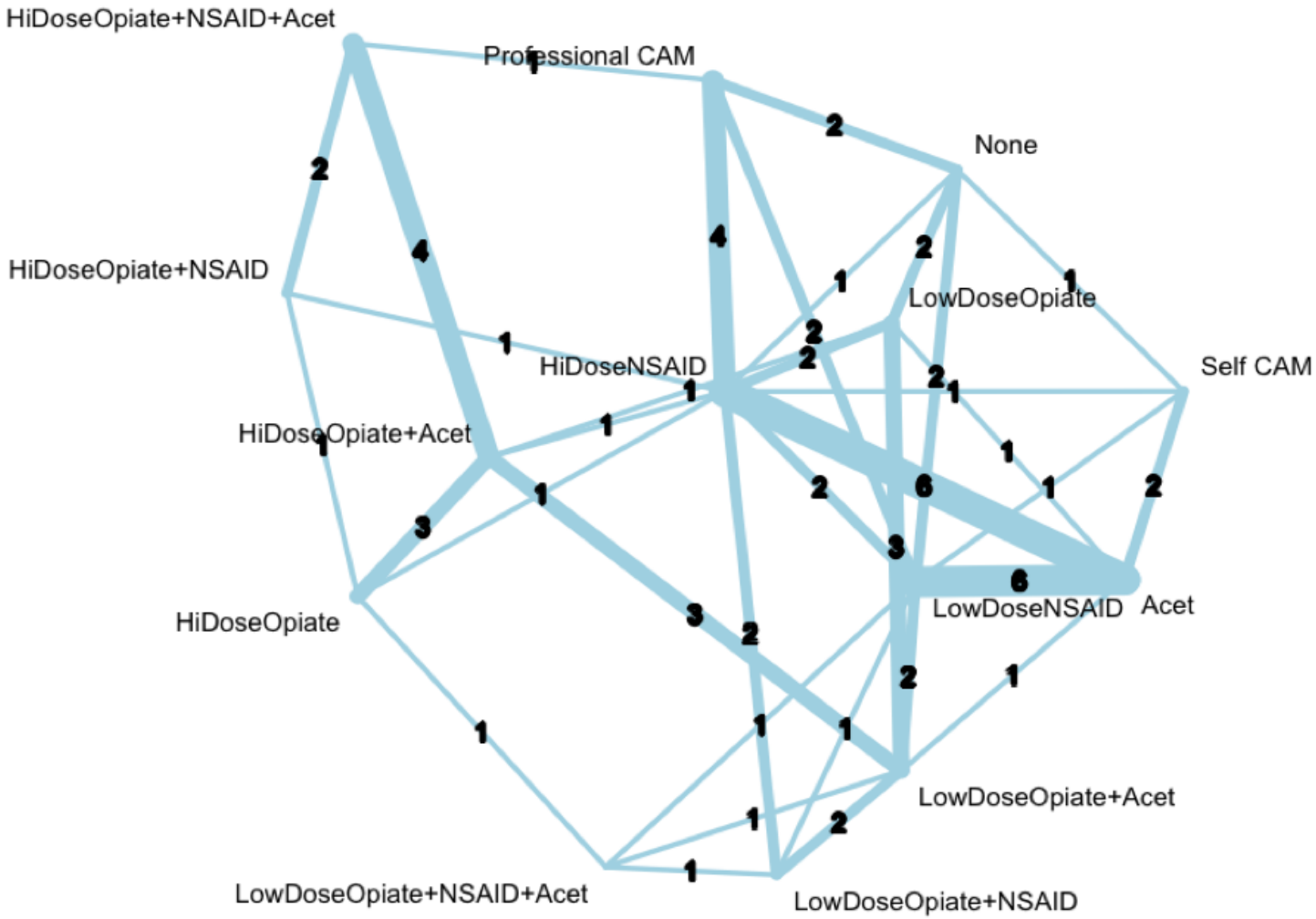
Zucker, Schmid, et al (1997), J Clin Epi

Network With Patient Chosen Treatment Comparisons



Treatment A	**Treatment B**	Concomitant Treatment
Naproxen 1000 mg	None	Hydrocodone 40 ME, Acet. 2600 mg

Expanded Network Using Concomitant Treatments

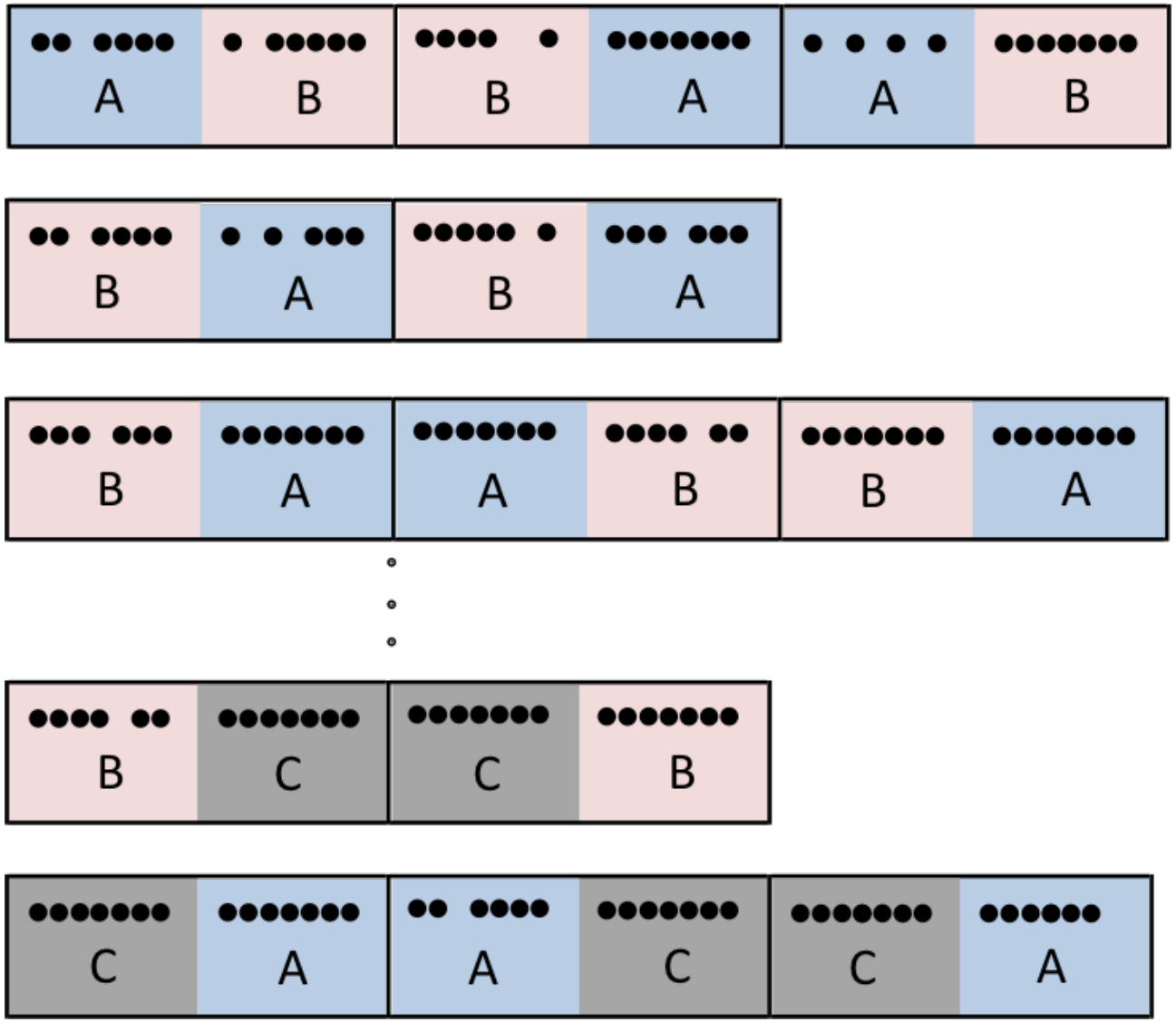


Network Meta-Analysis

- Combine direct + indirect estimates of multiple treatment effects
- Internally consistent set of estimates that respects randomization
- Estimate effect of each intervention relative to every other whether or not there is direct comparison in studies
- Calculate probability that each treatment is most effective
- Compared to conventional pair-wise meta-analysis:
  - Greater precision in summary estimates
  - Ranking of treatments according to effectiveness or safety

Lu and Ades (2006, JASA)

N-of-1 Network Data Structure



Extension to Network of N-of-1 Trials

- $\mathcal{R} = \{1, 2, ..., K\}$: complete treatment set
- $\mathcal{R}_i = \{r_{i1}, ..., r_{ik_i}\}$: treatment set for patient i
- r_{i1}: base treatment for patient i
- k_i: total number of treatments for patient i

Extension to Network of N-of-1 Trials

$$y_{ij} = G(Z_{ij}) + F(t_{ij}) + \pi_{z_{i(j-u)}, z_{ij}} + \alpha y_{i(j-1)} + \epsilon_{ij}, i = 1, \ldots, N; j = 1, 2, \ldots, J$$

where

$$G(Z_{ij}) = \begin{cases} \mu_i \text{ if } z_{ij} = r_{i1}, \\ \mu_i + \delta_{i, r_{i1} z_{ij}} \text{ if } z_{ij} \succ r_{i1}, \end{cases}$$

$$\delta_i = \left(\delta_{i, r_{i1} r_{i2}}, \ldots, \delta_{i, r_{i1} r_{ik_i}} \right) \sim N \left(P_i \Delta, P_i \Sigma P_i^T \right)$$

$$\Delta = (d_{r_1 r_2}, \ldots, d_{r_1 r_K})$$

Under consistency,

$$d_{r_{ij} r_{ij'}} = d_{1 r_{ij'}} - d_{1 r_{ij}}$$

with $d_{11} = 0$ and Σ is a matrix often simplified to have constant variances on the diagonal and a correlation of 0.5 satisfying the consistency equations

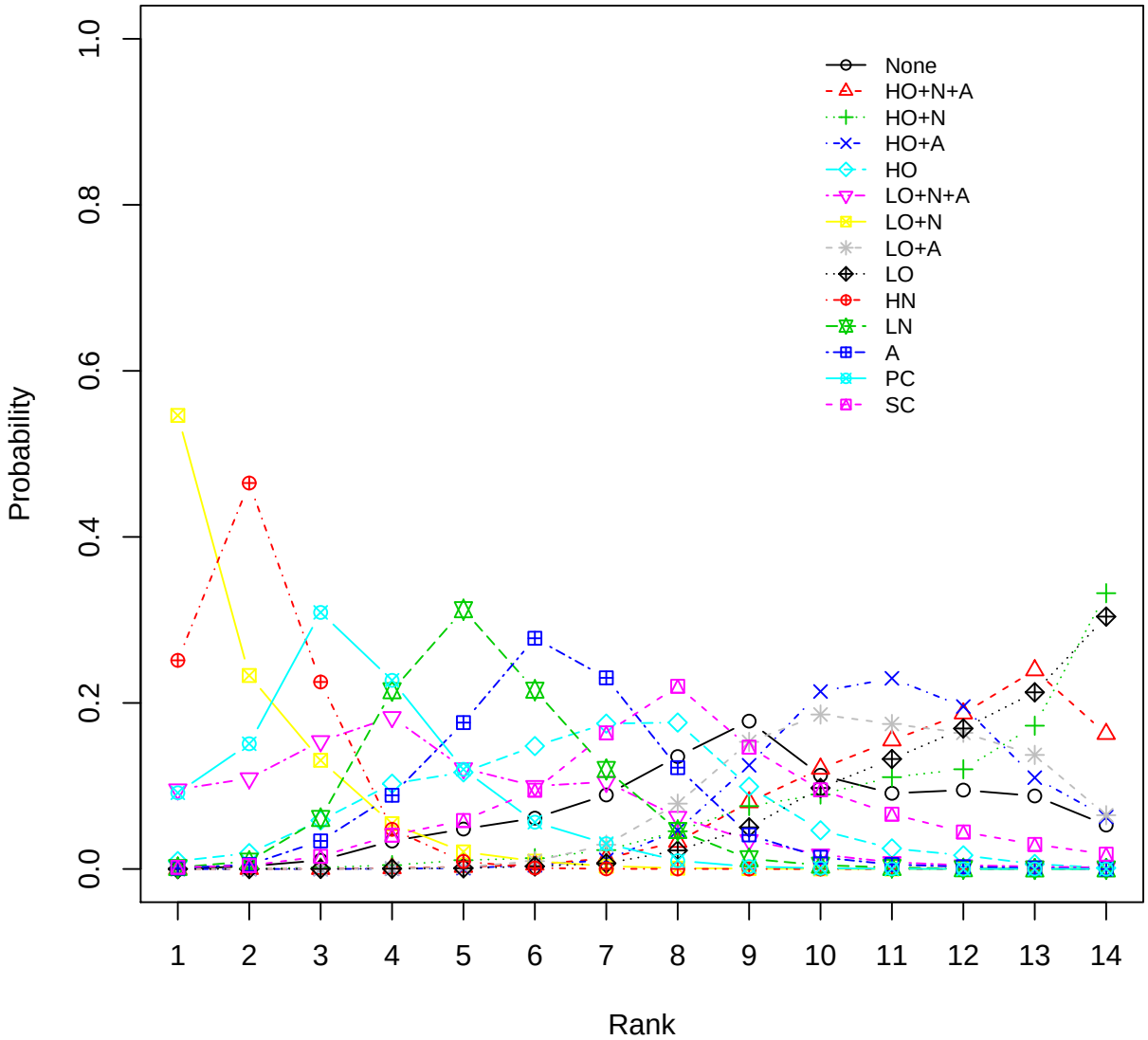
Results: Network Meta-Analysis Basic Treatment Effects

	Posterior Percentile		
Treatment	**2.5**	**50**	**97.5**
2	-1.56	0.83	3.66
3	-1.87	1.06	4.41
4	-1.66	0.56	2.98
5	-3.56	-0.95	1.87
6	-4.64	-1.76	1.25
7	**-5.60**	**-3.08**	**-0.59**
8	-1.82	0.51	2.92
9	-1.16	1.08	3.38
10	**-5.09**	**-2.78**	**-0.61**
11	-3.40	-1.46	0.64
12	-3.33	-1.10	1.17
13	-4.58	-2.14	0.18
14	-2.99	-0.51	2.40

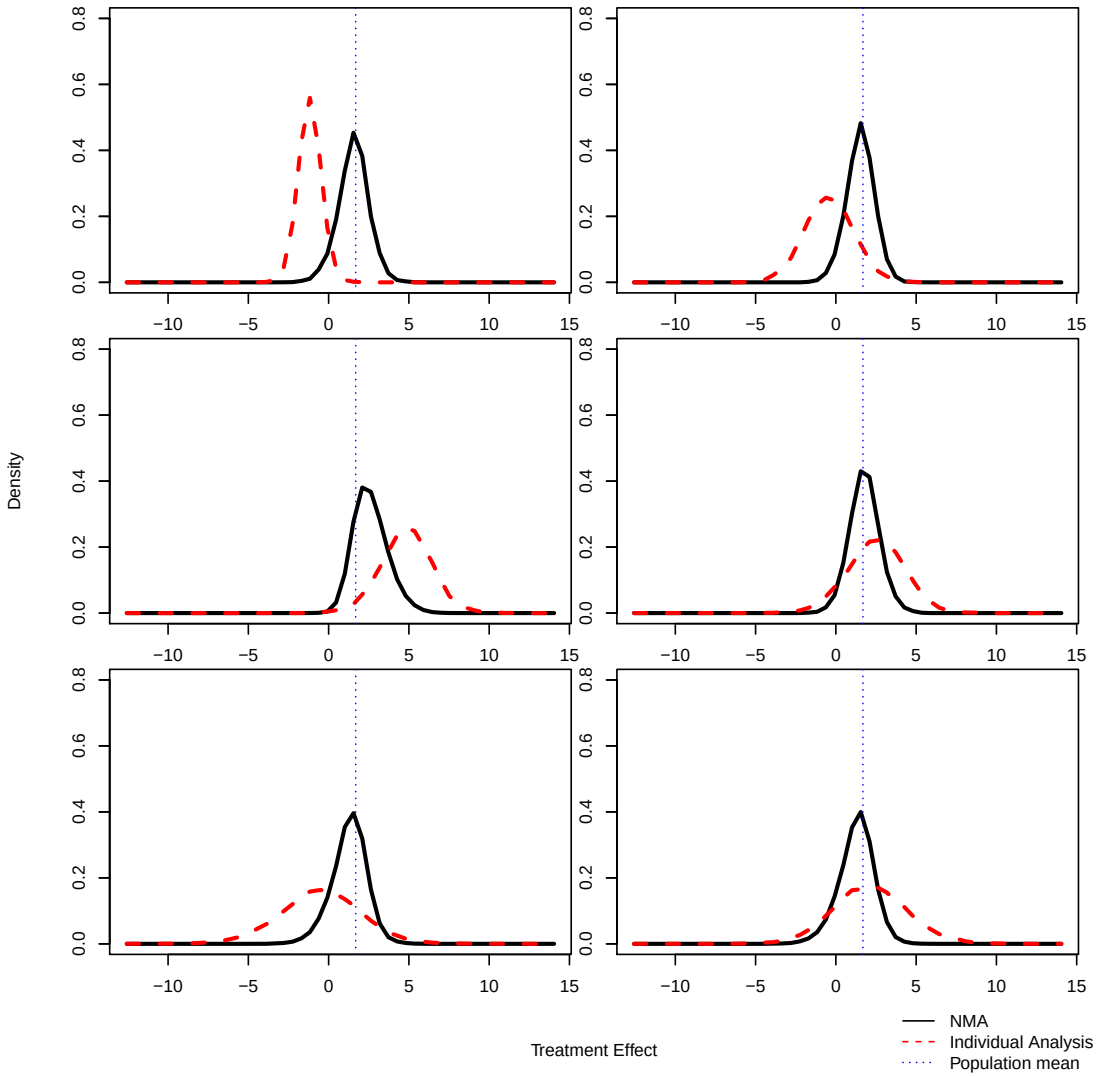
Results: Network Meta-Analysis Treatment Effects

	2	3	4	5	6	7	8	9	10	11	12	13	14
1	0.91	1.10	0.60	-0.90	-1.74	-3.09	0.54	1.10	-2.78	-1.41	-1.10	-2.16	-0.42
2		0.18	-0.31	-1.81	-2.66	-4.00	-0.37	0.18	-3.70	-2.33	-2.01	-3.08	-1.33
3			-0.50	-2.00	-2.84	-4.19	-0.56	0.00	-3.88	-2.51	-2.19	-3.26	-1.51
4				-1.50	-2.35	-3.69	-0.06	0.49	-3.39	-2.02	-1.70	-2.77	-1.02
5					-0.85	-2.19	1.44	1.99	-1.89	-0.52	-0.20	-1.27	0.48
6						-1.35	2.29	2.84	-1.04	0.33	0.65	-0.42	1.33
7							3.63	4.18	0.31	1.68	1.99	0.93	2.67
8								0.55	-3.33	-1.96	-1.64	-2.71	-0.96
9									-3.88	-2.51	-2.19	-3.26	-1.51
10										1.37	1.69	0.62	2.37
11											0.32	-0.75	1.00
12												-1.07	0.68
13													1.75

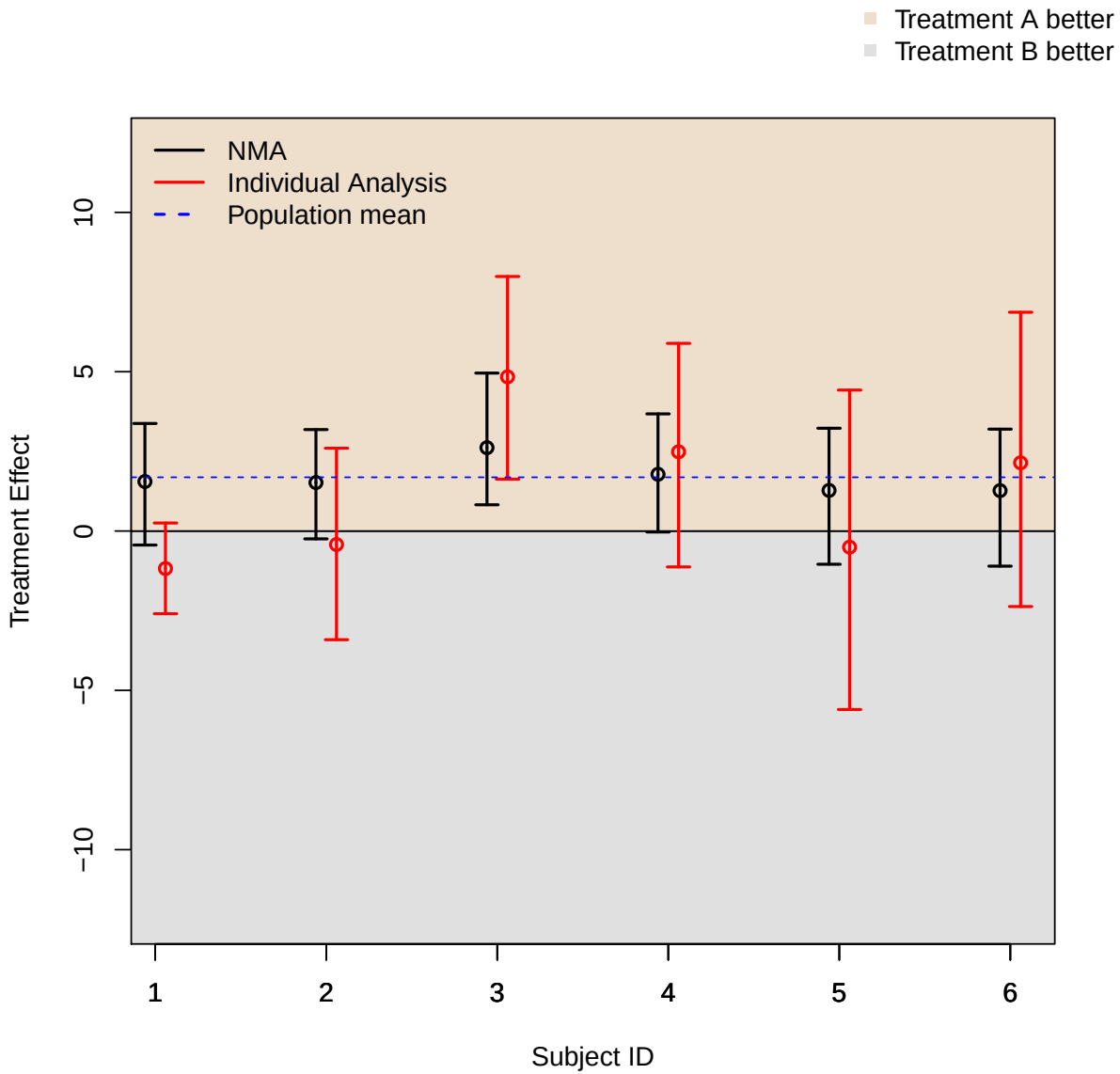
Network Meta-Analysis Treatment Rankings



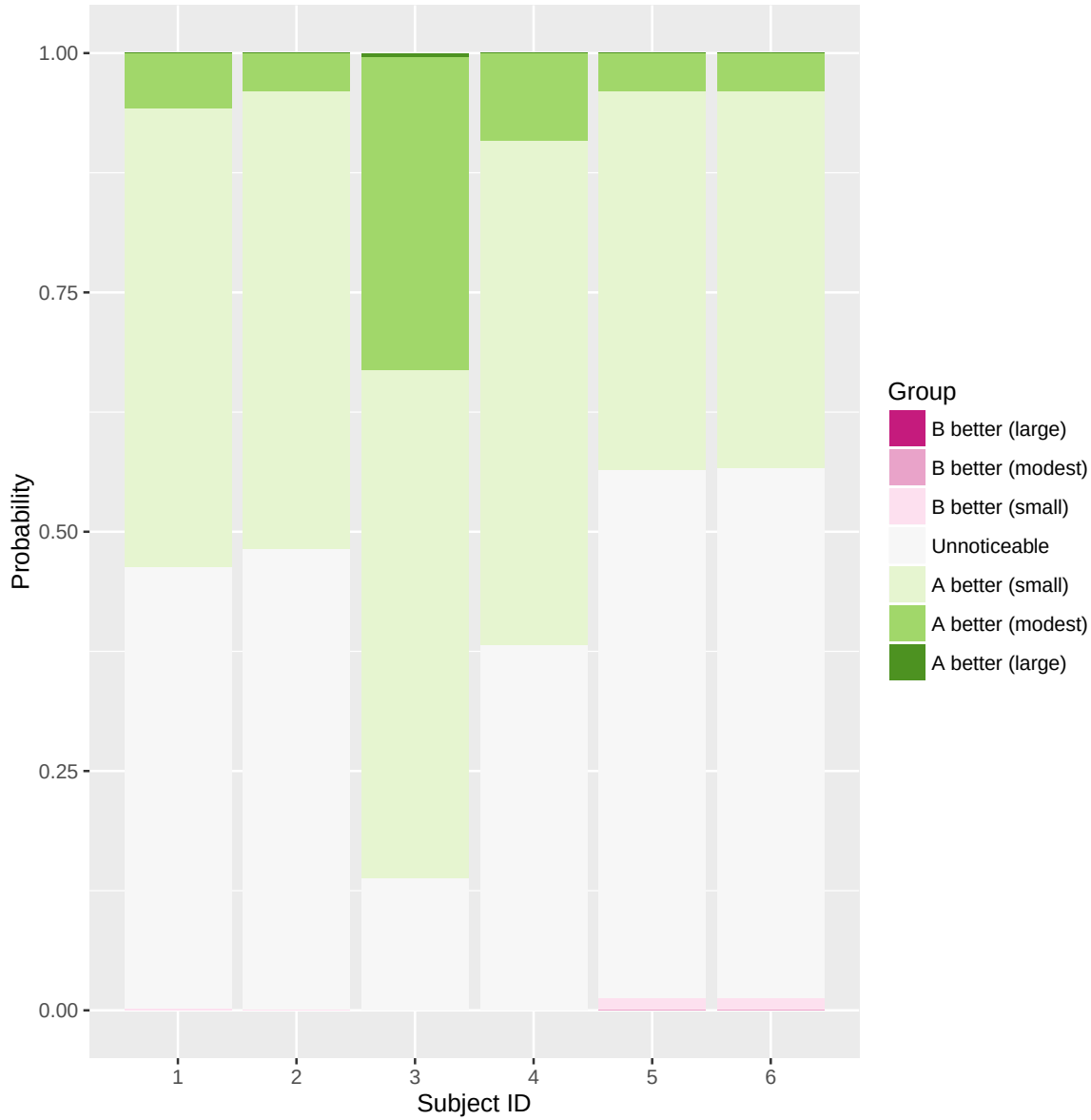
Density Plots for Six Patients who compared high dose NSAIDs vs. acetominophen



Meta-Analysis vs Individual Analysis



Posterior Probabilities of Six Patients from Meta-Analysis



Ongoing Work

- Categorical outcomes
- Inconsistency models
- Missing data
- Simulations
- Improved computing
- Software

Thank you!