Hierarchical models for combining N-of-1 trials

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ICHPS
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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 Musculoskeletal 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

<table>
<thead>
<tr>
<th>Condition</th>
<th>Sponsor</th>
<th>Outcome</th>
<th>Comparison</th>
</tr>
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<tbody>
<tr>
<td>Fibromyalgia</td>
<td>NIH</td>
<td>Impact scale</td>
<td>AM vs. AM + FL</td>
</tr>
<tr>
<td>ADHD</td>
<td>Australia</td>
<td>Sleep (kids)</td>
<td>Melatonin vs. None</td>
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<tr>
<td>Chronic Pain</td>
<td>NIH</td>
<td>Various</td>
<td>Various</td>
</tr>
<tr>
<td>IBD</td>
<td>PCORI</td>
<td>Various</td>
<td>Strict vs. relaxed diet</td>
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<tr>
<td>Atrial Fibrillation</td>
<td>PCORI</td>
<td>Episodes</td>
<td>Trigger vs. no trigger</td>
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<tr>
<td>Behavioral</td>
<td>WNYC</td>
<td>Various</td>
<td>Various</td>
</tr>
</tbody>
</table>
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

\[ y_j = \mu + \delta z_j + \epsilon_j; \quad j = 1, 2, \ldots, J \]

\[ \epsilon_j \sim N(0, \sigma^2) \]

\( y_j \): 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

\[ y_j = \mu + \delta z_j + \epsilon_j; j = 1, 2, \ldots, J \]
\[ \epsilon_j \sim N(0, \sigma^2) \]

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 \( j \)th measurement
Basic N-of-1 Models

Treatment Effect Model

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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. \( F(t_j) = B(t_j)\gamma = \sum_{m=1}^{M} \gamma_m B_m(t_j) \) 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
Extension to Multiple N-of-1 Trials

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

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

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

\[ i = 1, \ldots, N; j = 1, 2, \ldots, J_i \]
Extension to Multiple N-of-1 Trials

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

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\[ i = 1, \ldots, N; j = 1, 2, \ldots, J_i \]

\( \pi_{z_{j-u},z_j} \): Carryover lasts for \( U \) time units after changing treatment

\( F(t_j) \): Time trend e.g. \( F(t_j) = B(t_j)\gamma = \sum_{m=1}^{M} \gamma_mB_m(t_j) \) is spline
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\[ i = 1, \ldots, N; j = 1, 2, \ldots, J_i \]

\( \pi_{Z_{j-u},Z_j} \): Carryover lasts for \( U \) time units after changing treatment

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

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

Network With Patient Chosen Treatment Comparisons

<table>
<thead>
<tr>
<th>Treatment A</th>
<th>Treatment B</th>
<th>Concomitant Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen 1000 mg</td>
<td>None</td>
<td>Hydrocodone 40 ME, Acet. 2600 mg</td>
</tr>
</tbody>
</table>
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
\( \mathcal{R} = \{1, 2, \ldots, K\} \) : complete treatment set
\( \mathcal{R}_i = \{r_{i1}, \ldots, r_{ik_i}\} \): 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

\[ y_{ij} = G(Z_{ij}) + F(t_{ij}) + \pi z_{i(j-u),z_{ij}} + \alpha y_i(j-1) + \epsilon_{ij}, \quad i = 1, \ldots, N; \quad j = 1, 2, \ldots, J \]

where

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

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

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

Under consistency,

\[ d_{r_{ij}r_{ij'}} = d_{1r_{ij'}} - d_{1r_{ij}} \]

with \( d_{11} = 0 \) and \( \Sigma \) 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

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<thead>
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<th>Treatment</th>
<th>2.5</th>
<th>50</th>
<th>97.5</th>
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<td>0.83</td>
<td>3.66</td>
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<tr>
<td>3</td>
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<td>1.06</td>
<td>4.41</td>
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<tr>
<td>4</td>
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<tr>
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<td>14</td>
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<td>-0.51</td>
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## Results: Network Meta-Analysis Treatment Effects

<p>| | | | | | | | | | | | | |</p>
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</tbody>
</table>
Density Plots for Six Patients who compared high dose NSAIDs vs. acetaminophen
Meta-Analysis vs Individual Analysis

![Graph showing treatment effects and subject IDs]

- Treatment A better
- Treatment B better

Christopher Schmid
11 January 2018
Posterior Probabilities of Six Patients from Meta-Analysis

<table>
<thead>
<tr>
<th>Subject ID</th>
<th>Probability</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.00</td>
<td>B better (large)</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>B better (modest)</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>B better (small)</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>Unnoticeable</td>
</tr>
<tr>
<td></td>
<td>0.25</td>
<td>A better (small)</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>A better (modest)</td>
</tr>
<tr>
<td></td>
<td>0.75</td>
<td>A better (large)</td>
</tr>
</tbody>
</table>

Group colors:
- B better (large) in purple
- B better (modest) in pink
- B better (small) in green
- Unnoticeable in yellow
- A better (small) in light green
- A better (modest) in medium green
- A better (large) in dark green
Ongoing Work

- Categorical outcomes
- Inconsistency models
- Missing data
- Simulations
- Improved computing
- Software
Thank you!