Longitudinal Designs in Therapeutic Designs in Rare Disorder -

Rima Izem, PhD
Acknowledgements and References

- Children’s National Research Institute: Robert McCarter, Urea Cycle Disorders Network
  - Izem, R., McCarter R, Randomized and non-randomized designs for causal inference with longitudinal data in rare disorders. To appear at Orphanet Journal of Rare Diseases

- Berkeley forum: rare diseases working group
Some innovations in design and analysis

- Design and analytical choices
  - Longitudinal designs (e.g., repeated measures studies)
  - Borrowing information (e.g., leveraging adult or historical data, use of external control)
  - Adaptive design strategies (e.g., adaptive randomization, master protocols)
  - Qualifying new biomarkers or new endpoints

- Leveraging novel resources (e.g., real-world-data, rare diseases networks, electronic data capture)
UCD Example

- **Urea Cycle Disorder (UCD)**
  - Rare, multiple mutations, varying clinical severity
  - Treatments include: medical management (nitrogen scavenger therapies, low protein diet), **liver transplant**

- Data source: UCD consortium Natural History Epidemiologic Database
  - Multicenter, multinational, longitudinal study*
  - >13 years of data on >800 subjects, 5-16 sites, 4 countries

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Randomized trial vs. epi study

- Randomized studies control for **all confounding through randomization**
  - Parallel Arms, factorial designs
  - Crossover, and N-1
  - Sequential randomization studies

- Epidemiological studies control for **some confounding through assumptions, matching, weighting, and/or modeling**
  - Cohort study or case control
  - Self-control case series or case-crossover
  - Sequential control for confounding

5
UDC: N-1 randomized Study

- Study subject OTCD female > 45 years of age, did not take L-arginine for a few months prior to study
- Trial over a 6-week period, 3 paired weeks (L-arginine and placebo pairs), blinded to treatment physician and patient

### Table 1
Weekly efficacy indicators comparing placebo and L-arginine treatments

<table>
<thead>
<tr>
<th>Efficacy indicator</th>
<th>Pair 1</th>
<th></th>
<th>Pair 2</th>
<th></th>
<th>Pair 3</th>
<th></th>
<th>Mean</th>
<th></th>
<th>Paired t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>0-Tail</td>
</tr>
<tr>
<td>Day</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>5</td>
<td>6</td>
<td>5 + 6</td>
<td>5 + 6</td>
<td>0.0162*</td>
</tr>
<tr>
<td>Questionnaire score</td>
<td>3.1</td>
<td>1.5</td>
<td>5.5</td>
<td>5.8</td>
<td>5.4</td>
<td>4.9</td>
<td>3.3</td>
<td>5.3</td>
<td>0.122</td>
</tr>
<tr>
<td>Plasma arginine μmol/L</td>
<td>102</td>
<td>156</td>
<td>60</td>
<td>148</td>
<td>91</td>
<td>108</td>
<td>84</td>
<td>138</td>
<td>0.061</td>
</tr>
<tr>
<td>Plasma glutamine μmol/L</td>
<td>716</td>
<td>611</td>
<td>628</td>
<td>539</td>
<td>690</td>
<td>471</td>
<td>678</td>
<td>540</td>
<td>0.039*</td>
</tr>
</tbody>
</table>

Plasma arginine reference range: 34–118 μmol/L.
Plasma glutamine reference range: 385–862 μmol/L.
* Significant at $P < 0.05$.

Risk set matching, illustration in UCD

Liver Transplant → ? → Quality of life

(Risk set analysis) Compared to medical management until cohort entry

Confounding
disease severity, patient medical history

(Risk set analysis) Control for confounding through sequential matching at different age of transplant

PedQL
Risk Set matching – illustration in UCD (continued)

At strata age = 63 days
Determine the eligible set for transplantation

**Match** those with liver transplant at age **63 days** with those without transplant in risk set

At strata age = 69 days
Determine the eligible set for transplantation

**Match** those with liver transplant at age **69 days** with those without transplant in risk set


General considerations in using longitudinal designs

- Incorporating self-control can increase analyses units and reduce heterogeneity.
- Longitudinal designs are better suited for short causal pathway between exposure and outcome.
- Duration of each observation period is a critical design attribute, and specific to outcome, population and therapies.
- Analytical considerations: matching or weighting to adjust for confounding; hierarchical models and adjustment for within subject association.
Thank you
UCD: Findings on liver transplantation and additional challenges with heterogeneity

- Liver transplant was curative in managing hyperammonemia
- After control for disease severity, there was no difference in mortality or quality of life between liver transplant and medical management
- Same groups emerged in eligibility set with different methods (ps matching/weighting, risk set matching):
  - “Comparable groups” of medically managed and transplanted.
  - Incomparable groups include: (1) those with severe medical history that died early (2) those with severe medical history that would always receive transplant (3) those with less severe medical history that did not receive liver transplant
  (How can we inform inference in these groups?)