Statistical Methodology and Consulting

Longitudinal Designs in Therapeutic Designs in Rare Disorder -

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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*
  - Ah Mew N, McCarter R, Izem R, et al. (2020). Comparing Treatment Options for Urea Cycle Disorders. Patient-Centered Outcomes Research Institute (PCORI).
- Berkeley forum: rare diseases working group

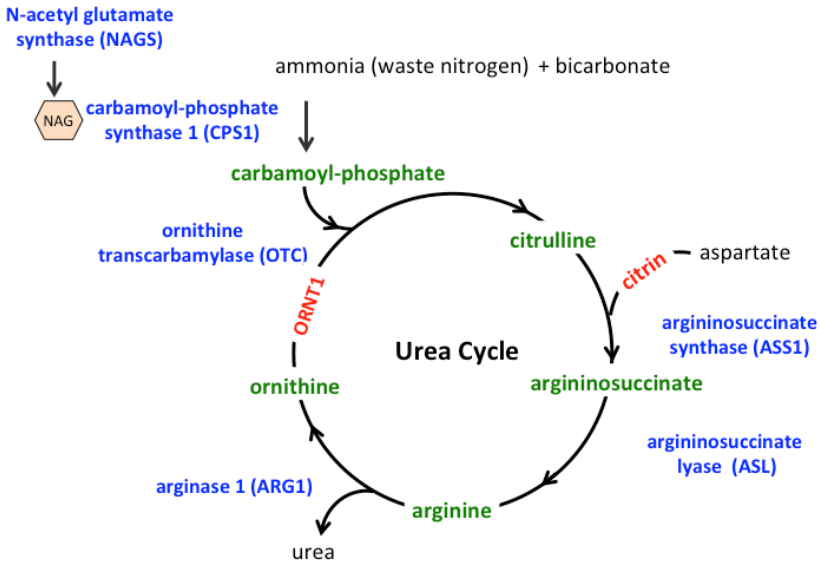
Some innovations in design and analysis

- 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



RARE CLINICAL DISEASES RESEARCH NETWORK
National Institutes of Health

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Randomized trial vs. epi study

- Randomized studies control for **all confounding** through **randomization**

- Epidemioligical studies control for **some confounding** through assumptions, **matching, weighting, and/or modeling**

- Parallel Arms, factorial designs → Cohort study or case control

- Crossover, and N-1 → Self-control case series or case-crossover

- Sequential randomization studies → Sequential control for confounding

UCD: 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

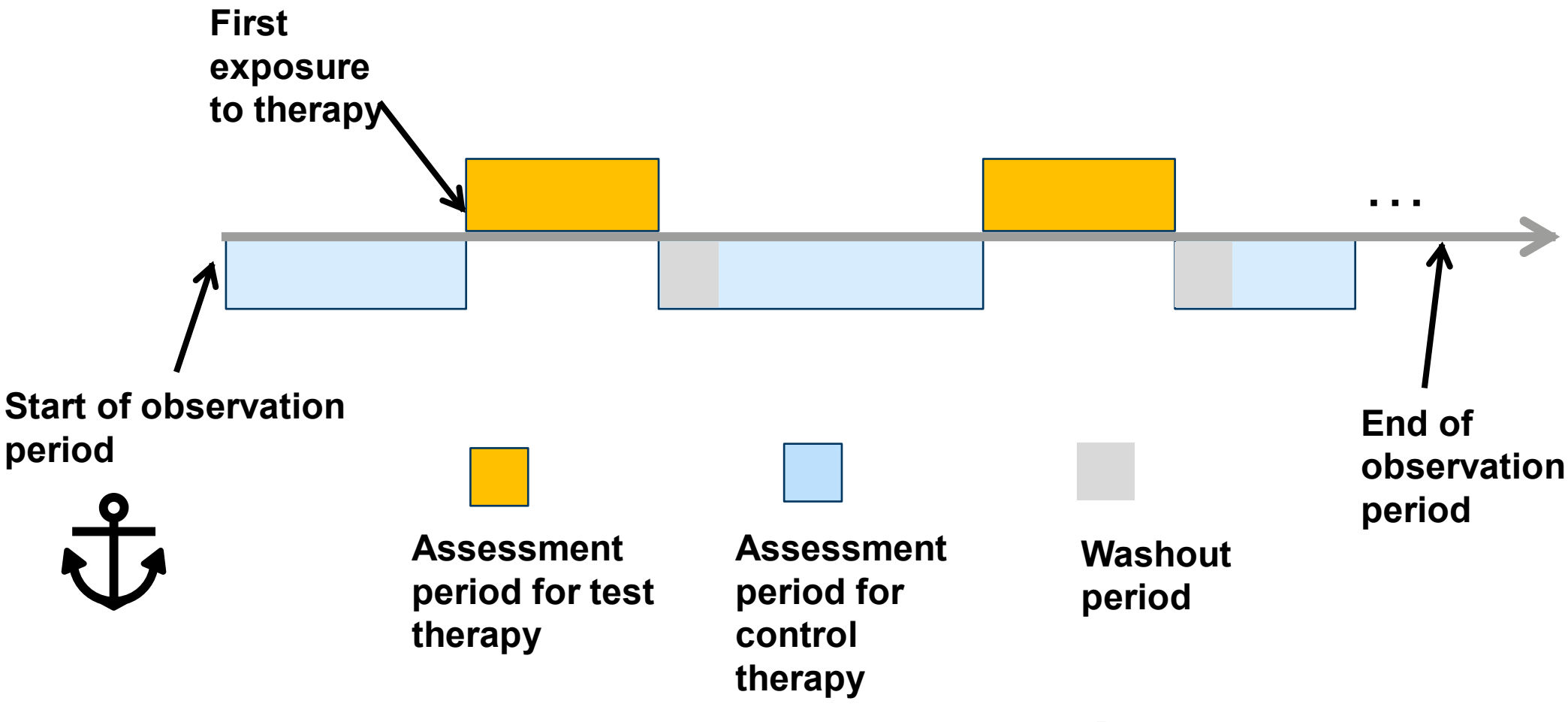
Table 1
Weekly efficacy indicators comparing placebo and L-arginine treatments

Efficacy indicator	Pair 1				Pair 2				Pair 3				Mean		Paired *t*-test	
	Placebo		Active		Placebo		Active		Placebo		Active		Placebo	Active	0-Tail	1-Tail
	Day				Day				Day							
	5	6	5	6	5	6	5	6	5	6	5	6	5 + 6	5 + 6		
Questionnaire score	3.1	1.5	5.5	5.8	5.4	4	5.7	4.9	2.7	3.2	5	5.1	3.3	5.3	0.0162*	
Plasma arginine μmol/L	102		156		60		148		91		108		84	138	0.122	0.061
Plasma glutamine μmol/L	716		611		628		539		690		471		678	540	0.078	0.039*

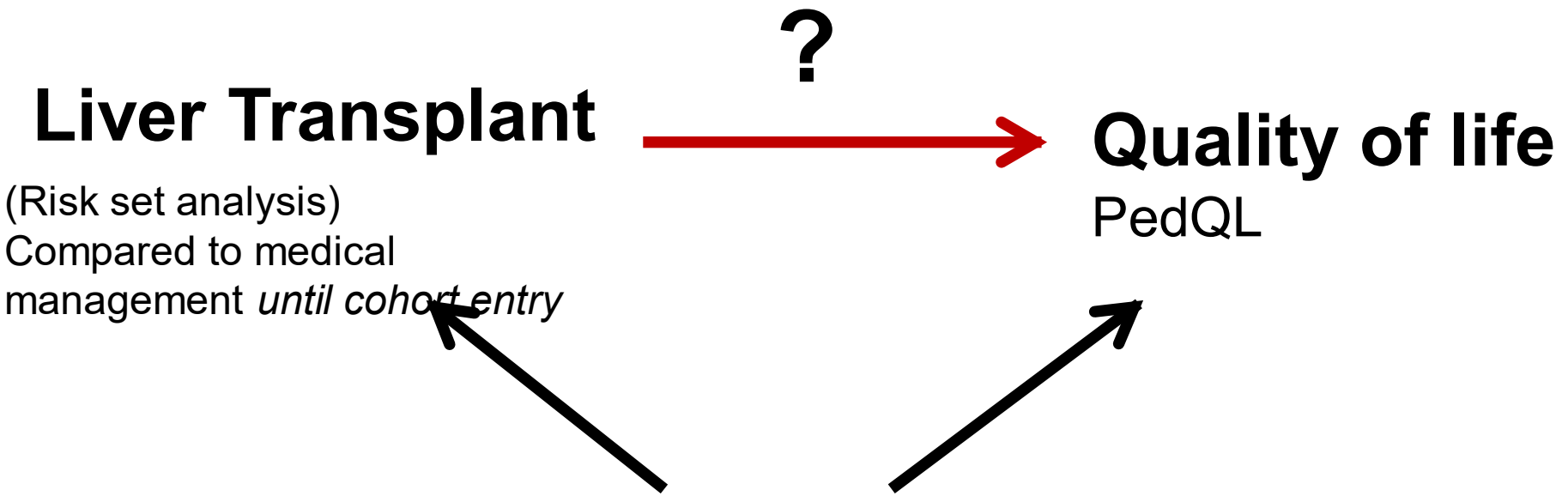
Plasma arginine reference range; 34–118 μmol/L.
Plasma glutamine reference range; 385–862 μmol/L.
* Significant at $P < 0.05$.

Source: Hackett A, Gillard J, Wilcken B: n of 1 trial for an ornithine transcarbamylase deficiency carrier. Mol Genet Metab 2008, 94:157–161.

Self-controlled designs, Case-series

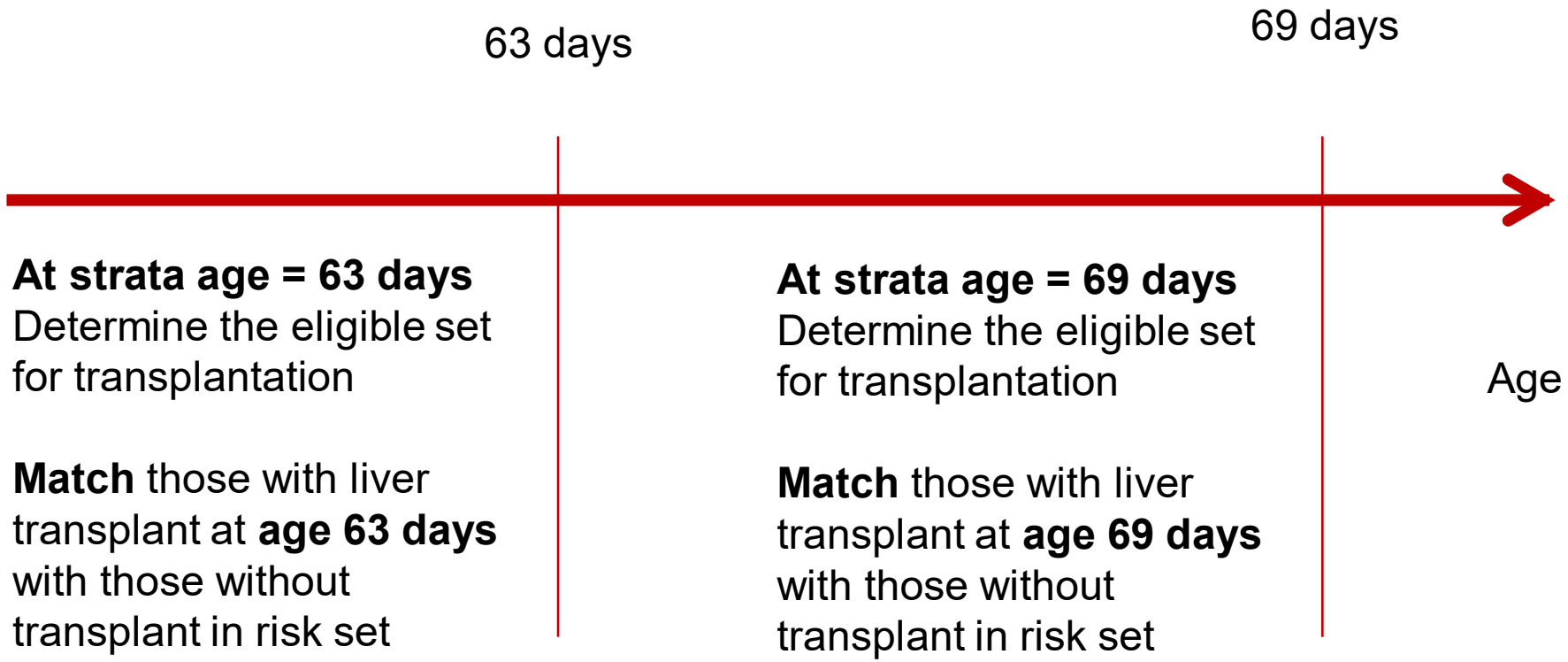


Risk set matching, illustration in UCD



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

Risk Set matching – illustration in UCD (continued)



Ref for risk set matching: Li, Y.F.P., K.J. Propert, and P.R. Rosenbaum, Balanced risk set matching. Journal of the American Statistical Association, 2001. 96(455): p. 870-882.

Application in UCDC: https://www.pcori.org/sites/default/files/AhMew325-Final-Research-Report.pdf

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; hierearchical models and adjustment for within subject association

Thank you

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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?)