Evaluation of the intact nephron hypothesis using design methodology

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Intact nephron hypothesis

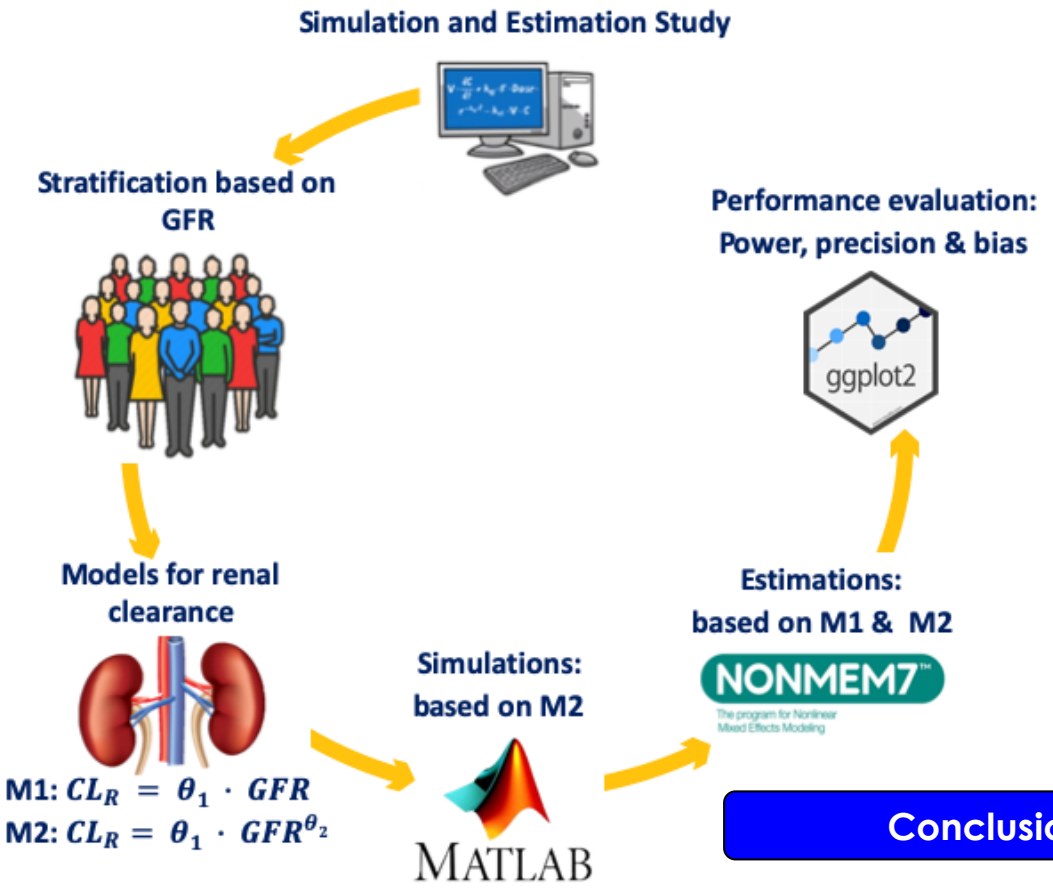
- Renal dose adjustment:
  $CL_R \propto GFR$
- Theory underpinning this practice is the intact nephron hypothesis (INH)
- Studies designed to test the INH do not generally consider optimization of design factors

Aim

- To construct an optimal study design that serves the dual purpose
  1. robust for parameter estimation
  2. discrimination between models for linear (INH) and non-linear (non-INH) renal drug handling

Methods

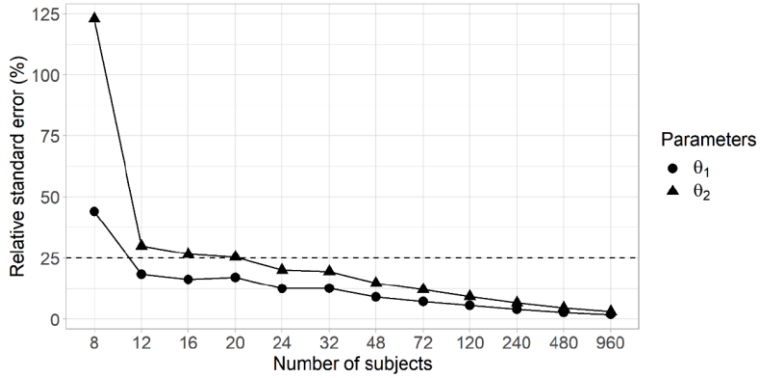
- Standard two-stage method common for Phase I studies
- Reviewed relationship between CL_R and GFR
- Design space: range of GFR across study population
- Models for CL_R:
  M1: $CL_R = \theta_1 \cdot GFR$
  M2: $CL_R = \theta_1 \cdot GFR^{\theta_2}$



Optimal design

- Robust compound optimality criterion:
  1. Hypercube ln D optimality criterion, robust design to account for parameter uncertainty
  2. Ds optimality criteria, discriminatory design between nested models

Results



Conclusion

- A standard sample size of 24 subjects was adequate to estimate parameters precisely
- Optimal design was efficient, requiring subjects from only three renal function groups