Clinical Trial Simulation in the Geriatric Population

NASEM Session 2:
Drug R&D for Older Adults

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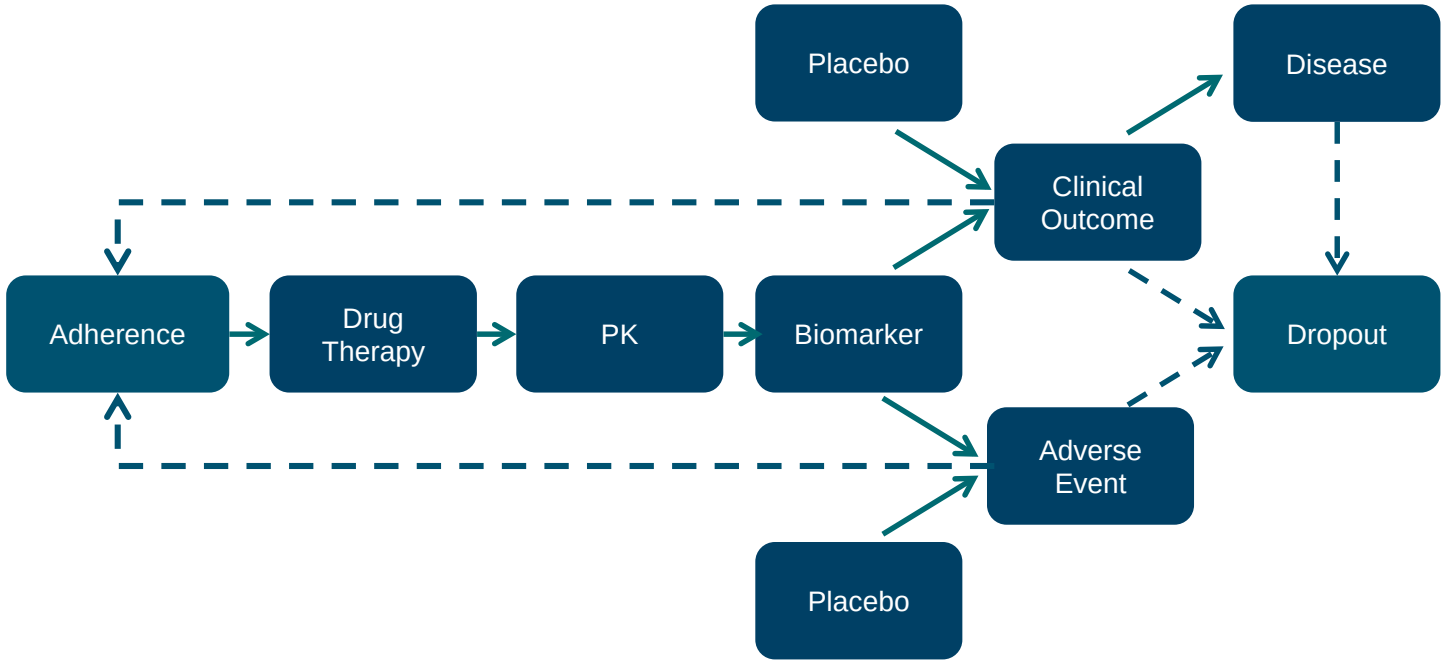
Clinical Trial Simulation

Overview of Modules

- Protocol Design & Inclusion/Exclusion Criteria
- Simulated Patients
  - › Covariate Distribution / Correlation
  - › Disease Progression Model
- Drug Model
  - › Dose → Pharmacokinetic → Pharmacodynamic → Response
- Protocol Deviations
  - › Adherence / Compliance
  - › Drop-out
- Statistical Analysis Plan / Results
- Simulation Scenarios

Goal of Optimizing the Clinical Trial Design

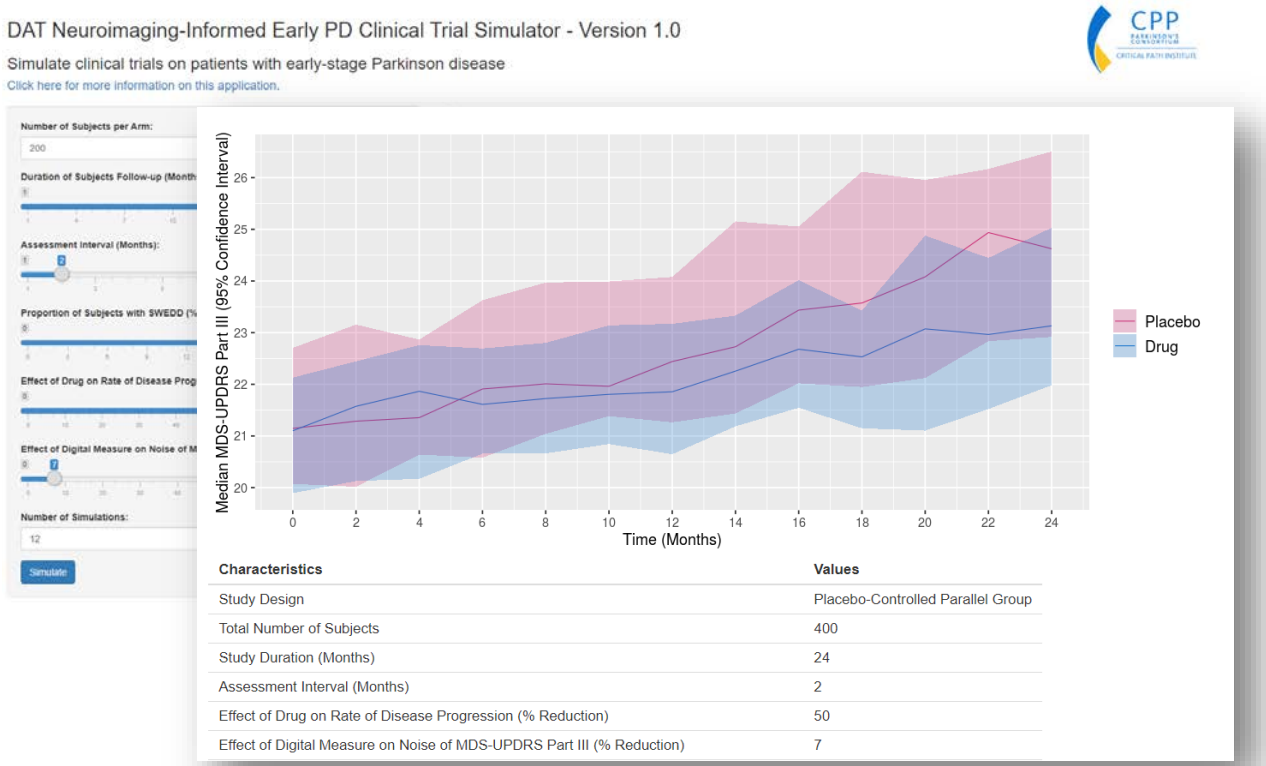


Reference: Kimko & Duffull. Simulation for Designing Clinical Trials.: A Pharmacokinetic-Pharmacodynamic Modeling Perspective. Marcel Dekker, New York, NY. 2003

Generating Elderly Patients for Clinical Trial Simulation

Virtual Subjects vs. Re-Sampling

- Re-sampling from an existing general database
  - **NHANES** (National Health and Nutrition Examination Survey)
  - **NHATS** (National Health and Aging Trends Study)
  - **NSHAP** (National Social Life, Health, and Aging Project)
- Therapeutic area specific databases / CTS tools
  - Specific NIH Institutes
    - › **NINDS** (National Institute of Neurological Disorders and Stroke)
  - Critical Path Institute
    - › **CPP** (Critical Path for Parkinson's)
    - › **CPAD** (Critical Path for Alzheimer's Disease)
  - Pharma placebo data
  - Associations (eg Alzheimer's)

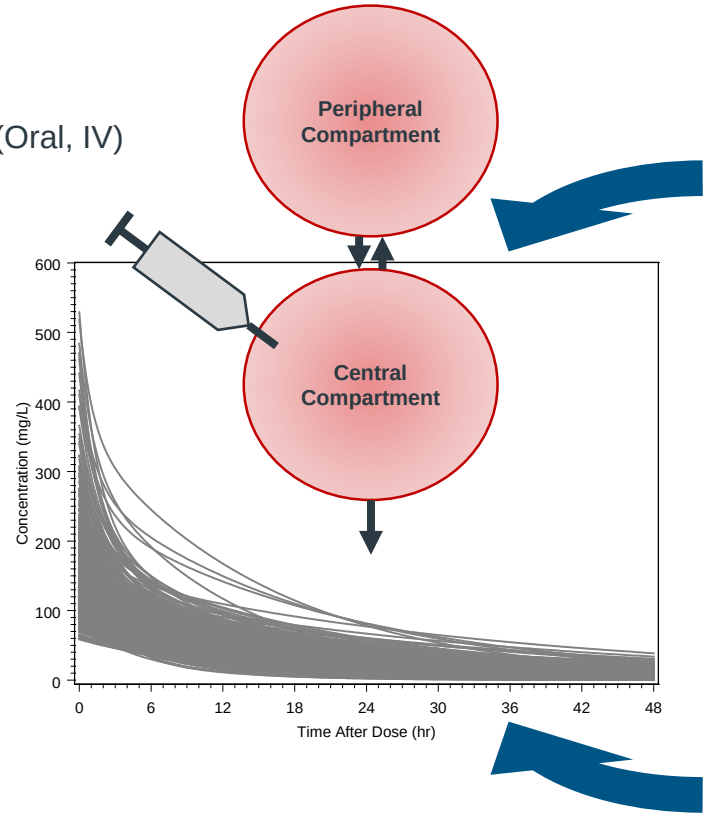


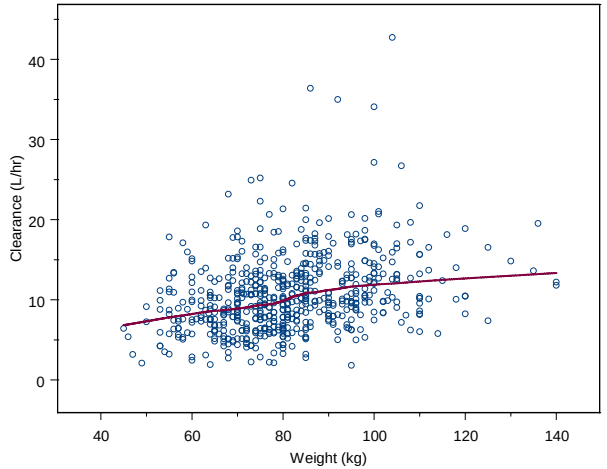
Source: https://cpath.shinyapps.io/dat_cts_v1/

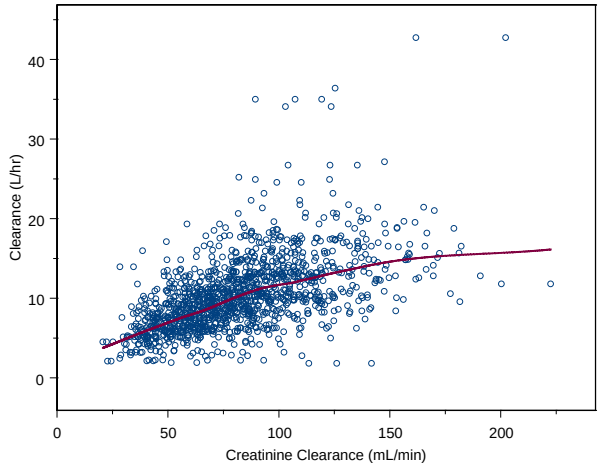
The Drug Model

Population PK–PD Models in the Elderly

- Basic Structural Model
  - Route of Administration (Oral, IV)
  - Analyte
    - › Parent
    - › Metabolite
    - › PK-PD
  - PK Parameters
    - › Absorption
    - › Distribution
    - › Metabolism
    - › Elimination
- Error Model
  - Variability Parameters
    - › Between Subject Error
    - › Within Subject Error
- Covariate Relationships







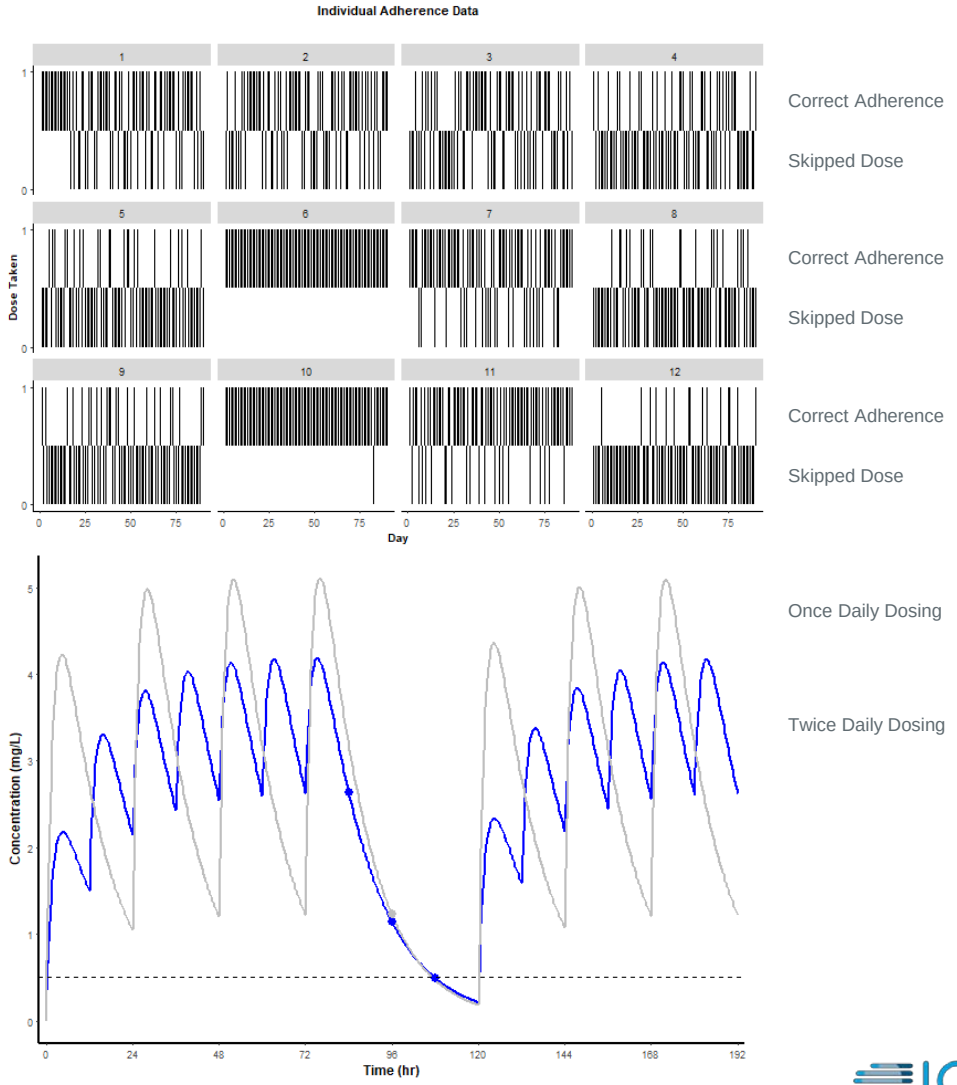
- Age-Related Changes
  - Gastrointestinal System
  - Body Composition
  - Cardiac Structure & Function
  - Liver
  - Renal System
- Pharmacokinetic Implications
  - Absorption
  - Distribution
  - Metabolism
  - Elimination
- Pharmacodynamic Implications

Reference: AA Mangoni & SHD Jackson. "Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications" British Journal of Clinical Pharmacology. 57(1): 6-14.

Adherence Patterns in the Elderly

Simulating Adherence – Markov Mixed Effects Regression Model

- John Urquhart's Rule of 6's
- In the Elderly:
  - Fairly low adherence, often due to difficulties with poly pharmacy issues.
  - Closely correlated with education level, significance of health-related problems, and dosing frequency
- Significance of Adherence
  - Adherence holidays can drop concentration levels below a threshold for therapeutic efficacy
  - Non-compliance with administration (eg, double dosing) can also raise concentration levels above toxicity thresholds, leading to potential adverse events
  - More frequent dosing provides a better level of forgiveness for missed doses.



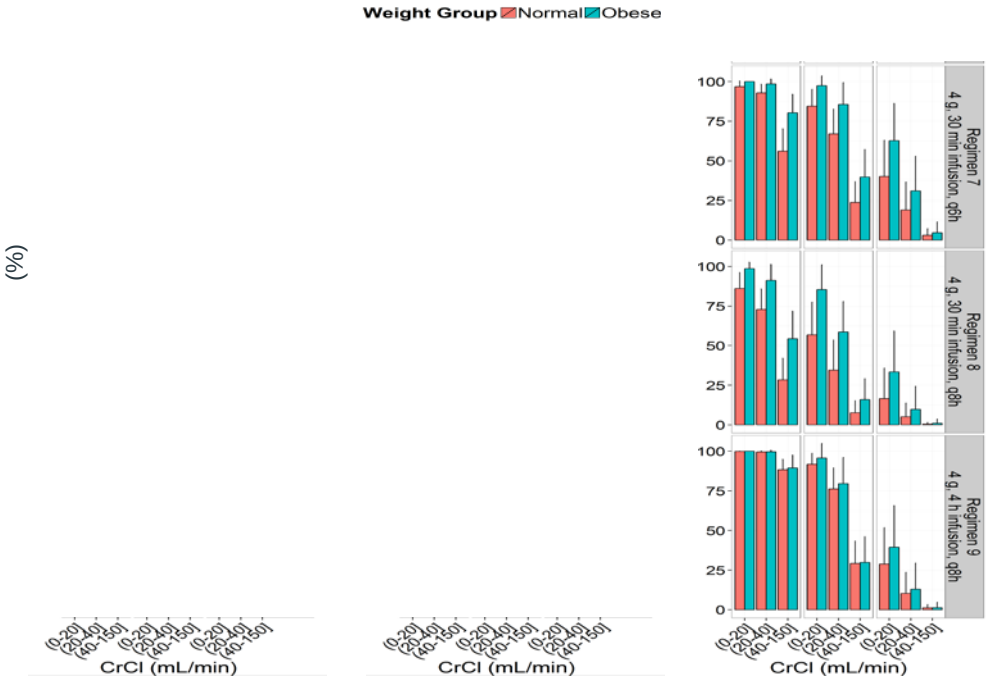
Reference: Girard, et. al. "A Markov Mixed Effect Regression Model for Drug Compliance", Statistics in Medicine.. Vol 17, pgs 2313-2333. (1998)
Comté, et. al. "Estimation of the comparative therapeutic superiority of QD and BID dosing regimens, based upon integrated analysis of dosing history and pharmacokinetics", Journal of Pharmacokinetics and Pharmacodynamics. Vol 34, pgs 549-558. (2007)

Simulation Scenarios

Case Study: Evaluation of Virtual Clinical Trial Results

Challenge	Solution	Results

• Background
  • Treatment:
  • Piperacillin / Tazobactam (PTZ)
  • Problem:
  • Obtain Probability of target attainment (PTA) > Minimum Inhibitory Concentration (MIC) for more than 50% of the dosing interval
  • Identify if dosing needs to be adjusted in the obese population (including adjustments for CrCL)
  • Compare traditional vs extended – infusion dosing regimens
	• Monte Carlo Simulations using Trial Simulator™ 2.2.2
	• Using a previously developed PTZ Population PK model, with covariates
		• No weight-based PTZ dose adjustments are required in obese population
		• Validates the use of extended-infusion regimens in both the normal and obese individuals

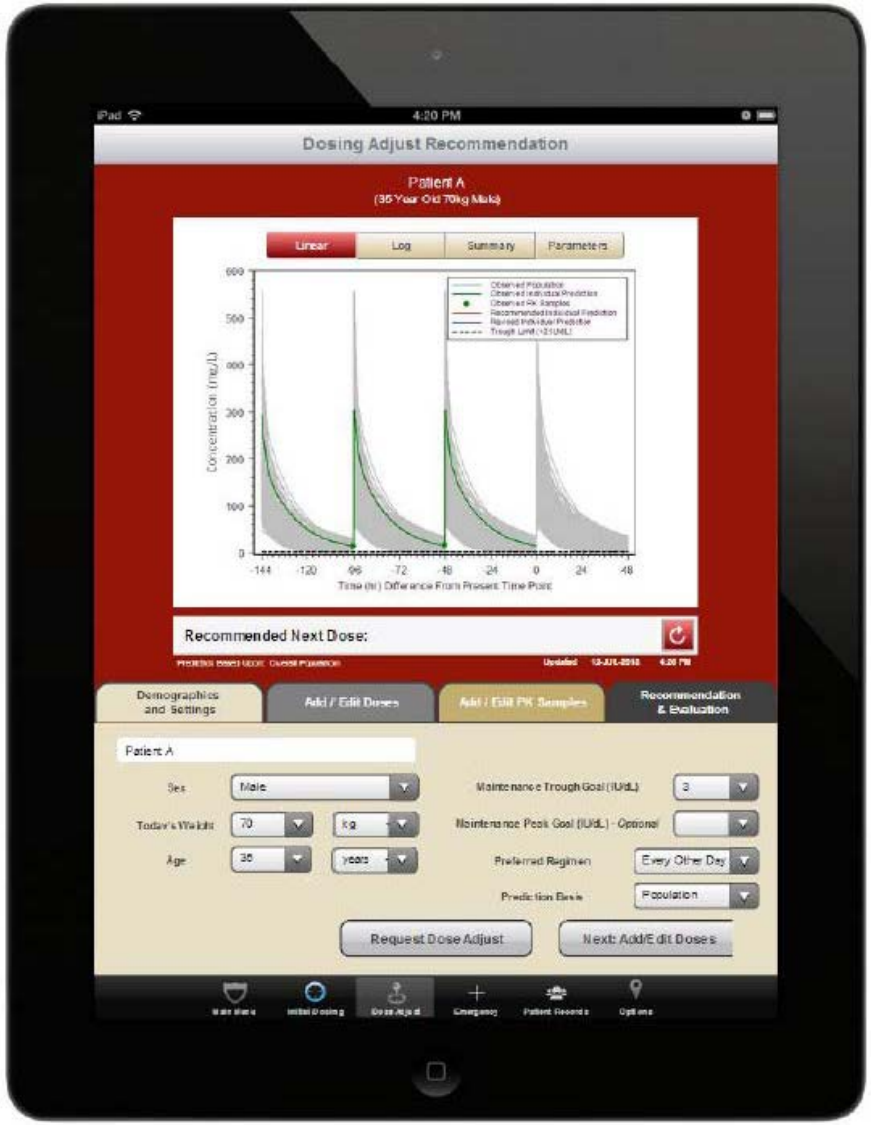


Reference: TP Dumitrescu, et. al. "Using Monte Carlo Simulations to Assess Dosing Regimen Adjustments of Piperacillin/Tazobactam in Obese Patients with Varying Renal Functions." *Journal of Pharmacokinetics and Pharmacodynamics*. May 2013.

Precision Dosing Applications

Use in the Elderly Population

- Ability to individualize dosing to optimize a patient's exposure and corresponding efficacy / safety response, especially for molecules with narrow therapeutic indices
- Bayesian update of model (ie, Adaptive Precision Dosing)
- Integration in Randomized Concentration- or Biomarker-Controlled Clinical Trials
  - > Reduce the down bias of dose-response trials due to confounding overlap for molecules with high PK variability.
  - > Reduce sample size
- Real-World health uses
  - > Connected to EMR and Health Care Provider
  - > Tie in with Adherence Devices, Wearables, Sensors
  - > Machine learning in poly-pharmacy (DDDDI)



Reference: Darwich, A, et al. "Why Has Model-Informed Precision Dosing Not Yet Become Common Clinical Reality? Lessons from the Past and a Roadmap for the Future." Clinical Pharmacology and Therapeutics. May 2017 101(5): 646-656.
International Medical Device Regulators Forum (IMDRF) N41 - Software as a Medical Device (SaMD): Clinical Evaluation (Draft – August 2016)

Thank You!