FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION & RESEARCH
OFFICE OF CLINICAL PHARMACOLOGY

Role of Disease Models in New Drug Development and Approval

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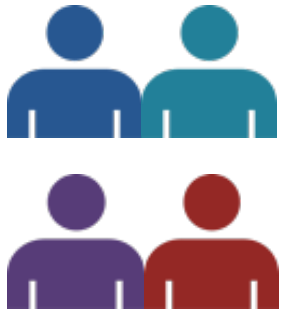
Best Practices for Development and Application of Disease Progression Models
November 19, 2021

Outline

- Introduction (MIDD and Disease-Drug-Trial Model)
- Disease Models at FDA and Case Examples
  - Disease Models at FDA
    (DPM Strategic Goals and Examples of Disease Models)
  - Case Examples
    - Pediatric Extrapolation: Schizophrenia Disease-Drug-Trial Model
    - Patient Selection: DMD Disease Model
    - Biomarker Change with Disease: Osteoporosis Disease-Drug Model
- Interaction with FDA on Disease Modeling
  - FPP Program
  - MIDD Paired Meeting Pilot Program
  - CID Program
- Opportunities for Collaboration
- Take Home Message

Quantitative Disease-Drug-Trial Models



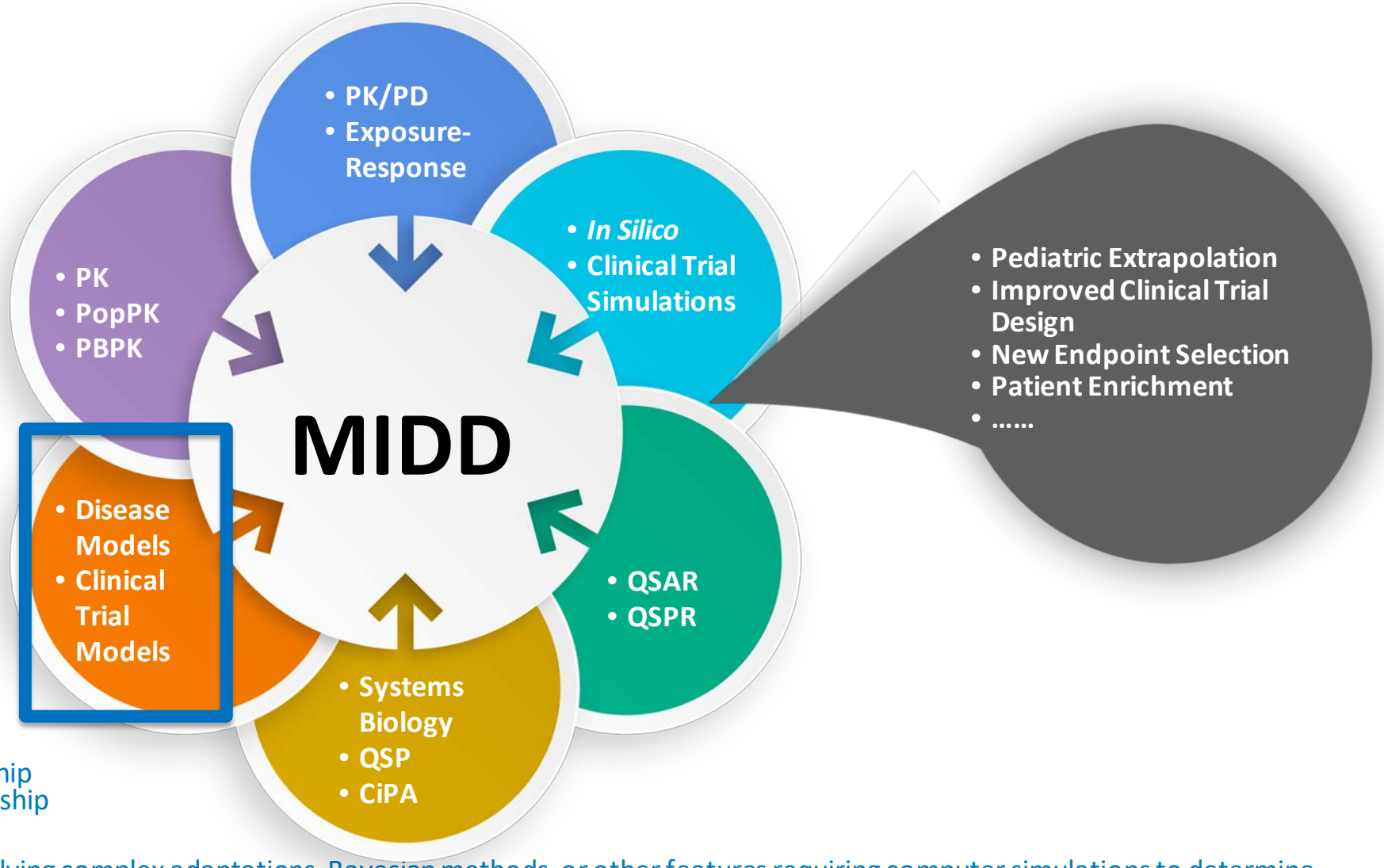
Disease Model → **Drug Model** → **Trial Model**

Disease Model	Drug Model	Trial Model
Natural Progression Biomarker vs. Outcome	Exposure-Response for Efficacy & Safety	Drop Out

*: Jogarao V S Gobburu, Lawrence J Lesko. **Quantitative disease, drug, and trial models.** *Annu. Rev. Pharmacol. Toxicol. 2009. 49:291–301.* doi: 10.1146/annurev.pharmtox.011008.145613.

Model-Informed Drug Development

Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues*



QSAR: Quantitative structure–activity relationship
QSPR: Quantitative structure–property relationship

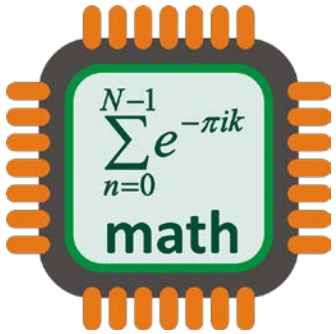
* From PDUFA 6; Excludes statistical designs involving complex adaptations, Bayesian methods, or other features requiring computer simulations to determine the operating characteristics of a confirmatory clinical trial.

Huang SM 2019 AAPS

Pharmacometrics 2020 Strategic Goals

Train 20 Pharmacometricians

Implement 15 Standard Templates



Develop 5 Disease Models

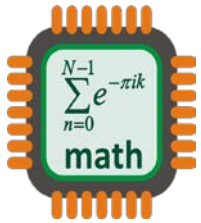
International Harmonization

Integrated Quantitative Clinical Pharmacology Summary

Design By Simulation

2010 2020

Disease Model Examples from FDA

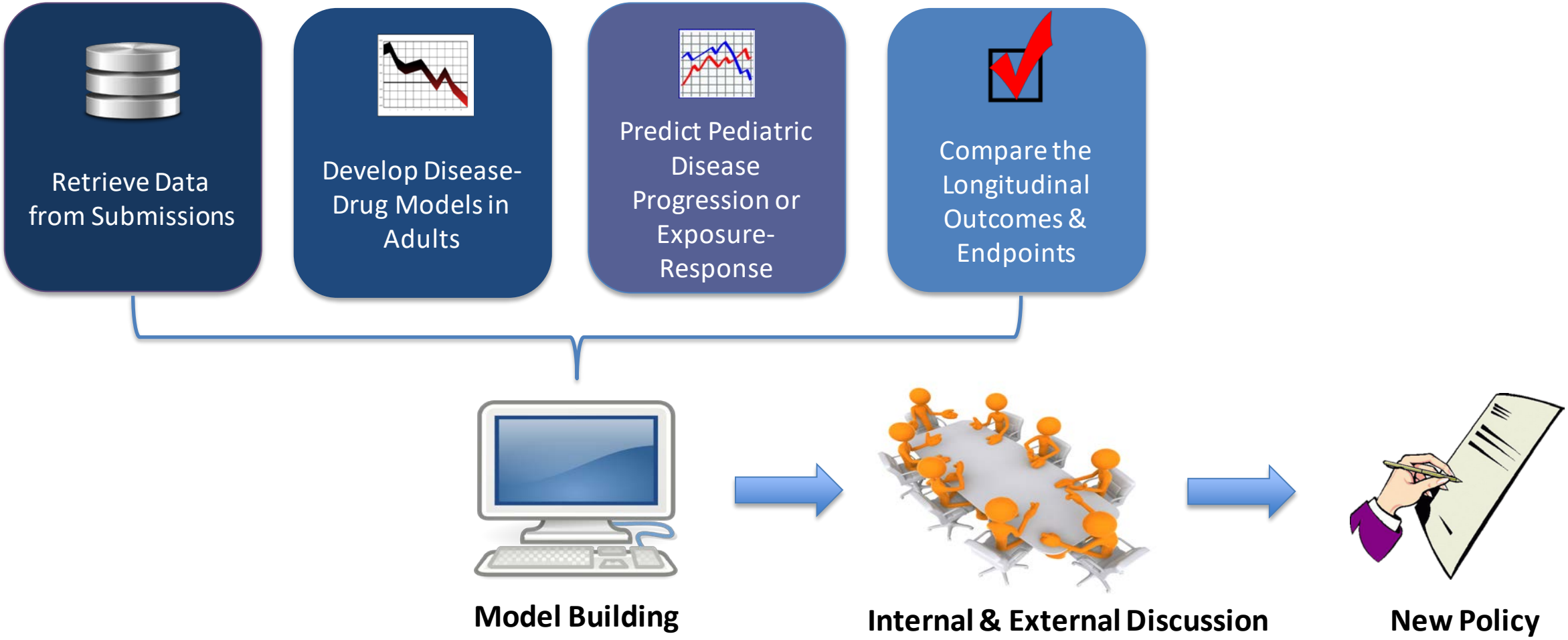


No	Disease Model	Use
1	NSCLC Model [1]	Late Phase Trial Design.
2	Parkinson's Disease Model [2]	Endpoint Selection and Clinical Trial Design
3	Alzheimer's Disease Model [3]	Endpoint Selection and Clinical Trial Design
4	Diabetes Disease Model [4]	Clinical Trial Design
5	Huntington's Disease Model [5]	Patient Enrichment, Clinical Trial Design
6	DMD Disease Model [6]	Patient Enrichment, Clinical Trial Design
7	HIV Model [4]	Clinical Trial Design
8	Schizophrenia Model [7]	Pediatrics Extrapolation
9	Bipolar I disorder Model [8]	Pediatrics Extrapolation
10	Weight Loss Model [9]	Clinical Trial Design
11	Bone Density Model [10]	Clinical Trial Design
12	Idiopathic Pulmonary Fibrosis Model [11]	Patient Enrichment, Clinical Trial Design
13	Rheumatoid Arthritis Model [12]	Patient Enrichment, Clinical Trial Design
14	Pulmonary Arterial Hypertension Model [13]	Endpoint Selection and Clinical Trial Design

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/division-pharmacometrics.

Case 1: Disease Model for Schizophrenia

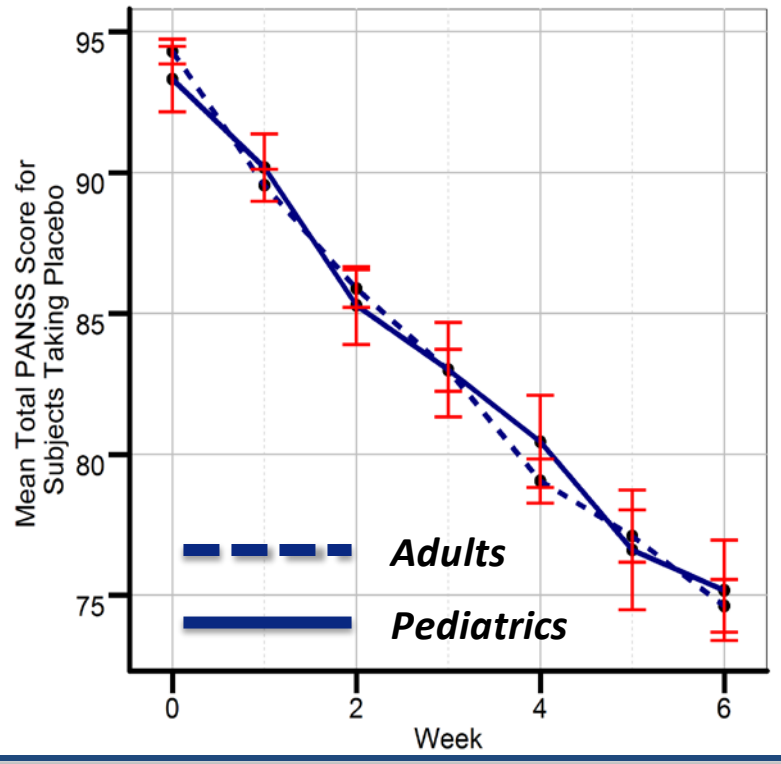
Characterize the Profile of the Disease Progression and ER



Qualitative Evidence to Demonstrate Disease Similarity

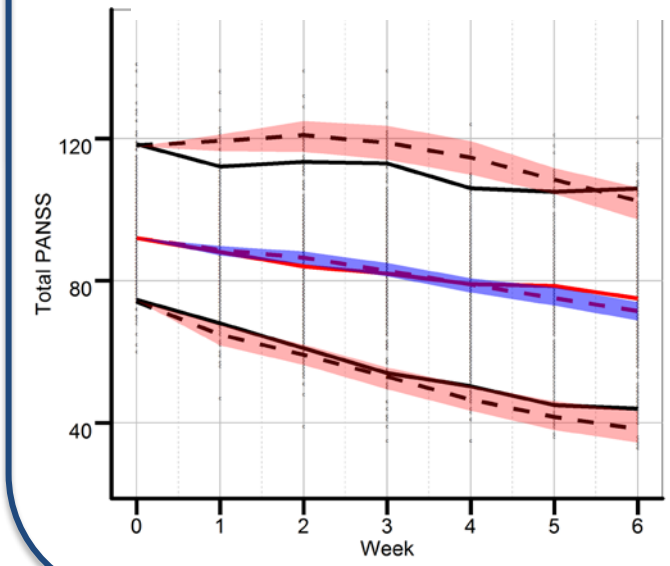
Disease Model

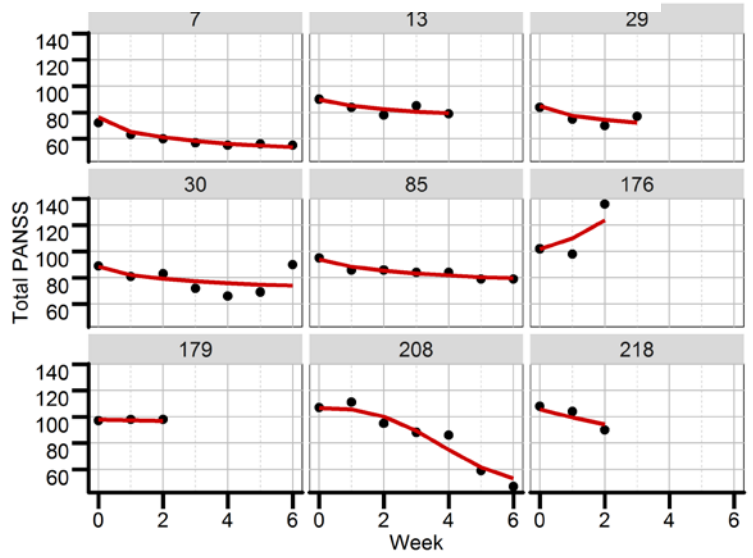
Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents Completers (Observed)



Disease Progression over a Typical 6-Week Trial is Similar Between Adults and Adolescents [Model Described]

$$PANSS(t) = Baseline\ PANSS \times \left[1 - Pmax \times \left(1 - exp^{-\left(\frac{t}{TD}\right)^{POW}}\right)\right]$$



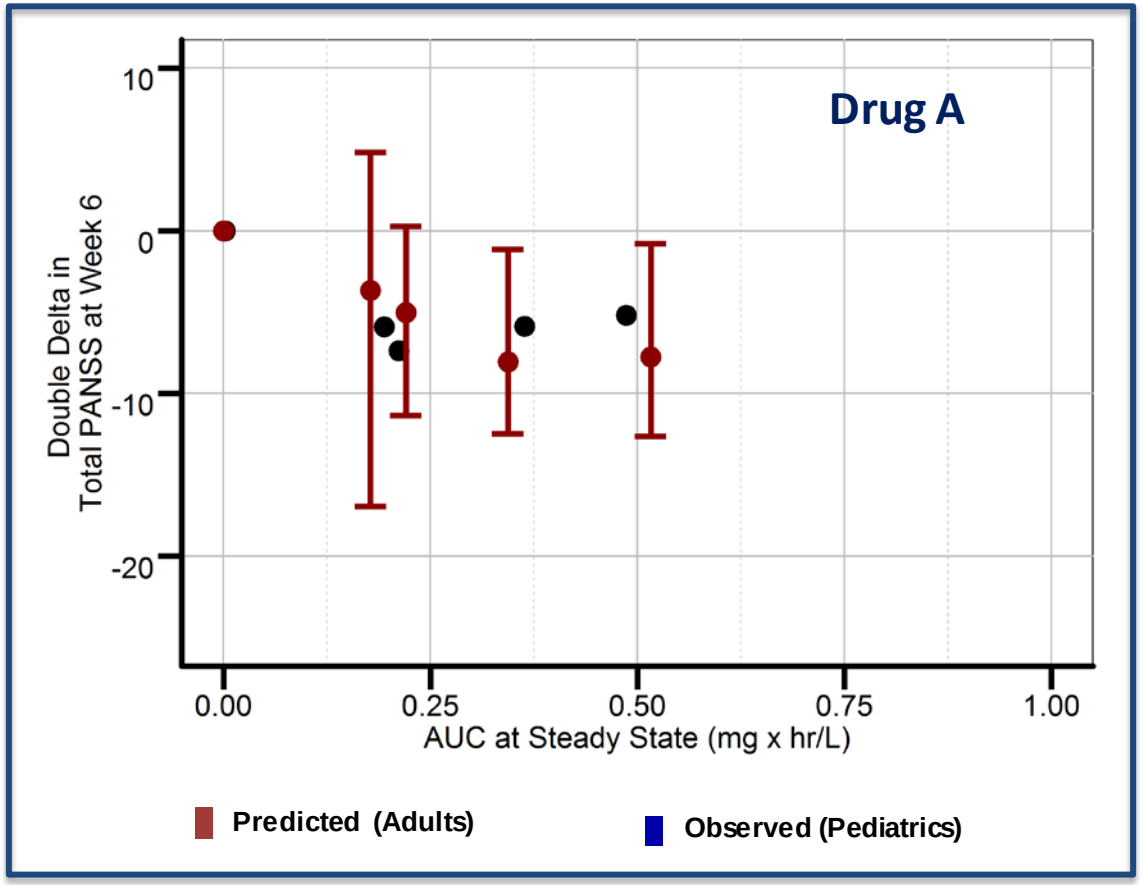


Shamir N Kalaria, Hao Zhu, Tiffany R Farchione, Mitchell V Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis. **A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials. Clin Pharmcol. Ther.** 2019 Nov;106(5):1046-1055. doi: 10.1002/cpt.1501. Epub 2019 Jul 3

Justification for Exposure Response Similarity

Drug Model

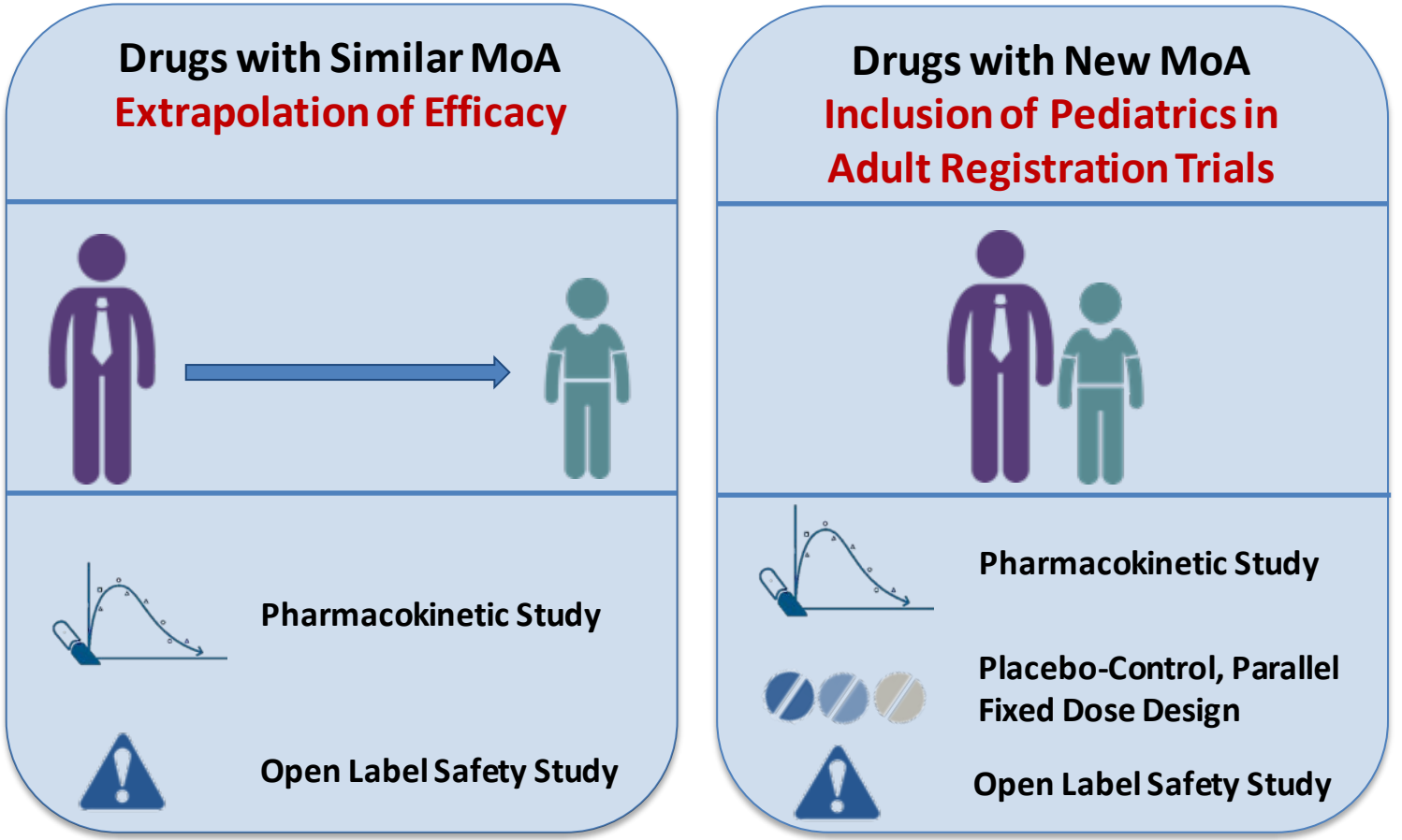
Drug	Age (yrs)	Dose in Adolescents (mg/day)	Dose in Adults (mg/day)
Paliperidone ER	12-17	Weight <51 kg: 3-6 Weight >51 kg: 3-12	3-12
Quetiapine	13-17	400-800	400-800
Risperidone	13-17	1-6	4-16
Aripiprazole	13-17	10-30	10-30
Lurasidone	13-17	40-80	40-160
Olanzapine	13-17	10	10



Shamir N Kalaria Tiffany R Farchione, Mitchell V Mathis, Mathangi Gopalakrishnan, Islam Younis, Ramana Uppoor, Mehul Mehta, Yaning Wang, Hao Zhu. **Assessment of Similarity in Antipsychotic Exposure-Response Relationships in Clinical Trials Between Adults and Adolescents With Acute Exacerbation of Schizophrenia. J Clin Pharmcol.** 2020 Jul;60(7):848-859. doi: 10.1002/jcph.1580. Epub 2020 Jan 28

Extrapolation of Efficacy from Adults to Pediatrics

Schizophrenia Program



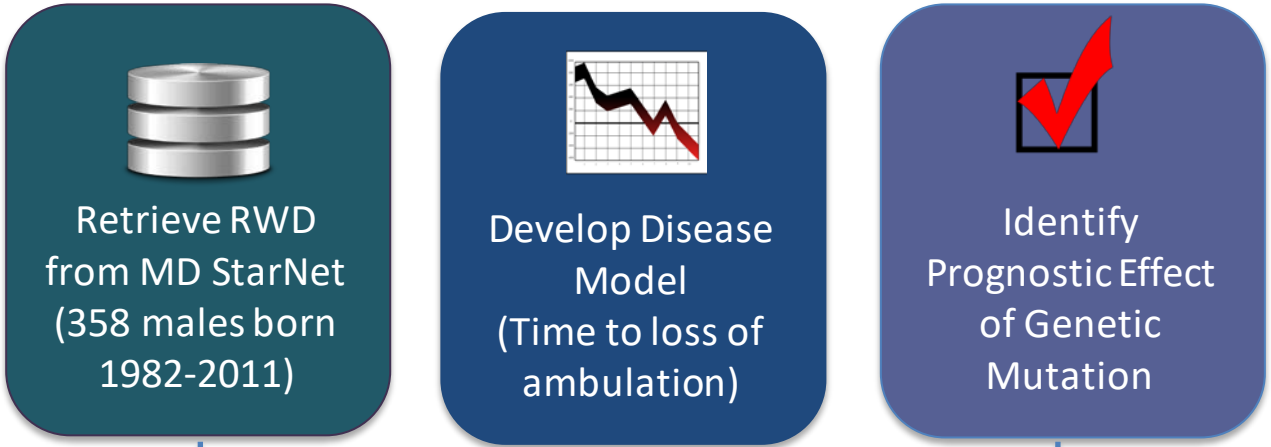
*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**Open label safety studies could concurrently enroll patients with bipolar I and schizophrenia adult and pediatric patients

Shamir N Kalaria, Tiffany R Farchione Ramana Uppoor, Mehul Mehta , Yaning Wang , Hao Zhu · **Extrapolation of Efficacy and Dose Selection in Pediatrics: A Case Example of Atypical Antipsychotics in Adolescents With Schizophrenia and Bipolar I Disorder. J Clin. Pharmcol.** 2021 Jun;61 Suppl 1:S117-S124. doi: 10.1002/jcph.1836

Case 2: Disease Model for Childhood-Onset Dystrophinopathy

Characterize Covariates



Joint effort from federal/state government & academia

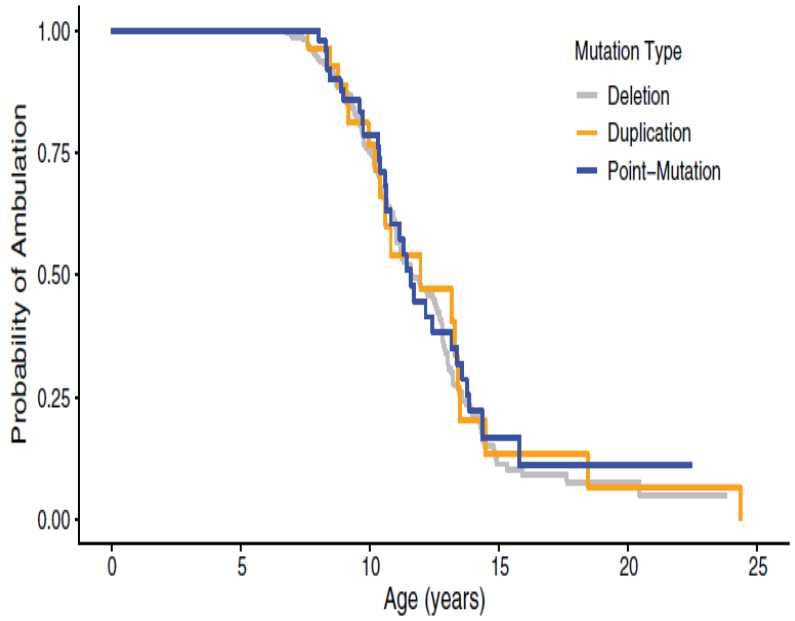
Model Building

New Protocol Design

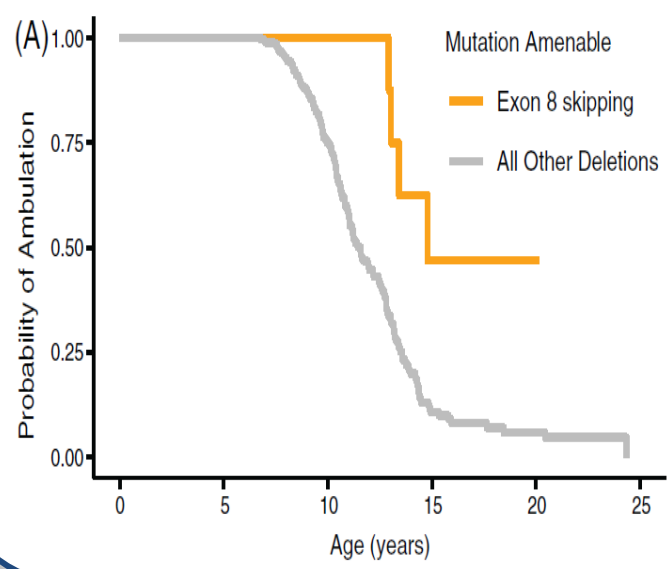
Identify Prognostic Effect of Genetic Mutation

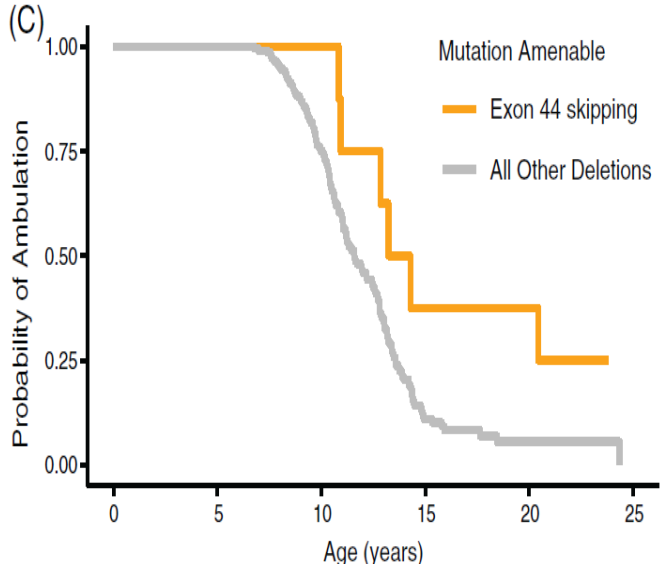
Disease Model with Covariate Effect

No Difference in Disease Progression by Genetic Mutation Type



Exon 8 and 44 Skippable Subgroups Showed Lower Risk of LoA Relative to Other Amenable Subgroups



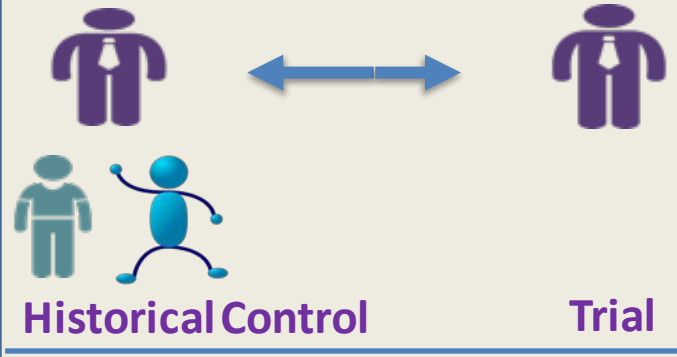


Gregory Haber Kristin M Conway, Pangaja Paramsothy, Anindya Roy, Hobart Rogers, Xiang Ling, Nicholas Kozauer Natalie Street, Paul A Romitti, Deborah J Fox, Han C Phan, Dennis Matthews, Emma Ciafaloni Joyce Oleszek, Katherine A James, Maureen Galindo Nedra Whitehead, Nicholas Johnson-, Russell J Butterfield, Shree Pandya Swamy Venkatesh, Venkatesh Atul Bhattaram **Association of genetic mutations and loss of ambulation in childhood-onset dystrophinopathy.** Muscle Nverve. 2021 Feb;63(2):181-191. doi: 10.1002/mus.27113. Epub 2020 Nov 17

Improve Patient Enrichment, Randomization, and Matching

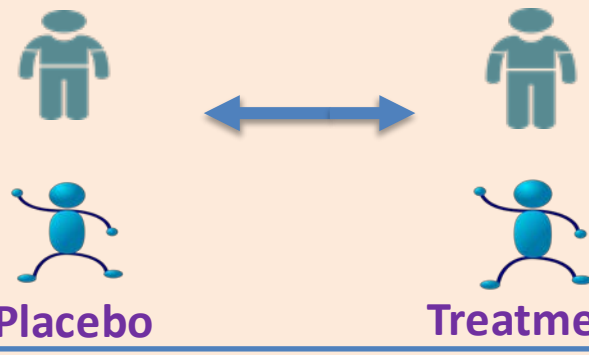
Duchenne Muscular Dystrophy

Matching Strategy



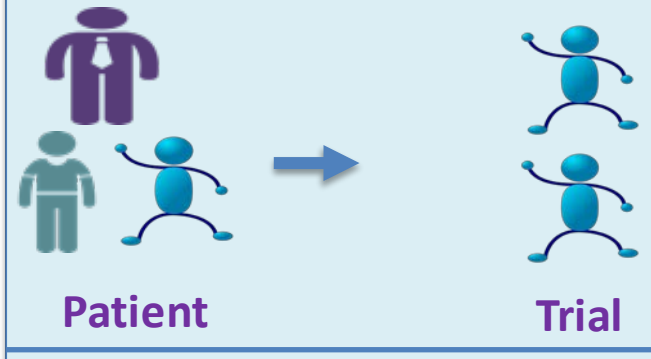
Using historical control subjects as a supplement to the placebo arm (Phase 2)

Randomization by Strata



Randomization by strata to ensure consistent disease progression in different arms.

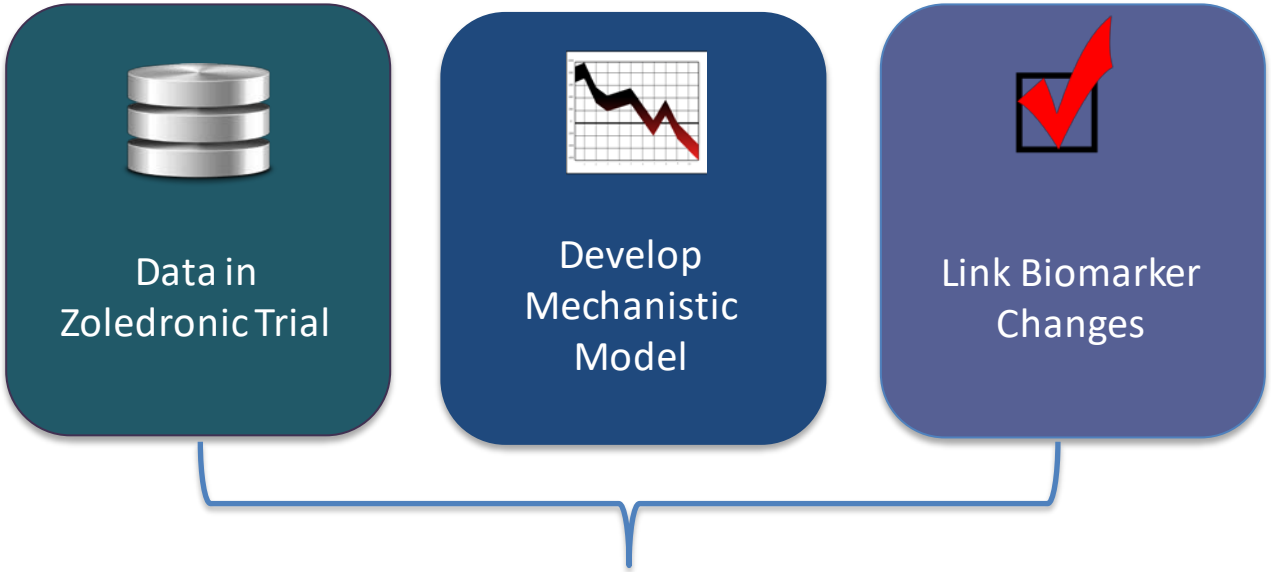
Patient Enrichment

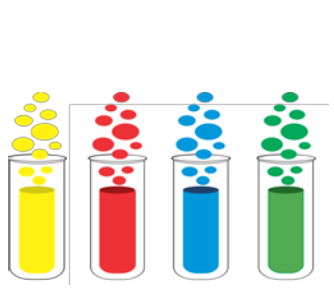


Enrich patients to reduce variability.

Case 3: Disease Model for Postmenopausal Osteoporosis

Link Short-Term Biomarker Changes





Short-Term Biomarkers

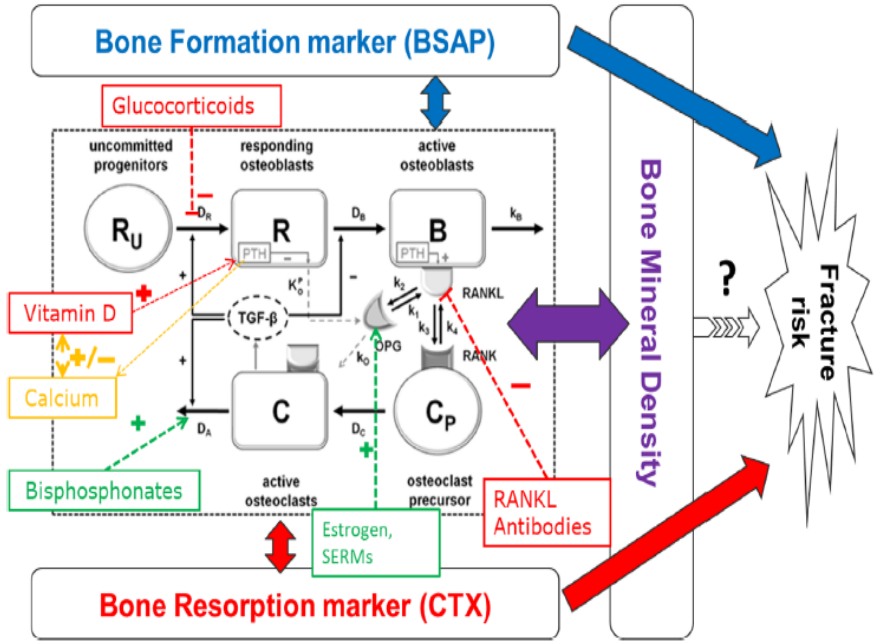
Model Building

Long-term Clinical Outcomes

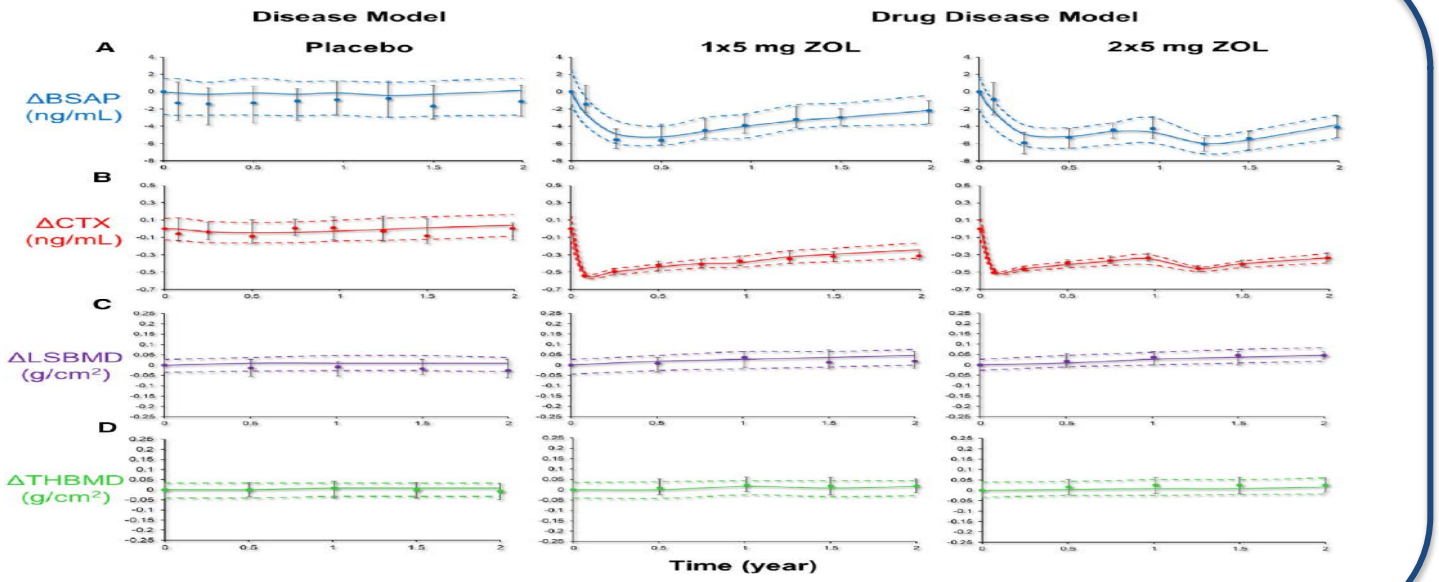
Identify Prognostic Effect of Genetic Mutation

Disease Model with Biomarkers

Schematic Diagram for Disease-Drug Model

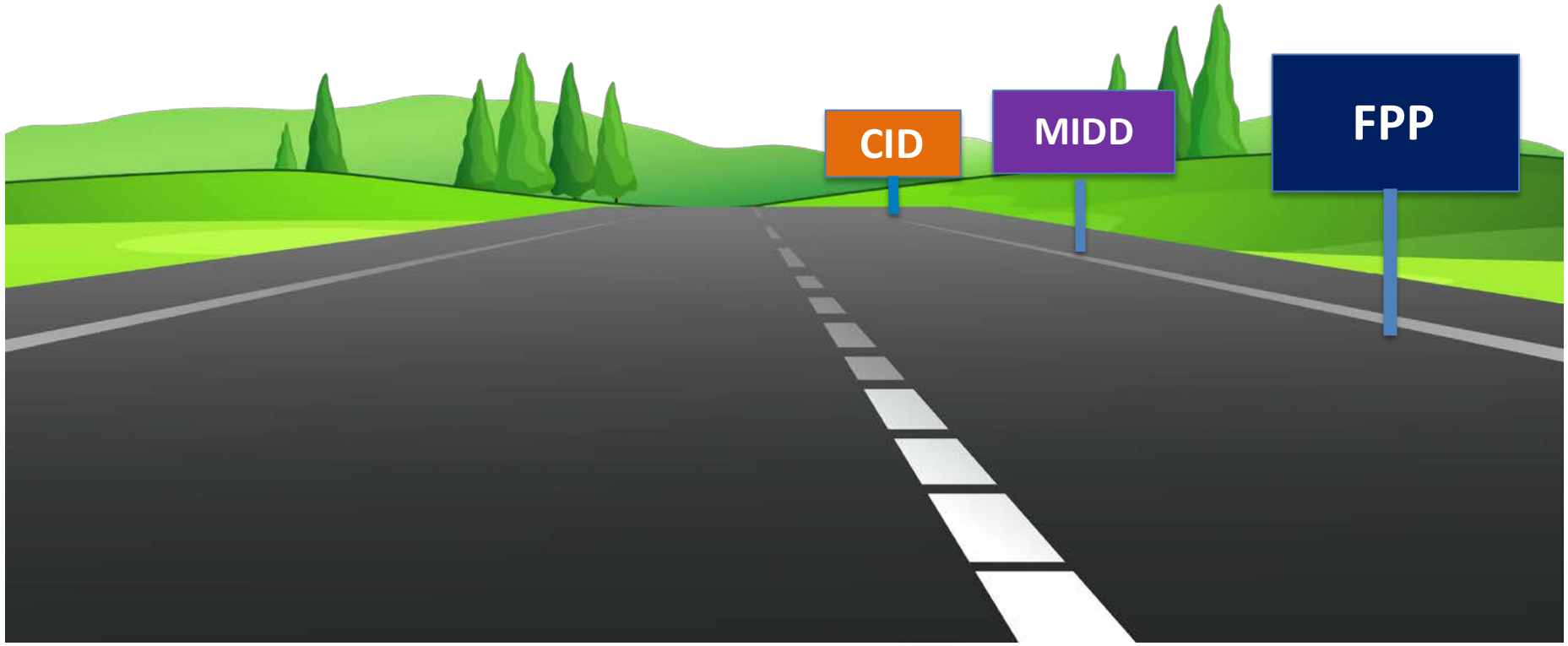


Various Biomarker Changes in Placebo and Treatment Arms



Yi Ting Kayla Lien , Kumpal Madrasi , Snehal Samant , Myong-Jin Kim , Fang Li , Li Li , Yaning Wang , Stephan Schmidt **Establishment of a Disease-Drug Trial Model for Postmenopausal Osteoporosis: A Zoledronic Acid Case Study. J Clin. Pharmcol.** 2020 Dec;60 Suppl 2:S86-S102. doi: 10.1002/jcph.1748

Avenues for Regulatory Interaction



Fit for Purpose (FPP) Initiative

- The Fit-for-Purpose (FFP) Initiative provides a pathway for regulatory acceptance of dynamic tools for use in drug development programs.
- A designation of 'fit-for-purpose' (FFP) will be established based on a thorough evaluation of the information provided.

Disease Area	Submitter	Tool	Trial Component
Alzheimer's Disease	The Coalition Against Major Diseases (CAMD)	Disease model: Placebo/ disease progression	Demographic & drop out
Multiple	Janssen Pharmaceuticals & Novartis Pharmaceuticals	Statistical model: MCP-Mod	Dose finding

Link to the FDA FPP initiative:
<https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative>

MIDD Paired Meeting Pilot Program

- This program is jointly administered by CDER and CBER.
- OCP is the point of contact.
- The sponsor should be a drug or a biologics developer.
- The product should be registered under an U.S. IND/NDA/BLA.
- FDA accepts requests on a continuous basis.
- FDA expects to grant 2-4 submissions on a quarterly basis.

Joint effort for:
(1) all stake holders
(2) multi-disciplinary review team members

Link to the FDA MIDD Program:
<https://www.fda.gov/drugs/development-resources/model-informed-drug-development-pilot-program>

Complex Innovative Trial Design (CID) Program

- To support the goal of facilitating and advancing the use of complex adaptive, Bayesian, and other novel clinical trial designs.
- Meetings will be conducted by FDA's CDER and CBER during fiscal years 2019 to 2022.
- Under the pilot meeting program, FDA will accept two primary meeting requests and two alternates per quarter.

- **The CID Pilot Meeting Program is designed to:**
  - **Facilitate the use of CID approaches in late-stage drug development.**
  - **Promote innovation by allowing FDA to publicly discuss the trial designs considered through the pilot meeting program, including trial designs for medical products that have not yet been approved by FDA.**

Link to FDA CID Program:
<https://www.fda.gov/drugs/development-resources/complex-innovative-trial-design-pilot-meeting-program>

Collaboration Opportunities

Academic Institutions

- Collaborative Agreements (e.g., **MOU**, CRADA)
- CDER Network of Experts (NoE) Program

Academic Faculty

- Faculty Sabbatical/Scientific Visit Program
- Advisory Committees (AC)/Special Government Employee (SGE)

Professional & Graduate Students

- Doctor of Pharmacy APPE Rotations
  - Clinical Pharmacology
- Pharmacy Student Experiential Program (PSEP)
- Student Summer Internships
  - Professional and Graduate Students
- ORISE Fellows

Industry, Non-Profit Organizations

- IQ consortium

Platform developers

Take Home Messages

- **Disease-Drug-Trial Models are important tools for MIDD.**
- **This modeling approach is widely used to support new drug development.**
- **FPP, MIDD, and CID programs allow direct interactions between industry and FDA on various modeling approaches.**
- **We look forward to collaborations with all stakeholders to improve modeling tools that can be used to facilitate new drug development.**

Acknowledgement

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- **Dr. Issam Zineh**
- **Dr. Maryanne Dingman**
- **DPM Members**
- **OCP Members**
- **Other Collaborators at FDA or Outside FDA**

Reference to Disease Models from FDA

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