Welcome to CTTI's Disease Progression Modeling Expert Meeting

- This meeting is being recorded for note taking purposes only.
- Masks are recommended if you are experiencing cold-like symptoms.
- Open discussion is encouraged and fostered by respect and collaboration.
- Do you have a comment during the open discussion?
  - Please tip your name tent card and a microphone will be delivered.
  - Virtual participants- please enter questions into the chat.

Here's to a great discussion!

CTTI

Agenda

Time (EST)	Content	Presenter
8:30 AM	Welcome Remarks and Introduction to CTTI	Sara Calvert (CTTI)
8:40 AM	Opening Comments	Issam Zineh (FDA)
9:00 AM	Trials in Clinical Practice Project Overview	Lindsay Kehoe (CTTI)
9:15 AM	Scoping review (Q&A and break to follow)	Summer Starling (CTTI)
10:15 AM	Panel Discussion	Hao Zhu (FDA) CJ Musante (Pfizer) Dave Miller (Unlearn.AI) Klaus Romero (Critical Path Institute) Moderator: Raj Madabushi (FDA)
11:20 PM	Break Out Groups *(Lunch then Debrief to follow)*	All Attendees
1:50 PM	Recommendations Needed: Open discussion	Bruce Burnett (Duke)
2:40 PM	Metrics Brainstorming: Open discussion	Sara Calvert (CTTI)
3:25 PM	Closing Comments and Adjourn	Lindsay Kehoe (CTTI)

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CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

March 6, 2023

Introduction to CTTI

Sara Calvert, CTTI Director of Projects

Clinical Trials Transformation Initiative

MISSION

To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials.

VISION

A high-quality clinical trial system that is patient-centered and efficient, enabling reliable and timely access to evidence-based therapeutic prevention and treatment options.

PUBLIC-PRIVATE PARTNERSHIP

- Co-founded in 2007 by FDA and Duke University
- Active collaboration with +500 individuals and groups
- Steering Committee with +80 member organizations

SCOPE

Focus on clinical trials of FDA-regulated medical products, recognizing that clinical trials are international and acting as a collaborative global citizen.

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CTTI Membership

*Version: February 20, 2023

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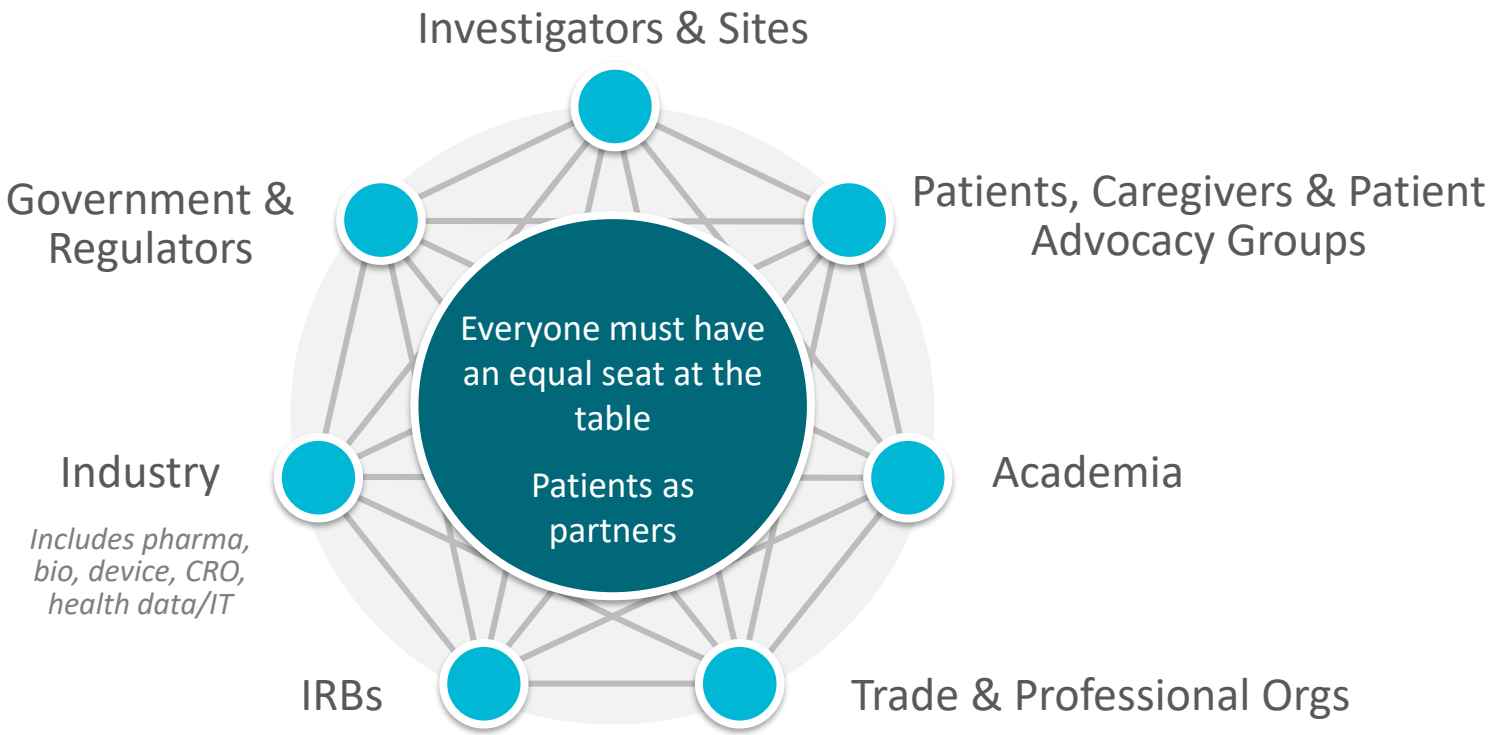
Multi-Stakeholder



CTTI Products

Recommendations

Evidence-based and actionable results from a CTTI project that are approved by the CTTI Executive Committee

Tools

Supportive resources developed by a CTTI project team to assist with the implementation and adoption of project recommendations

Publications

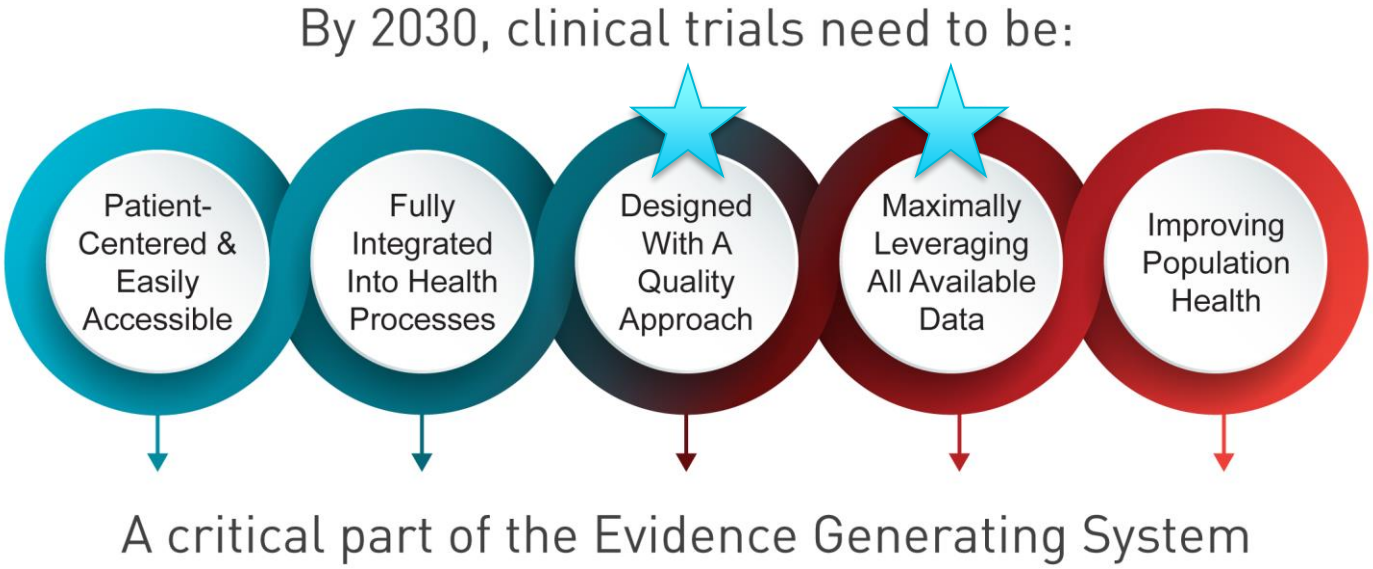
Reports

Case Studies

Webinars

Presentations

TRANSFORMING TRIALS 2030



https://ctti-clinicaltrials.org/who_we_are/strategic-vision/

CTTI

Today's Meeting Objectives

- Discuss disease progression modeling (DPM) and its current applications
- Explore opportunities, barriers, and best practices for advancing the use of disease progression modeling to aid in decision making
- Brainstorm relevant metrics to monitor and evaluate the recognition, value and consistent use of disease progression modeling

Issam Zineh

Director, Office of Clinical Pharmacology
U.S. Food & Drug Administration

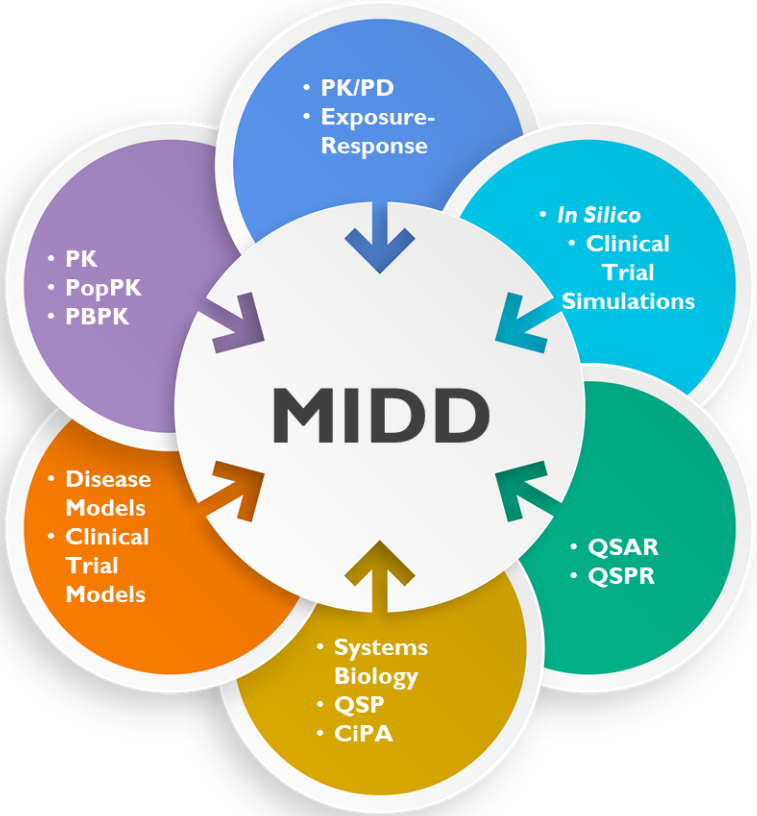
U.S. FOOD & DRUG ADMINISTRATION

Model-Informed Drug Development: From Translation to Transformation

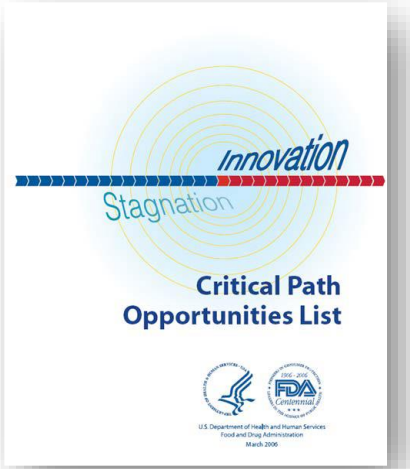
Issam Zineh, PharmD, MPH, FCP, FCCP
Director, Office of Clinical Pharmacology
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

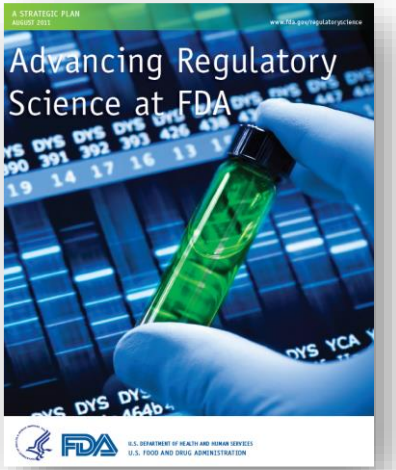
Model-informed Drug Development (MIDD)

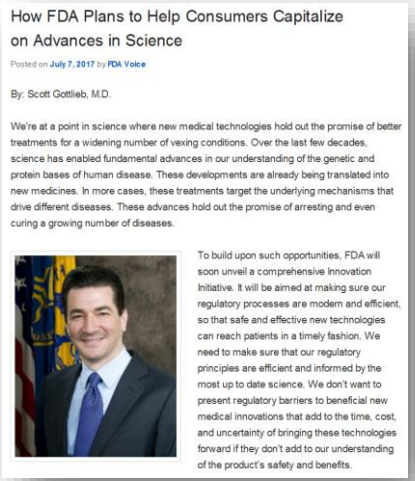
Development and application of exposure-based, biological, and statistical models derived from preclinical and clinical data sources to address drug development or regulatory issues



Modeling & Simulation on the Critical Path





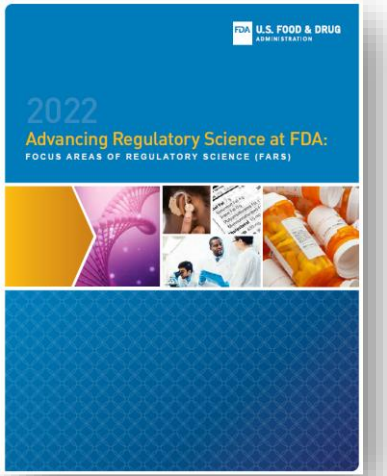

How FDA Plans to Help Consumers Capitalize on Advances in Science

Posted on July 7, 2017 by FDA Voice

By: Scott Gottlieb, M.D.

We're at a point in science where new medical technologies hold out the promise of better treatments for a widening number of vexing conditions. Over the last few decades, science has enabled fundamental advances in our understanding of the genetic and protein bases of human disease. These developments are already being translated into new medicines. In more cases, these treatments target the underlying mechanisms that drive different diseases. These advances hold out the promise of arresting and even curing a growing number of diseases.

To build upon such opportunities, FDA will soon unveil a comprehensive Innovation Initiative. It will be aimed at making sure our regulatory processes are modern and efficient, so that safe and effective new technologies can reach patients in a timely fashion. We need to make sure that our regulatory principles are efficient and informed by the most up to date science. We don't want to present regulatory barriers to beneficial new medical innovations that add to the time, cost, and uncertainty of bringing these technologies forward if they don't add to our understanding of the product's safety and benefits.

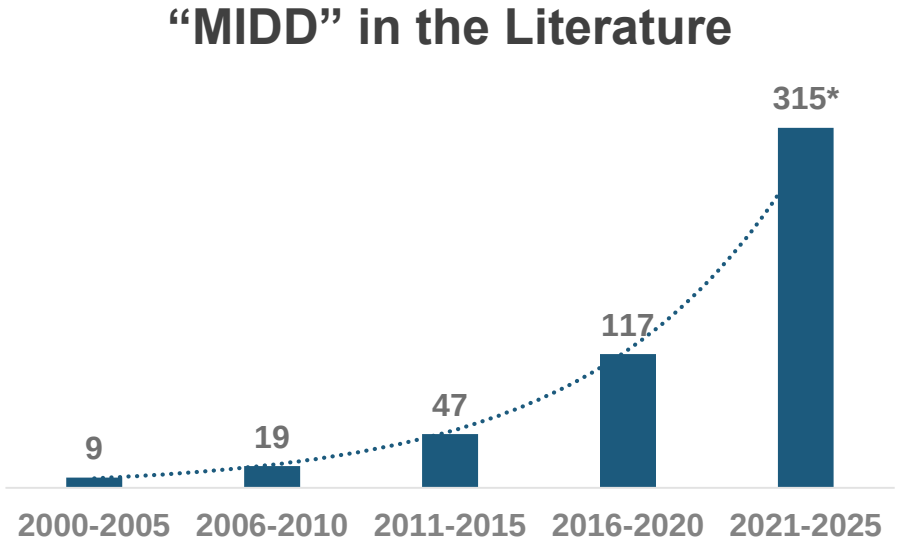


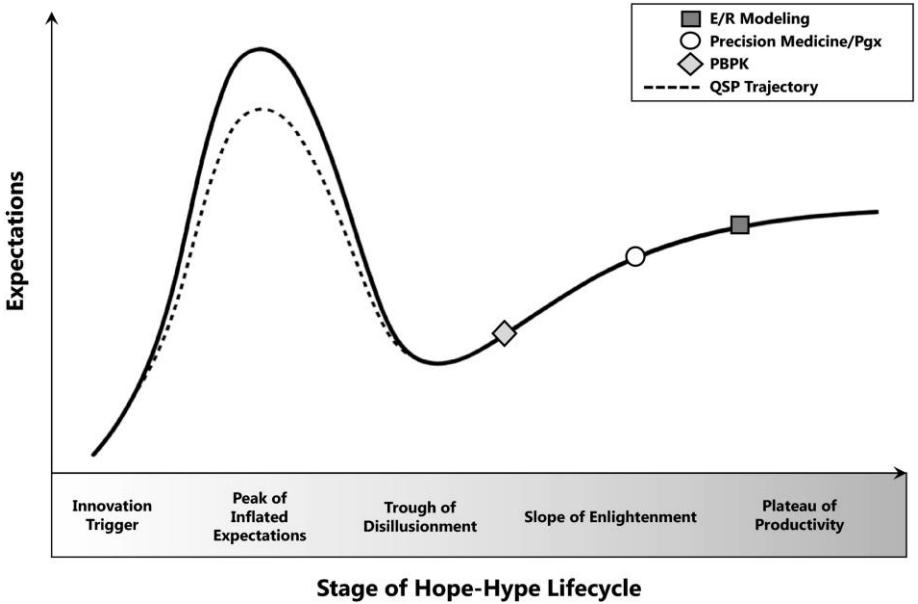
Recognized pathway for lowering drug attrition and dealing with regulatory uncertainty

<u>Problem Statement</u>:

Opportunistically applied, heterogeneously accepted, no dedicated pathways for engagement

MIDD: Hope or Hype?





* Projected | "MIDD;" "MBDD;" "MID3"

Zineh 2019 [PMID 30924594]

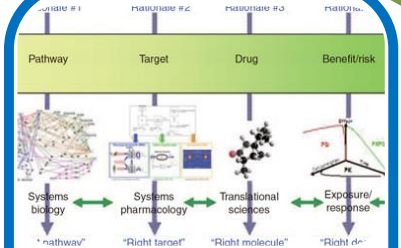
Barriers to Translation

- Constraints of the science
- A steep learning curve among non-technical experts + very few instructive cases
- High organizational activation energy required to integrate new approaches

PDUFA 6: Regulatory Decision Tools

Patient Voice

Complex Innovative Trial Designs



Model-Informed Drug Development

Analysis Data Standards

Benefit/Risk Assessment

Biomarker Qualification

COMMENTARY

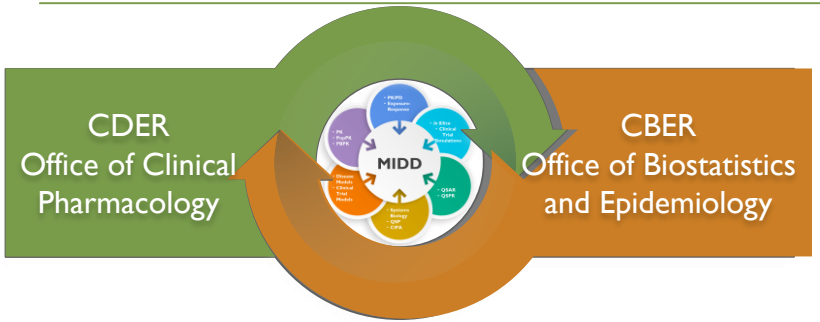
A Holistic and Integrative Approach for Advancing Model-Informed Drug Development

Rajanikanth Madabushi[1,*], Yaning Wang[1] and Issam Zineh[1]

1. Creating an environment that increases stakeholder acceptance of MIDD approaches
2. Developing standards and best practices that lead to consistent application and evaluation
3. Increasing capacity and expertise to address growing demands and innovation

Madabushi 2019 [PMID 30582301]

MIDD Paired Meeting Program

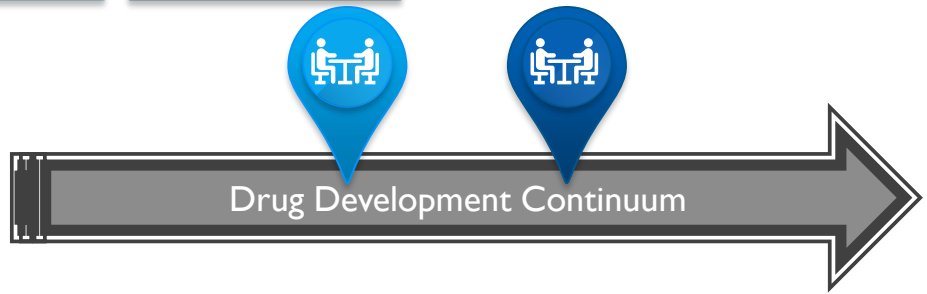


A dedicated forum for regulatory interaction on MIDD applications in specific drug development programs

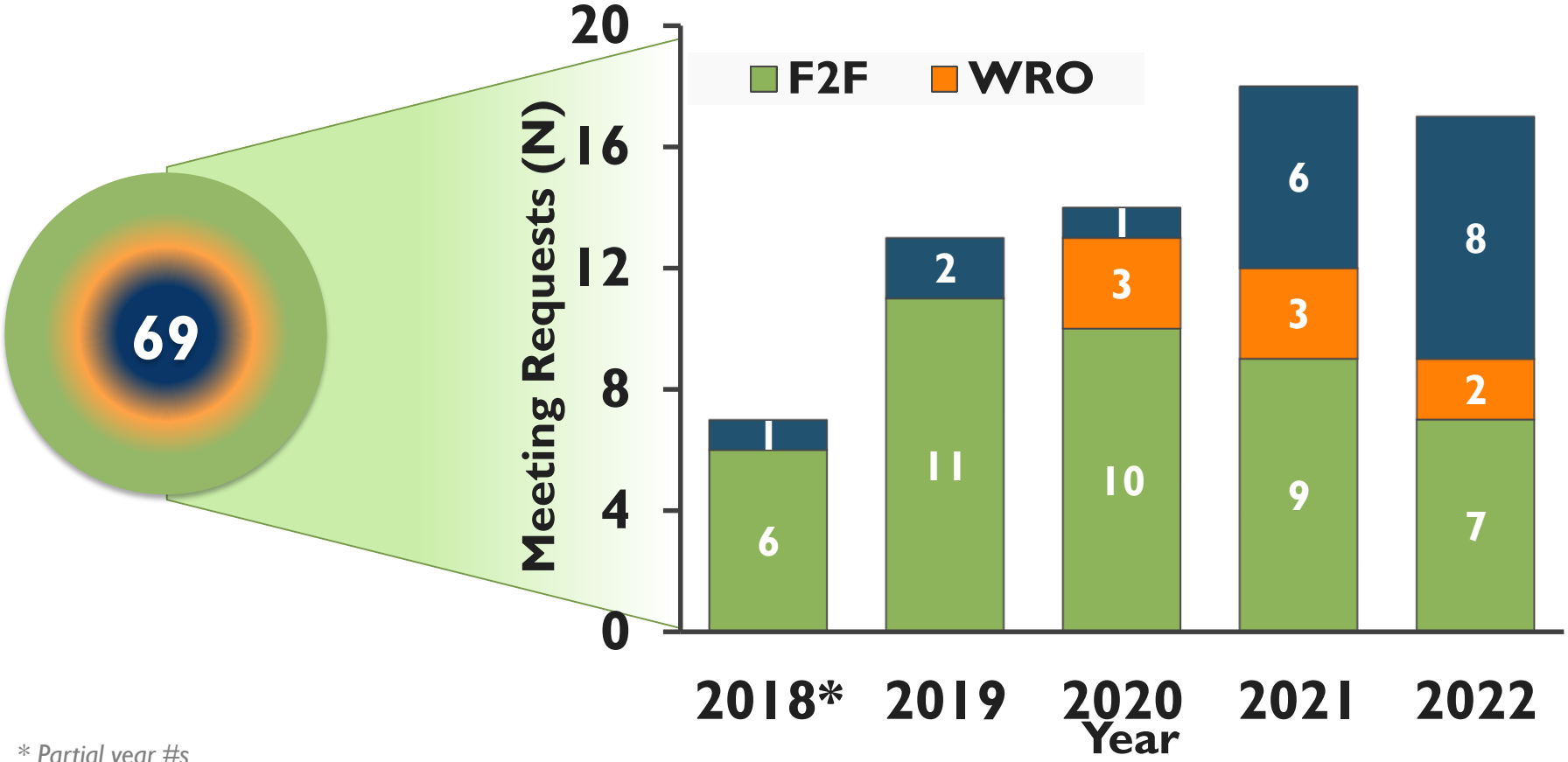
Dose Section and Optimization

Clinical Trial Simulation

Mechanistic Safety Evaluation

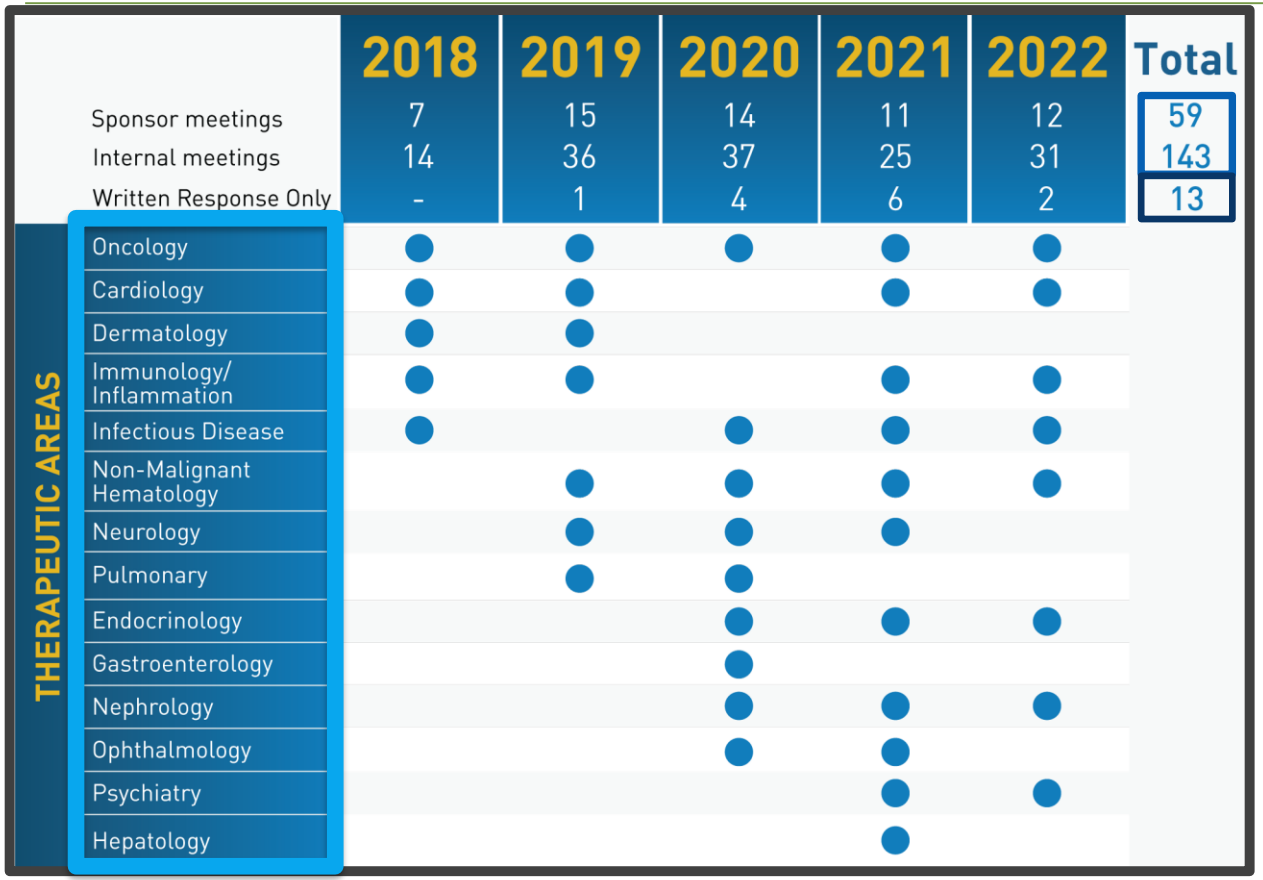


High Demand for Engagement



* *Partial year #s*

CDER/OCP MIDD Program Overview



Applicable across wide spectrum of therapeutic areas

Resource intensive and involves engagement of multidisciplinary stakeholders

Flexibility, transparency, and clarity in feedback

Office of Clinical Pharmacology – 2022 Annual Report https://www.fda.gov/media/164793/download

Impact

FDA U.S. FOOD & DRUG ADMINISTRATION

Drug Development

Model validation & clinical trial simulation to inform trial design and patient selection

Strategies for dose selection, optimization and risk mitigation

Alternative approaches for therapeutic individualization

Regulatory pathway seeking approval of new dose, dosing regimen, formulation, etc.

TIME
- Accelerated timelines
- Reduced sample size, faster recruitment
- Getting to right dose faster

COST
- Savings est. up to $70M
- M/S replacing trials
- Path to potential new indications

ALIGNMENT
- Study design
- Modeling approach
- Technical feasibility
- Traction gained

CLARITY
- Direct feedback
- Technical expectations
- Additional data needs
- Engaged scrutiny

Fit-for-Purpose (FFP) Initiative

U.S. FOOD & DRUG ADMINISTRATION

Pathway for regulatory acceptance of dynamic tools for use in drug development programs

Disease Area	Submitter	Tool	Trial Component
Alzheimer's Disease	The Coalition Against Major Diseases (CAMD)	Disease Model: Placebo/Disease Progression	Demographics, Drop-out
Multiple	Janssen Pharmaceuticals and Novartis Pharmaceuticals	Statistical Method: MCP-Mod	Dose-Finding
Multiple	Ying Yuan, PhD The University of Texas MD Anderson Cancer Center Department of Biostatistics	Statistical Method: Bayesian Optimal Interval (BOIN) Design	Dose-Finding
Multiple	Pfizer	Statistical Method: Empirically Based Bayesian Emax Models	Dose-Finding

https://www.fda.gov/drugs/development-approval-process-drugs/drug-development-tools-fit-purpose-initiative

Toward the Aspirational State

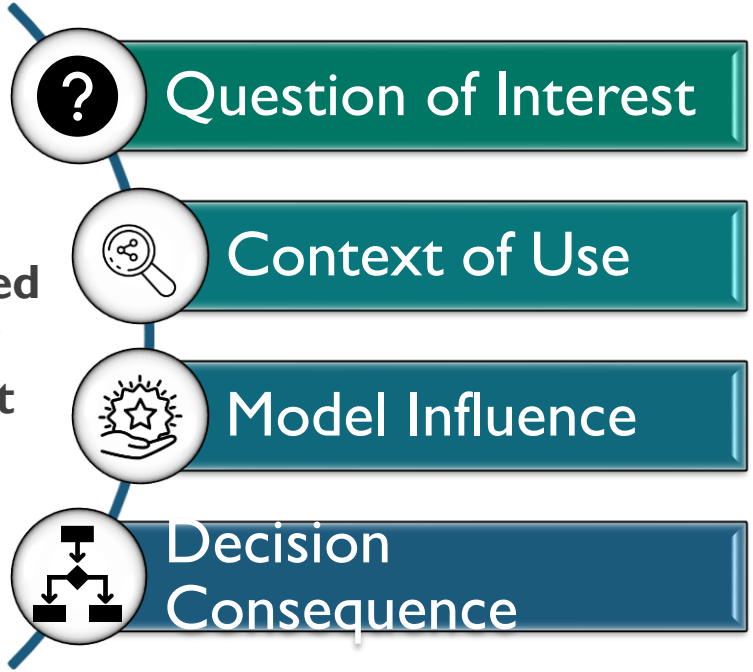
- "Slope of enlightenment" driven by continued scientific advancement and lessons learned from the accumulating experience
- Increase in and growing championship of these approaches among decision- and policy-makers
  - Motivated by more tangible examples
- Public engagement
  - Broad discussion of the contexts for high probability of success
- Processes and workflows
  - Created more predictable and transparent interactions
- Institutional support and collaboration among pharmaceutical companies and academic institutions/consortia
  - Development of best practices and regulatory guidance

Challenges & Opportunities

- Best practices for determining a model is fit-for-purpose (validation, performance/sensitivity metrics, platform independence)
- Identification and transparent communication of knowledge gaps
- Data/knowledge warehouses
- Varying degrees of comfort by end-users
- Clarity on regulatory expectations

What is the Question?

Risk-Informed Credibility Assessment



Standardizes terminology and streamlines assessment

Aids in communication and increase transparency

De-risks and advances MIDD applications

Kuemmel *et al* 2020 PMID: 31652029; Viceconti *et al* 2020 PMID: 31991193

Key Points

- MIDD has matured and is enjoying routine application
- Enabling and limiting factors are known and surmountable
- There is a global convergence which presents an opportunity
- Success depends on well-articulated goals and community effort

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

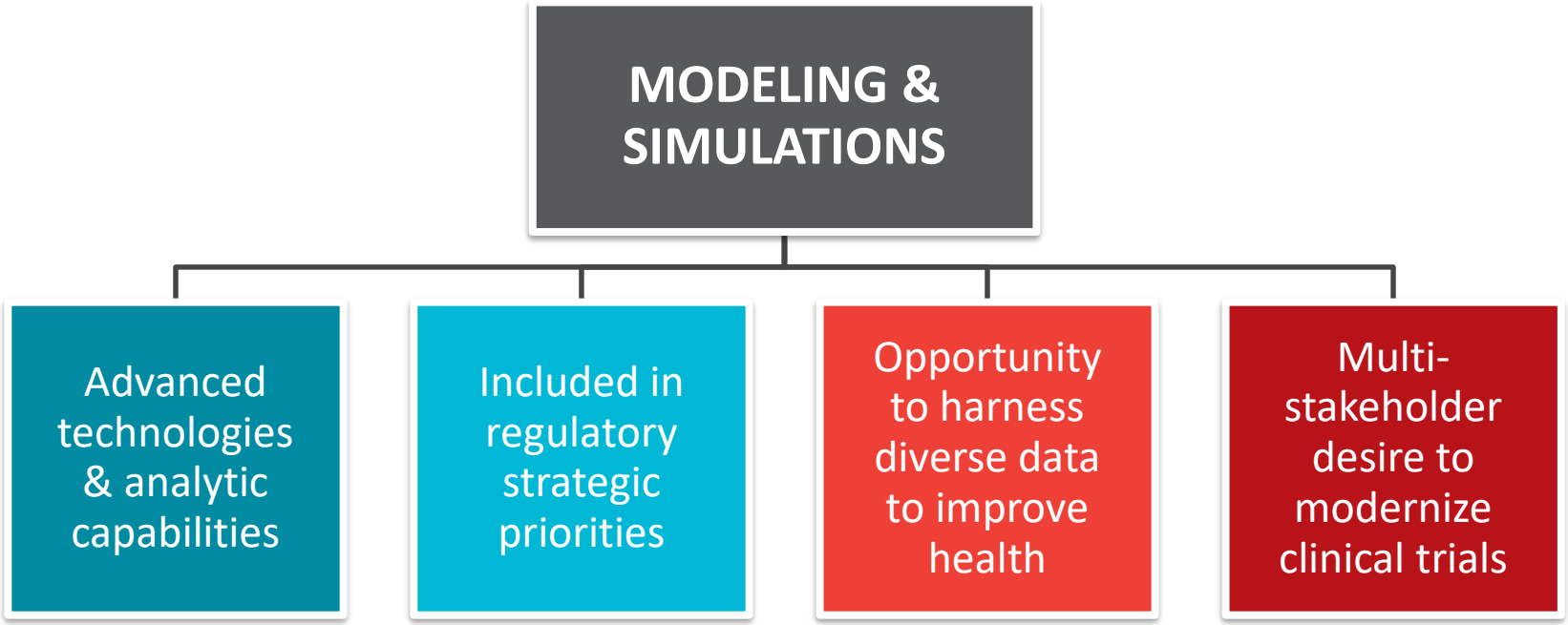
March 6, 2023

Disease Progression Modeling to Advance Clinical Trial Decision Making

Project Overview

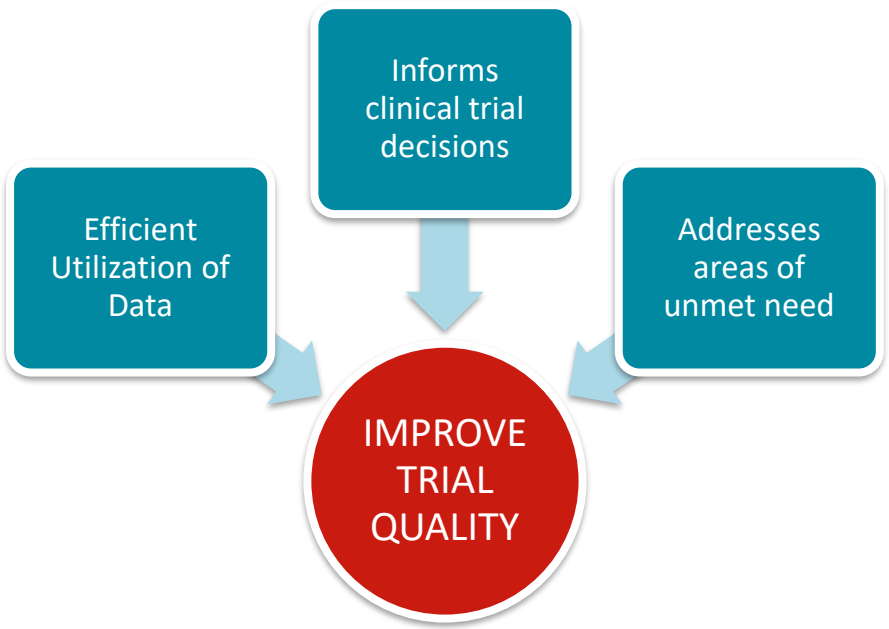
Lindsay Kehoe, CTTI, Senior Project Manager

Optimal Time for Modeling & Simulation



Why focus on Disease Progression Modeling (DPM)?

- M&S and MIDD are broad topics
- Scoped to DPM because it:
  - has applications across various stages of medical product development
  - integrates information from a wide variety of sources enabling efficient utilization of prior data
  - informs evidence generation in areas of unmet need



DPM: A model that quantitatively describes the time course or trajectory of a disease

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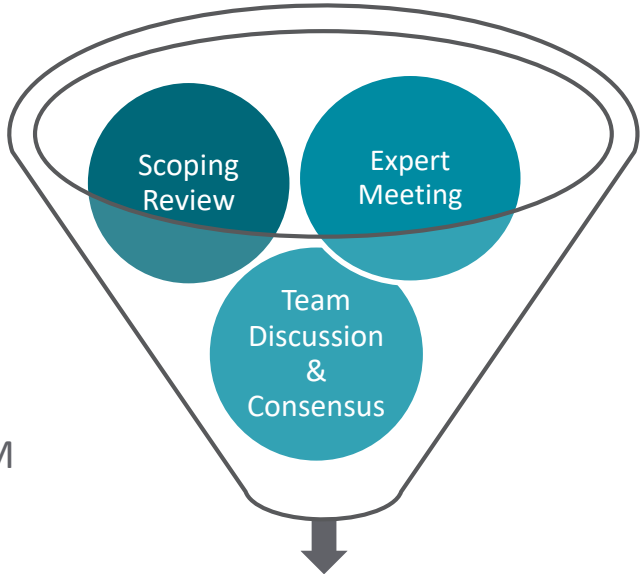
Disease Progression Modeling Project

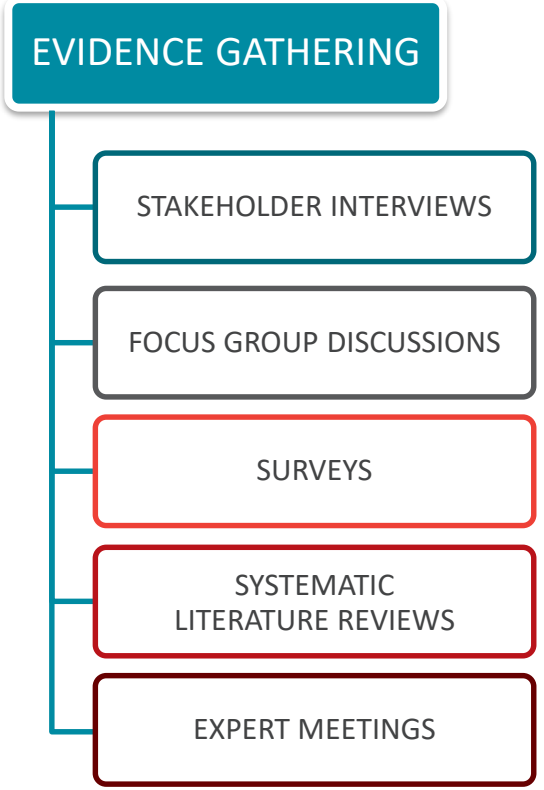
- **Purpose**: Clarify how DPM can advance decision making* throughout the medical product development lifecycle and accelerate the process of bringing treatments to patients
- **Objectives:**
  - Describe DPM and its current applications/contexts of use (COUs)
  - Identify and catalog examples of DPM that point to areas where it could be valuable in advancing decision making
  - Develop and disseminate recommendations that address DPM best practices
- **Anticipated Impact**: Improve trial and clinical development efficiency through the increased recognition, value, and consistent use of DPM



*decision making includes trial design, regulatory, development, and business decision making

Evidence guides the journey to solutions

- Select quantitative & qualitative research methods that best align with each project's objectives, to:
  - Identify and describe "what is going on" to gain a better understanding of a particular phenomenon
  - Move beyond individual views to more complete and objective understanding of disincentives and motivators for change
- Equipped with data, we then challenge assumptions, identify roadblocks, build tools, and develop recommendations to change the way people think about and conduct clinical trials.



CTTI Methodology: https://journals.sagepub.com/doi/10.1177/1740774518755054

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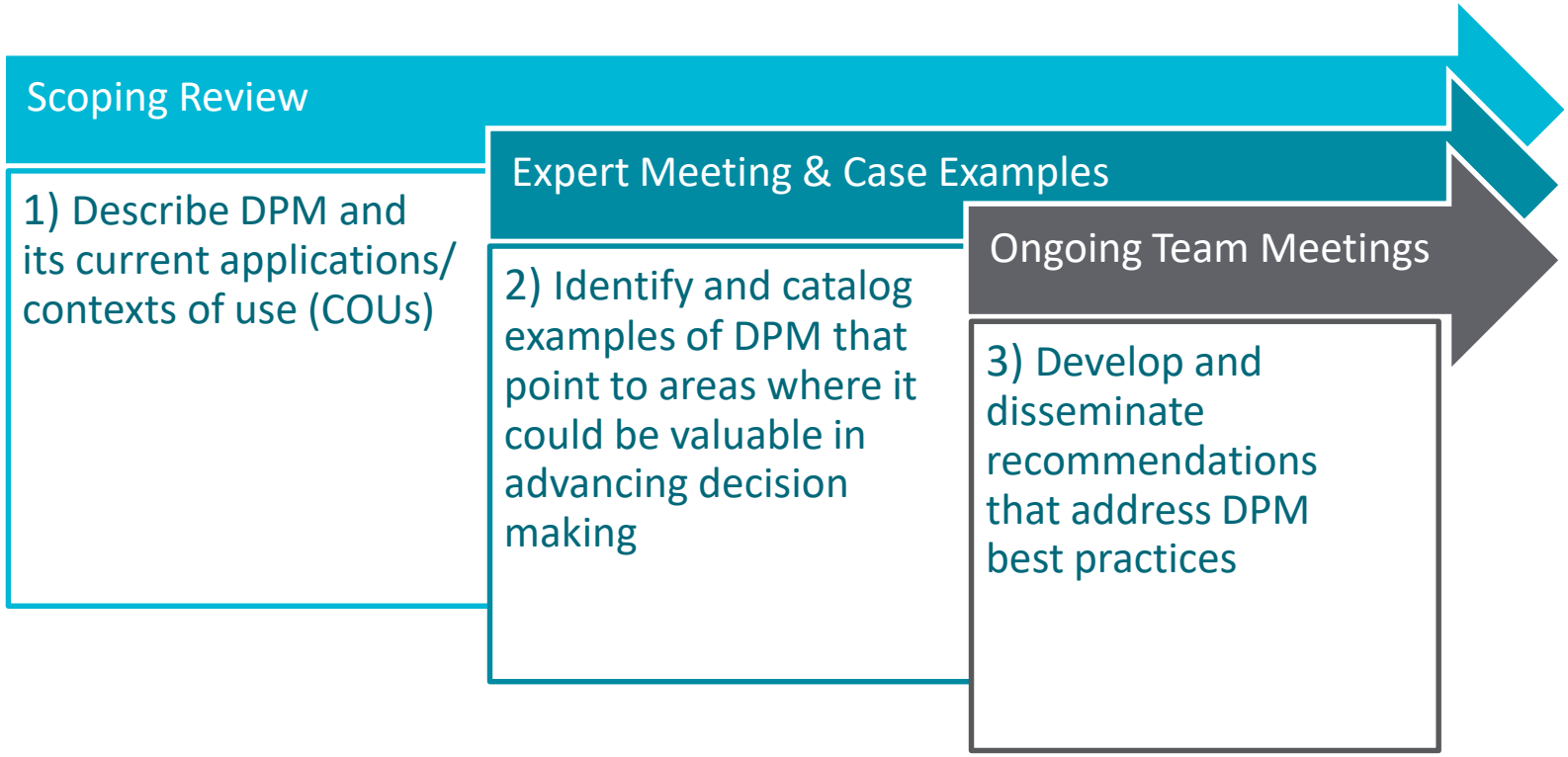
CTTI DPM Project Objectives & Approach



Multi-Stakeholder Project Team

Team Leads

Malidi Ahamadi (Amgen)

Bruce Burnett (Duke)

Phil Green (individual patient)

Raj Madabushi (FDA)

Executive Committee Champion

Theodore Lystig (BridgeBio)

Social Science Team

Summer Starling (CTTI/Duke)

Brian Perry (Duke)*

Team Members

Jenny Chien (Eli Lilly and Company)

Zifang Guo (Merck)

Matus Hajduk (Mind Medicine)*

Tony Jiang (Amgen)

Scott Kollins (Holmusk)*

Jiang Liu (FDA)

Qi Liu (FDA)

Eftyhmios Manolis (EMA)

Mark Palmer (Medtronic)

Herb Pang (Genentech)

Etienne Pigeolet (Novartis)

John Roberts (CSL Behring)*

Camelia Thompson (Biotechnology Innovation Organization)

Karthik Venkatakrishnan (EMD Serono)

Tiffany Westrick-Robertson (AiArthritis)

Reem Yunis (Medable)

Theo Zanos (Northwell Health)

Writer

Sav Miller (Duke)

Communications Lead

Rae Holliday (CTTI)

Project Manager

Lindsay Kehoe (CTTI)

Event Planner

Susan Morris (CTTI)

*former team lead or member

CTTI

Expectations for Today

- Provide examples of DPM applications that have been or could be valuable in advancing decision making in clinical trials
- Highlight challenges and potential solutions to using DPM for decision making
- Discuss recommendations/best practices needed from CTTI to advance DPM use and acceptance
- Brainstorm measures of progress

CLINICAL
TRIALS
TRANSFORMATION
INITIATIVE

@CTTI_Trials

THANK YOU

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

March 6, 2023

Project Scoping Review Approach and Results

Summer Starling, CTTI Project Manager

Today’s presentation

- Overview of objectives & methods for scoping review
- Presentation of scoping review results
- Description and discussion of DPM current applications or contexts of use observed in our scoping review

Scoping review objectives and approach

RQ: What is the scope of how disease progression modeling (DPM) is being used (applications) to inform clinical trial design, support regulatory decision making, and support U.S. global trials of drugs, biologics, and devices?

- Objectives:
  - Assess literature landscape
  - Describe different DPM potential applications
  - Identify unique or illustrative case examples of DPM for trials
- Approach:
  - Scoping review
  - Collaboration: Social Science Team, Duke SOM Library Sciences, CTTI DPM Project Team
  - Iterative data decisions

Criteria for inclusion

Inclusion criteria:

- Applications of disease progression modeling in humans in any therapeutic area at any clinical phase of the drug development process
- Original research, case studies, consortia papers, and white papers included
- Published in English since 2012

Exclusion criteria:

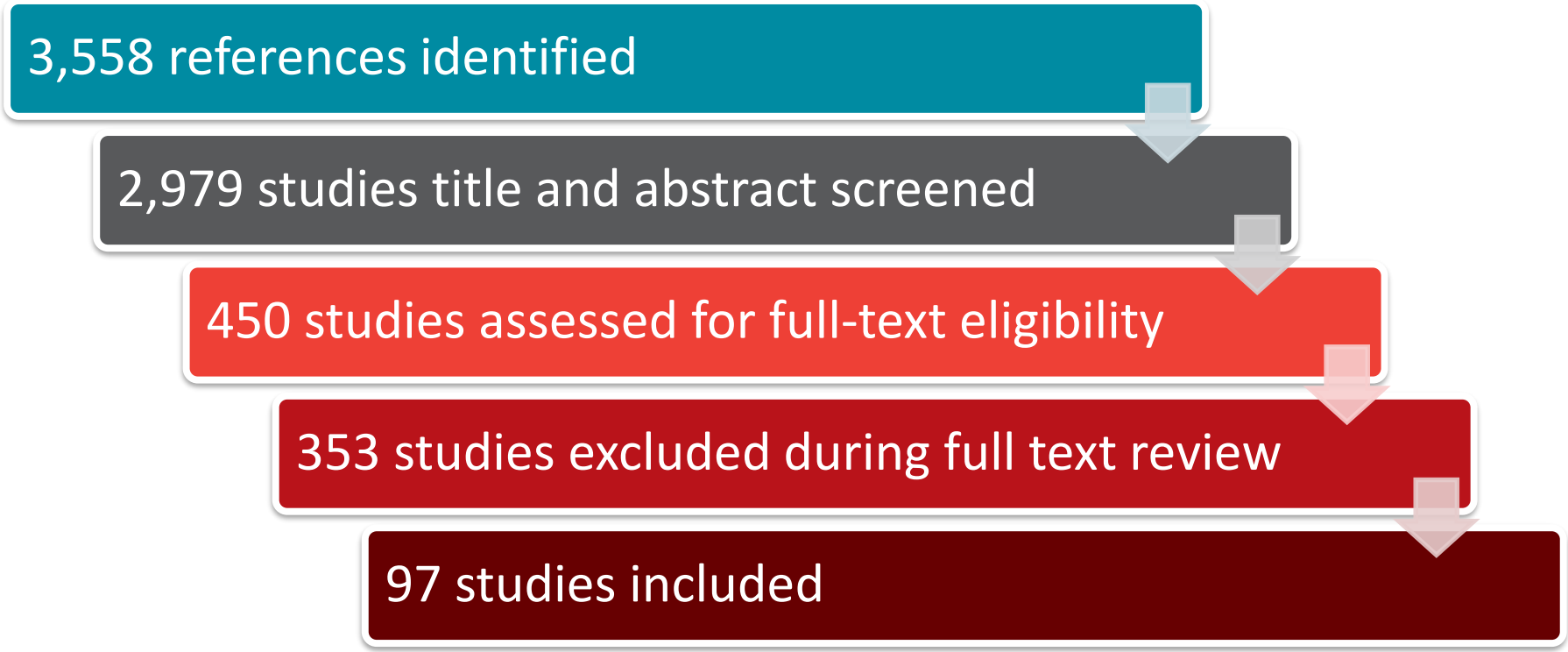
- Does not relate to clinical trials
- Does not address a disease
- Does not reflect a disease progression component
- Related to medical diagnosis or prediction of diagnostic outcomes
- Not related to humans
- Methodology paper only

Targeted searches and evidence gathering

- Search string keywords, phrases iteratively developed with Project Team
- Search executed in 3 databases
  - PubMed, Embase, and Scopus

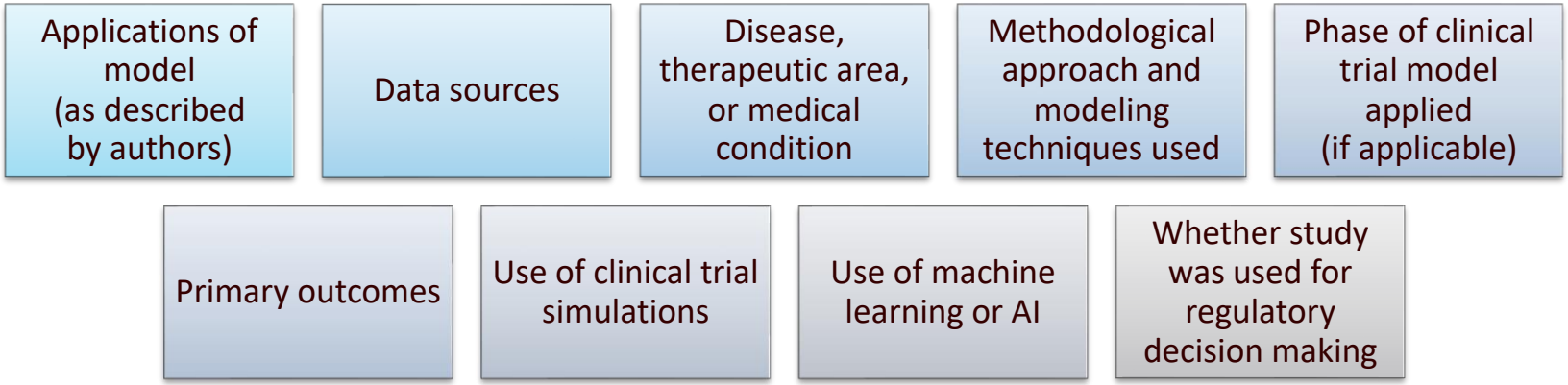
- Data screened using Covidence
- Data organized using MaxQDA

PRISMA process for data selection



Data extraction

- With our final sample (n=97), we:
  - Extracted 9 data points from each study and coded in MaxQDA



Data refinement and synthesis

- With our final sample (n=97), we:
  - Reviewed codes for accuracy
  - Refined code definitions and thematic groupings
  - Cross tabulated and explored data intersections, relationships
  - Flagged illustrative or unique studies of interest

Results: Overview

- Disease focus or therapeutic areas
- Methodologies and modeling techniques
- Data sources
- Common phases of CTs model used
- Use of CT simulations
- Model applications

Results: Diseases or therapeutic areas

- 34 unique disease or medical conditions in final sample set
  - Including neurodegenerative diseases, cancers, neuromuscular disorders, mental health disorders, and COVID-19
  - 56% neurodegenerative diseases or cognitive impairments (n=54)

Most frequent diseases or medical conditions (n=97)	n(%)
Alzheimer's disease	26(27)
Parkinson's disease	12(12)
Huntington's disease	6(6)
Amyotrophic lateral sclerosis (ALS)	6(6)
Osteoporosis	5(5)

Results: Model methodologies and techniques

Model methodologies (n=97)	n(%)
Empirical or statistical	87(90)
Mechanistic (QSP, etc.)	10(10)

- Diverse array, 100+ unique DP modeling techniques employed
- Regression analysis and nonlinear mixed effects modeling most common statistical modeling techniques
- Machine learning used in >10% of final sample set (n=12)
- Time-to-event modeling techniques also used (n=11)

Results: Data sources

Data sources used for model application (n=97)	n(%)
Real world data (RWD)	63(65)
Randomized clinical trials data (RCT)	44(51)
Literature	8(8)
Preclinical data	4(4)

- 16 studies used multiple data source types (16%)

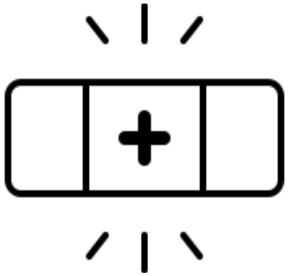
Results: Additional observations

- Majority had no applicable CT phase for model application (n=69, 71%)
  - 17 applied to Phase III trials; 8 to Phase II; 2 to preclinical

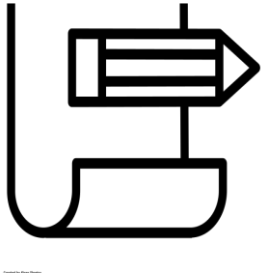
- More than a third (n=38, 39%) conducted CT simulations as part of model exploration or application

Thematic groupings for applications

13 applications for trials identified across scoping review results



Characterize treatment effects or inform dose selection



Enhance trial design

Identification or qualification of biomarkers or endpoints

Inform patient selection

Observed applications for trials, All studies (n=97)

Thematic grouping (4)	Applications (13)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization
	Treatment effect characterization
Enhance trial design	Inform study duration
	Inform study power
	Predict dropout rates
	Quantify impact of dropout
	Use for virtual control arm
Identification or qualification of biomarkers or endpoints	Endpoint identification
	Identification of prognostic or predictive biomarkers
Inform patient selection or population sources of variability	Improve characterization of patients
	Inform trial enrichment strategies
	Quantify impact of co-variates / inform stratification factors
	Support cross-population extrapolation or pooling

Frequencies of applications for trials, All studies (n=97)

Application		Studies (*n*)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization	11
	Treatment effect characterization	32
Enhance trial design	Inform study duration	6
	Inform study power	28
	Predict dropout rates	9
	Quantify impact of dropout	2
	Use for virtual control arm	2
Identification or qualification of biomarkers or endpoints	Endpoint identification	3
	Identification of prognostic or predictive biomarkers	31
Inform patient selection or population sources of variability	Improve characterization of patients	25
	Inform trial enrichment strategies	23
	Quantify impact of co-variates, inform stratification factors	23
	Support cross-population extrapolation or pooling	3

Frequencies of applications for trials, All studies (n=97)

Application		Studies (*n*)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization	11
	Treatment effect characterization	32
Enhance trial design	Inform study duration	6
	Inform study power	28
	Predict dropout rates	9
	Quantify impact of dropout	2
	Use for virtual control arm	2
Identification or qualification of biomarkers or endpoints	Endpoint identification	3
	Identification of prognostic or predictive biomarkers	31
Inform patient selection or population sources of variability	Improve characterization of patients	25
	Inform trial enrichment strategies	23
	Quantify impact of co-variates, inform stratification factors	23
	Support cross-population extrapolation or pooling	3

Frequencies of applications for trials, Empirical or statistical models (n=87)

Application		Empirical or statistical models (*n*)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization	8
	Treatment effect characterization	25
Enhance trial design	Inform study duration	6
	Inform study power	28
	Predict dropout rates	9
	Quantify impact of dropout	2
	Use for virtual control arm	1
Identification or qualification of biomarkers or endpoints	Endpoint identification	2
	Identification of prognostic or predictive biomarkers	30
Inform patient selection or population sources of variability	Improve characterization of patients	23
	Inform trial enrichment strategies	21
	Quantify impact of co-variates, inform stratification factors	22
	Support cross-population extrapolation or pooling	1

Frequencies of applications for trials, Empirical or statistical models (n=87)

Application		Empirical or statistical models (*n*)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization	8
	Treatment effect characterization	25
Enhance trial design	Inform study duration	6
	Inform study power	28
	Predict dropout rates	9
	Quantify impact of dropout	2
	Use for virtual control arm	1
Identification or qualification of biomarkers or endpoints	Endpoint identification	2
	Identification of prognostic or predictive biomarkers	30
Inform patient selection or population sources of variability	Improve characterization of patients	23
	Inform trial enrichment strategies	21
	Quantify impact of co-variates, inform stratification factors	22
	Support cross-population extrapolation or pooling	1

Frequencies of applications for trials, Mechanistic models (n=10)

Application		Mechanistic models (*n*)
Characterize treatment effects or inform dose selection	Inform dose/regimen selection & optimization	3
	Treatment effect characterization	7
Enhance trial design	Inform study duration	-
	Inform study power	-
	Predict dropout rates	-
	Quantify impact of dropout	-
	Use for virtual control arm	1
Identification or qualification of biomarkers or endpoints	Endpoint identification	1
	Identification of prognostic or predictive biomarkers	1
Inform patient selection or population sources of variability	Improve characterization of patients	2
	Inform trial enrichment strategies	2
	Quantify impact of co-variates / inform stratification factors	1
	Support cross-population extrapolation or pooling	2

Special thanks

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Research Practice Manager, Duke SOM

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Associate Dean for Library Services & Archives, Duke Medical Center Library & Archives

DPM Project Team Leads and Members

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Summer Starling, CTTI Project Manager

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Q & A

BREAK

Return to …at 10:10 am

Session II: Challenges and Solutions for Advancing DPM Uptake

Moderator: **Raj Madabushi**, Associate Director, Guidance and Scientific Policy, Office of Clinical Pharmacology, FDA

CTTI

Welcome Back!

Session II Objectives:

- Explore barriers for advancing the use of disease progression modeling to aid in decision making
- Discuss essential needs to advance the use of disease progression modeling

Approach: Panel → Break Out Groups

- Panel focus: DPM Applications & Decision Making
- Break Out Group focus: Essentials to Advance DPM & Accountability

Panel: DPM Applications & Decision Making

Hao Zhu

FDA

CJ Musante

Pfizer

Dave Miller

Unlearn.Ai

Klaus Romero

Critical Path Institute

Moderator: **Raj Madabushi**, FDA, CTTI Project Team Lead

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OFFICE OF CLINICAL PHARMACOLOGY

Use of Disease Progression Models to Support New Drug Development

Hao Zhu, Ph.D., M.stat.
Division Director
Division of Pharmacometrics
Office of Clinical Pharmacology
OTS/CDER/FDA

CTTI
March 6, 2023

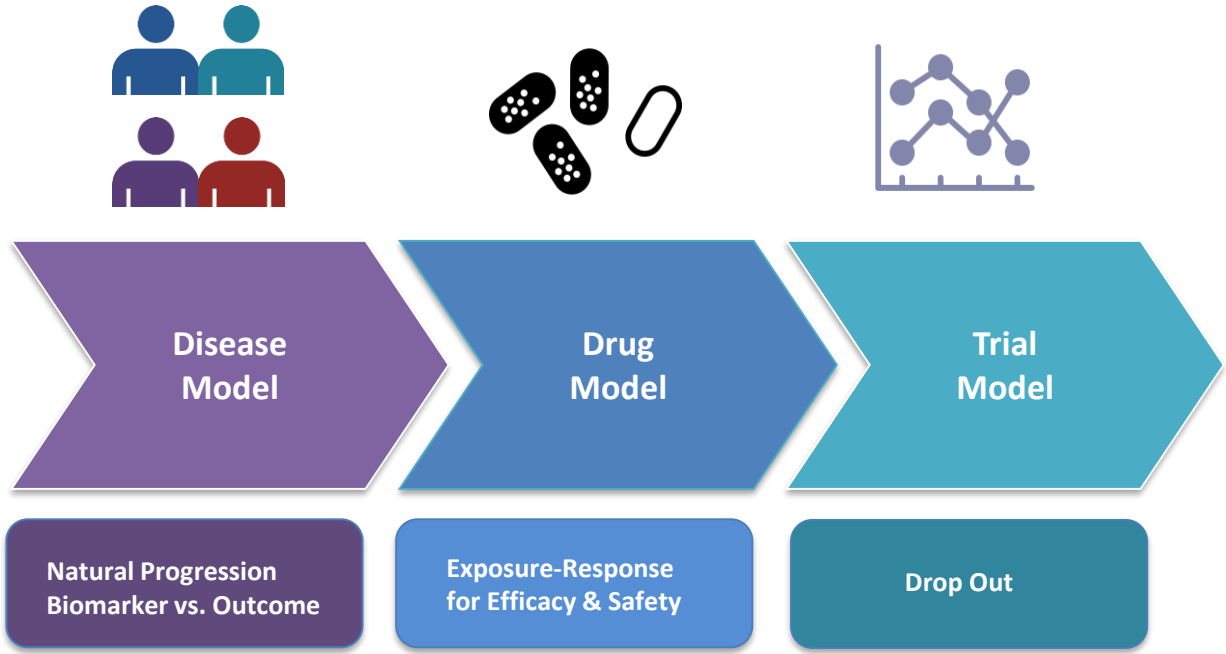
* Disclaimer: The views in this presentation are my personal and should not be construed as the official position of the US Food and Drug Administration.

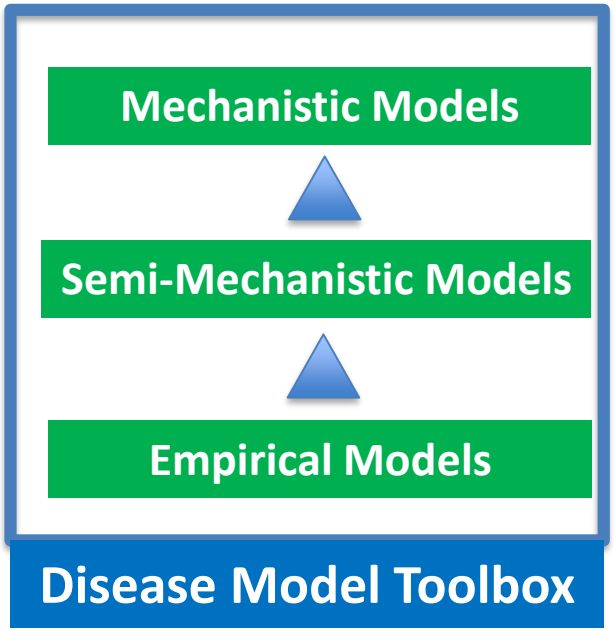
Outline

- Introduction
  - Disease Progression Models
- Disease Models at FDA and Case Examples
  - Disease Models at FDA

    (OCP's Efforts and Examples of Disease Models)
  - Case Examples
    - Pediatric Extrapolation: Schizophrenia Disease-Drug-Trial Model
- General Considerations for Disease Progression Models
- Take Home Message

Quantitative Disease-Drug-Trial Models



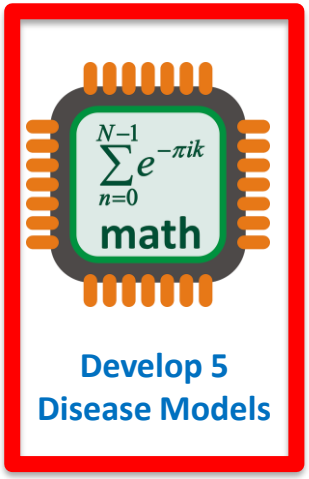


*: Jogarao V S Gobburu, Lawrence J Lesko. **Quantitative disease, drug, and trial models.** *Annu. Rev. Pharmacol. Toxicol. 2009. 49:291–301.* doi: 10.1146/annurev.pharmtox.011008.145613.

History: 2020 Strategic Goals

Train 20 Pharmacometricians

Implement 15 Standard Templates



Develop 5 Disease Models

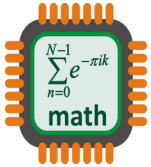
International Harmonization

Integrated Quantitative Clinical Pharmacology Summary

Design By Simulation

2010 2020

Disease Model Examples from FDA

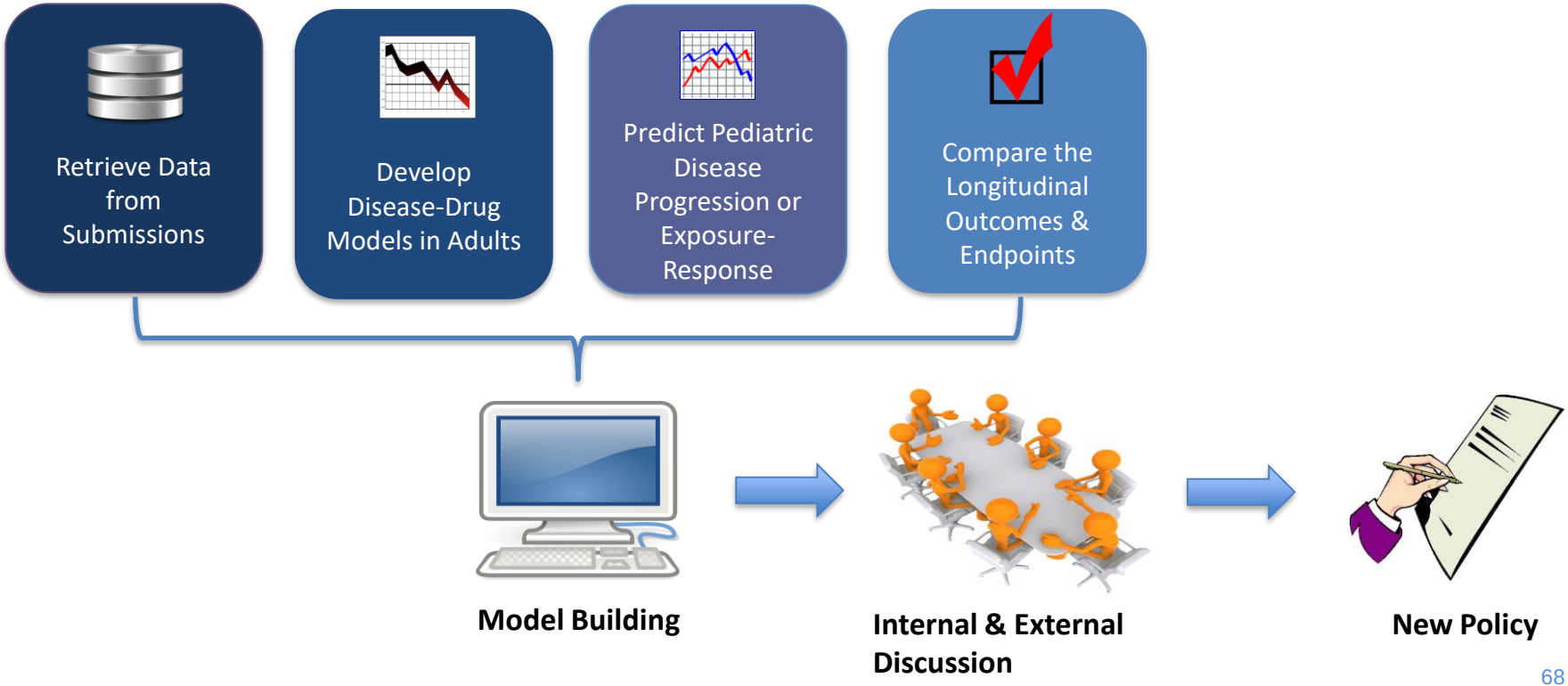


No	Disease Model	Use
1	NSCLC Model [1]	Late Phase Trial Design.
2	Parkinson's Disease Model [2]	Endpoint Selection and Clinical Trial Design
3	Alzheimer's Disease Model [3]	Endpoint Selection and Clinical Trial Design
4	Diabetes Disease Model [4]	Clinical Trial Design
5	Huntington's Disease Model [5]	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 Example: Disease Model for Schizophrenia

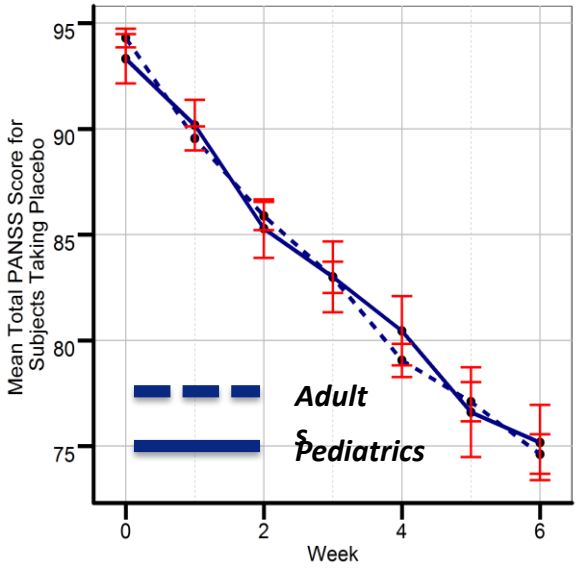
Characterize the Profile of the Disease Progression and ER

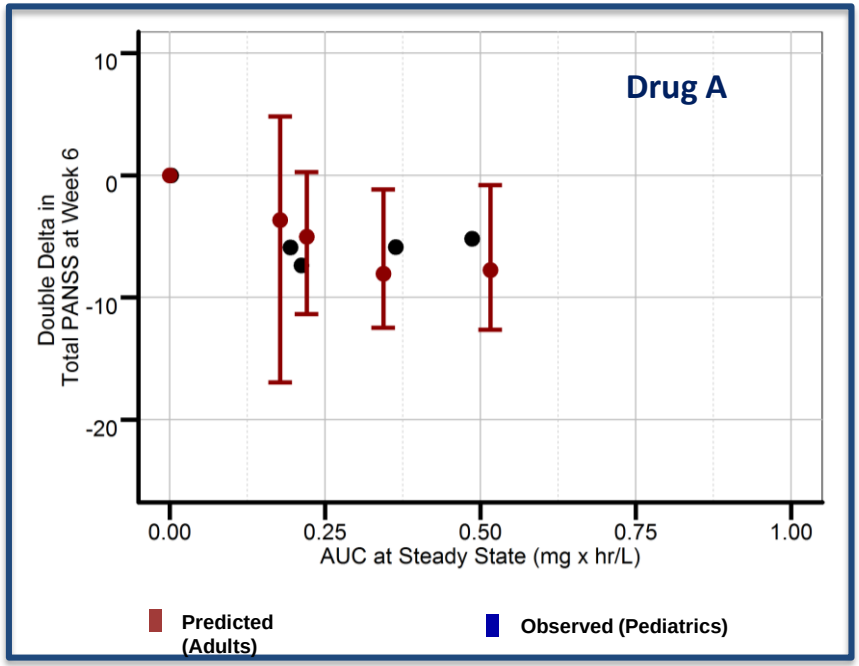


Evidence to Demonstrate Disease Similarity and Response

Disease Model

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

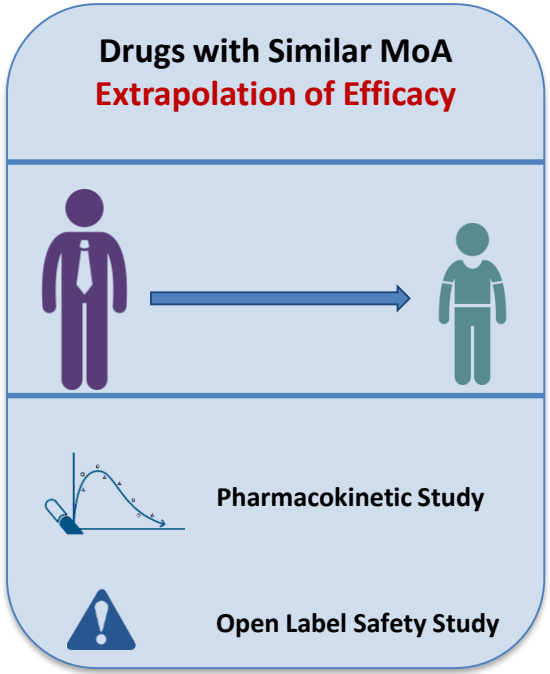


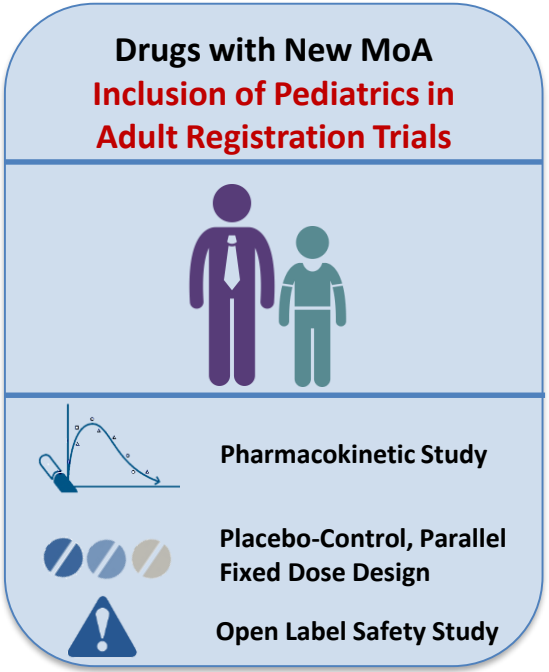


Shamir N Kalaria, Hao Zhu, Tiffany R Farchione, Mitchell V Mathis, Mathangi Gopalakrishnan, Ramana Uppoor, Mehul Mehta, Islam Younis. **A Quantitative Justification of Similarity in Placebo Response Between Adults and Adolescents With Acute Exacerbation of Schizophrenia in Clinical Trials. Clin Pharmcol.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

Extrapolation of Efficacy from Adults to Pediatrics

Schizophrenia Program





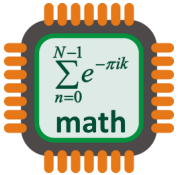
*Juvenile animal studies needed for bipolar I indications less than 12 years of age

**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

General Considerations for Disease Modeling

- Modeling Objectives: (critical to determine subsequent actions)
- Data: (General principles for meta-analysis: source, information collected, endpoints, assay, study design, enrollment criteria, observational study vs. clinical trial, patient subgroups, handling of missing values, outliers, etc)
- Assumptions: (mathematical / statistical assumptions, biological assumptions, assumptions for information borrowing, etc)
  - Model Structure (e.g., linear vs. non-linear, current understanding of mechanism)
  - Covariate selection (e.g., missing covariates, imbalanced information from trials)
  - Parameters (e.g., borrowing information from different sources)
- Validation and verification (inline with the context of use, needed level of validation needs to be adjusted)
- Decision making (risk-based, factor in uncertainty)
- Reporting



Take Home Messages

- Disease-Drug-Trial Models are important tools for MIDD.
- FFP, MIDD, and CID programs allow direct interactions between industry and FDA on various modeling approaches.
- Several steps should be considered to ensure that the established disease model can be applied to support the targeted usage.

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- DPM Members
- OCP Members
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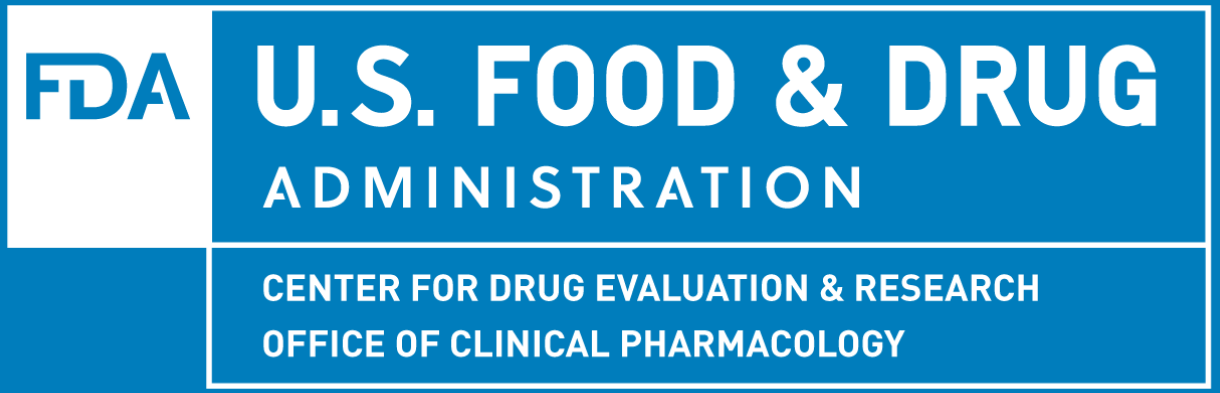
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March 6, 2023

Applications of DPM: Attributes and Limitations – Sponsor perspective

C.J. Musante, VP & Global Head of QSP, Pfizer

Disclaimer

- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative or the presenter's employer.
- The presenter is an Employee of Pfizer Inc.

Quantitative Systems Pharmacology (QSP) Examples

DPM to Advance Decision Making Throughout the Medical Product Development Lifecycle

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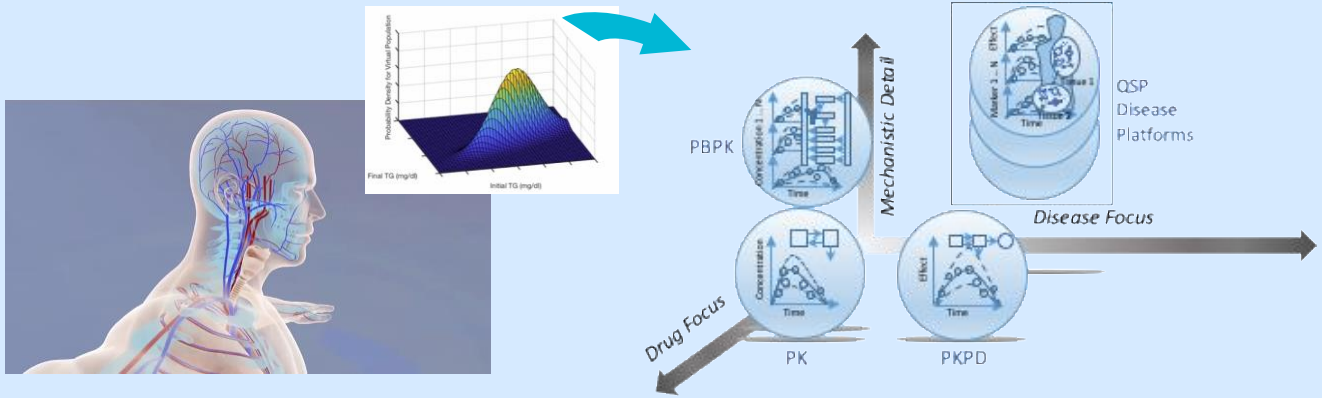
What is a QSP DPM?

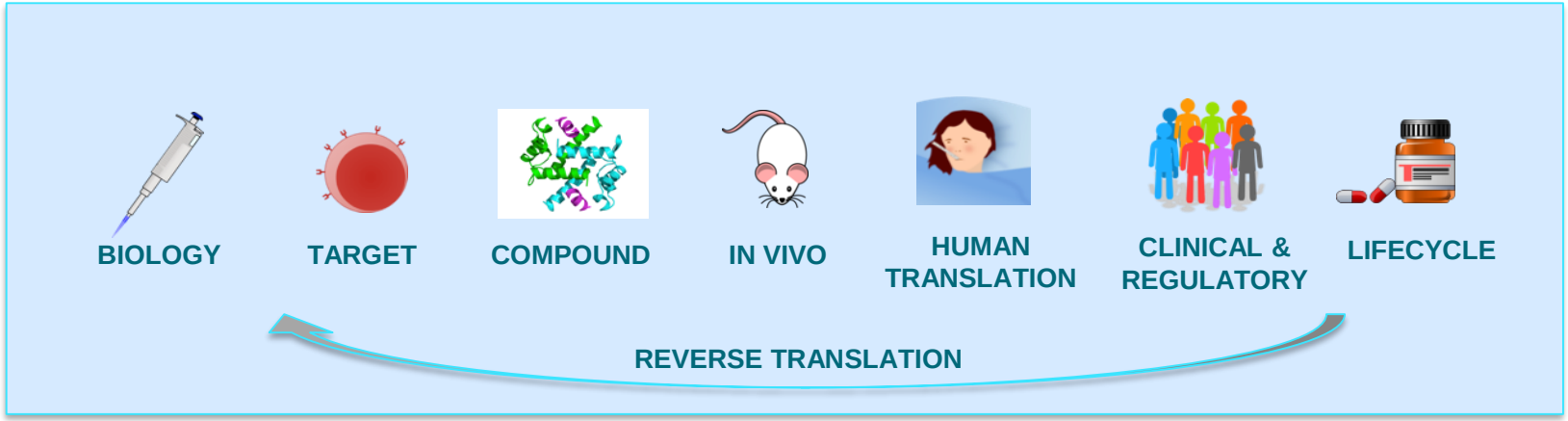
… a modeling & simulation approach that mathematically describes the mechanistic relationships between target modulation and disease biomarkers & outcomes over time…



Musante, CJ, Ramanujan S, et al (2017), Quantitative Systems Pharmacology: A Case for Disease Models. Clin. Pharmacol. Ther., 101: 24-27.

…to predict and interpret clinical responses to pharmacological intervention as part of a model informed drug development (MIDD) paradigm.

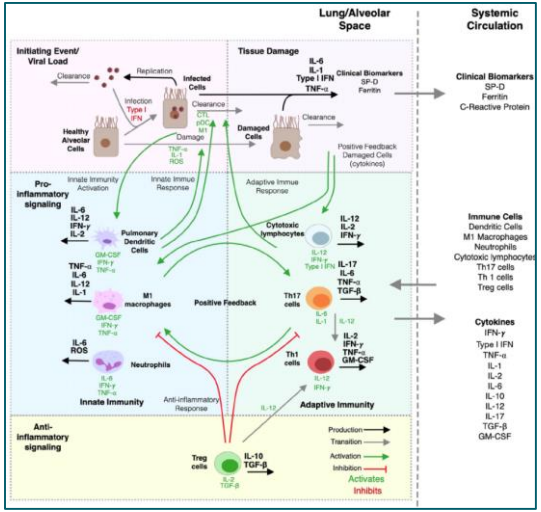
QSP DPM Applications in MIDD



SOURCE: Adapted from Ramanujan et al., Systems Pharmacology & Pharmacodynamics, ed. D Mager & H. Kimko, 2016.

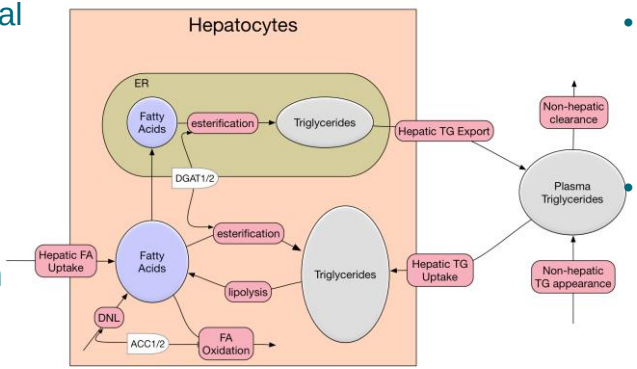
Different Examples - Common Themes

QSP Model of the Immune Response to SARS-CoV-2



- Preclinical to clinical translation
- Dose-response predictions
- Dose timing and treatment duration vs time of infection
- Comparative efficacy
- Efficacy predictions in different populations

QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)



- Predicting combo efficacy in NAFLD based on healthy data for single agents
- Clinical trial simulations for single & combo arms in Ph 2 trial
  - Study duration
  - Doses
- Comparative efficacy

Left: Dai, W., Rao, R., et al. (2021), "A Prototype QSP Model of the Immune Response to SARS-CoV-2 for Community Development." CPT Pharmacometrics Syst. Pharmacol., 10: 18-29. https://doi.org/10.1002/psp4.12574

Right: Rieger, T. "Development of virtual populations for prediction of the response to treatments for non-alcoholic fatty liver disease." Presented at the 9th American Conference on Pharmacometrics, October 2019.

Key Common Themes

- Each model
  - was based on mechanistic understanding (*at the time of development)* of the target and disease
  - was used to extrapolate to new conditions
  - informed clinical trial design and accelerated the programs
  - predictions were subsequently confirmed by trial results

Key Common Themes & One Difference

- Each model was based on mechanistic understanding (*at the time of development)* of the target and disease
- Each model was used to extrapolate to new conditions
- Each model informed clinical trial design and accelerated the programs
- Predictions from each model were subsequently confirmed by trial results
  - However, the QSP NAFLD model initially mis-predicted a change in a key biomarker, resulting in a missed opportunity to address earlier in development

What can we learn from these examples?

Two Examples: Compare & Contrast

QSP Model of the Immune Response to SARS-CoV-2

- Novel infectious disease of global concern
- Many biotech/pharma advancing vaccines & anti-virals, at unprecedented speed, several with EUA
- Clinical trial and real-world data rapidly emerging and submitted for peer-review publication and/or included in EUA submissions

- At the time of our clinical trial simulations, mAb and preliminary competitor anti-viral summary data were publicly available
- Relative confidence in mechanism of action, based on preclinical and clinical data

QSP Model of Non-Alcoholic Fatty Liver Disease (NAFLD)

- Under-studied/diagnosed disease with unmet need
- Highly competitive field with many agents in development; several fast-tracked
- Limited data available on disease progression in published literature; RWE lacking

- At the time of initial simulations, clinical data were not publicly available for this mechanism of action (MoA)
- Preclinical data did not translate to understanding the regulation of hepatic lipid metabolism in humans
- Once competitor data with same MoA were published, model was updated & successfully used to inform Phase 2

Summary: QSP DPMs

- Represent complex interactions *in time* between multiple drug targets, pathways, tissues, and organs/systems
- Mechanistically link target modulation to biomarker response &/or clinical outcomes
- Include untreated and treated patients and a range of disease phenotypes via virtual patients, populations, and trial simulations
- Allows for hypothesis testing & extrapolation beyond available data

- “Success” largely dependent on confidence in the target and the mechanism(s) in the context of human disease

Acknowledgments

- Rohit Rao
- Richard Allen
- Theodore Rieger

- Gianluca Nucci
- Brian Corrigan

- Project team members and clinical trial participants

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C.J. Musante

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March 6, 2023

AI/ML: Value for DPM and Adoption Challenges

David P. Miller

Chief Science Officer, Unlearn.ai

Disclaimer

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- The presenter is an Employee of Unlearn.ai and owns equity in Unlearn.ai.

AI/ML → Deep Learning

- What is it?
- What is it good for?
- Why aren’t we already using it broadly today?

Deep Learning
What Is It?

← Thread

Yann LeCun
@ylecun

Some folks still seem confused about what deep learning is. Here is a definition:

DL is constructing networks of parameterized functional modules & training them from examples using gradient-based optimization....
facebook.com/722677142/post...

7:32 AM · Dec 24, 2019

Clear enough?

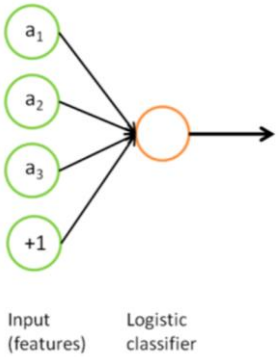
CTTI

Can you tell the difference between a cat and a dog?

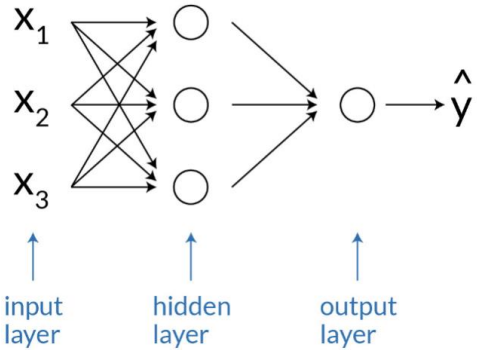
How do you know the cat is a cat?
Size? Color? Posture? Ears? Fluffiness?

Features and Parameters

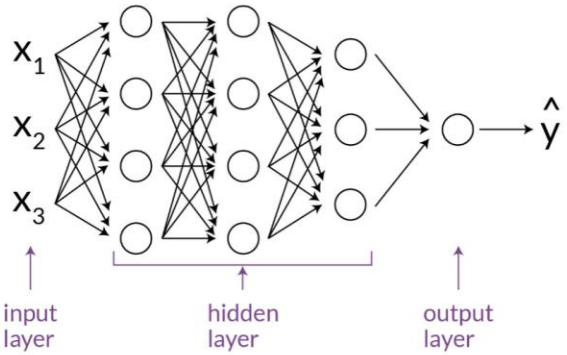
Logistic Regression



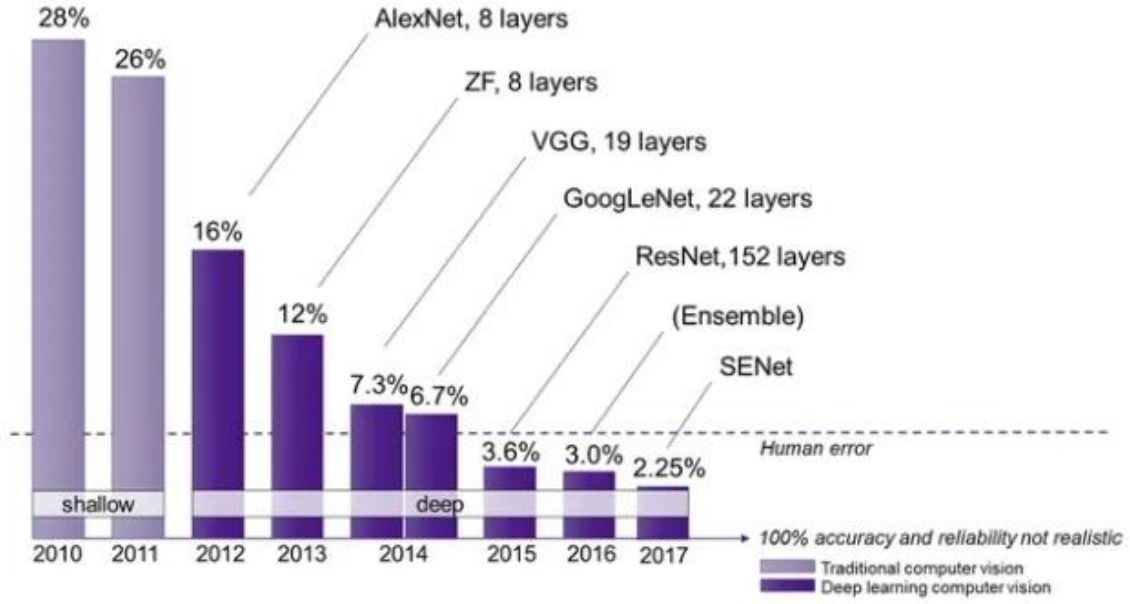
Shallow Neural Network



Deep Neural Network



What if pictures had more than cats and dogs?



AlexNet Ushered in a New Era of ML in 2012

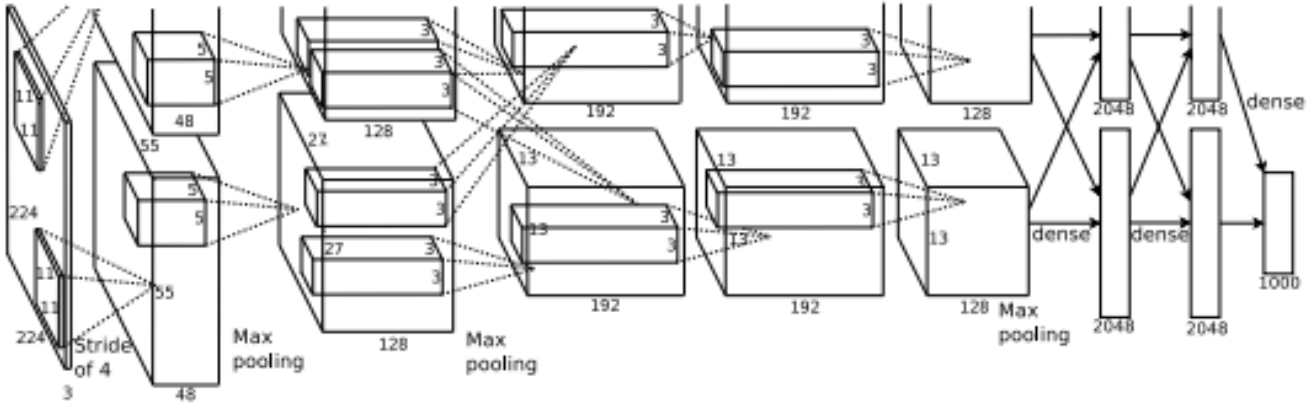


Figure 2 from Krizhevsky, Sutskever, and Hinton

Deep Learning
What Is It Good For?

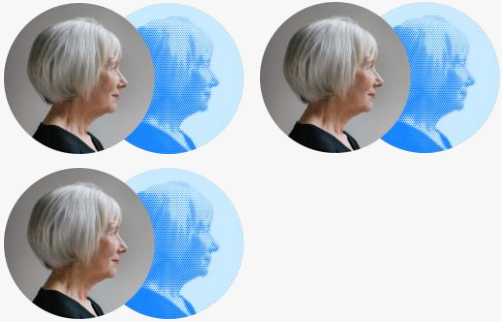
AI-generated Digital Twins provide a rich set of explanatory data for every participant in an RCT

Control Arm

Treatment Arm

AI-Generated Digital Twins + Real Participants = Faster, Smaller Trials

Control Arm



Treatment Arm

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

CHMP qualifies PROCOVA

What are the key points in the qualification?

- Suitable for primary analysis of phase 3 pivotal studies
- Unbiased estimation of treatment effect
- Increased power
- Reduced sample size

The PROCOVA™ Procedure has 3 Steps

Step 1

"Training and evaluating a prognostic model to predict control outcomes"

Step 2

"Accounting for the prognostic model while estimating the sample size required for a prospective study"

Step 3

"Estimating the treatment effect from the completed study using a linear model while adjusting for the control outcomes predicted by the prognostic model"

Deep Learning
Why Aren't We Already Using It Broadly Today?

Charles Fisher

Founder and CEO

Unlearn.AI

Unlearn is accelerating clinical trials with AI.

"The biggest challenge in commercializing AI-based tech in healthcare is "the discernment problem" – most prospective customers can't easily distinguish between companies using sophisticated AI and other companies selling nonsense as AI.

As a result, they assume you're guilty until proven innocent. To overcome this, you need to do something big to stand out from the crowd.

In Unlearn's case, we've focused on paving the regulatory path and became the first company to receive a regulatory qualification for an AI-based approach to accelerating clinical trials. What can you do to show you're a cut above the rest?

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EMA vs FDA

- Submission April, 2021
- First meeting May, 2021
- Comments from EMA May, 2021
- Updated submission June, 2021
- EMA formal questions Sep, 2021
- Additional questions Dec, 2021
- Draft qualification Feb, 2022
- Public consult March, 2022
- Qualification Sep, 2022

- CPIM meeting March, 2020
- ISTAND submission June, 2021
- Eleven separate updates that there was no update (July, 2021 through June, 2022)
- Communication that there would be no more applications accepted in 2022 (July, 2022)
- Confirmation that ISTAND was the right path and there are no available resources to review (Dec 2022)

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Disease Progression Modeling Without Tears

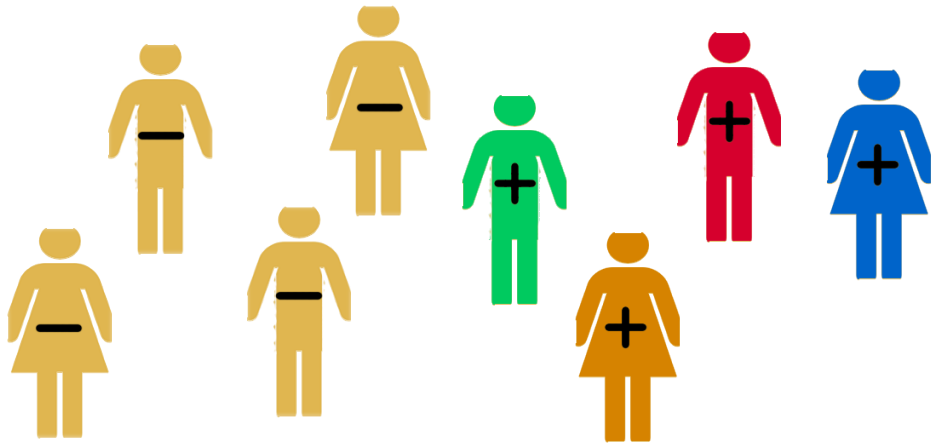
Transforming data into actionable knowledge for drug development

Klaus Romero MD MS FCP
Chief Science Officer

CRITICAL PATHH INSTITUTE

Critical questions for trial design

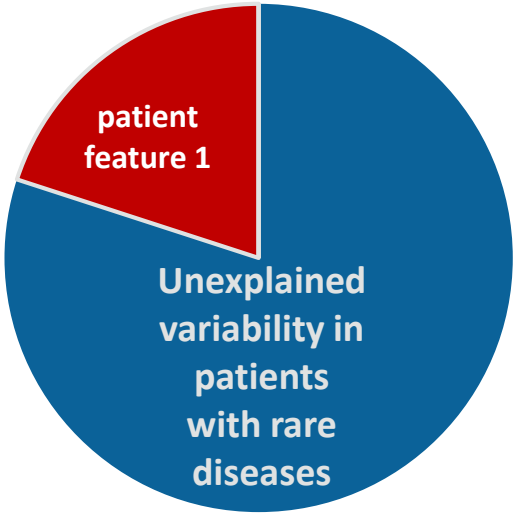
- How many patients should be recruited to properly power the trial?
- What should be the inclusion criteria?
- Can the control arm be optimized?
- What types of progression rates are expected for different subpopulations?
- What measures of progression are most adequate, at which stages of the disease continuum?
- How long should the trial duration be?
- How often should I assess?
- What is the time-varying probability of dropouts, and what are their predictors?

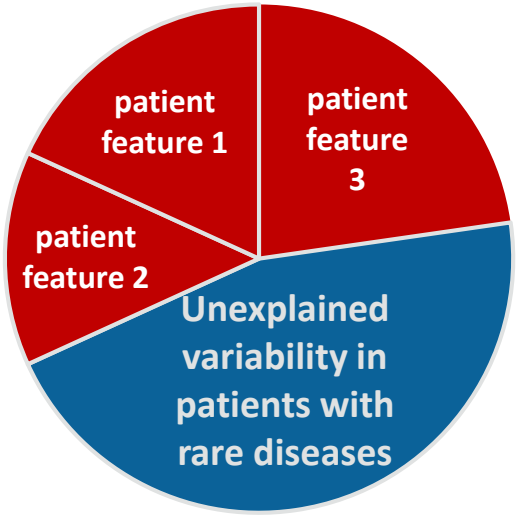


How should one go about providing sound quantitative answers to these questions?

Answer 1: Quantifying variability

Quantifying multiple sources of variability simultaneously within the patient population reduces overall unexplained variability



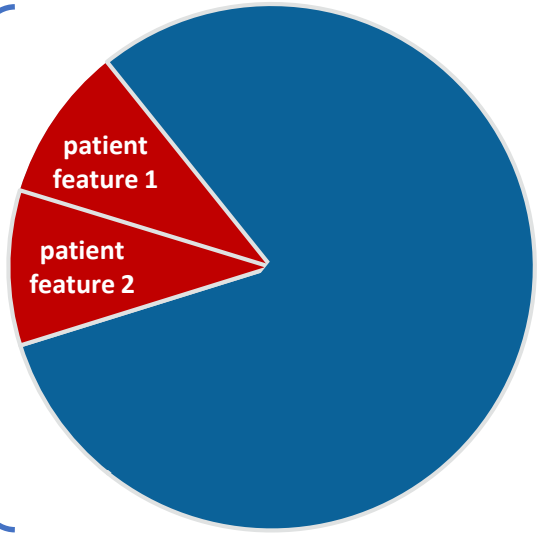


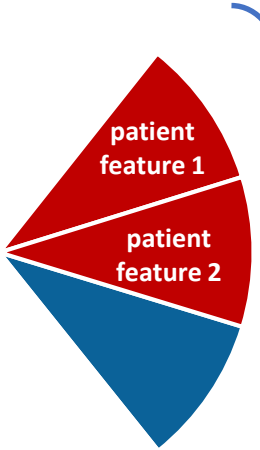
Result: The ability to predict more accurate progression rates for heterogeneous subpopulations of patients in clinical trials

Answer 2: Multiple data sources

Understanding the 'universe' of a given disease's heterogeneity

Unexplained variability in <u>ALL</u> patients with rare diseases

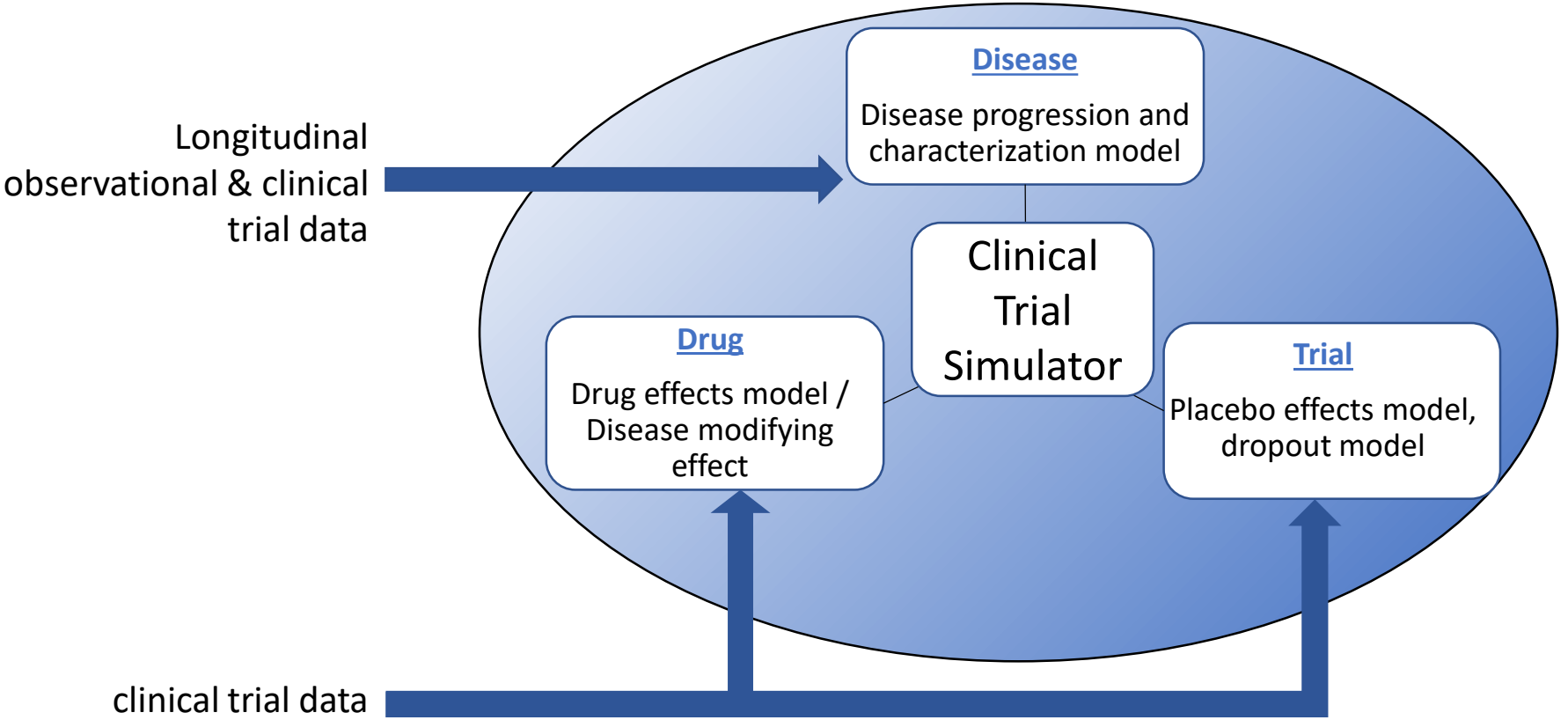




Unexplained variability in patients with rare diseases from <u>a single study</u>

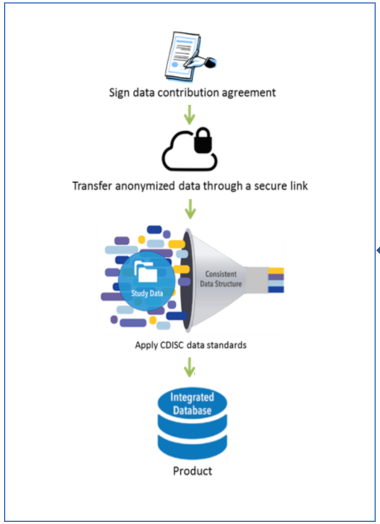
Result: The ability to more accurately account for the heterogeneity in rare diseases and avoid biased conclusions on few data sources

Answer 3: Drug-disease-trial modeling



Putting it altogether

- Start with an understanding of what sponsors can practically use to design clinical trials, and reverse engineer



STUDYID	USUBJID	AGE	SEX	ARM	ACTARM	SITEID	SWEDD
PD-1000	PD-1000/(	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/(	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/(	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/(	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/(	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/(	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/(	65	0	Parkinson	Parkinson	NA	NA
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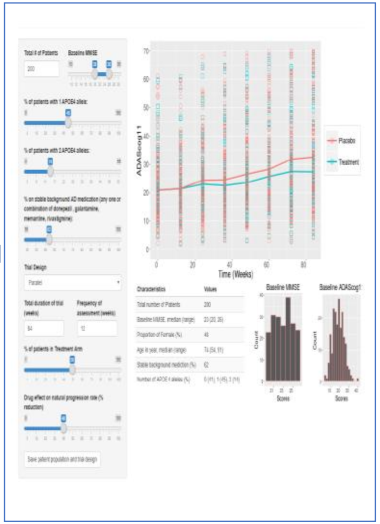
PD-1000	PD-1000/(	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/(	67	1	Parkinson	Parkinson	NA	NA

$$S(t) = \frac{S_0}{\left[S_0^{\beta} + \left(1 - S_0^{\beta}\right) e^{-\beta r t}\right]^{1/\beta}}$$

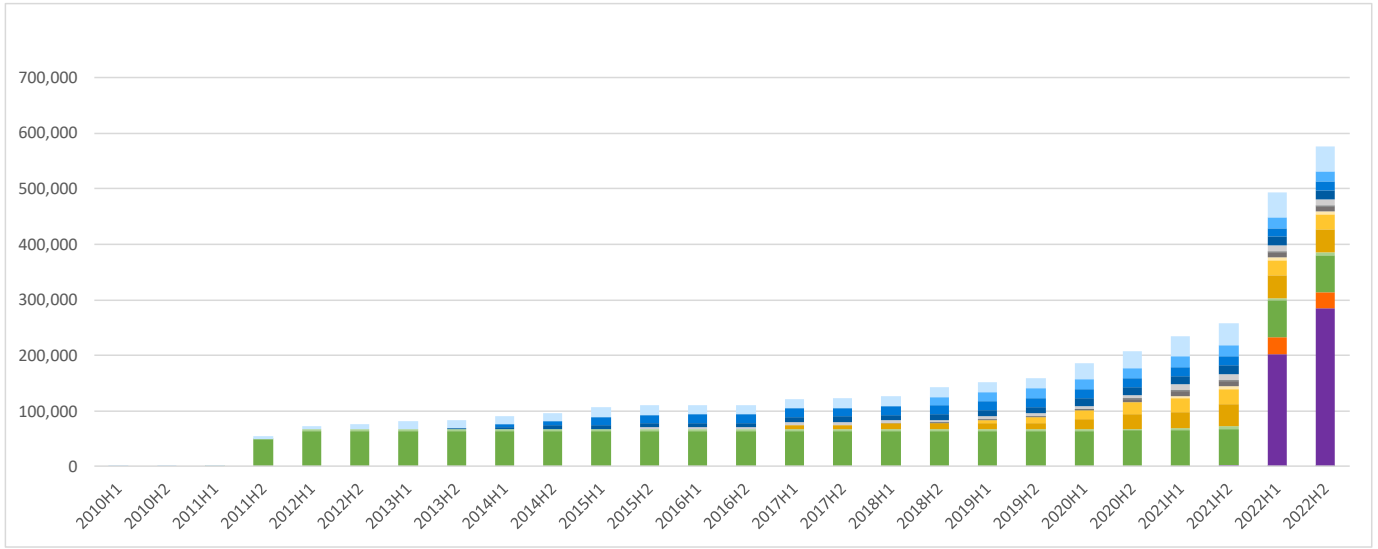
$$TVP_i = \theta_i \left(\frac{cont_i}{ref}\right)^{\theta_{power}} \theta_{coeff}^{cat_i}$$

$$f(S;\ \alpha, \beta) = \frac{\Gamma(\alpha+\beta)}{\Gamma(\alpha)+\Gamma(\beta)} \cdot S^{(\alpha-1)} \cdot (1-S)^{(\beta-1)}$$



Execution

Total Data Contributed



Clinical Data	
Studies	390
Participants	605,708

Non-Clinical Data	
Studies	148
Participants	11,084

Neuro	
Alzheimer's Disease	44,131
Huntington's Disease	19,665
Multiple Sclerosis	15,626
Parkinson's Disease	15,926

Rare	
Duchenne's Muscular Dystrophy	11,442
Friedreich's Ataxia	1,572
Rare Diseases	8,196

IHP	
Sickle Cell Disease	6,240
Transplant Therapeutics	26,264
Type 1 Diabetes	42,287

TSSP	
Polycystic Kidney Disease	4,422
Safety Testing	66,295

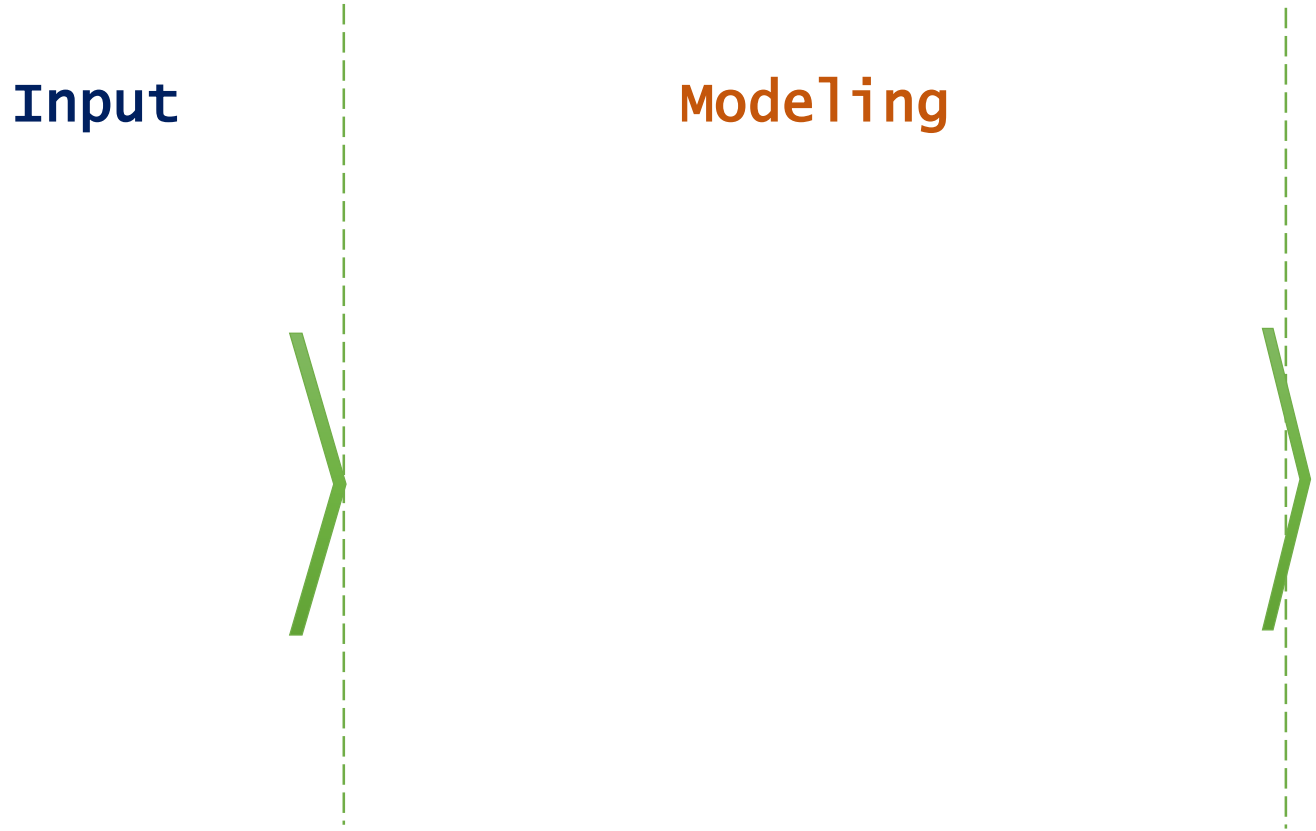
CURE Drug Repurposing	29,618

Neonatal	283,565

Tuberculosis	829

Note: Studies currently undergoing curation are only counted in Total Studies until evaluated.

Disease Progression Model



Disease Progression Model

Input

Patient-level data

Modeling

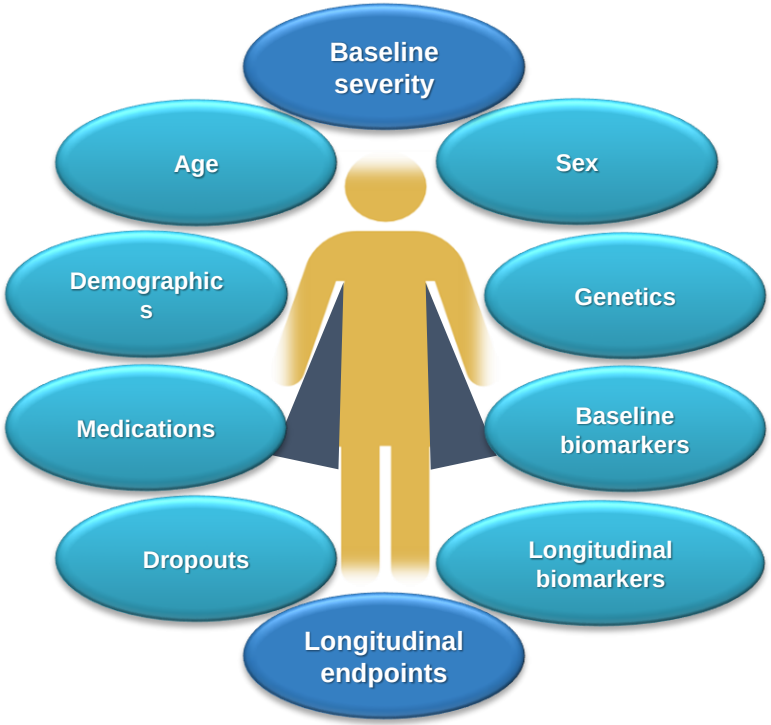
Output

Disease Progression Model

Input

Patient-level data

Modeling



Output

Disease Progression Model

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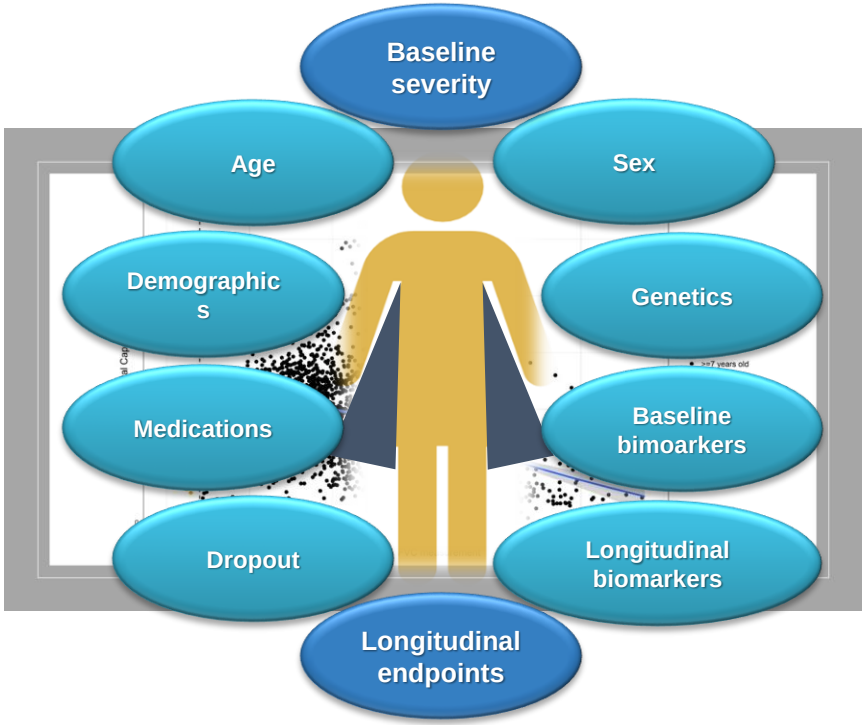
Input

Clinical studies

Modeling



Output

Understanding of disease worsening

Trajectory

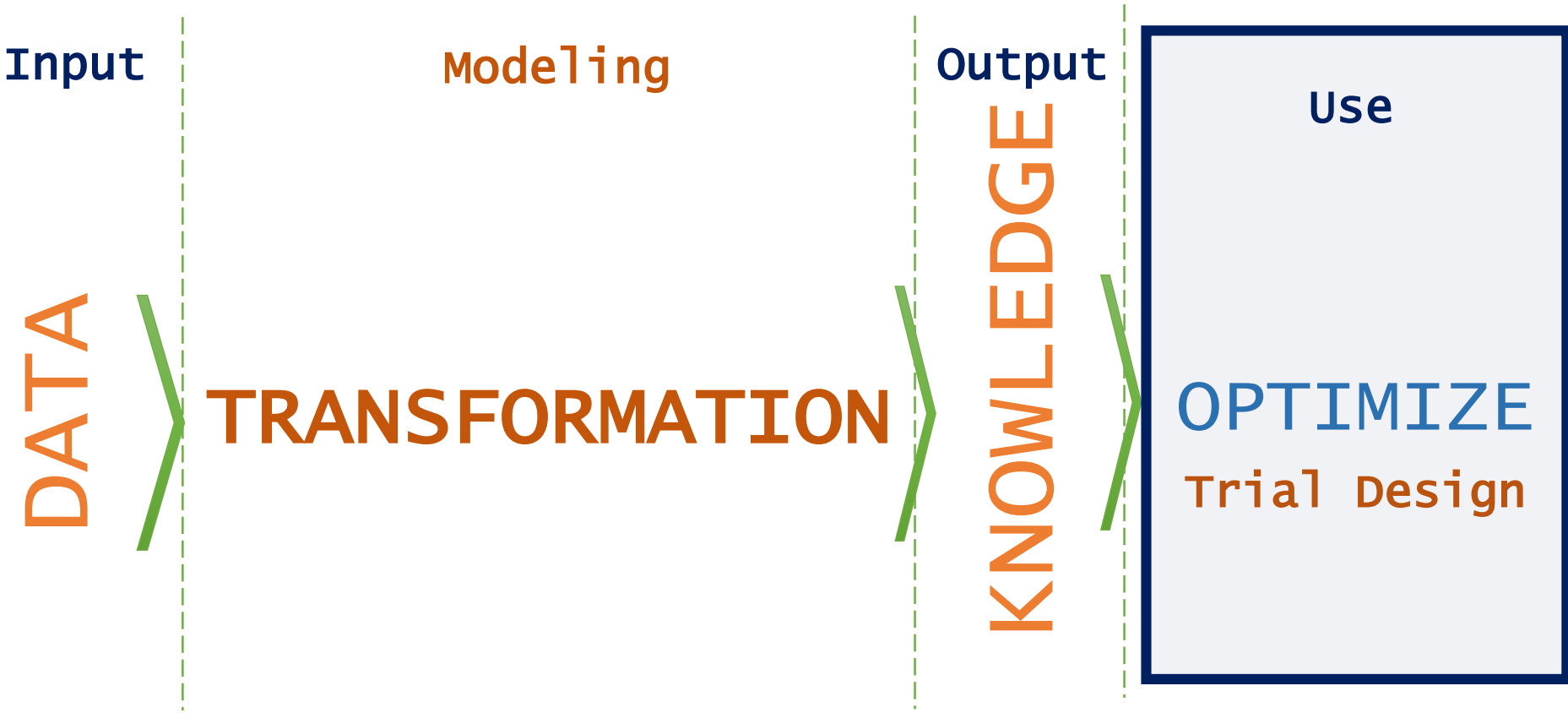
Rate

Predictors

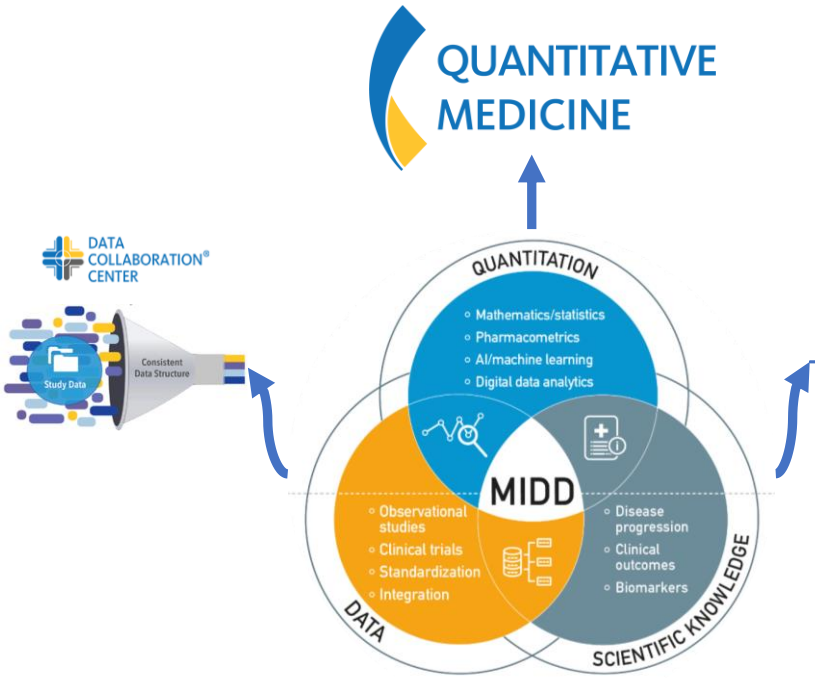
Web Clinical Trial Simulator

Disease Progression Model

Disease Progression Model



From data, to solutions, to impact



Indication	Solutions	Impact
Alzheimer's disease	2CTS tools, 2 biomarkers	First 2 disease-modifying drugs
Tuberculosis	Multiple quantitative tools	First new drug and drug regimen
PKD	PKD	First disease-modifying drug
Type 1 Diabetes	Model-based biomarkers	First prevention drug
Duchenne Muscular Dystrophy	5 disease progression models	Transformed trial design paradigm
Kidney Transplantation	Composite biomarker endpoint	Transformed trial design paradigm
Parkinson's disease	3 CTS tools, 1 biomarker, multiple DHT solutions	Transformed trial design paradigm
Huntington's disease	Staging system, 3 disease progression models	Transformed trial design paradigm

Thank you!

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collaborate · innovate · accelerate

Q & A

Break Out Group Overview

- **4 Break Out Groups** designated by colored dots on back of your name tag:
  - Group 1 = red  General Session Room (Chinese Room) with Summer
  - Group 2 = yellow  Massachusetts Room with Lindsay
  - Group 3 = green  New Jersey Room with Sara
  - Group 4 = virtual Zoom/Virtual Room with Sav
- Duration = 60 minutes (11:30am - 12:30pm) then break for Lunch
- Debrief (20 mins) post Lunch

CTTI

Break Out Group Questions

Essentials to Advance DPM

What are the key areas that need to be addressed to incorporate DPM approaches more effectively in:

- medical product development (drug, *device*, biologics)?
- regulatory decision making?

For the question above, which items can be addressed in the

- short term?
- long-term?

Are there illustrative examples and/or tools that you can share?

CTTI

Break Out Group Questions

Accountability

Who should be involved in driving the recognition, value, and use of DPM?

What actions should they take to facilitate change?

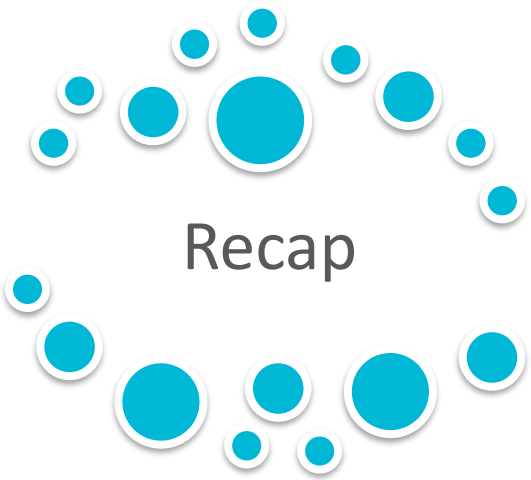
What's CTTI's role in driving the recognition, value & use of DPM?

**Plan 5-10 mins at the end to add to if needed and prepare a read out*

LUNCH

Return to General Session at 1:30 pm ET

Session II Break Out Debrief



Session III: Facilitating Progress

Moderator: **Bruce Burnett**, Director of Regulatory Affairs, Duke, CTTI Project Team Lead

CTTI

Open Discussion Questions

Recommendations & Resources Needed

What recommendations and resources should CTTI develop to advance DPM acceptance and use to support decision making?

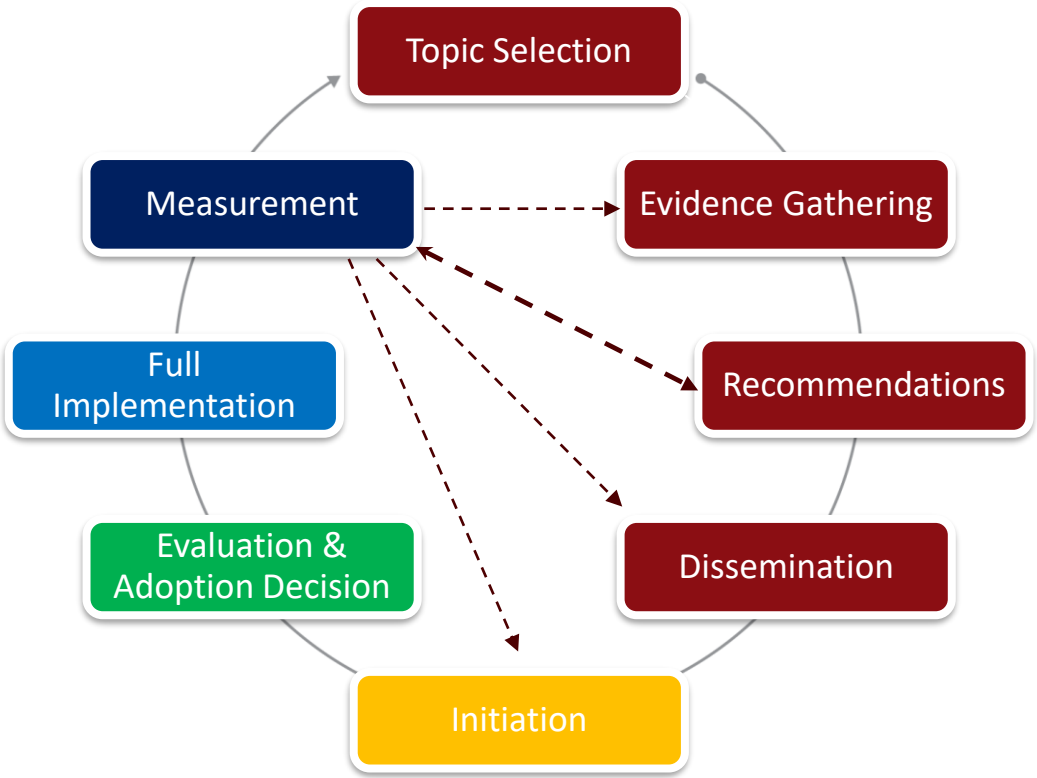
To whom should those recommendations target?

Metrics to Measure Change

Sara Calvert, CTTI Director of Projects

Looking at CTTI's Role in Adoption

CTTI & Clinical Trial Enterprise

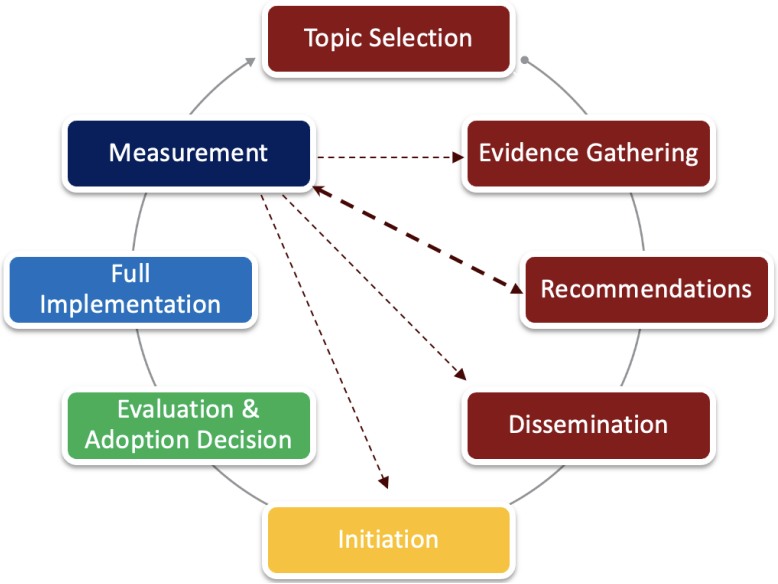


CTTI Staff & Members

Clinical Trial Enterprise
(including CTTI Members)

CTTI's Evolving Role in Measurement

- We are interested in assessment at the organizational scale:
  - *How does an individual **adopter** of CTTI recommendations assess their progress?*
- We also care about the full CTE:
  - *How can we quantify the uptake in disease progression modeling across the entire clinical trial **enterprise**?*
  - *How will we know if adoption of DPM is **improving the quality and/or efficiency of trials**?*



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How Can We Measure Progress in DPM?

	Organizational	Enterprise-wide
Tracking (Process)	How can we know whether change is happening at the organizational level?	How can we know that change is happening across the entire trial enterprise?
Outcomes (Value)		

Open Discussion Questions

Metrics to Measure **Organizational** Change

What would you look at within an organization to measure adoption of DPM?

How would you measure the ROI from DPM adoption? (i.e. What measure from similar organizations would convince you to adopt or scale DPM?)

Open Discussion Questions

Metrics to Measure **Enterprise-Wide** Change

How would you measure if change is happening at the clinical trial enterprise level?

What are the benefits of this change?

Next Steps & Potential Timeline

Expert Meeting Summary

- Key themes from meeting will be posted on CTTI Website in early April

Draft Recommendations & Supporting Tools

- DPM Project Team will assess whether additional evidence gathering is necessary
- DPM Project Team drafts recommendations and develops supporting tool(s)

Launch Recommendations

- CTTI convenes a Recommendations Advisory Committee to refine recommendations
- CTTI hosts public webinar to launch recommendations and supporting tools

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TRIALS
TRANSFORMATION
INITIATIVE

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THANK YOU

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