CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

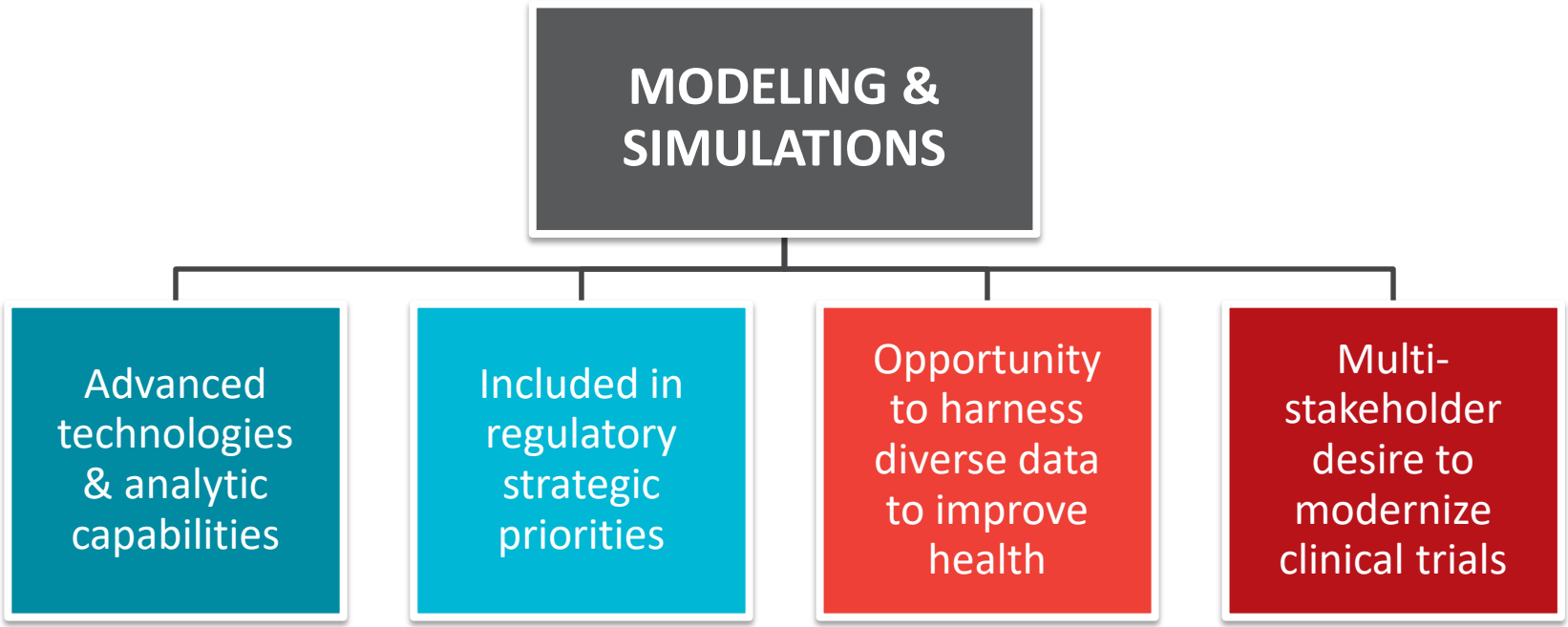
March 6, 2023

Disease Progression Modeling to Advance Clinical Trial Decision Making

Project Overview

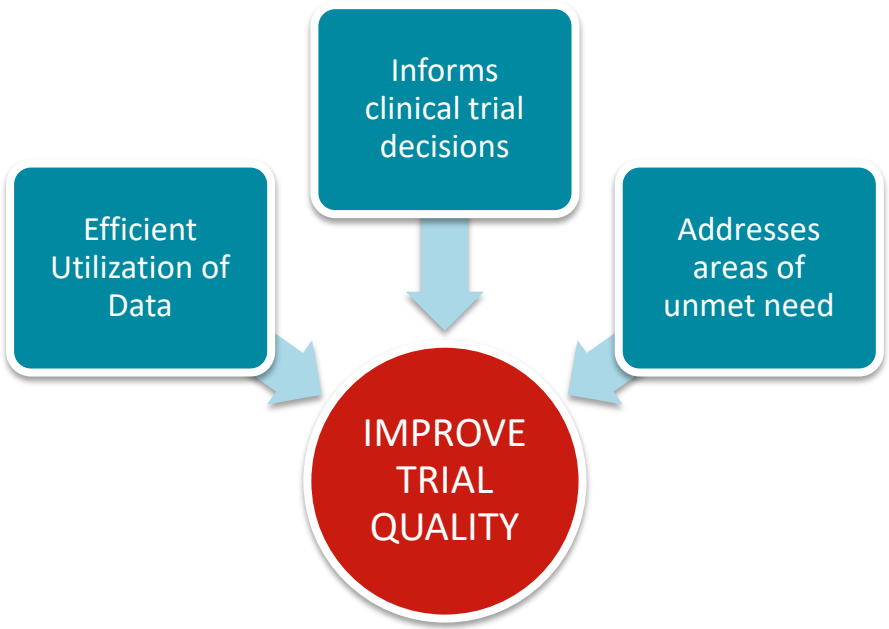
Lindsay Kehoe, CTTI, Senior Project Manager

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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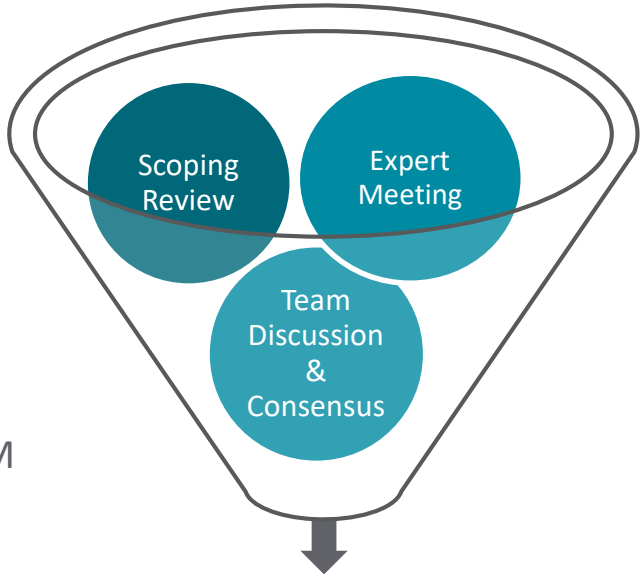
Disease Progression Modeling Project

- **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

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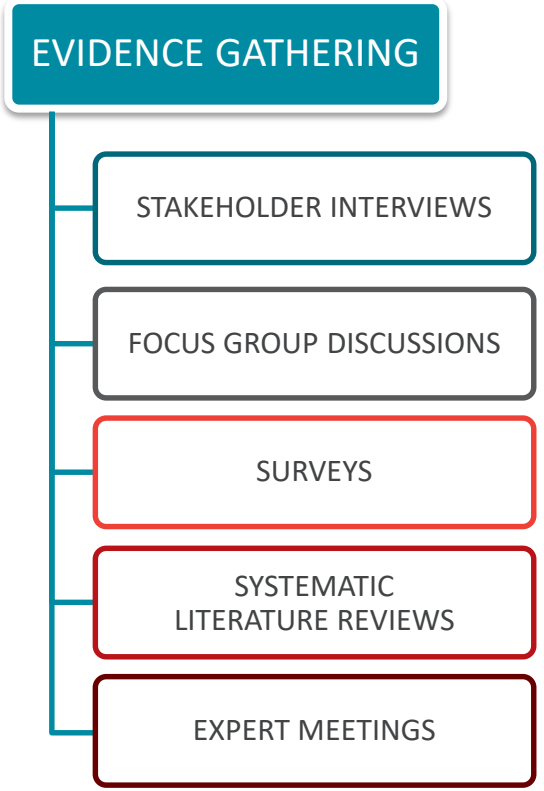
Evidence guides the journey to solutions

- 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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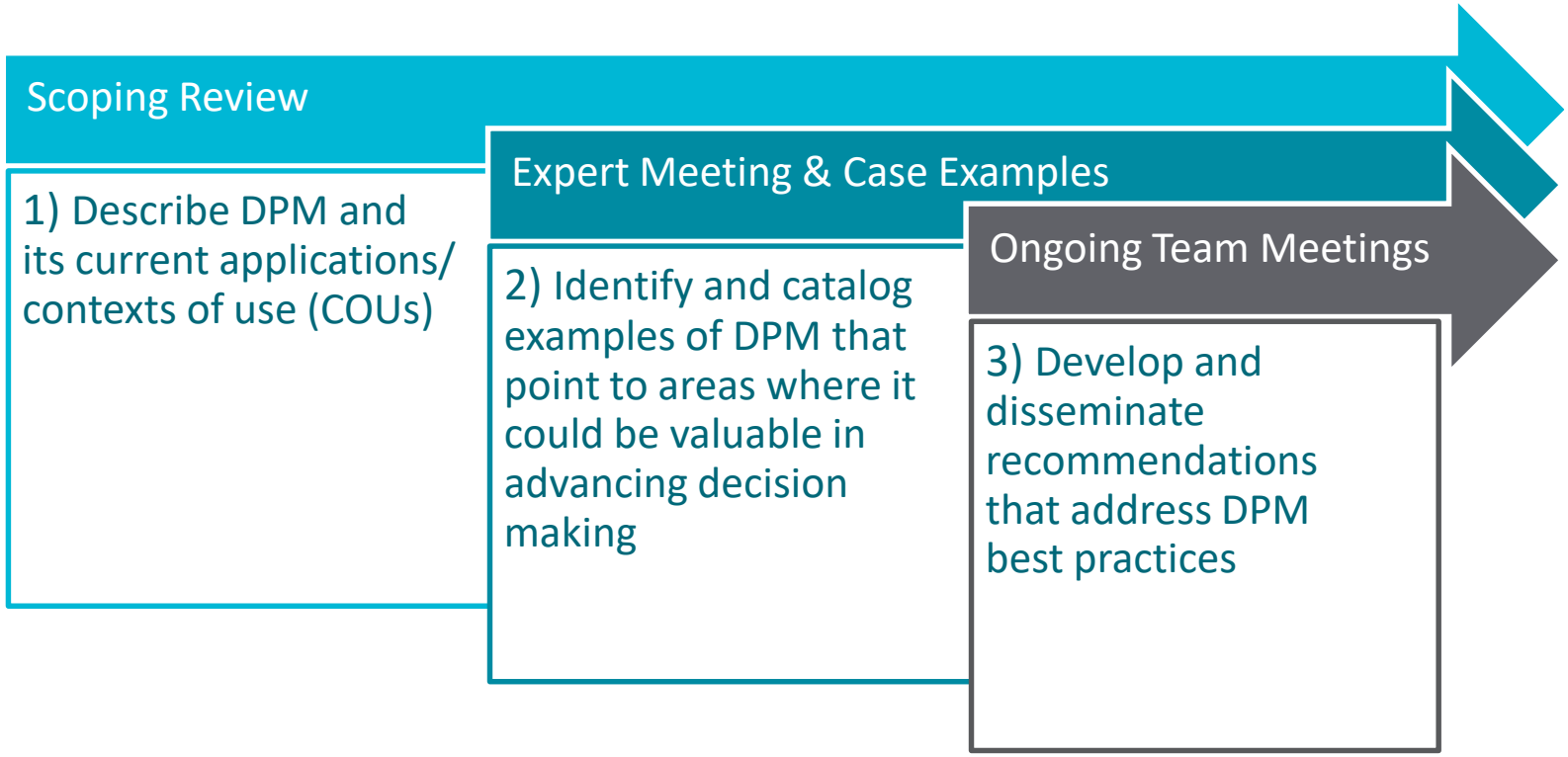
CTTI DPM Project Objectives & Approach



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

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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

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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:

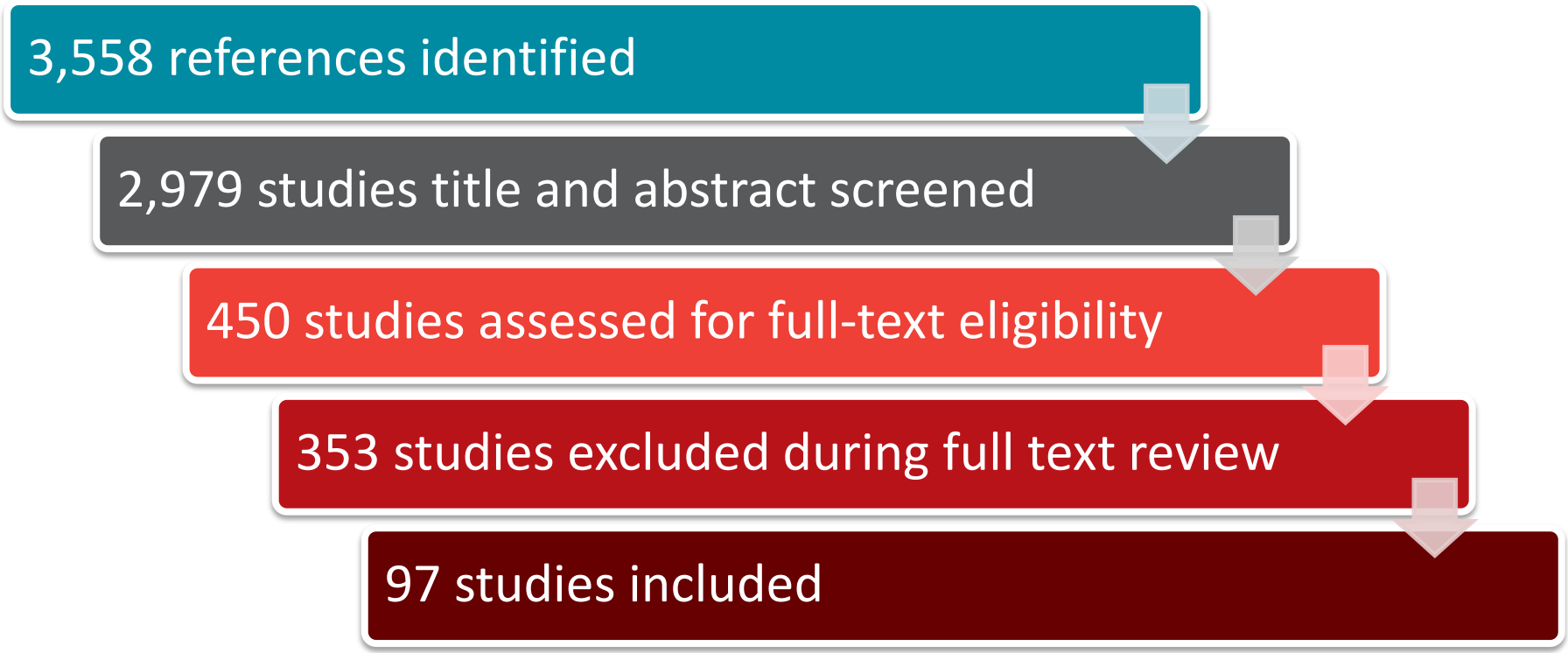
- Does not relate to clinical trials
- Does not address a disease
- Does not reflect a disease progression component
- Related to medical diagnosis or prediction of diagnostic outcomes
- Not related to humans
- Methodology paper only

Targeted searches and evidence gathering

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

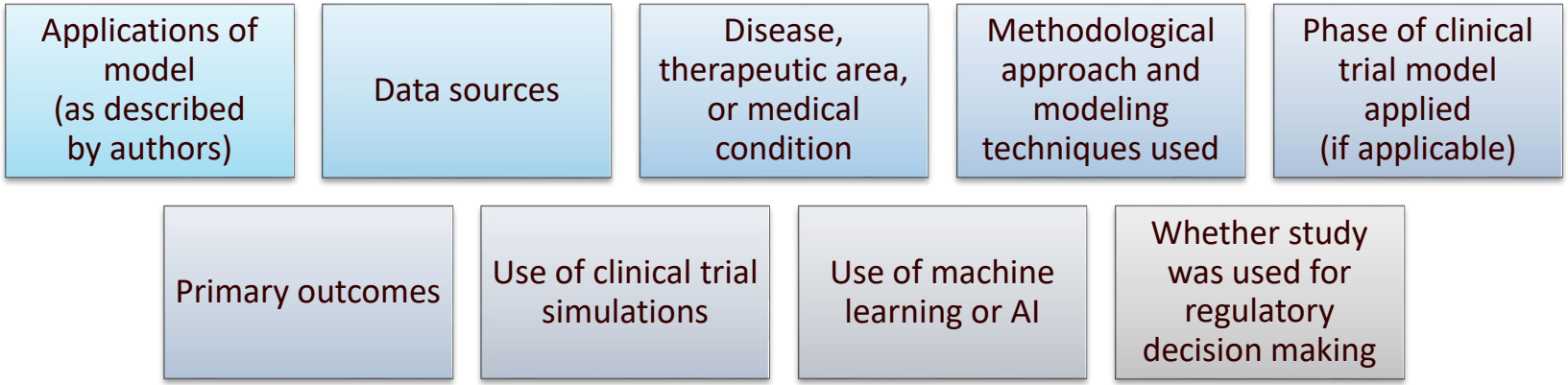
- Data screened using Covidence
- Data organized using MaxQDA

PRISMA process for data selection



Data extraction

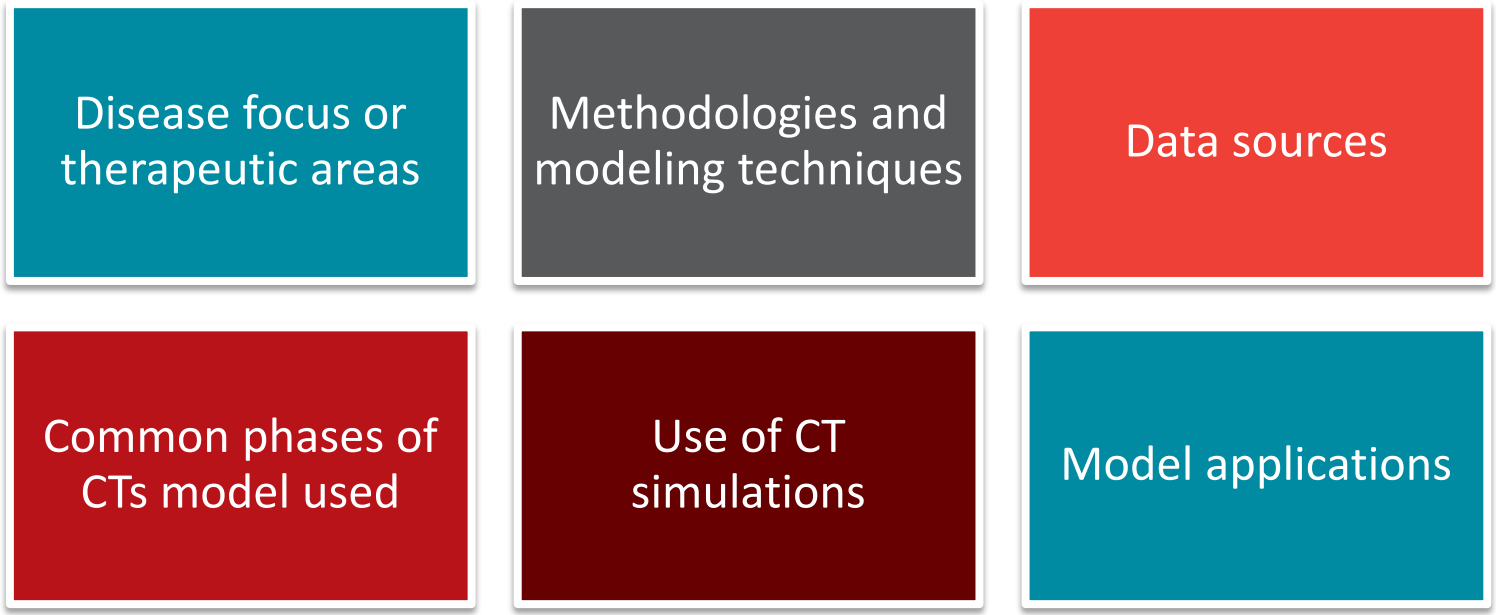
- With our final sample (n=97), we:
  - Extracted 9 data points from each study and coded in MaxQDA



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



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%)

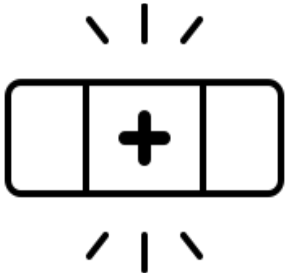
Results: Additional observations

- 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

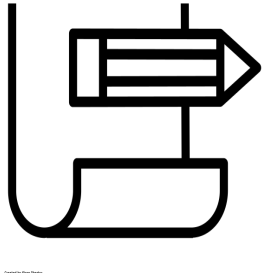
- More than a third (n=38, 39%) conducted CT simulations as part of model exploration or application

Thematic groupings for applications

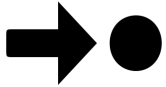
13 applications for trials identified across scoping review results



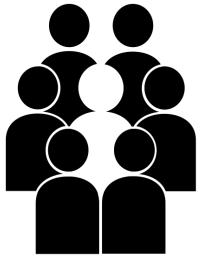
Characterize treatment effects or inform dose selection



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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CTTI Project Manager

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Research and Education Librarian, Duke Medical Center Library & Archives

Megan von Isenburg
Associate Dean for Library Services & Archives, Duke Medical Center Library & Archives

DPM Project Team Leads and Members

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THANK YOU

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