C-Path's Data Science

Transforming data into actionable knowledge for drug development

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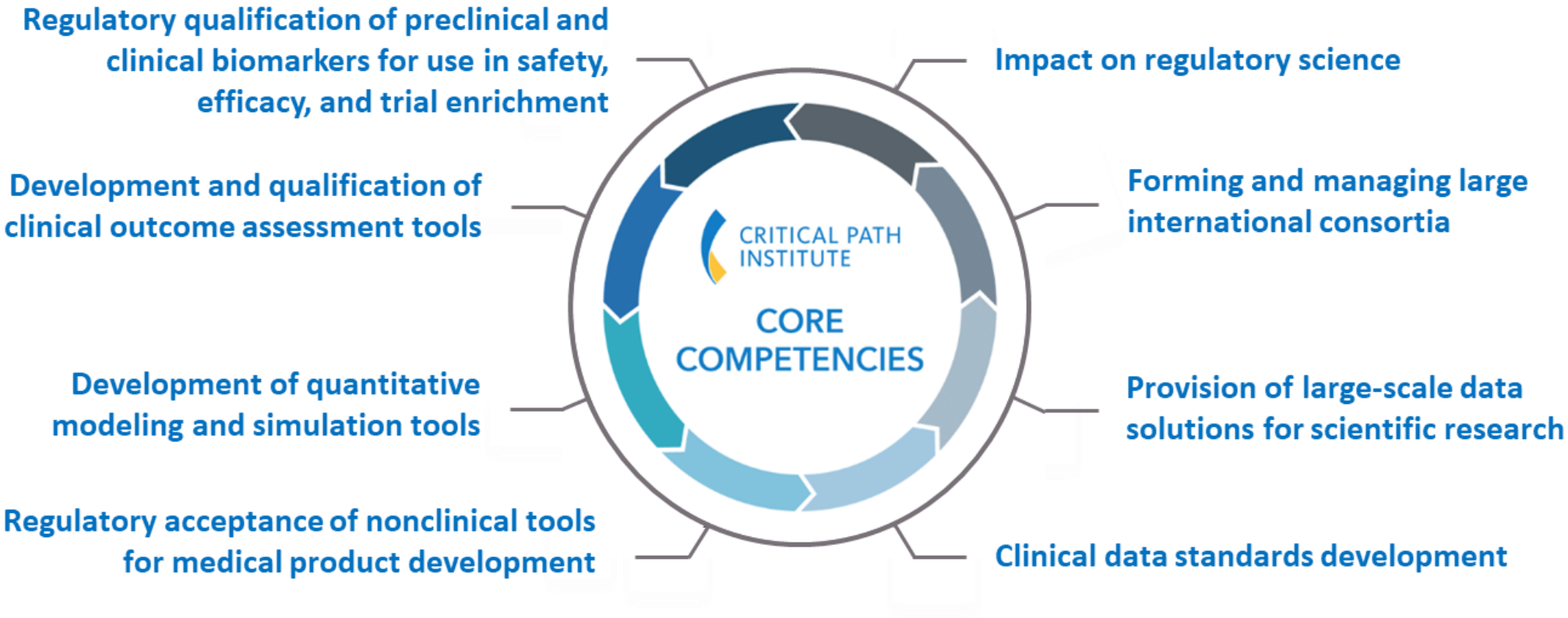
Impact on Regulatory Science

- 15 global, pre-competitive, public-private partnerships with
- Participation from industry, academia, advocacy groups, and regulators



How C-Path Works: A Public-Private Partnership

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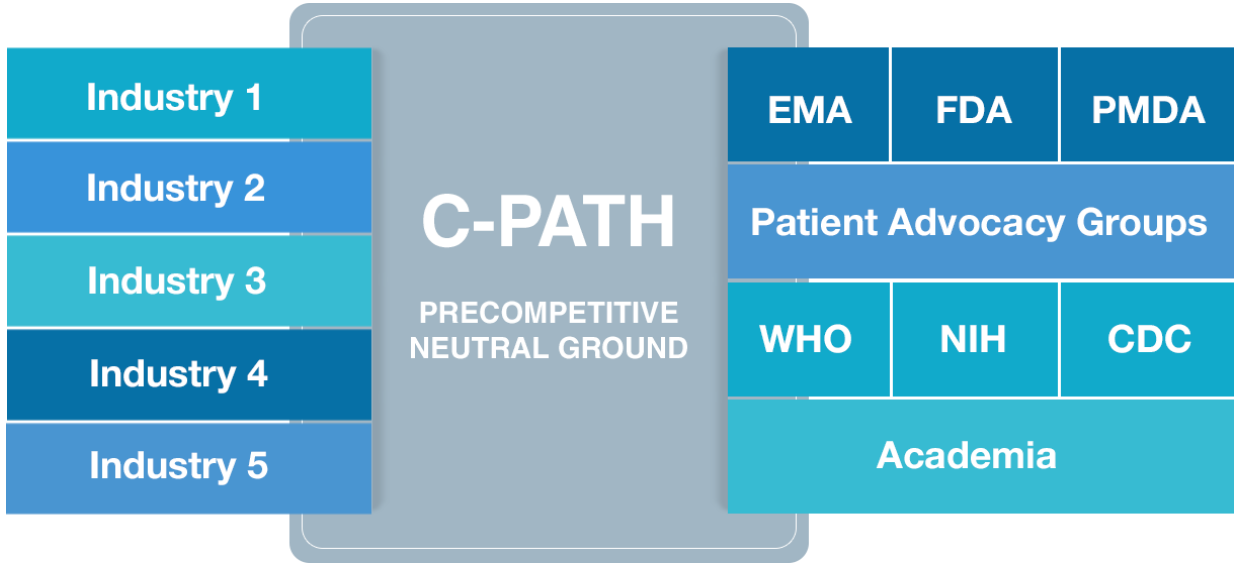
- Act as a trusted, neutral third party
- Convene scientific consortia of industry, academia, and government for sharing of data/expertise
  - ✓ The best science
  - ✓ The broadest experience
  - ✓ Active consensus building
  - ✓ Shared risk and costs
- Enable iterative FDA/EMA/PMDA participation in developing new methods to assess the safety and efficacy of medical products



Official regulatory endorsement of novel methodologies and drug development tools

What is Model-Informed Drug Development?

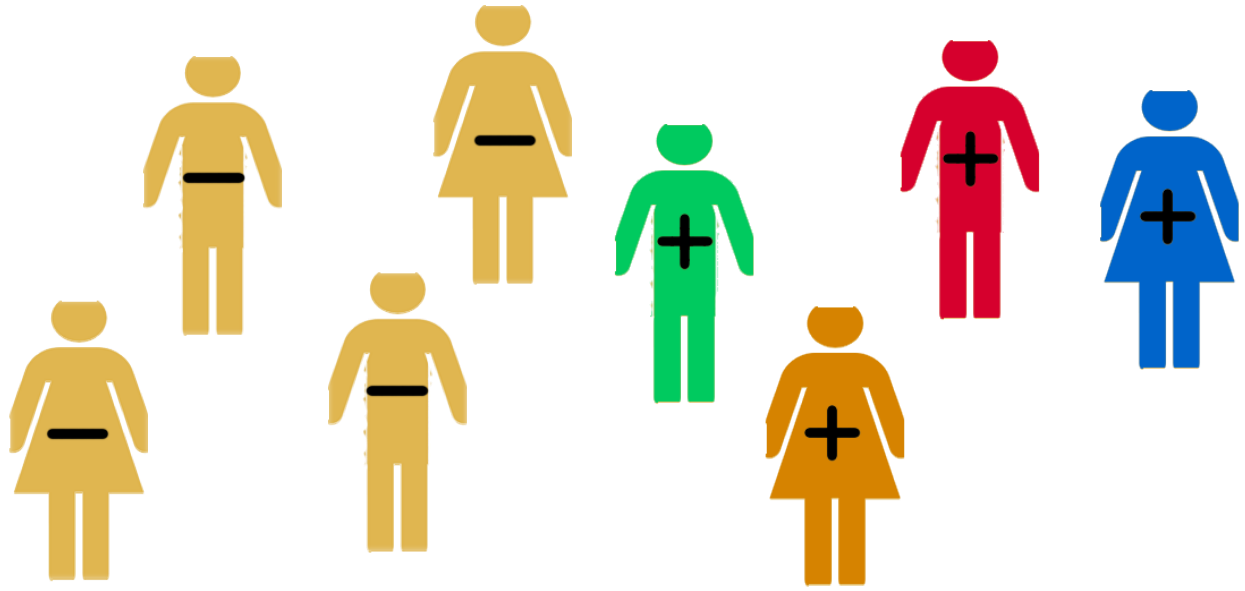
- Development and application of pharmaco-statistical models of drug efficacy and safety from preclinical and clinical data to improve drug development knowledge management and decision-making[1]

- Quantitative framework for prediction and extrapolation, centered on knowledge and inference generated from integrated models of compound-, mechanism-, and disease-level data and aimed at improving the quality, efficiency and cost effectiveness of decision making[2]

1 Lalonde 2007 [PMID 17522597] | 2 Marshall 2016 [PMID 27069774]

Critical questions for trial design

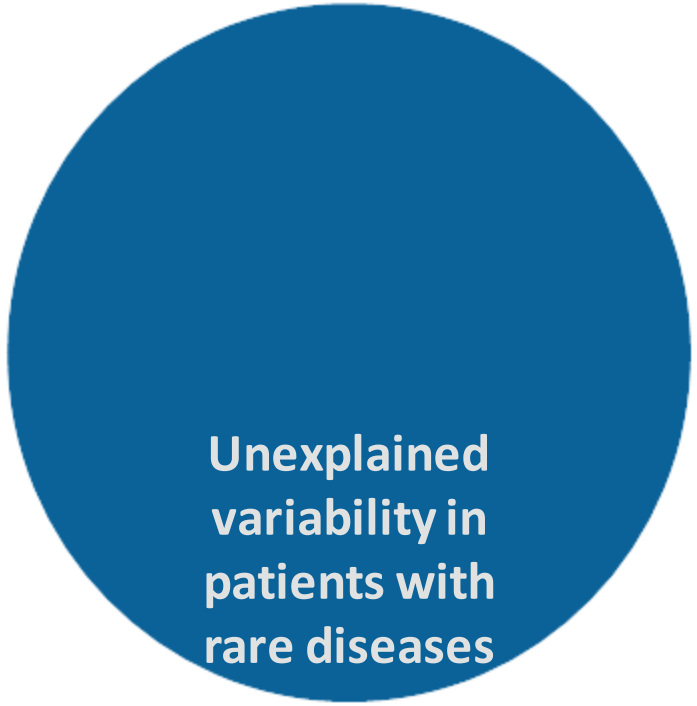
- How many patients should be recruited to properly power the trial?
- What should be the inclusion criteria?
- Can the control arm be optimized?
- What types of progression rates are expected for different subpopulations?
- What measures of progression are most adequate, at which stages of the disease 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?

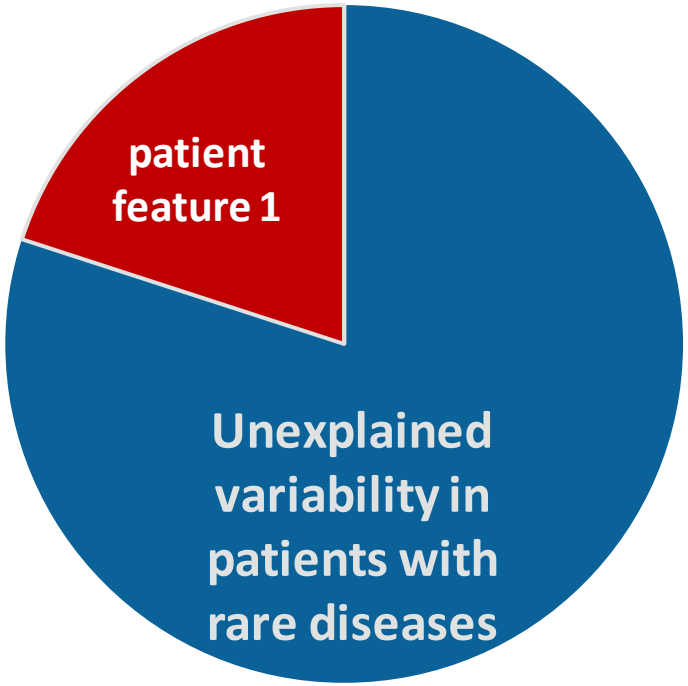


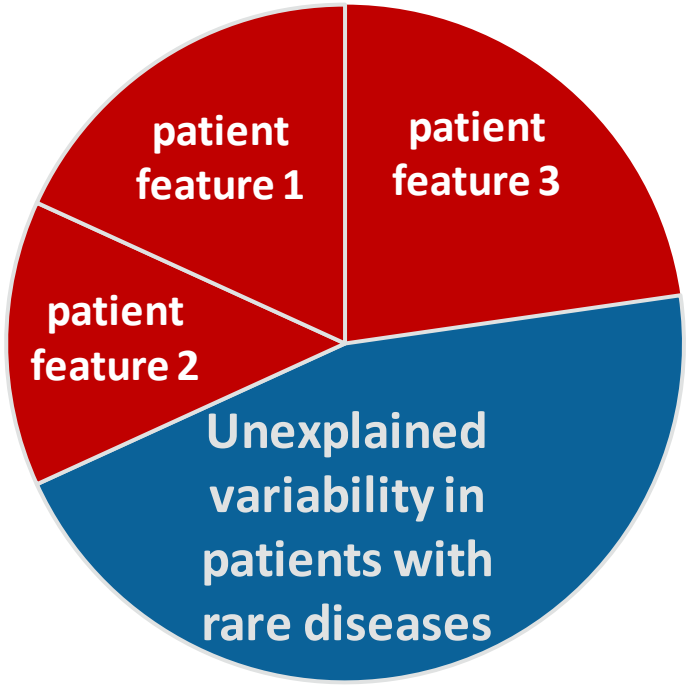
How should one go about providing sound quantitative answers to these questions?

Answer 1: Quantifying variability

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





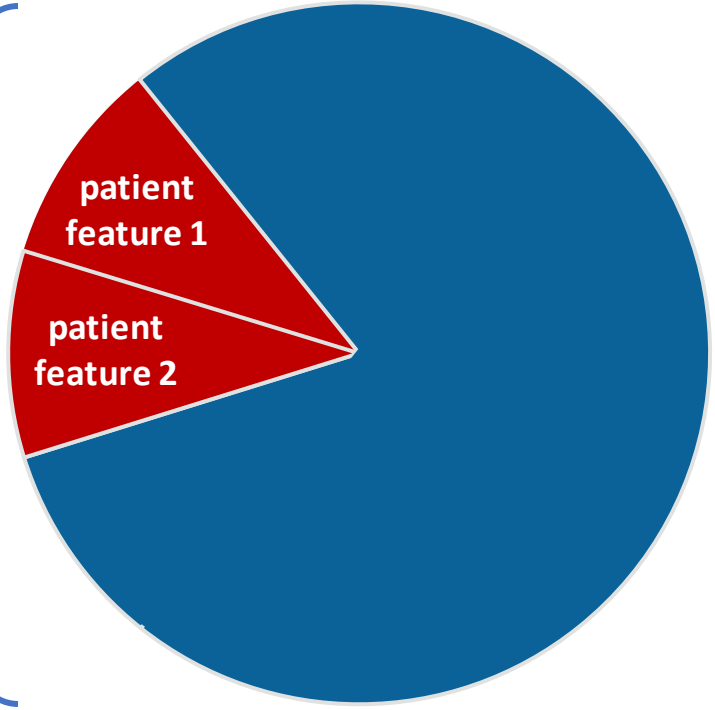


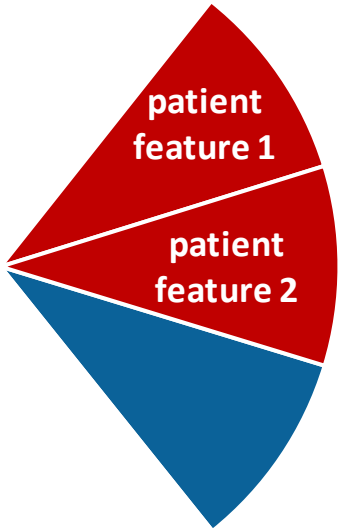
Result: The ability to predict more accurate progression rates for heterogeneous subpopulations of patients in clinical trials

Answer 2: Multiple data sources

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

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

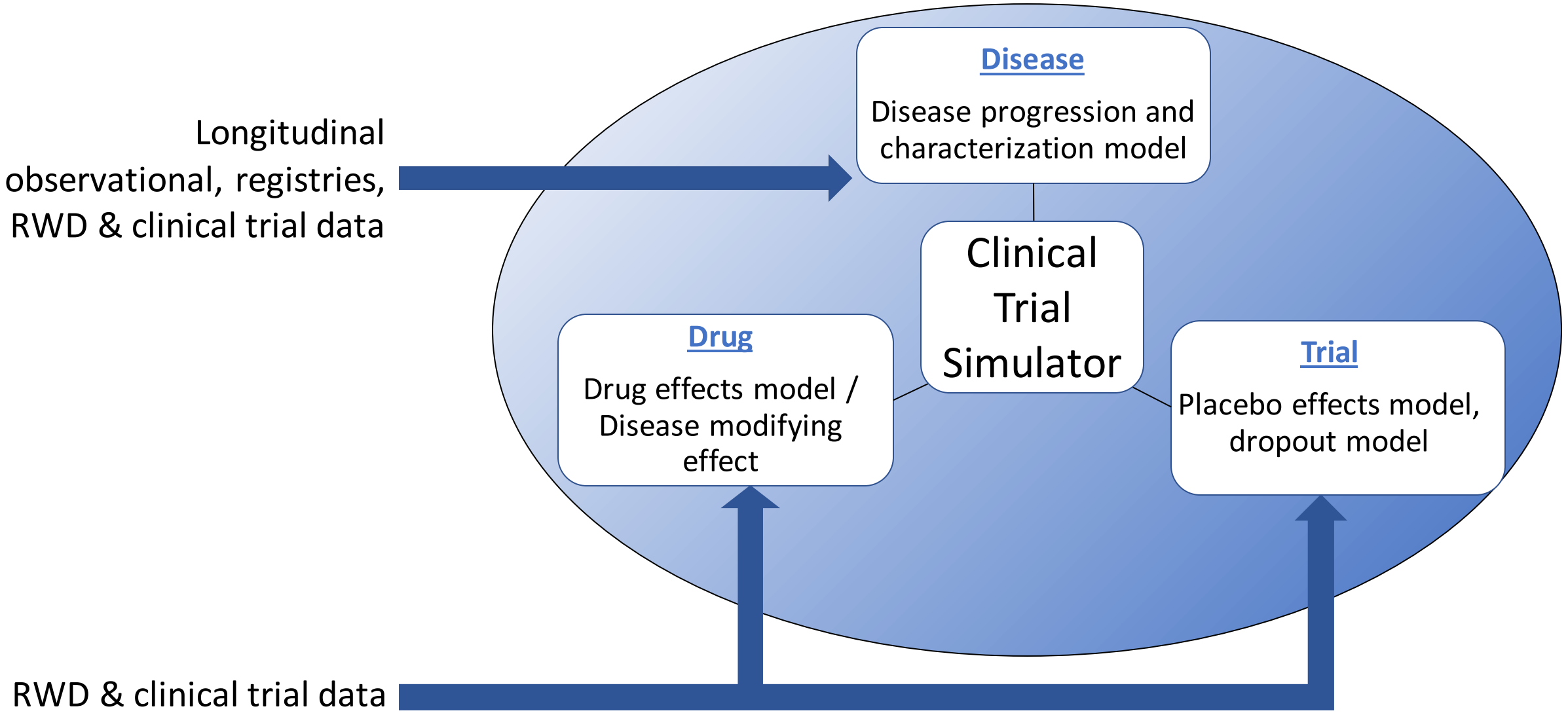




Unexplained variability in patients with rare diseases from <u>a single study</u>

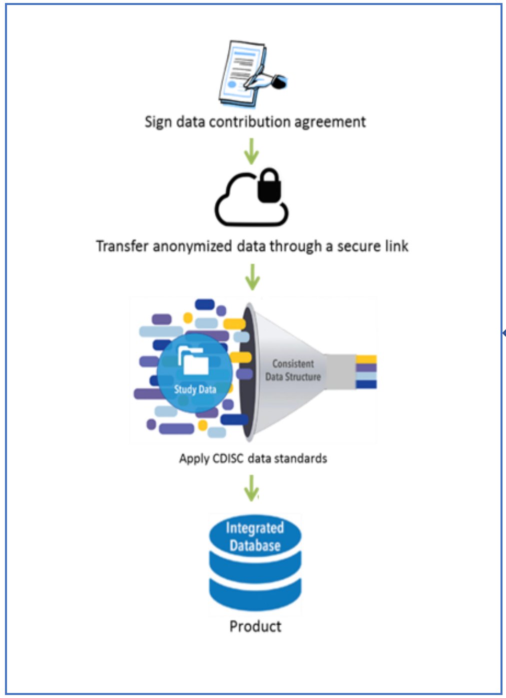
Result: The ability to more accurately account for the heterogeneity in rare diseases and avoid biased conclusions on few data sources

Answer 3: Drug-trial-disease 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-1000/0	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/0	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/0	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/0	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/0	69	1	Healthy C	Healthy C	NA	NA
PD-1000	PD-1000/0	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/0	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/0	65	0	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/0	65	0	Parkinson	Parkinson	NA	NA
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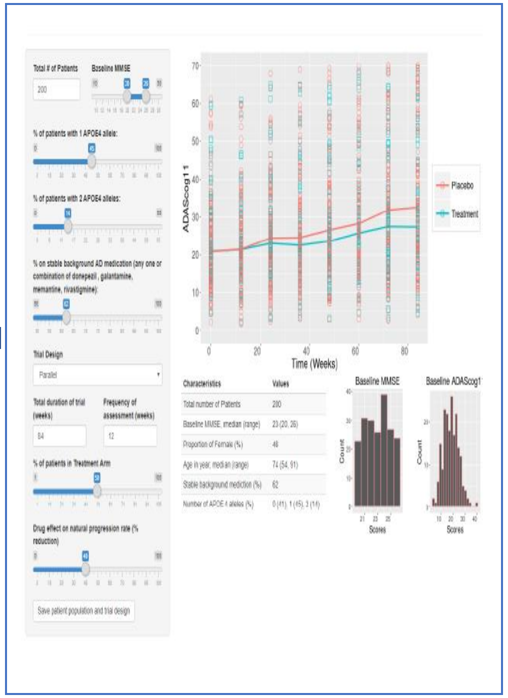
PD-1000	PD-1000/0	67	1	Parkinson	Parkinson	NA	NA
PD-1000	PD-1000/0	67	1	Parkinson	Parkinson	NA	NA

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

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

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



Execution

Clinical Data Shared with C-Path

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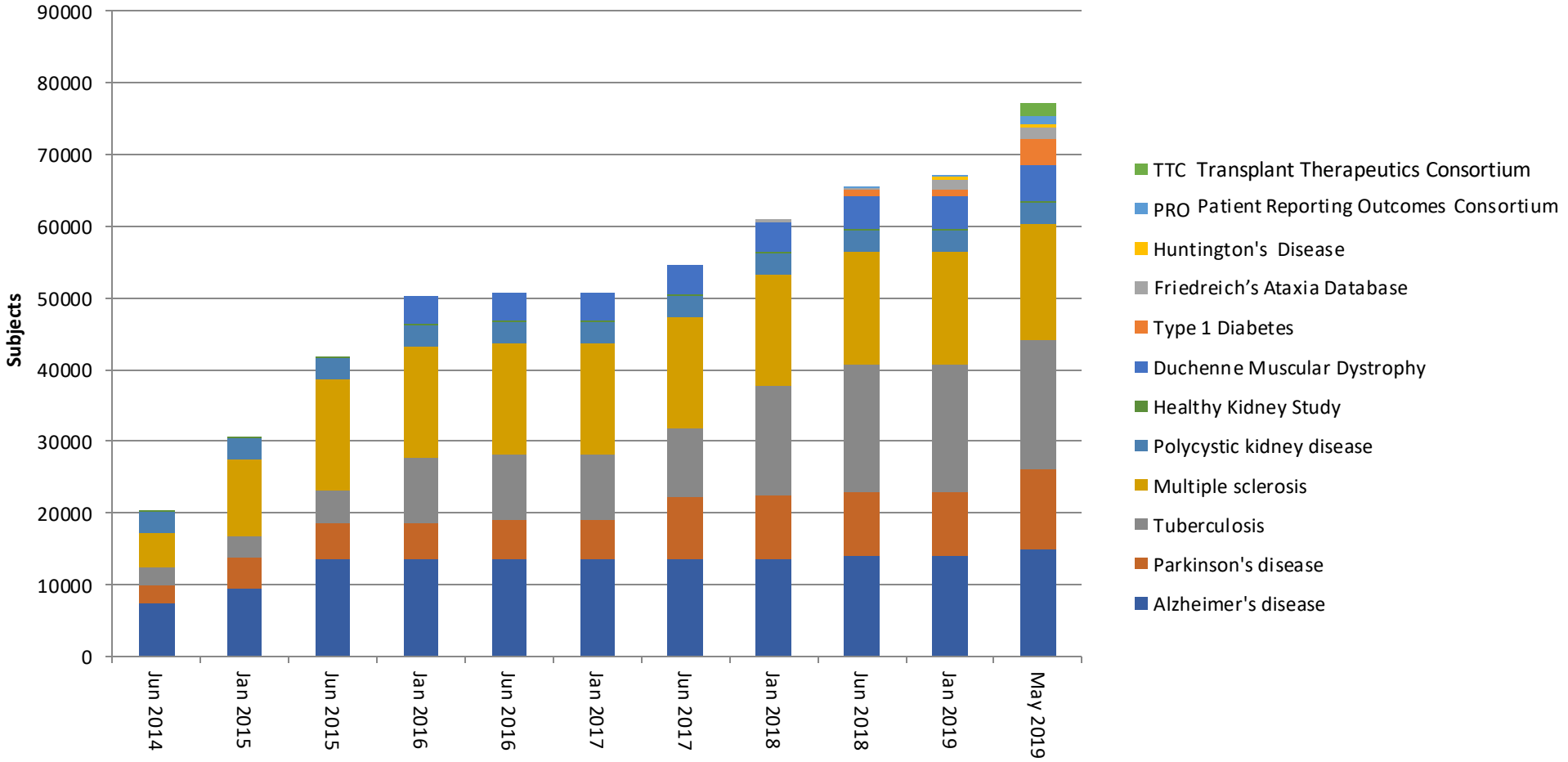
Clinical data: 146 studies: 77,054 subjects



Nonclinical: 179 studies; 11775 subjects.
ReSeqTB: 9215 Individual Isolates

RDCA-DAP: A resource for the future of drug development in rare diseases

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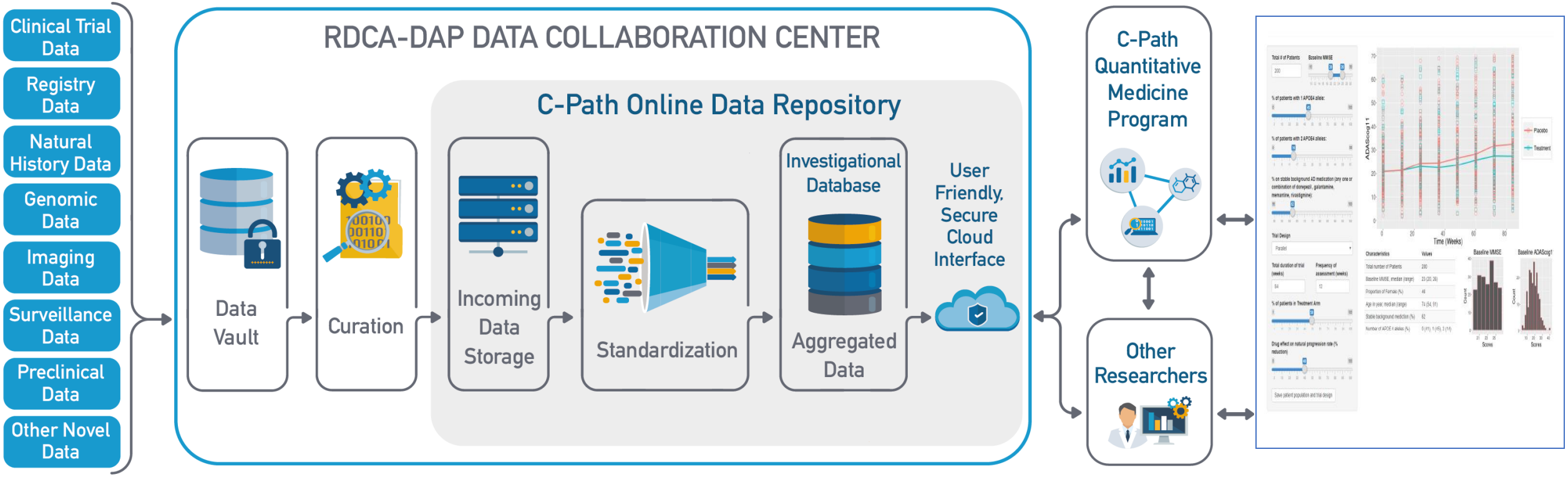
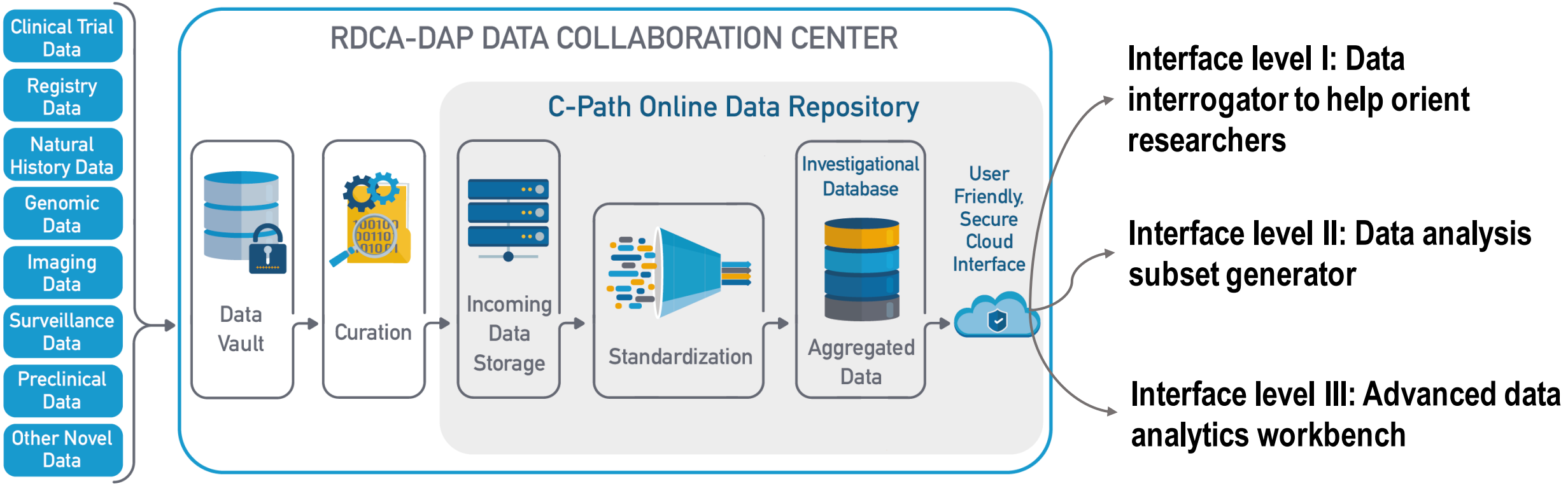
Actionable rare disease drug development solutions



RDCA-DAP: A resource for the future of drug development in rare diseases



Clinical Study Simulations

Evaluate different design options

Drug-Trial-Diosease Models

$$\frac{dFVC}{dAge} = k_{in} \times (1 + AgeIn) - (1 + AgeOut) \times FVC \times k_{out}$$

$$P_{01} = \frac{\exp(logit_{01})}{(1 + \exp(logit_{01}))}$$

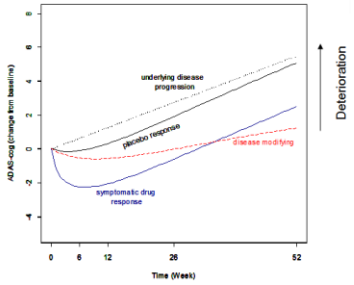
Study Execution

- X dose
- N
- Frequency of observations
- Inclusion/exclusion criteria

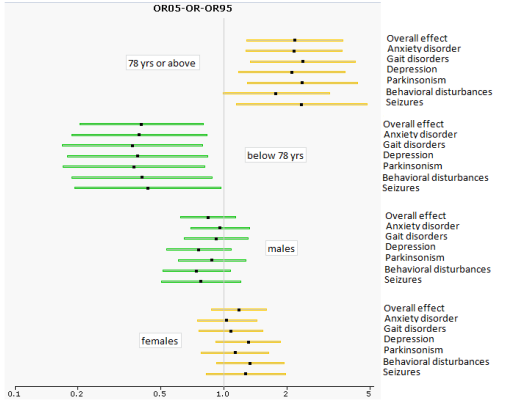
Trial optimization through simulations

Design selection

Simulated results



Statistical Analysis



Disease Progression Model

Input

Modeling

Output

Disease Progression Model

Input

Patient-level data

Modeling

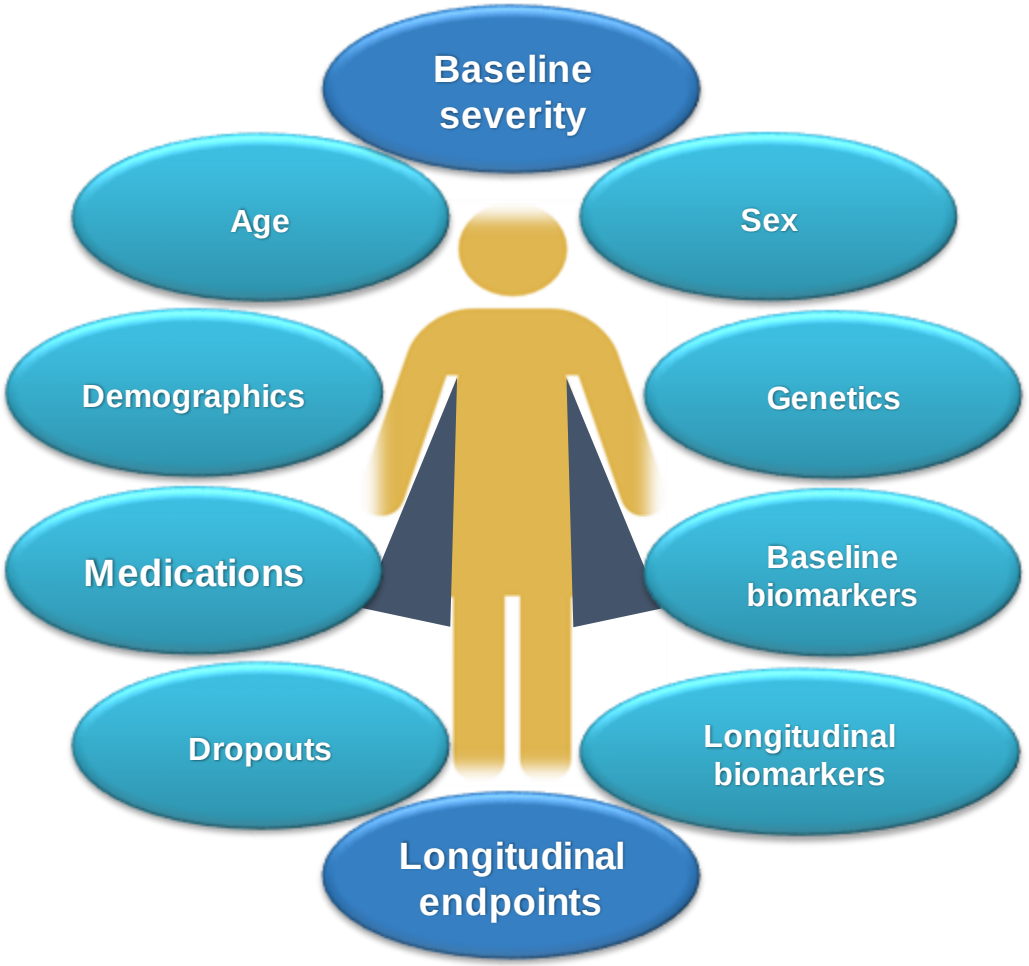
Output

Disease Progression Model

Input

Patient-level data

Modeling



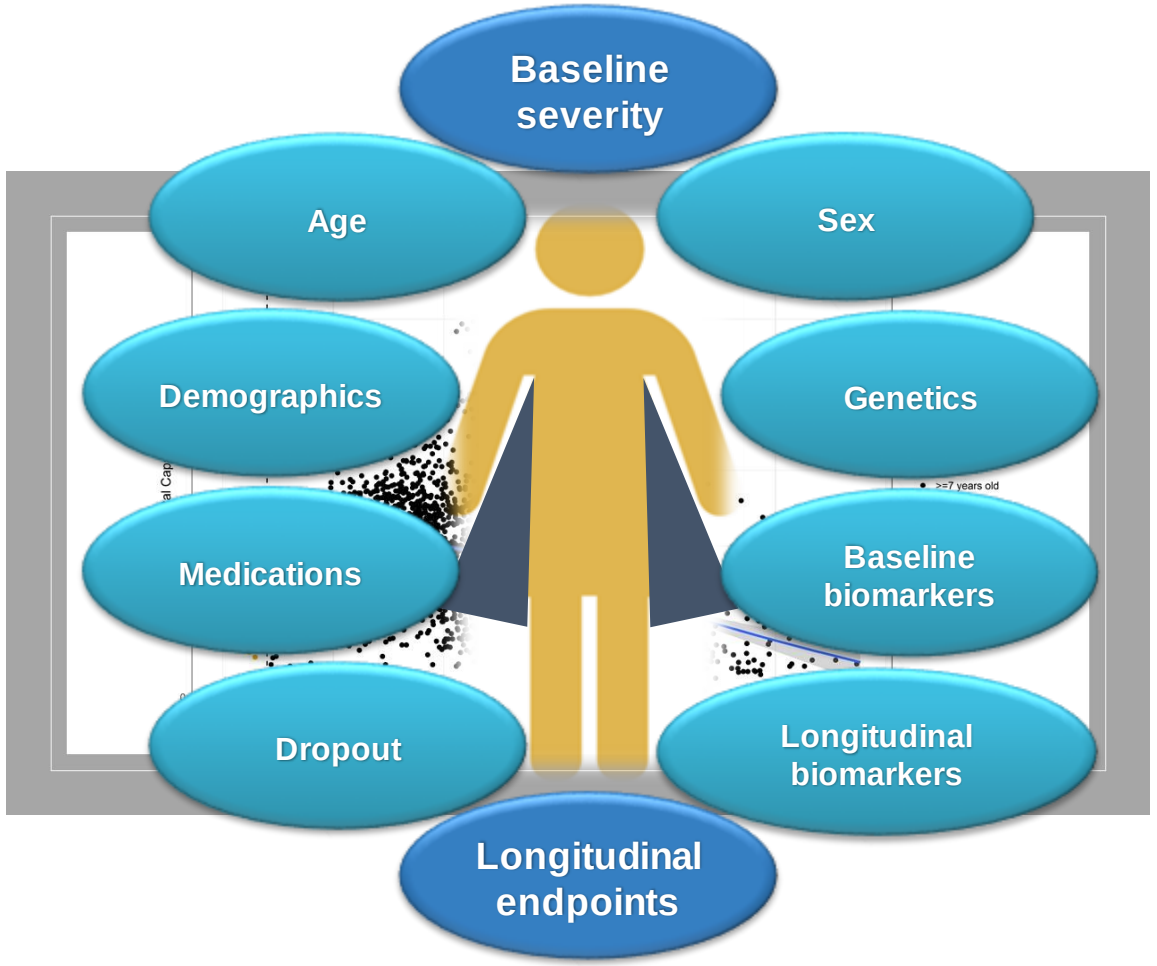
Output

Disease Progression Model

Input

Clinical studies

Modeling



Output

Understanding of disease worsening

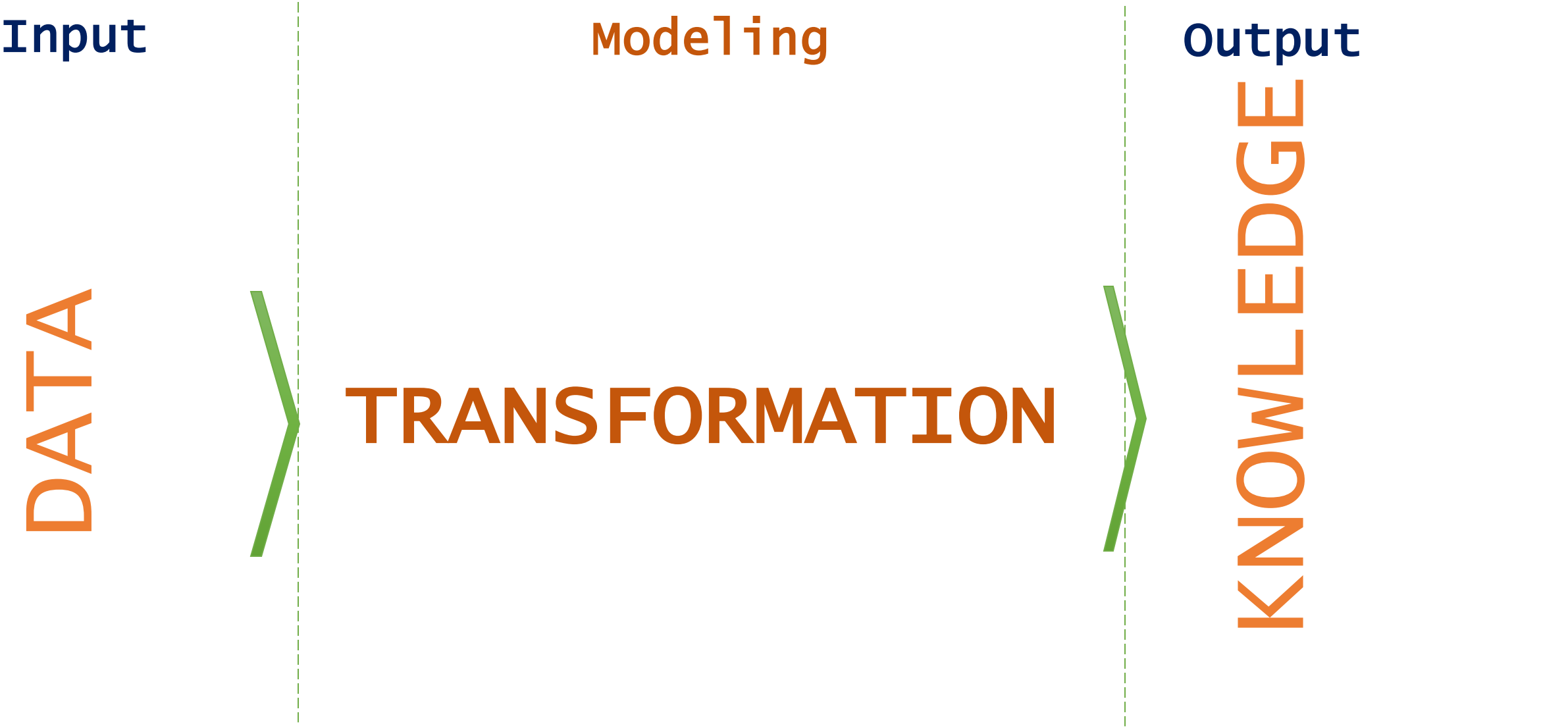
Trajectory

Rate

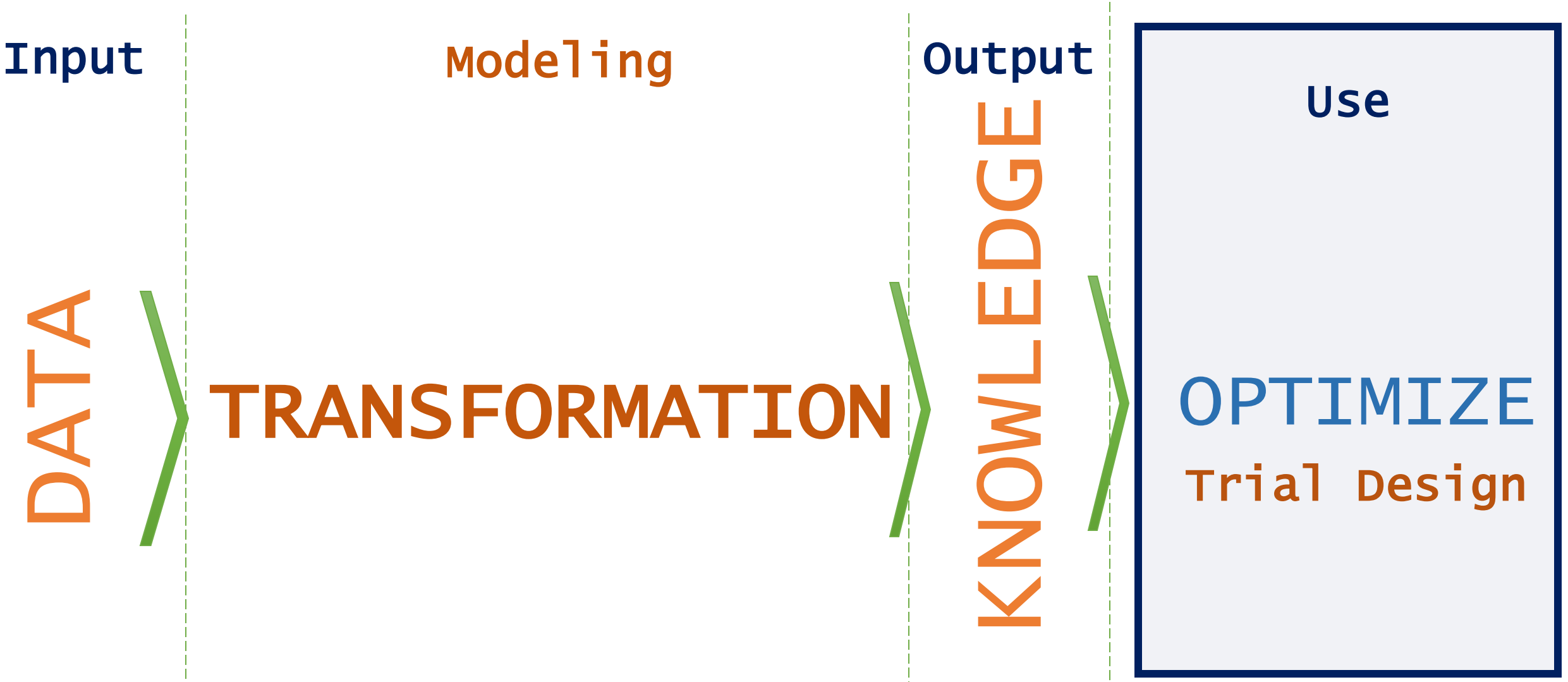
Predictors

Web Clinical Trial Simulator

Disease Progression Model

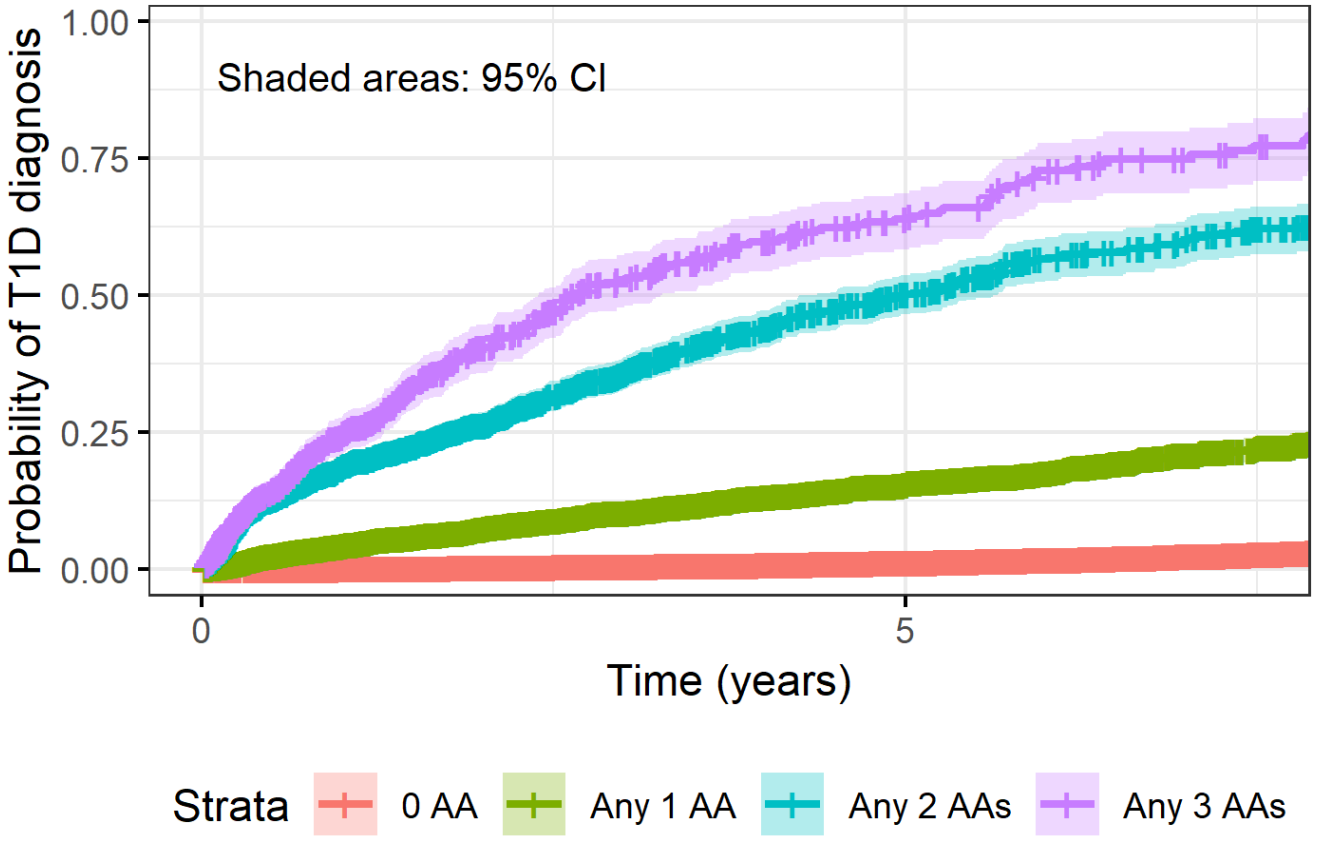


Disease Progression Model



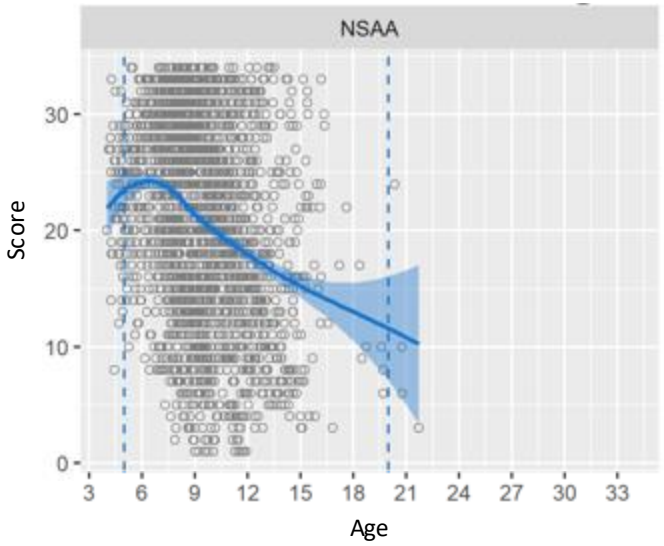
C-Path's impact in MIDD

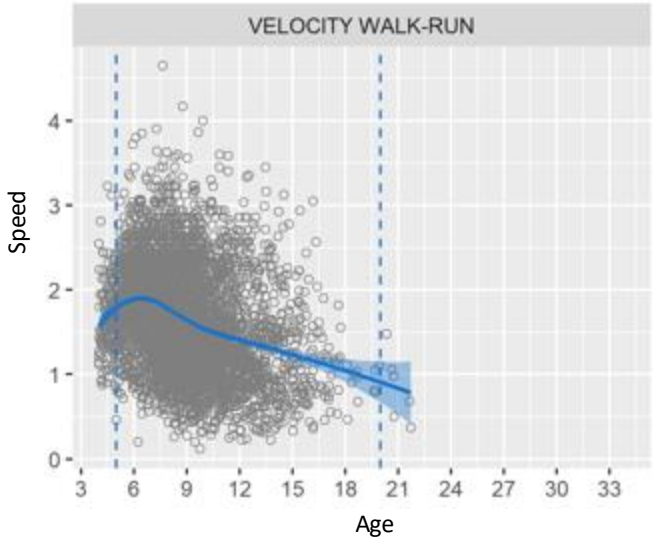
- Survival model to predict T1D diagnosis, based on islet AA positivity.
- A model that changes the landscape for RCTs for T1D prevention.

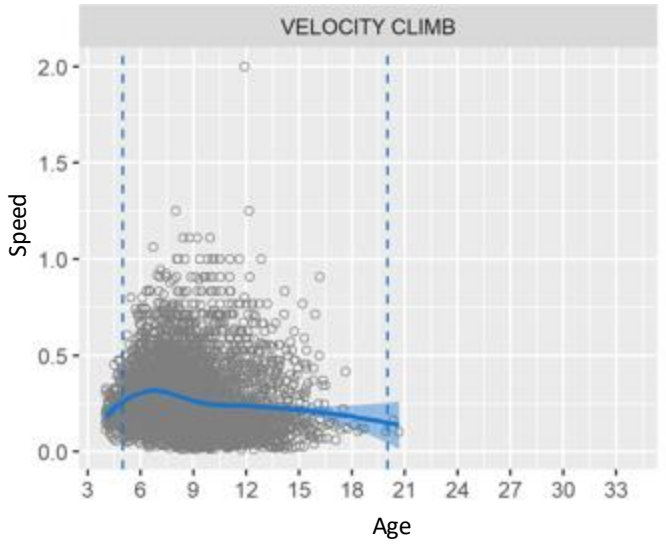


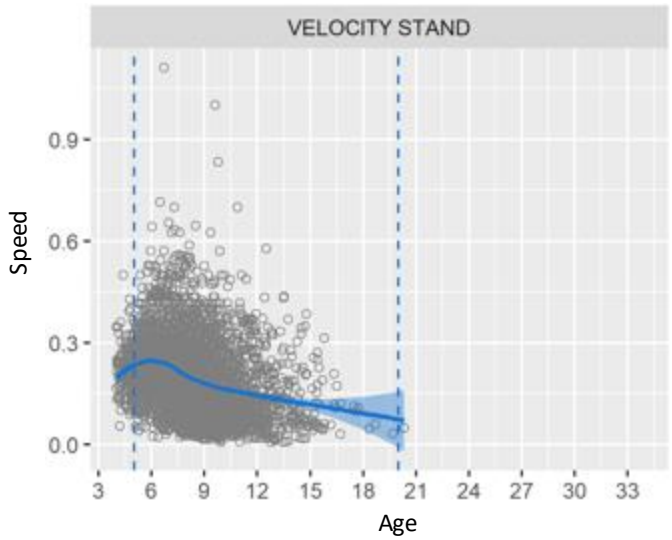
C-Path's impact in MIDD

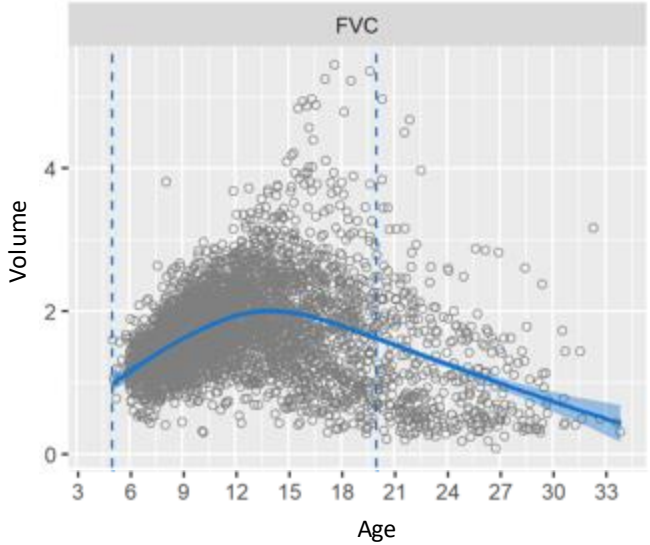
- Multiple endpoints over time in Duchenne Muscular Dystrophy (DMD).

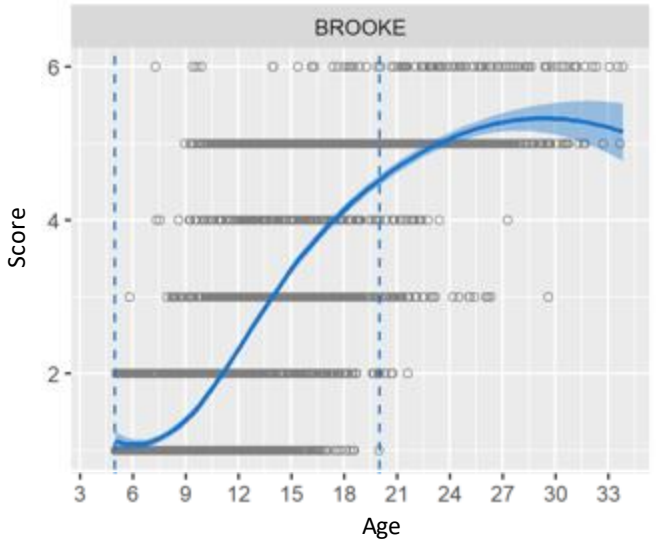




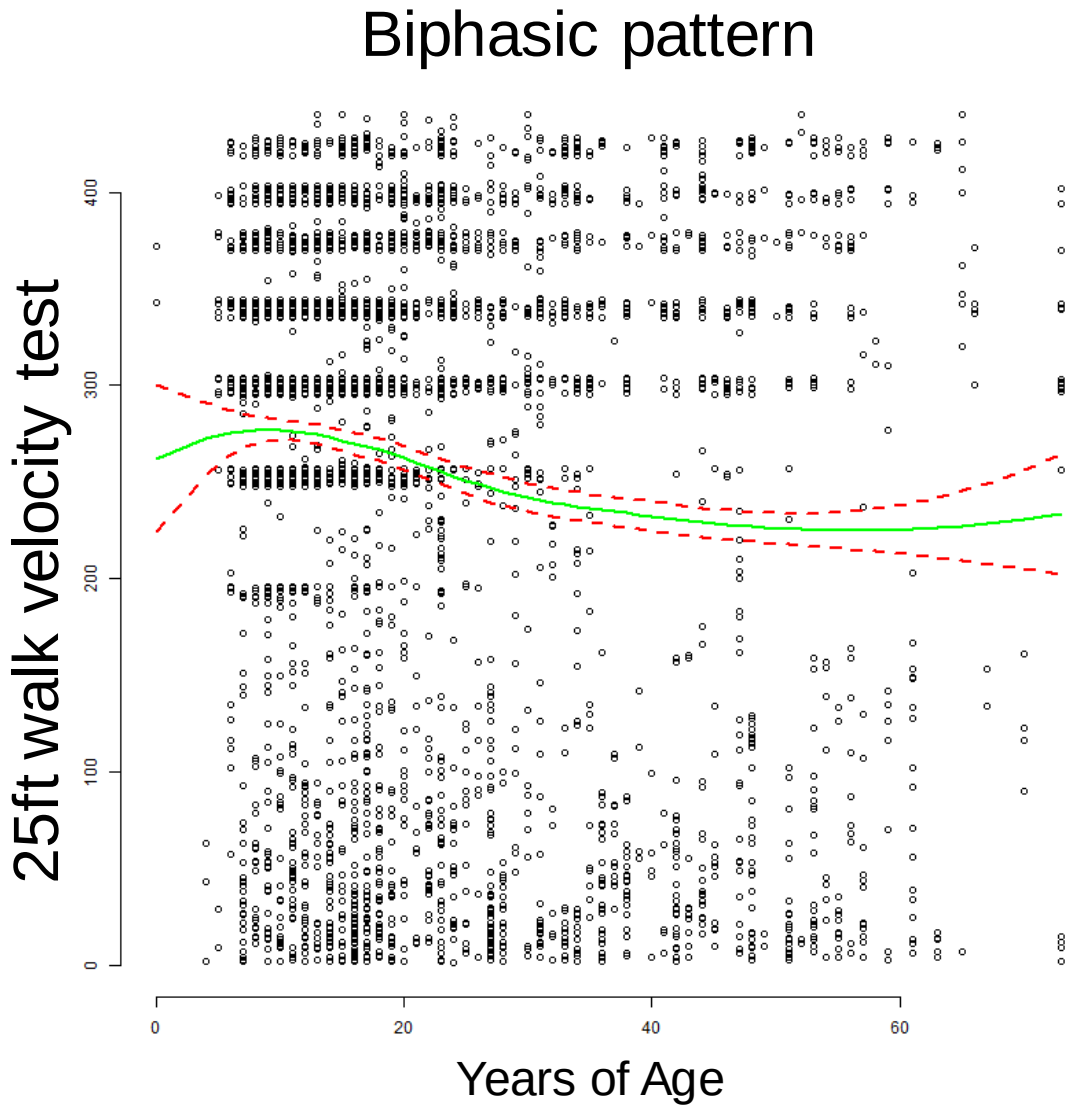








Preliminary findings from the FA database



So…

Models, trials and endpoints?

- Quantitatively understanding sources of variability, multiple measures and markers across a disease continuum can streamline the pathway towards regulatory acceptance of quantitative solutions that can inform clinical trial design questions.

AD CTS: n=50

Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 50

Baseline MMSE: 14 – 26

% with 1 APOE4 allele: 20

% with 2 APOE4 alleles: 0

% on stable background medication: 70

Trial Design: Parallel

Include Patient dropout rate? (•) Yes ( ) No

Include Bayesian uncertainty? (•) Yes ( ) No

Duration: 52

Assessment: 5

% of patients in Treatment Arm: 41

Drug effect (% reduction on slope): 50

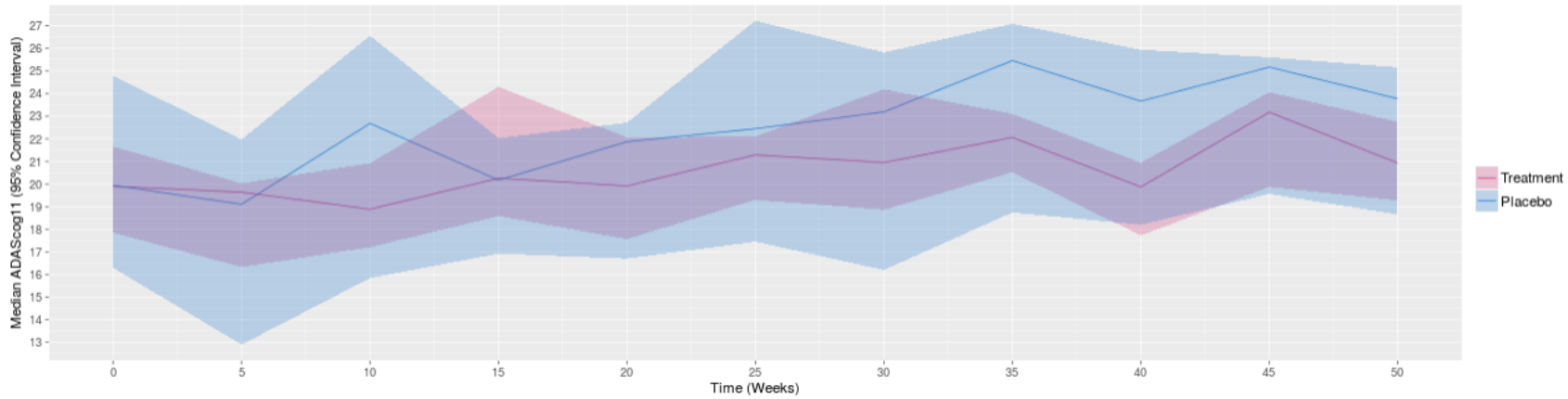
# of simulations: 3

Seed: 1

Alpha (slope difference): 95

Confidence Interval (%): 95

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	5
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Sample size	50
Age, (mean,sd)	(75.33,0.84)
Percentage of Male (mean,sd)	(0.42,0.09)
Number of APOE e4 alleles (%)	0 (80), 1 (20)
Baseline MMSE, median (range)	(14,26)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(45.84,0.61)
Trial Power (%)	0
Monte Carlo Error (%)	0
Confidence Interval of Monte Carlo Error	(0,0)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

AD CTS: n=50, with genetic enrichment

Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 50

Baseline MMSE: 14 – 26

% with 1 APOE4 allele: 100

% with 2 APOE4 alleles: 0

% on stable background medication: 70

Trial Design: Parallel

Include Patient dropout rate? Yes / No

Include Bayesian uncertainty? Yes / No

Duration: 52

Assessment: 5

% of patients in Treatment Arm: 41

Drug effect (% reduction on slope): 50

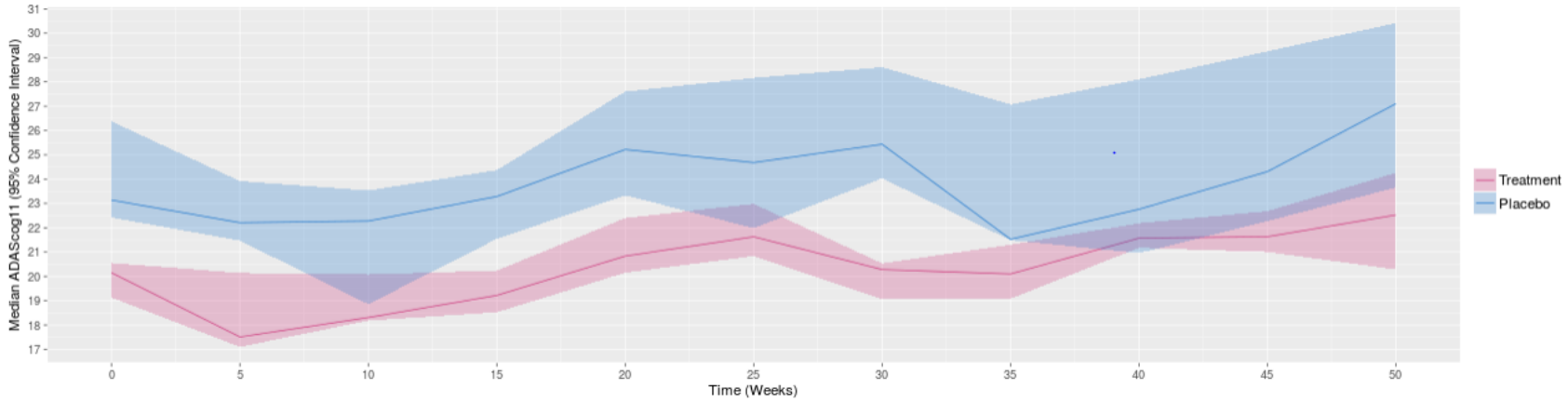
# of simulations: 3

Seed: 1

Alpha (slope difference): 95

Confidence Interval (%): 95

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	5
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Sample size	50
Age, (mean,sd)	(74.31,1.16)
Percentage of Male (mean,sd)	(0.41,0.06)
Number of APOE e4 alleles (%)	1 (100)
Baseline MMSE, median (range)	(14,26)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(45.41,0.58)
Trial Power (%)	0
Monte Carlo Error (%)	0
Confidence Interval of Monte Carlo Error	(0,0)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

AD CTS: n=50, with genetic enrichment, and baseline severity characterization

Mild-to-Moderate Alzheimer Disease Clinical Trial Simulator (beta v2.0)

Total # of Patients: 50

Baseline MMSE: 20 – 24

% with 1 APOE4 allele: 100

% with 2 APOE4 alleles: 0

% on stable background medication: 70

Trial Design: Parallel

Include Patient dropout rate? Yes / No

Include Bayesian uncertainty? Yes / No

Duration: 52

Assessment: 5

% of patients in Treatment Arm: 41

Drug effect (% reduction on slope): 50

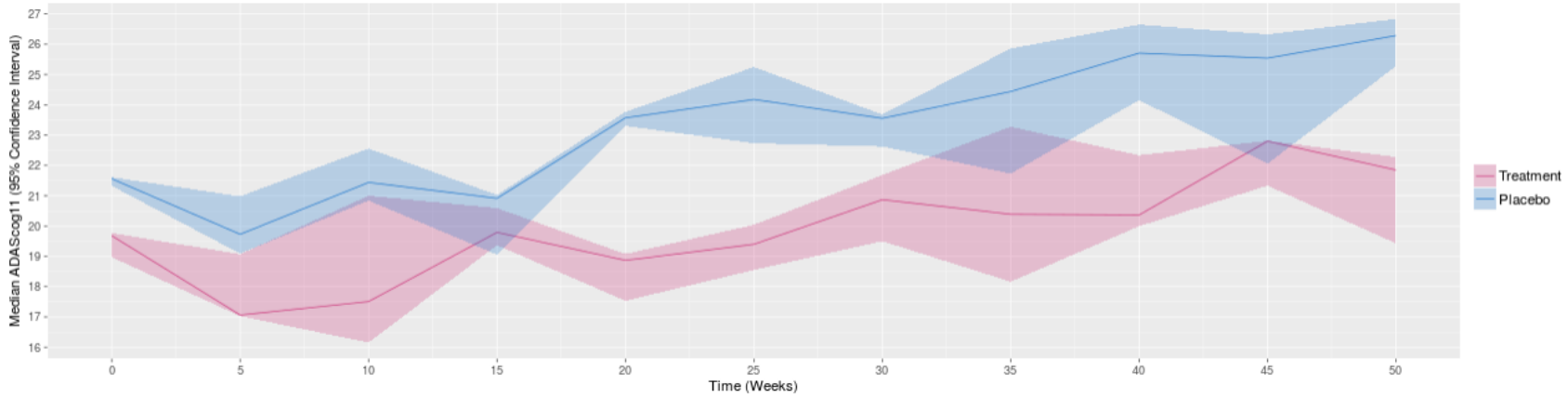
# of simulations: 3

Seed: 1

Alpha (slope difference): 95

Confidence Interval (%): 95

Simulate Trials



Characteristics	Values
Study Design	Parallel Design
Study Duration (weeks)	52
Assessment Interval (weeks)	5
Effect of Drug on Rate of Disease Progression (% Reduction)	50
Sample size	50
Age, (mean,sd)	(74.2,0.9)
Percentage of Male (mean,sd)	(0.36,0.11)
Number of APOE e4 alleles (%)	1 (100)
Baseline MMSE, median (range)	(20,24)
Concomitant medication use (%)	1
Dropout: Weeks at last assessment (mean,sd)	(46.84,1.32)
Trial Power (%)	0
Monte Carlo Error (%)	0
Confidence Interval of Monte Carlo Error	(0,0)

By Jackson Burton (model and app developer) and Daniela Conrado (model developer) on behalf of the Critical Path for Alzheimer Disease (CPAD) consortium. E-mail JBurton@c-path.org with questions or comments.

So…

Models, trials and biomarkers?

- It's all about the sources of variability
- Unless dealing with safety or diagnosis, biomarkers are either:
  - Covariates in a model
  - One of many endpoints in a model
- Quantitatively understanding disease progression helps improve the understanding of biomarkers and other relevant sources of variability, and can streamline the pathway towards regulatory acceptance of quantitative solutions to improve clinical trial design efficiency

RDCA-DAP: A resource for the future of drug development in rare diseases

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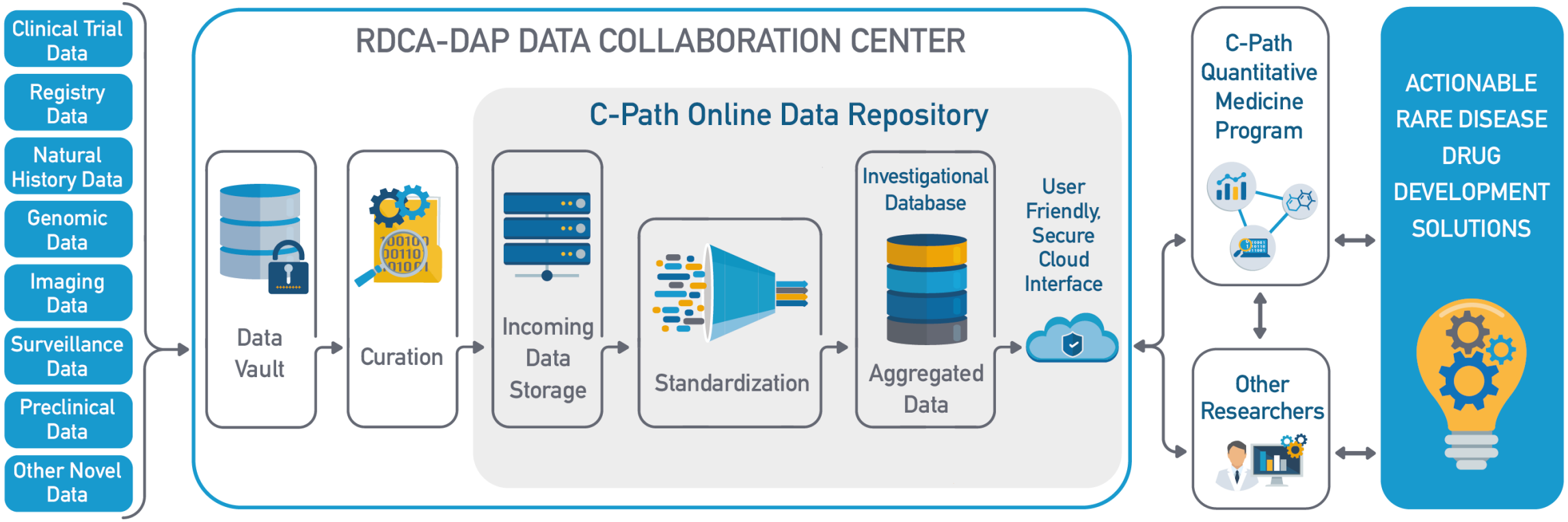

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$$S = f(t, p)$$

Thank you!

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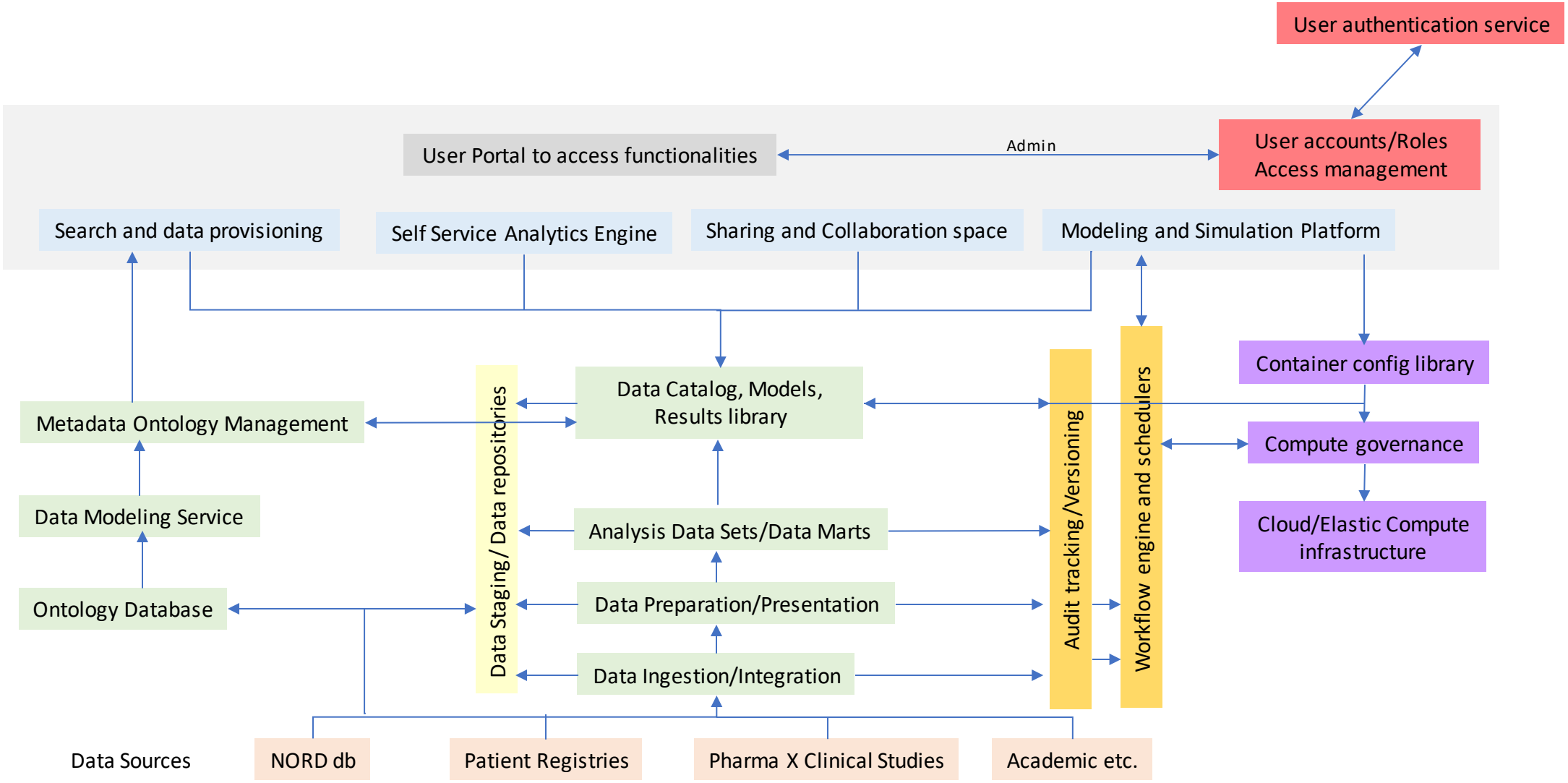
collaborate · innovate · accelerate

Rare Disease Cures Accelerator Platform

Reference architecture with key components/services/tools



Rare Disease Cures Accelerator Platform

Reference architecture with key components/services/tools: Some proposed examples