



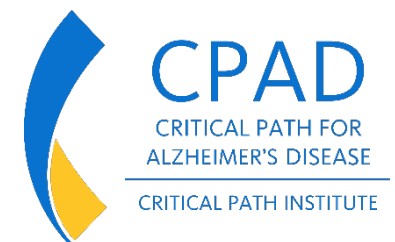
# Solving Measurement Gaps

**CPAD Annual Meeting – October 29, 2019**

**Klaus Romero MD MS FCP**

**Executive Director, Clinical Pharmacology and Quantitative Medicine**

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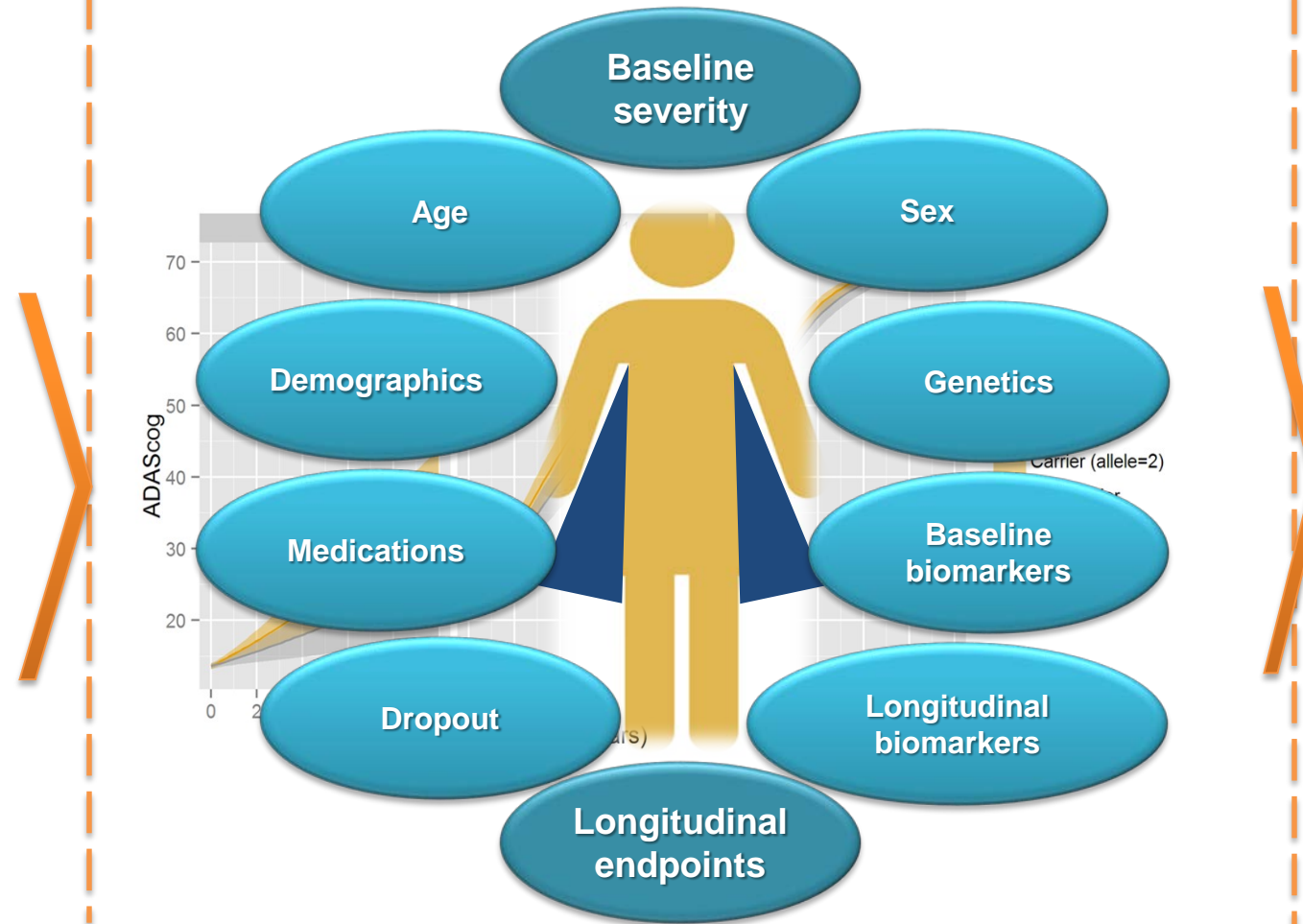


# Quantification of disease dynamics

## Input

Clinical studies

## Modeling



## Output

Understanding of disease worsening

Trajectory

Rate

Predictors

Web Clinical Trial Simulator



# CONTEMPORARY LARGE AND DEEP AD DATASETS PROVIDE AN UNPRECEDENTED OPPORTUNITY TO REALIZE THE VISION

- The following datasets are of greatest relevance to the development of an early AD progression model

**>30,000**

**Additional patient-level records**

Sponsor	Trial	Treatment	Participants
Biogen	EMERGE/ENGAGE	Aducanumab	3,200+
Eisai/Biogen	MissionAD1/MissionAD2	Elenbecestat	1,900+
Eisai/Biogen		BAN2401	800
Eisai/Biogen	Clarity AD	BAN2401	1,500+
Eli Lilly	EXPEDITION/EXPEDITION2/ EXPEDITION3	Solanezumab	4,100+
Eli Lilly/AstraZeneca	AMARANTH/DAYBREAK-ALZ	Lanabecestat	3,900+
Janssen/Pfizer		Bapineuzumab	3,300+
Janssen	EARLY	Atabecestat	500+
Merck	EPOCH/APECS	Verubecestat	3,600+
Novartis/Amgen	GENERATION S1/GENERATION S2	Umibecestat	1,600+
Roche	CREAD/CREAD2	Crenezumab	1,500+
Roche	GRADUATE1/GRADUATE2	Gantenerumab	1,500+
Takeda/Zinfandel	TOMMORROW	Pioglitazone	3,000+

# D-RSC Datasets



Database	Type of data	No. patients	Age range	Length of follow up	Types of variables
Santhera DMD 1004	Placebo arm of trial	34	10-18 years	up to 420 days	Respiratory measures, myometry, cardiac
Lilly* DMD 1005	Placebo arm of trial	115	7-14 years	up to 395 days	Functional measures, respiratory measures, cardiac measures
PTC -1 DMD 1009	Placebo arm of trial	57	older than 5	48 weeks	Functional measures, myometry, respiratory measures
PTC -2 DMD 1010	Placebo arm of trial	114	7-16 years	48 weeks	Functional measures, myometry, respiratory measures, Northstar
CHOP* DMD 1006	Clinical	66	13-33 years	up to 3 years	Respiratory measures
CCHMC DMD 1002	Clinical	97	7-16 years	up to 5 years	Functional measures, respiratory measures, cardiac measures
ImagingDMD DMD 1007	Natural history	100	5-18 years	up to 7 years	Functional measures, myometry
CINRG DNHS DMD 1003	Natural history	440	2-30 years	up to 12 years	Functional measures, respiratory measures, myometry
CINRG Steroid DMD 1011	Steroid Clinical Trial	64	4- 12 years	608 days	Functional measures, respiratory measures, myometry
UC Davis* DMD 1000	Natural history	73	2 -31 years	up to 10 years	Functional measures, respiratory measures, myometry
UC Davis 2* DMD 1000A	Test/re-test data for COA	24	4-14 years	1 year	Functional measures, respiratory measures
LUMC* DMD 1008	Biomarker study	14	5-18 years	Up to 5 years	FVC, drug effects, protein biomarkers
Duchenne Registry* DMD 1001	Patient Reported Registry	3736	Reports 1-115 years	none	Questionnaire
Summit *– DMD 1012	Clinical trial data	40	5-10	52-56 weeks	Respiratory measures, MRI/MRS measures, functional measures, PODCI, Northstar

# NOT ALL MEASURES NEED TO BE PRESENT IN ALL DATA SOURCES

Measure	1000	1000A	1002	1003	1004	1005	1006	1007	1009	1010	1011
North Star			X	X		X				X	
Velocity Stand	X	X		X		X		X	X	X	X
Velocity Climb	X	X	X	X		X		X	X	X	X
Velocity Walk-Run	X	X	X	X		X		X	X	X	X
FVC	X		X	X	X	X	X				X
Brooke	X		X	X	X	X	X				X

**Baseline covariates proposed to be included in the analyses:** Age, BMI, RACE, Steroid use, Age at start of steroid use, Genetic mutation, Study type

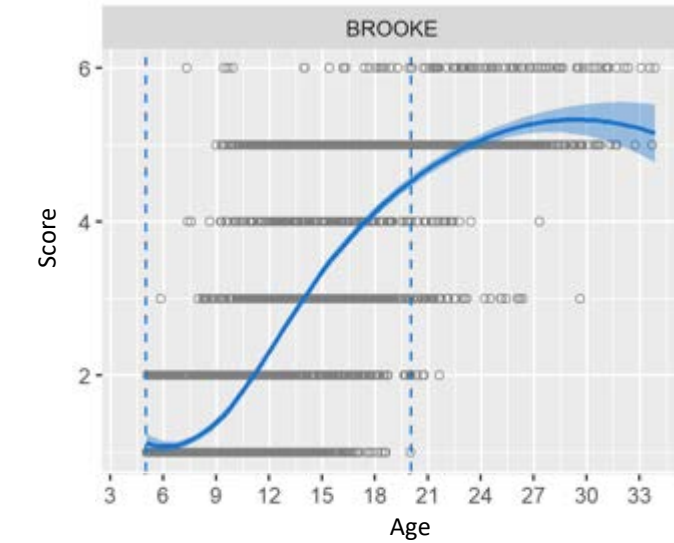
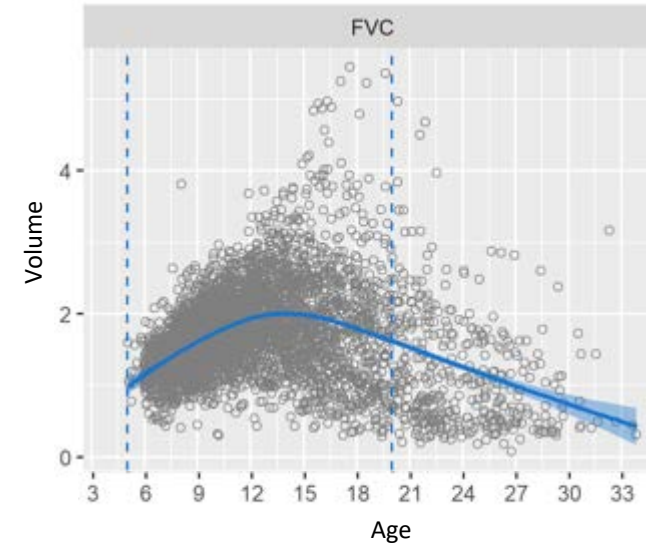
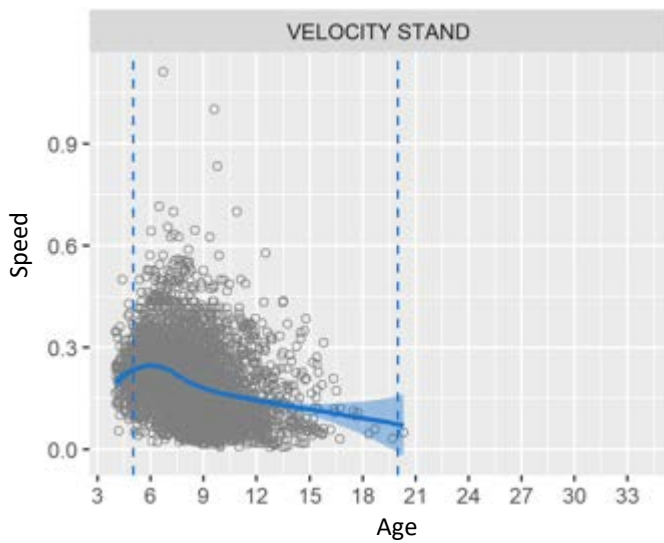
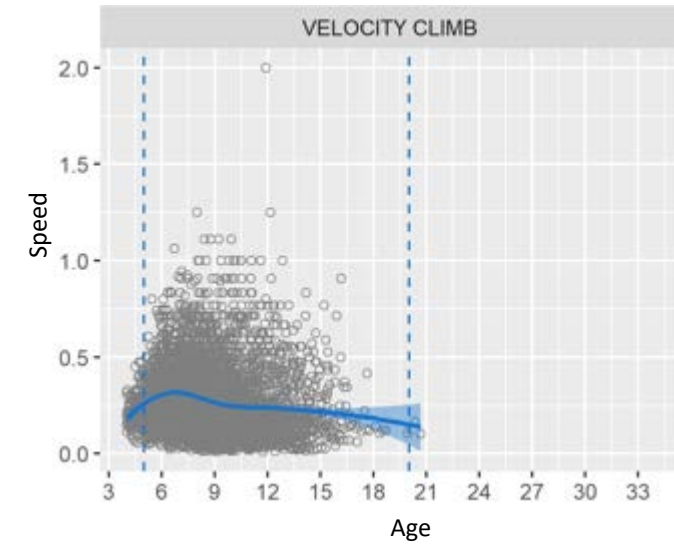
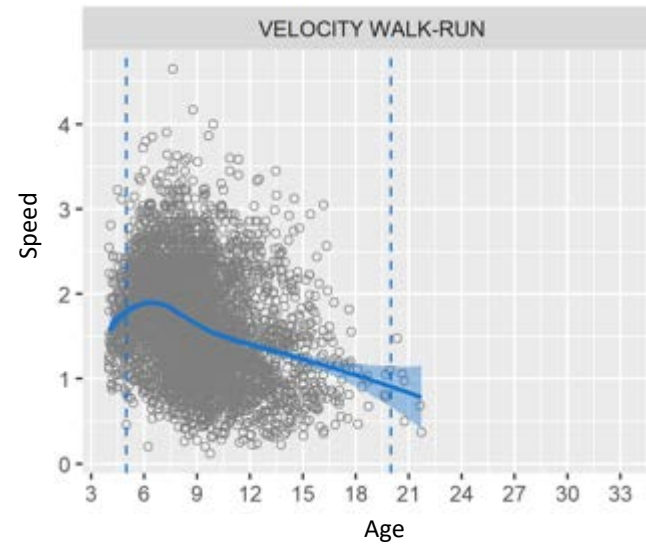
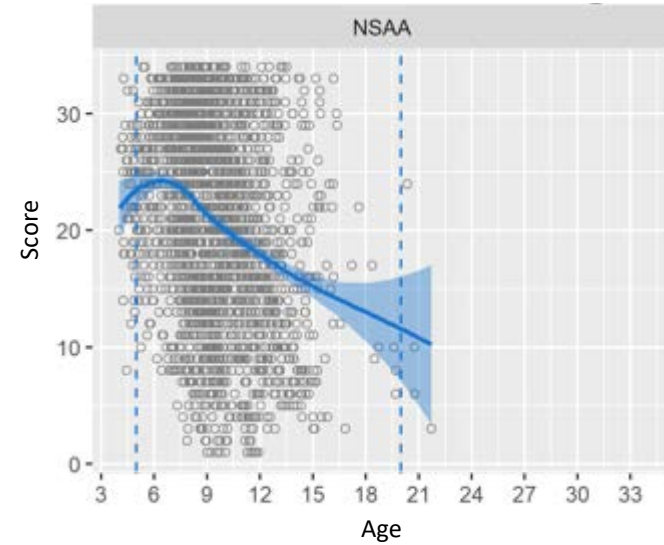
**The power of numbers:** 1139 individuals with DMD with a total of 24210 (non-missing) observations of the selected measures, from 4 to 34 years of age

## Lessons from Duchenne

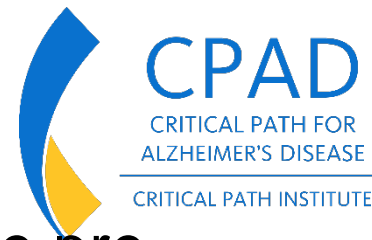
- Velocity of completion of the supine-stand test
- Velocity of completion of the 4-stair climb test,
- Velocity of completion of the 10-meter walk/run test / 30-foot walk/run test
- North Star Ambulatory Assessment
- Forced vital capacity
- Transition between scores in the Brooke scale

# Dynamic changes in a disease continuum

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



# CPP Digital Drug Development Tools (3DT) Team



- A subset of CPP member organizations\* have convened to collaborate pre-competitively with the goal of optimizing the efficiency of paths for developing digital tools for PD drug development.
- 3DT is leveraging a prospective study called WATCH-PD (Wearable Assessments in The Clinic and Home in PD), a 12-month multi-center, longitudinal, digital assessment study of PD progression in subjects with early, untreated PD as an exemplar pilot study to collect digital data in an early PD target population for the purpose of facilitating discussion and alignment with regulatory agencies.
- Face to face meetings with FDA and EMA have taken place and advice is being adopted into multiple digital device clinical studies

*Biogen, Takeda, UCB, Merck, Roche, Lundbeck, GSK  
Academic advisors: University of Rochester, Rush  
University, Parkinson's UK, Michael J Fox Foundation*

*Ray Dorsey,  
Principal Investigator*



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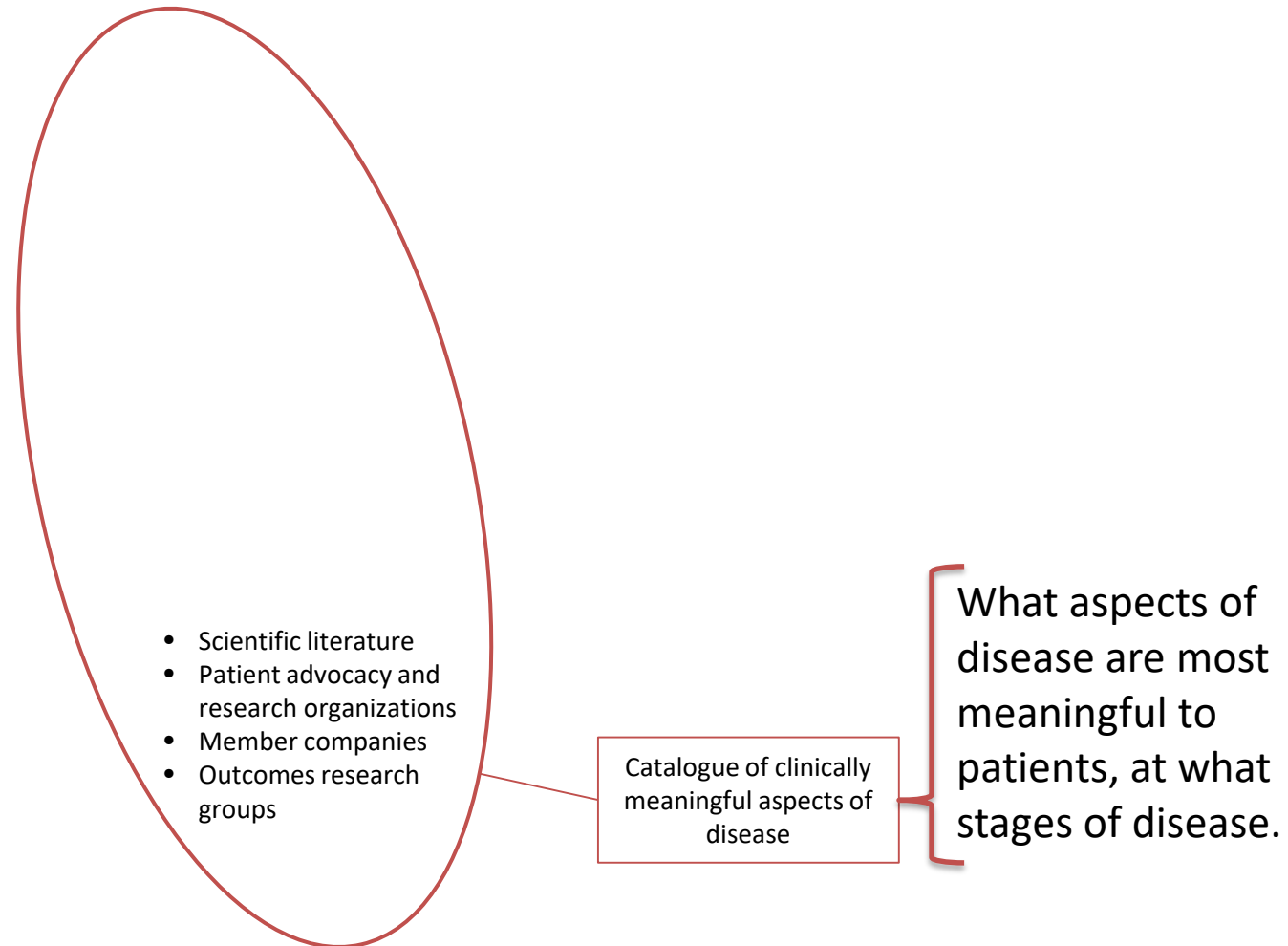
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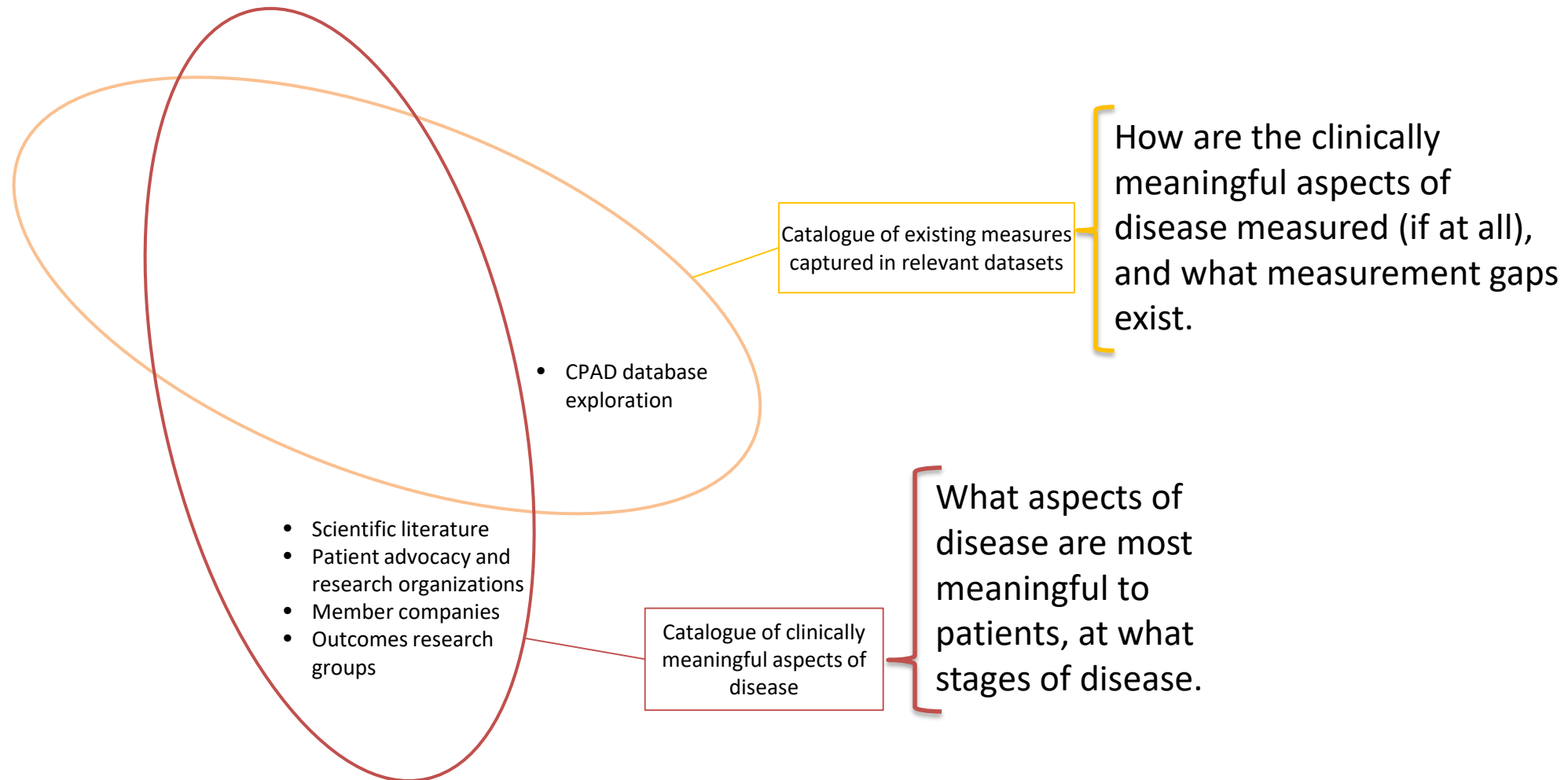
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Novartis/Amgen	GENERATION S1/GENERATION S2	Umibecestat	1,600+
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# Triangulation approach: part I



# Triangulation approach: part II



# Triangulation approach: part III

What outcomes can address measurement gaps for clinically meaningful aspects of disease.

Prioritization of which outcomes to model

• Active dialogue

- Scientific literature
- Patient advocacy and research organizations
- Member companies
- Outcomes research groups

• CPAD database exploration

Catalogue of existing measures captured in relevant datasets

How are the clinically meaningful aspects of disease measured (if at all), and what measurement gaps exist.

Catalogue of clinically meaningful aspects of disease

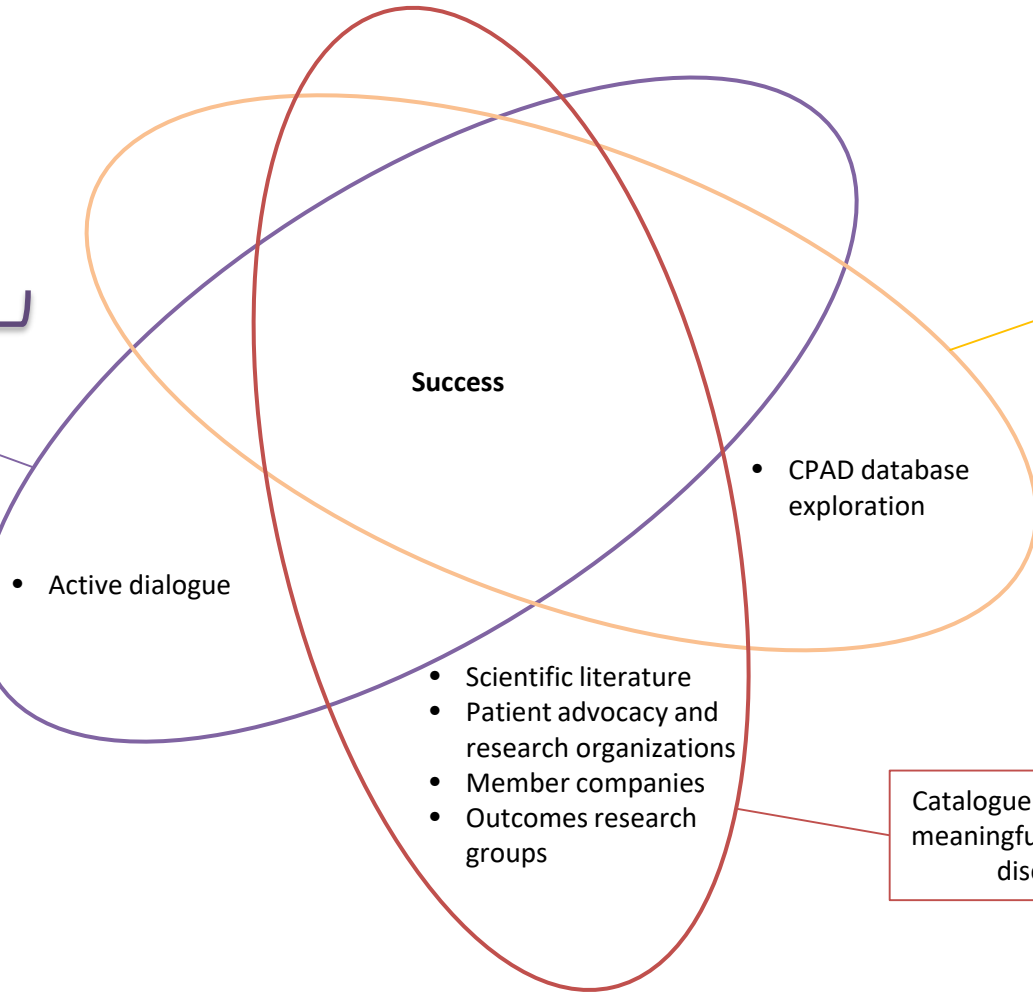
What aspects of disease are most meaningful to patients, at what stages of disease.



# Triangulation approach: integration of knowledge

What outcomes can address measurement gaps for clinically meaningful aspects of disease.

Prioritization of which outcomes to model



Catalogue of existing measures captured in relevant datasets

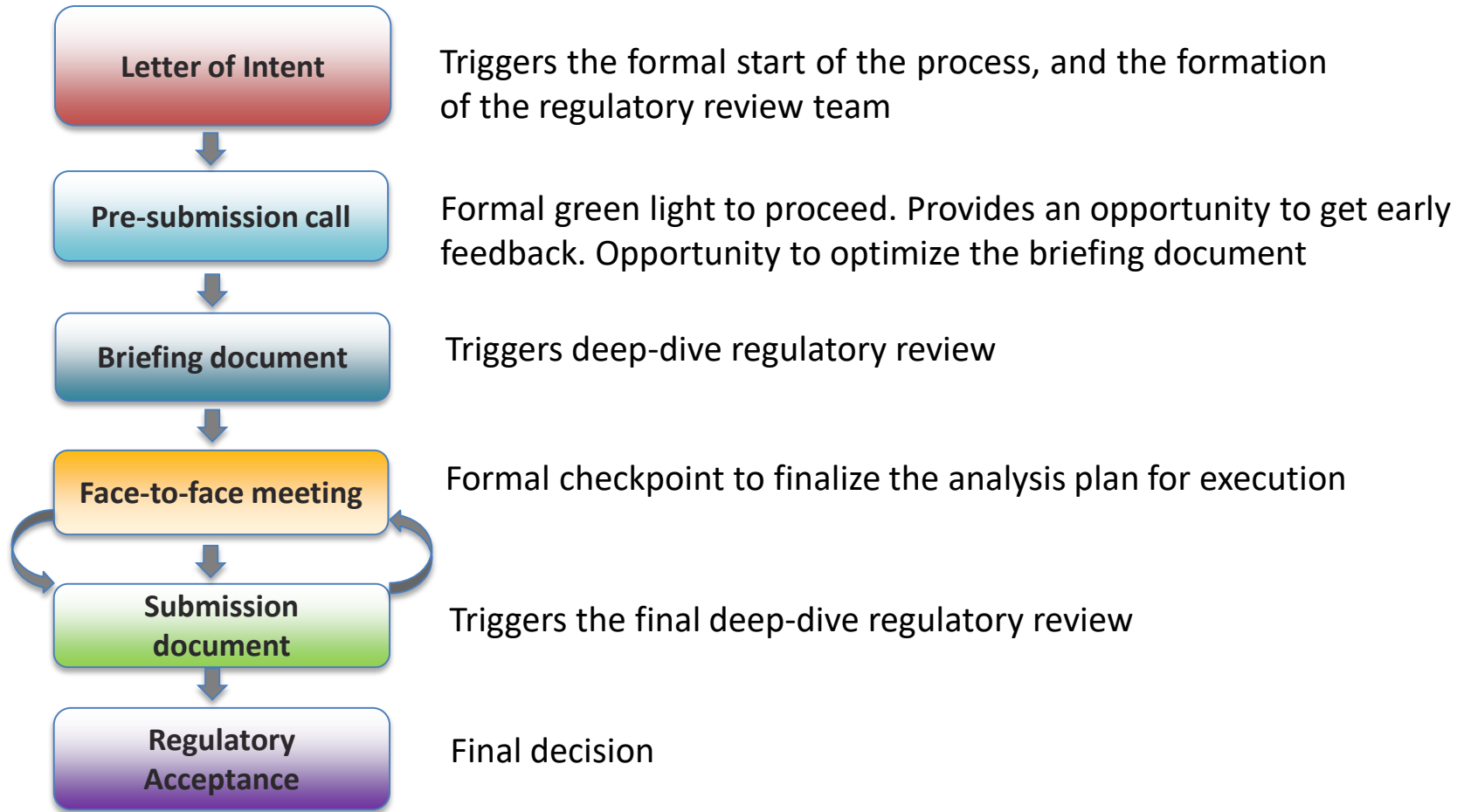
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Catalogue of clinically meaningful aspects of disease

What aspects of disease are most meaningful to patients, at what stages of disease.

# Regulatory Pathway Strategy (FDA)

## Fit-for-Purpose Initiative

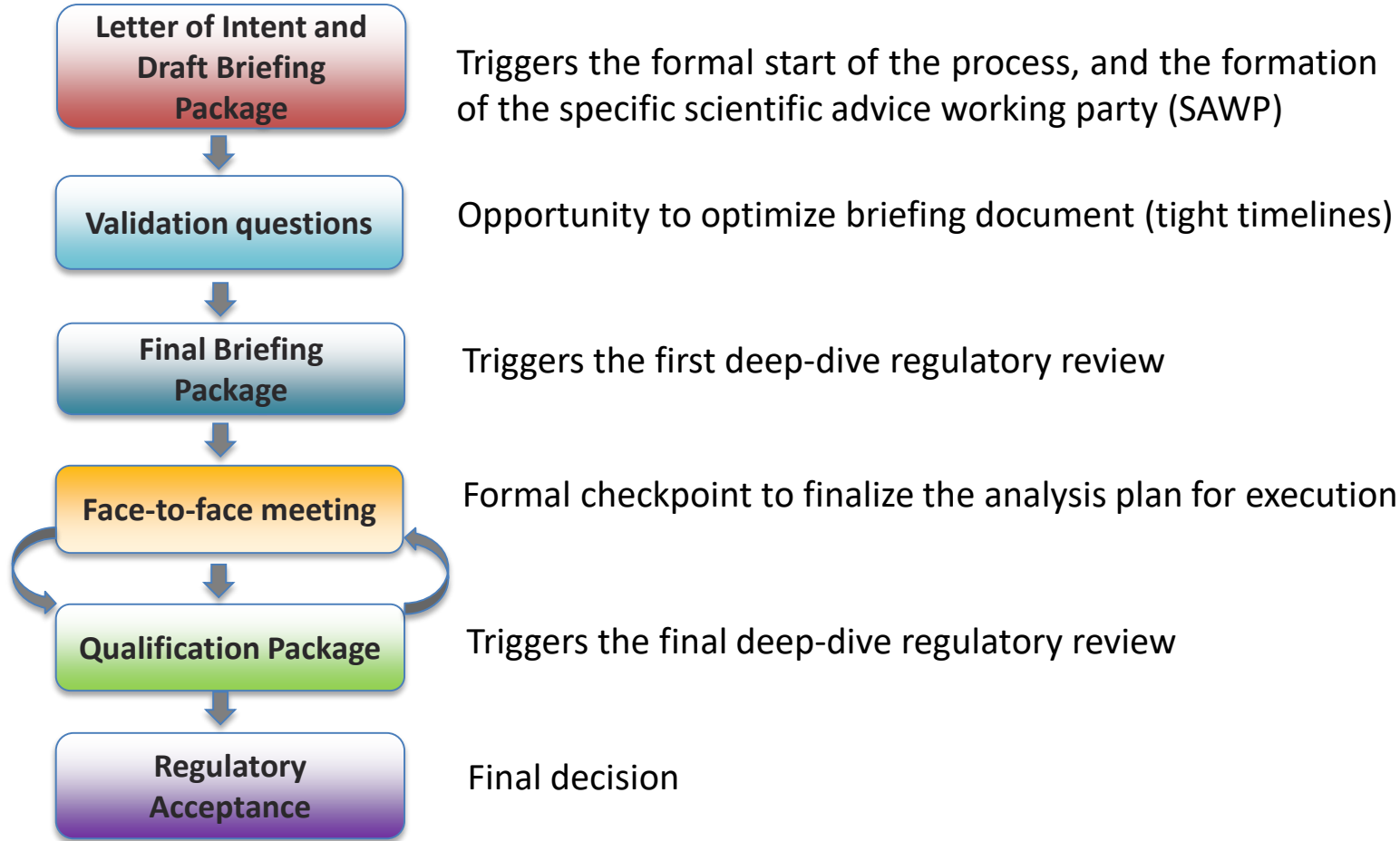


### Briefing Document

- ❖ Summary
- ❖ Regulatory history
- ❖ COU
- ❖ Modeling analysis plan:
  - ❖ Data sources and management
  - ❖ Data analytics
- ❖ Q&A:
  - ❖ Questions to the Agency
  - ❖ Consortium position on the questions

# Regulatory Pathway Strategy (EMA)

## Qualification of novel methodologies steps



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**Thank you!**

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