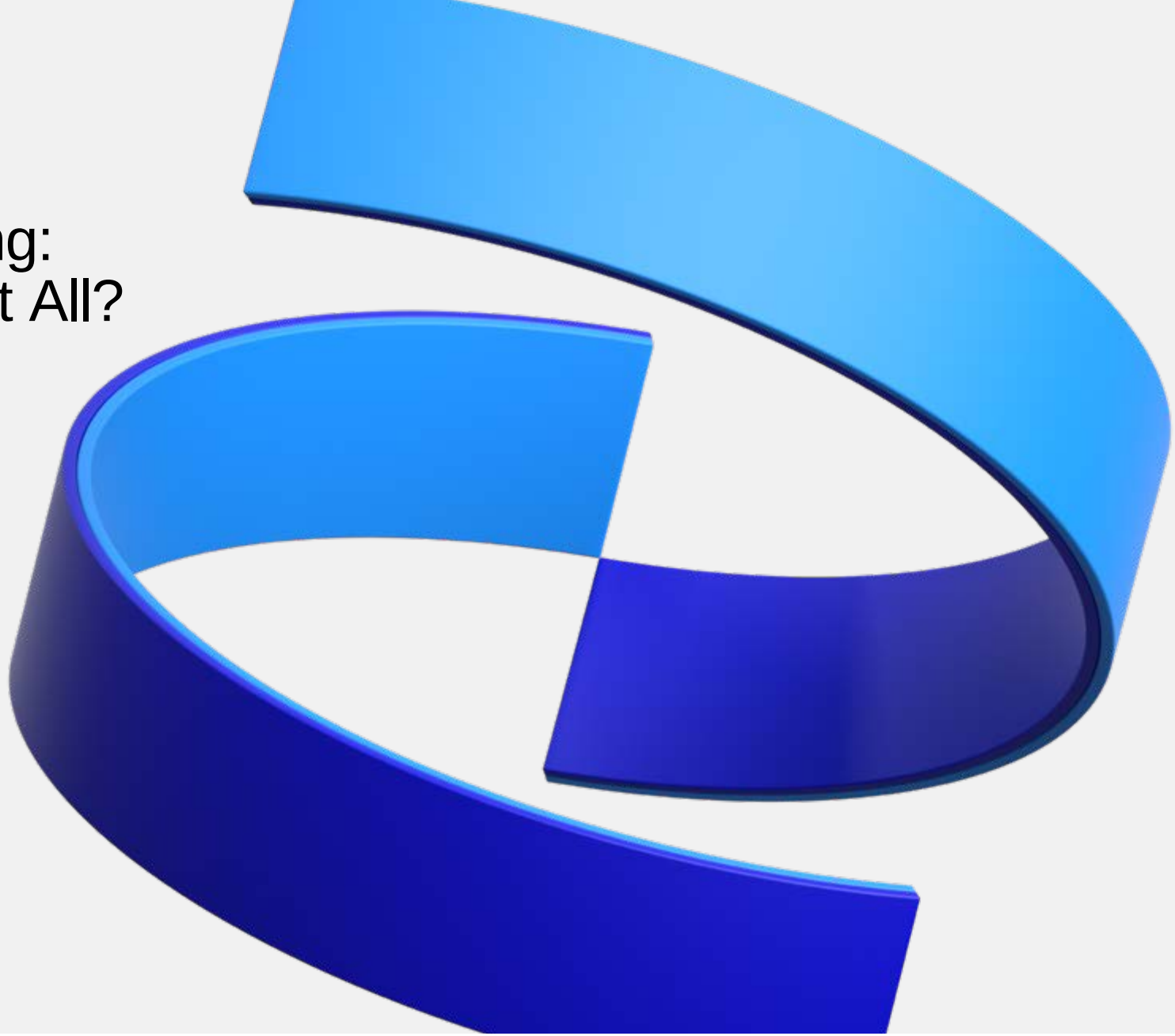
The Science and Fiction of Disease Progession Modeling: Can One “Best Practices” Fit All?



FDA Workshop on Best Practices for Development and Application of Disease Progression Models

November 19, 2021

C.J. Musante, Ph.D.
Vice President of Scientific Research
Head of Quantitative Systems Pharmacology

Towards a Best Practice for Disease Progression Modeling

1. Challenges (not exhaustive):
   - Heterogenity of modeling approaches, disease understanding, biomarkers/endpoints
   - Availability/accessibility of relevant disease-specific data
   - Data quality
2. Opportunities (not exhaustive):
   - Education & awareness
   - Community & stakeholder engagement
   - Data standards & sharing
3. Call for Action based on IQ Consortium survey results

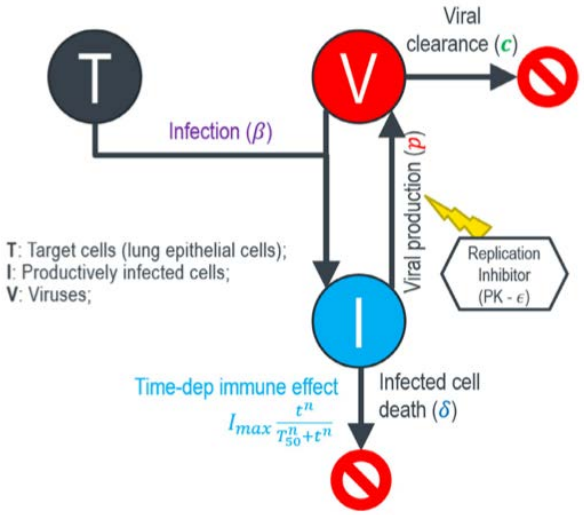
Challenge: Heterogeneity of modeling approaches

Modeling approach determined by research question and biomarkers/endpoints of interest

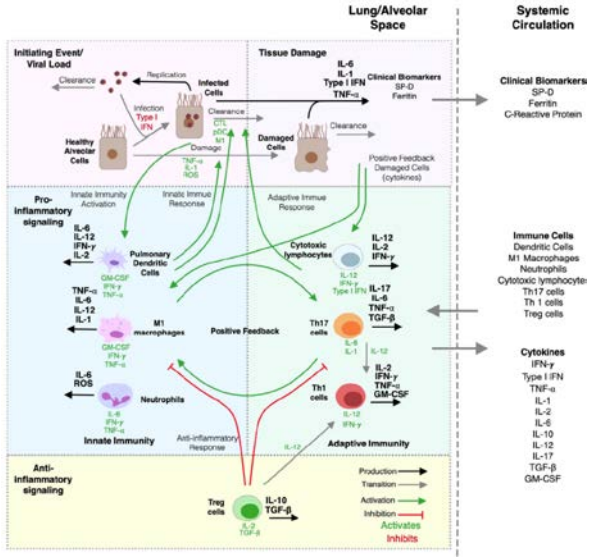
Parametric

Outcome= -36.898-0.020 AGE+0.894 COMORBID-0.048 Viral Load-0.004 IFN+0.444 Fever -0.003 IL6+0.271 D-Dimer+0.000 Ferritin-0.000 Lymphocyte Count-0.037 O2 saturation- 2.57034e-006 NAB

Semi-Mechanistic



QSP



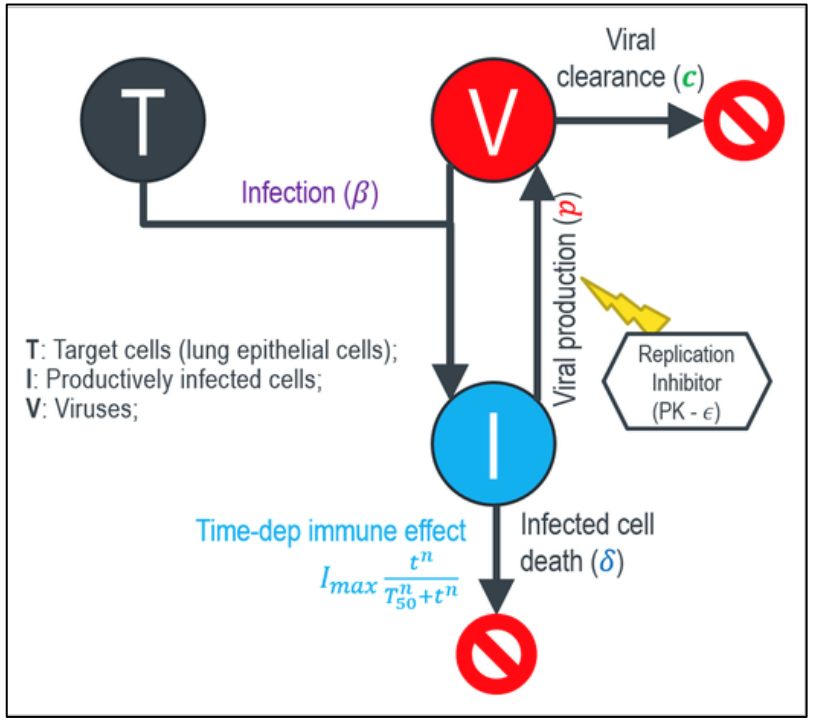
Data Driven — ***Complexity*** — **Biology Driven**

Left: Chirmule N. et al. (2021) Predicting the Severity of Disease Progression in COVID-19 at the Individual and Population Level: A Mathematical Model. J Clin Exp Pharmacol. 11:283.
Middle: Cao, Y et al.. Immune-viral dynamics modeling for SARS-CoV-2 drug development. *Clin Transl Sci*. 2021; 00: 1– 12. https://doi.org/10.1111/cts.13099
Right: 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

Challenge: Heterogeneity of modeling approaches

Modeling approach determined/limited by disease understanding & biomarkers

Infectious Diseases (Viral Dynamics)



Neurological Diseases (Parkinson's)

Citation: Clin Transl Sci (2018) 11, 63–70; doi:10.1111/cts.12492

ARTICLE

Dopamine Transporter Neuroimaging as an Enrichment Biomarker in Early Parkinson's Disease Clinical Trials: A Disease Progression Modeling Analysis

Daniela J. Conrado[1,*], Timothy Nicholas[2], Kuenhi Tsai[3], Sreeraj Macha[3], Vikram Sinha[3], Julie Stone[3], Brian Corrigan[2], Massimo Bani[4], Pierandrea Muglia[1], Ian A. Watson[5], Volker D. Kern[1], Elena Sheveleva[1,6], Kenneth Marek[7], Diane T. Stephenson[1] and Klaus Romero[1] on behalf of the Critical Path for Parkinson's (CPP) Parkinson's Disease Modeling and Simulation Working Group

Given the recognition that disease-modifying therapies should focus on earlier Parkinson's disease stages, trial enrollment based purely on clinical criteria poses significant challenges. The goal herein was to determine the utility of dopamine transporter neuroimaging as an enrichment biomarker in early motor Parkinson's disease clinical trials. Patient-level longitudinal data of 672 subjects with early-stage Parkinson's disease in the Parkinson's Progression Markers Initiative (PPMI) observational study and the Parkinson Research Examination of CEP-1347 Trial (PRECEPT) clinical trial were utilized in a linear mixed-effects model analysis. The rate of worsening in the motor scores between subjects with or without a scan without evidence of dopamine transporter deficit was different both statistically and clinically. The average difference in the change from baseline of motor scores at 24 months between biomarker statuses was –3.16 (90% confidence interval [CI] = –0.96 to –5.42) points. Dopamine transporter imaging could identify subjects with a steeper worsening of the motor scores, allowing trial enrichment and 24% reduction of sample size.

Clin Transl Sci (2018) **11**, 63–70; doi:10.1111/cts.12492; published online on 27 July 2017.

Left: Cao, Y et al.. Immune-viral dynamics modeling for SARS-CoV-2 drug development. *Clin Transl Sci*. 2021; 00: 1– 12. https://doi.org/10.1111/cts.13099

Challenge: Context of use and decision risk

Rigor/robustness may vary

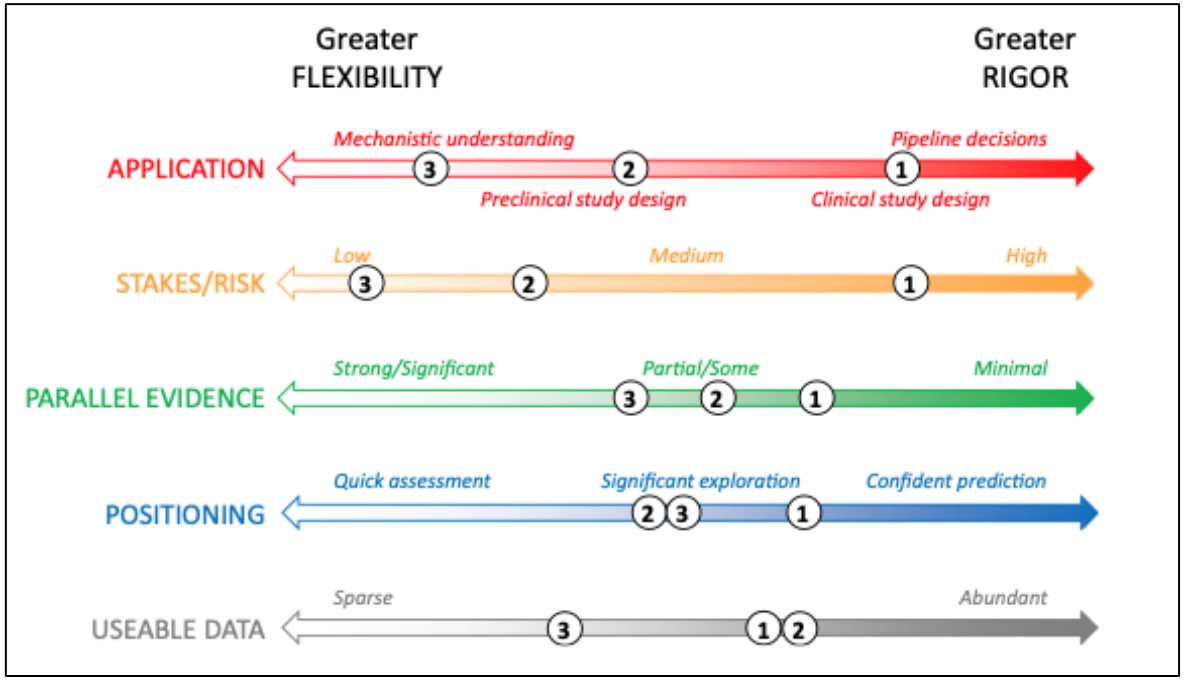


Table 1 Key terminology in the risk-informed credibility assessment framework

Term	Definition
Applicability	Relevance of the validation activities to support use the computational model for a specific context of use
Comparator	Test data that are used for validation; may be data from *in vitro* or *in vivo* studies. Selection should be based on context of use
Context of use	Statement that defines the specific role and scope of the computational model used to address the question of interest
Credibility	Trust, established through the collection of evidence, in the predictive capability of a computational model for a context of use
Credibility factors	Elements of the verification and validation process, including applicability, used to establish credibility (listed in **Table 2**)
Decision consequence	Significance of an adverse outcome resulting from an incorrect decision
Model influence	Contribution of the computational model relative to other contributing evidence in making a decision
Model risk	Possibility that the computational model and the simulation results may lead to an incorrect decision and adverse outcome
Question of interest	The specific question, decision, or concern that is being addressed
Validation	Process of determining the degree to which a model or simulation is an accurate representation of the real world
Verification	Process of determining a model or simulation represents the underlying mathematical model and its solution from the perspective of the intended uses of modeling and simulation

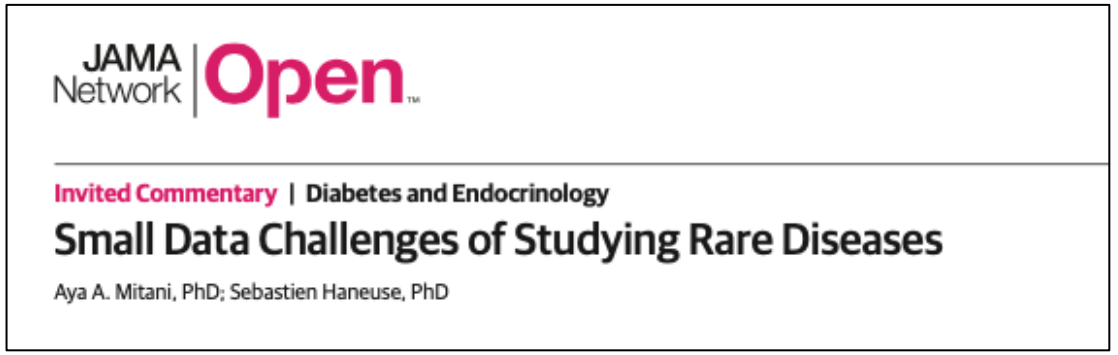
Terms and definitions are specified from the American Society of Mechanical Engineers verification and validation 40.[13]

Left: Ramanujan, S. et al. (2019). A flexible approach for Context-Dependent assessment of quantitative systems pharmacology models. *CPT: Pharmacometrics & Systems Pharmacology, 8*(6), 340-343. doi:http://dx.doi.org/10.1002/psp4.12409
Right: Kuemmel, C. et al. (2020), Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation. CPT Pharmacometrics Syst. Pharmacol., 9: 21-28. https://doi.org/10.1002/psp4.12479

DPM Challenge: Data availability and accessibility

Rare Diseases as Example

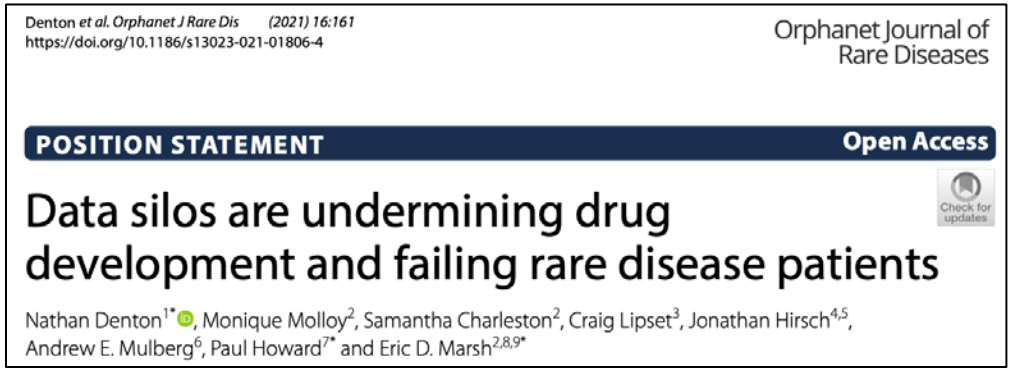
- **Patients are scarce**
  - Insufficient clinical information
  - Inadequate power
- Many rare diseases **lack of well-defined** and/or **fit-for-purpose outcome measures and biomarkers**
- More than half of patients with rare disease are **children**


JAMA Network Open

Invited Commentary | Diabetes and Endocrinology

Small Data Challenges of Studying Rare Diseases

Aya A. Mitani, PhD; Sebastien Haneuse, PhD


Denton et al. Orphanet J Rare Dis (2021) 16:161
https://doi.org/10.1186/s13023-021-01806-4

Orphanet Journal of Rare Diseases

POSITION STATEMENT Open Access

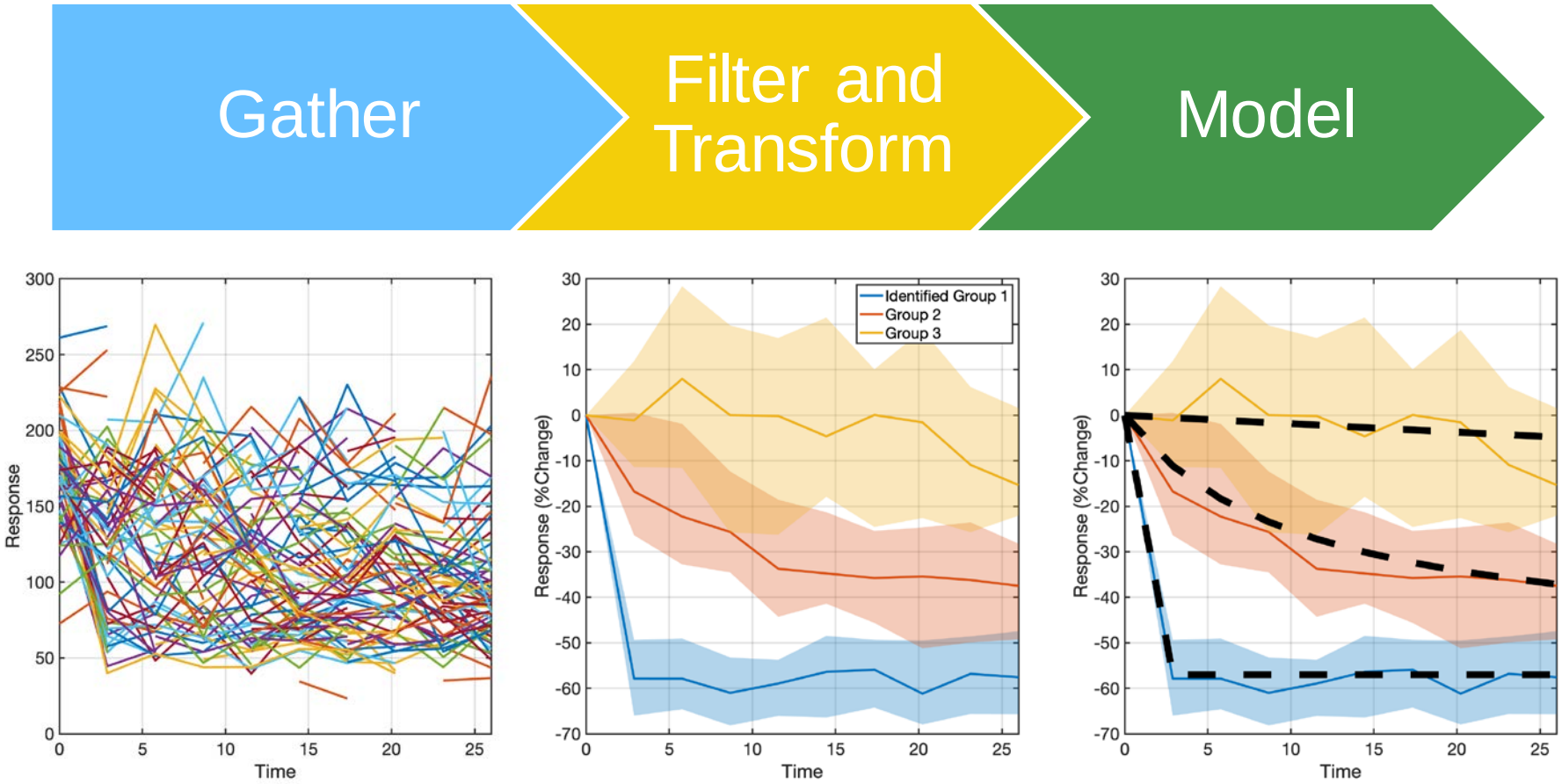
Data silos are undermining drug development and failing rare disease patients

Nathan Denton[1*], Monique Molloy[2], Samantha Charleston[2], Craig Lipset[3], Jonathan Hirsch[4,5], Andrew E. Mulberg[6], Paul Howard[7*] and Eric D. Marsh[2,8,9*]

Upper right: https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2763223

Challenge: Data quality

80% of analysis can be data-wrangling



DPM Opportunity: Education & Awareness

Science and Impact

- Define the scope: Consensus definition
- Establish scientific credibility
  - Peer-reviewed DPM publications for different diseases, different model types, different endpoints/biomarkers
  - Transparency
    - Methods and assumptions/limitations clearly described
    - Reproducible code provided
    - Datasets provided
- Establish value proposition
  - Published reports of high-impact case studies and examples
  - Include patient and HCP perspectives, especially for hard-to-recruit/treat diseases

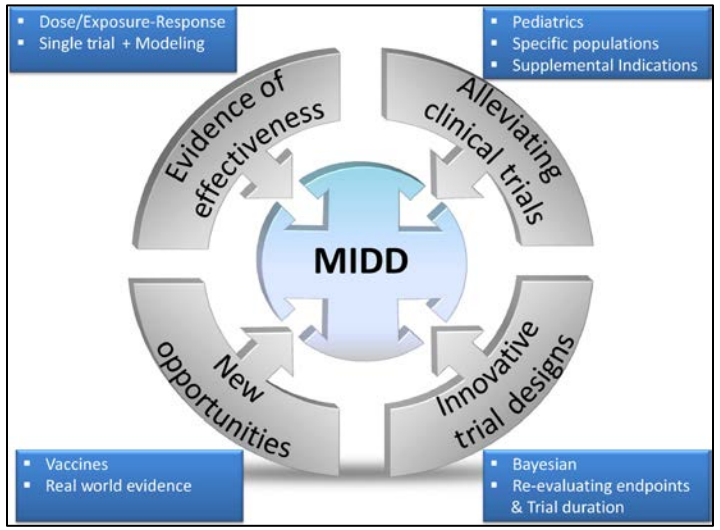


Table 1 Some examples of the high-level efficiencies gained over historical designs and data analytics following MBDD implementation

Indication	MBDD approach adopted	Efficiencies gained over historical designs and analysis
Thromboembolism[a]	Omit phase IIa, model-based dose–response relationship, adaptive phase IIb design	2,750 Fewer patients, 1 year shorter study duration
Hot flashes	Model-based dose–response relationship	1,000 Fewer patients
Fibromyalgia	Prior data supplementation, model-based dose–response relationship, sequential design	760 Fewer patients, 1 year shorter study duration
Type 2 diabetes	Prior data supplementation, model-based dose–response relationship	120 Fewer patients, 1 year shorter study duration
Gastroesophageal reflux	Model-based dose–response relationship	1,025 Fewer patients
Rheumatoid arthritis	Model-based dose–response relationship	437 Fewer patients, increased probability of success
Global anxiety disorder	Omit phase IIb	260 Fewer patients, 1 year shorter study duration
Lower urinary tract symptoms	Meta-analysis	Increased probability of success
Urinary incontinence	Meta-analysis	Increased probability of success

MBDD, model-based drug development.

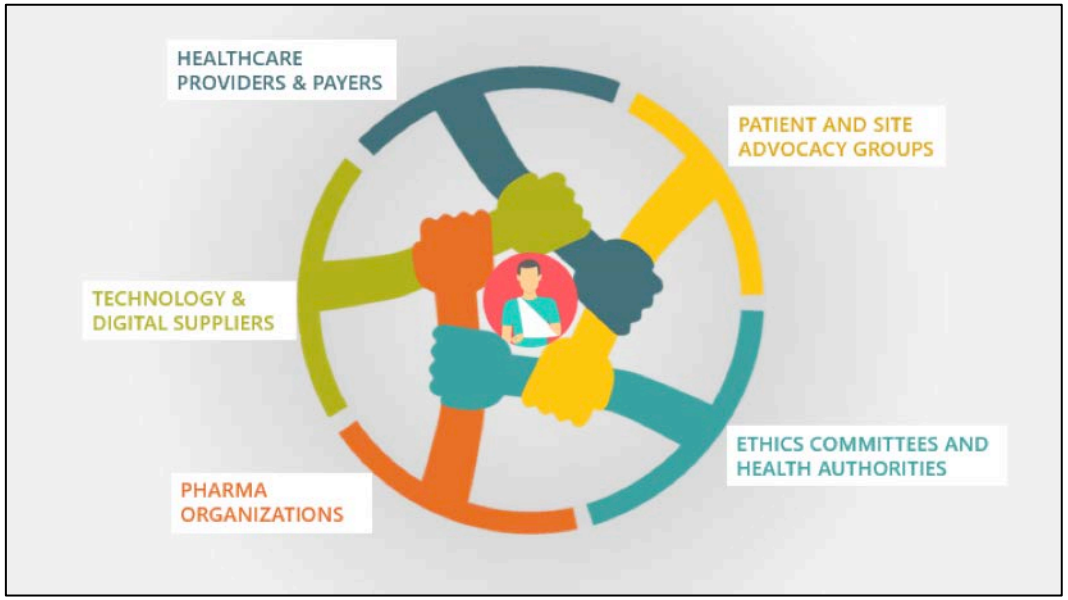
[a]This application is discussed further in the text as example 4, "Adaptive dose-finding phase II study designed using clinical trial simulations."

Left Top: Jain, Let al. (2019), PDUFA VI: It Is Time to Unleash the Full Potential of Model-Informed Drug Development. CPT Pharmacometrics Syst. Pharmacol., 8: 5-8. https://doi.org/10.1002/psp4.12365
Left Bottom: Milligan, P.A. et al. (2013), Model-Based Drug Development: A Rational Approach to Efficiently Accelerate Drug Development. Clinical Pharmacology & Therapeutics, 93: 502-514. https://doi.org/10.1038/clpt.2013.54

Opportunity: Community & stakeholder engagement

MIDD is a team “sport”

Active collaboration is key



Left: https://www.pharmavoice.com/contributed-article/modern-technologies-partnerships-enabling-next-generation-patient-centric-research/

Learnings from many areas

TransCelerate Special Section: Original Article

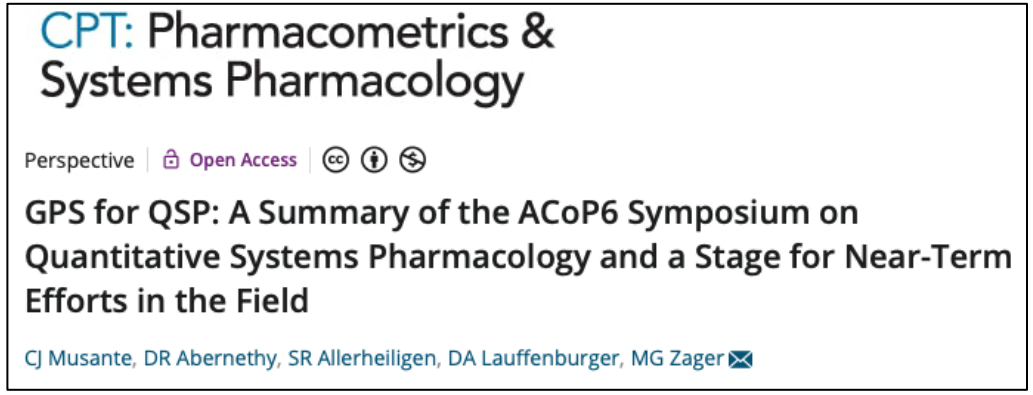
DIA

Awareness and Collaboration Across Stakeholder Groups Important for eConsent Achieving Value-Driven Adoption

Therapeutic Innovation & Regulatory Science
2019, Vol. 53(6) 724-735

DOI: 10.1177/2168479019861924
tirs.sagepub.com

Hilde Vanaken, Ir, MsC, PhD[1], and Shirley N. Masand, PhD[2]



CPT: Pharmacometrics & Systems Pharmacology

Perspective | Open Access

GPS for QSP: A Summary of the ACoP6 Symposium on Quantitative Systems Pharmacology and a Stage for Near-Term Efforts in the Field

CJ Musante, DR Abernethy, SR Allerheiligen, DA Lauffenburger, MG Zager

Opportunity: Data standards & sharing

Many efforts, many opportunities

Data standards & best practices

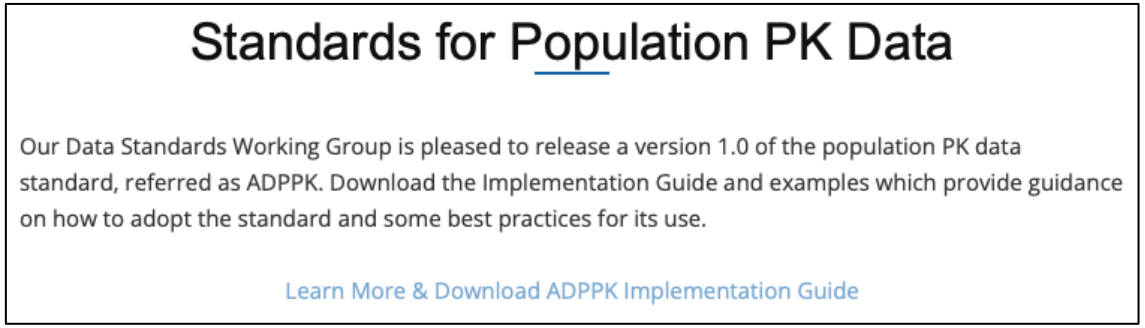

Clinical Pharmacology & Therapeutics

Opinion | Full Access

The ISoP Standards and Best Practices Committee

R Bruno, F Mentré, S Tannenbaum, Y Wang, B Corrigan, D E Mager

First published: 12 March 2014 | https://doi.org/10.1038/clpt.2014.65 | Citations: 1

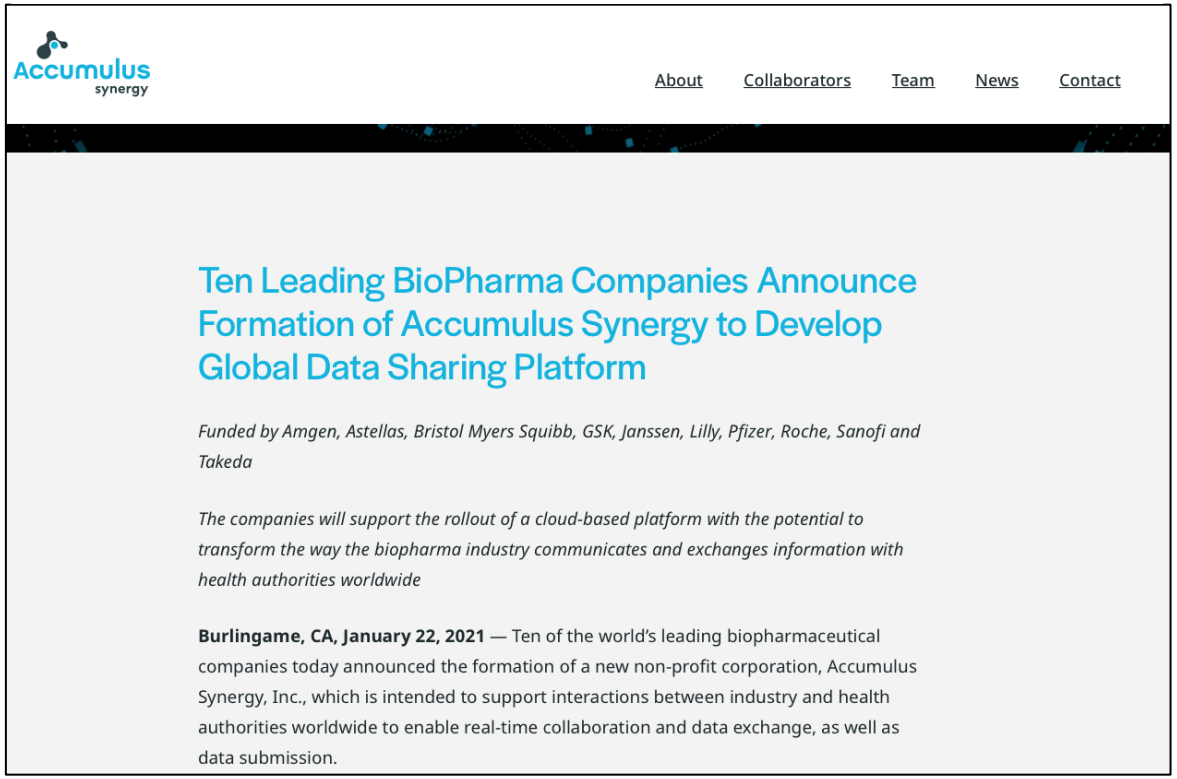

Standards for Population PK Data

Our Data Standards Working Group is pleased to release a version 1.0 of the population PK data standard, referred as ADPPK. Download the Implementation Guide and examples which provide guidance on how to adopt the standard and some best practices for its use.

Learn More & Download ADPPK Implementation Guide

Right: www.go-isop.org
Left: https://www.accumulus.org/#team

Data sharing platforms


Accumulus synergy

About Collaborators Team News Contact

Ten Leading BioPharma Companies Announce Formation of Accumulus Synergy to Develop Global Data Sharing Platform

Funded by Amgen, Astellas, Bristol Myers Squibb, GSK, Janssen, Lilly, Pfizer, Roche, Sanofi and Takeda

The companies will support the rollout of a cloud-based platform with the potential to transform the way the biopharma industry communicates and exchanges information with health authorities worldwide

Burlingame, CA, January 22, 2021 — Ten of the world's leading biopharmaceutical companies today announced the formation of a new non-profit corporation, Accumulus Synergy, Inc., which is intended to support interactions between industry and health authorities worldwide to enable real-time collaboration and data exchange, as well as data submission.

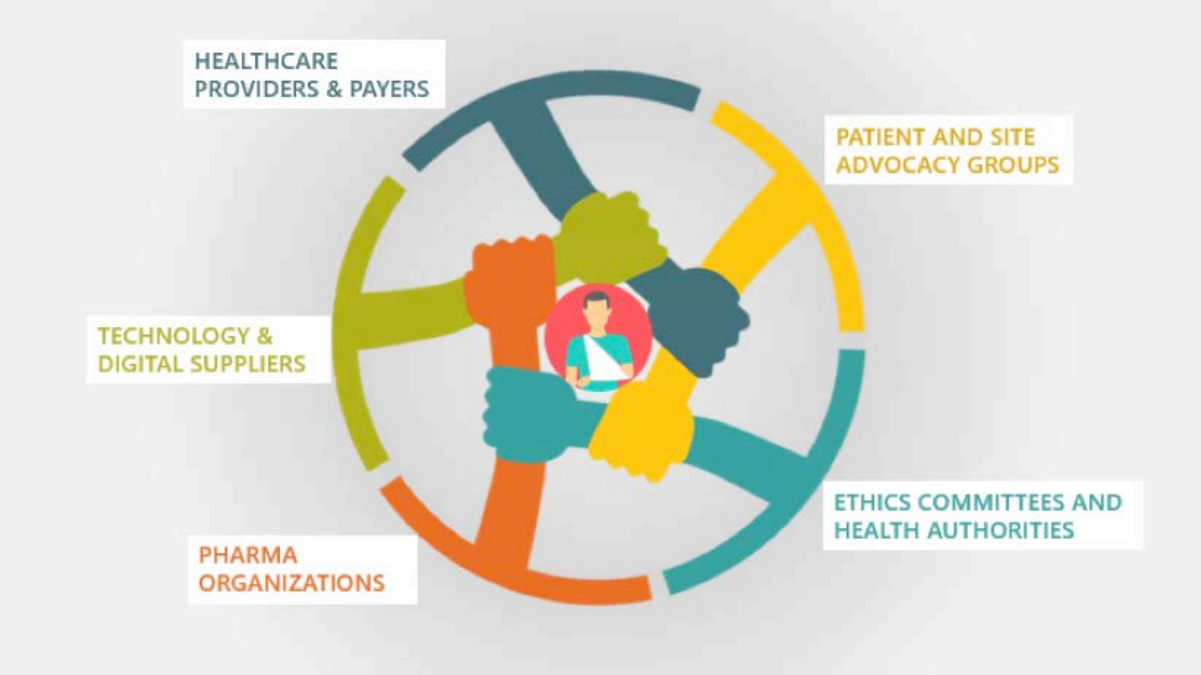
Current Status and Call for Action

IQ CPLG DPM Working Group

DPM has been **developed** using various data and modeling approaches in many TAs and **applied** at all development stages, but the **science is still evolving** and successful **impact is not certain**	Clear **DPM definition** and aligned **best practice** for convincing cross-functional and regulatory communication
Easy access to **relevant and high quality data** for model development/validation is critical and is still limited	Making more disease specific **datasets** and **models** available (especially for **placebo and SoC**) to ensure timely impact
Details are lacking in some DPM publications for full **reproducibility**, and publication of successful **impact examples** are currently limited	More **publications** of **reproducible models** as well as **case examples** with demonstrated drug development and/or regulatory decision-making impact are needed
Consortiums exist for only a few TAs/indications and are generally slow moving	Timely **collaborations, consortiums, shared learning** are critical, and could be facilitated by regulatory agency
Lack of clear **regulatory guidance and path** for DPM, and **regulatory submissions** are limited	More **presentation/publication** and **data/model sharing by regulatory agency** on DPM to enhance acceptability and impact for regulatory application and decision-making

CPLG – Clinical Pharmacology Leadership Group; DPM – disease progression modeling; SoC – standard of care; TA – therapeutic area

Disease Progression Modeling: Can One Best Practices Fit All?



https://www.pharmavoice.com/contributed-article/modern-technologies-partnerships-enabling-next-generation-patient-centric-research/

Thank You

cynthia.j.musante@pfizer.com

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  - Esp. Jin Jin & Kosalaram Goteti
- FDA Workshop organizers
  - Esp. Hao Zhu, Qi Liu, & Maryanne Dingman