The Healthcare business of Merck KGaA, Darmstadt, Germany
operates as EMD Serono in the U.S. and Canada.

Partnerships among quantitative sciences to optimize drug development

ASA Regulatory-Industry Statistics Workshop Sept 27th

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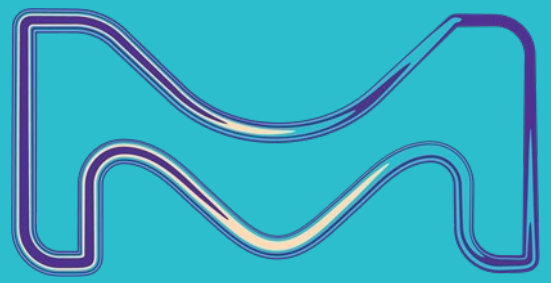

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Outline

- Intro/Background
- Opportunities for collaboration
- Applications
- A few examples
- Conclusion- Key messages

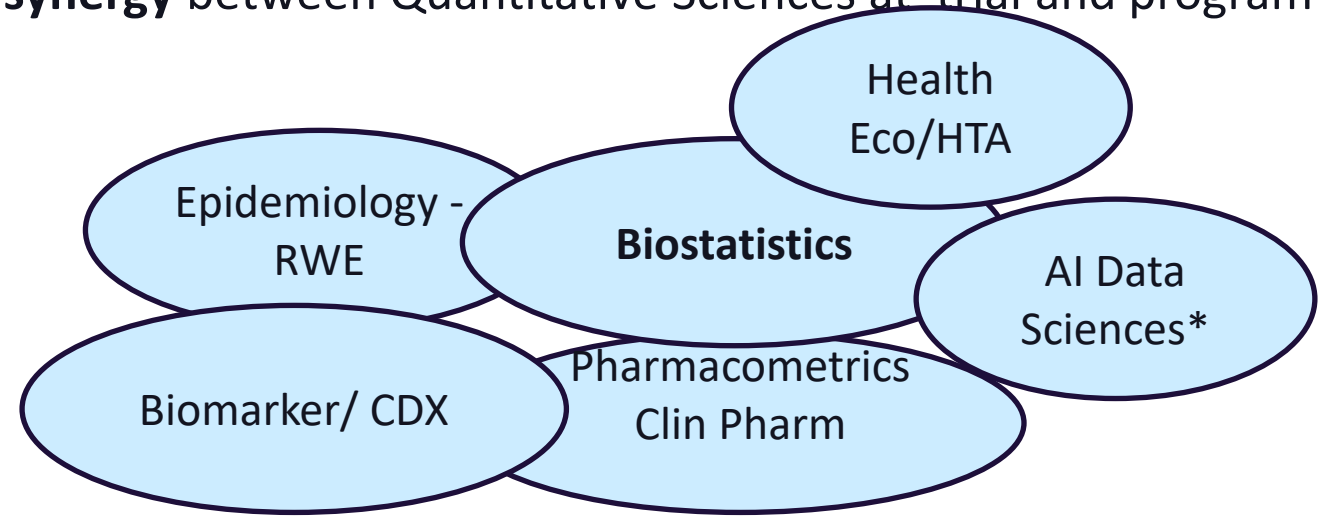
Introduction/background

Biopharmaceutical industry challenges of pipeline growth :

Drug development is more complex, more expensive and riskier.

- Integration of more quantitative expertise to **impact timely decision making** and to **leverage data** removing uncertainty to generate evidence.

- More **synergy** between Quantitative Sciences at trial and program level

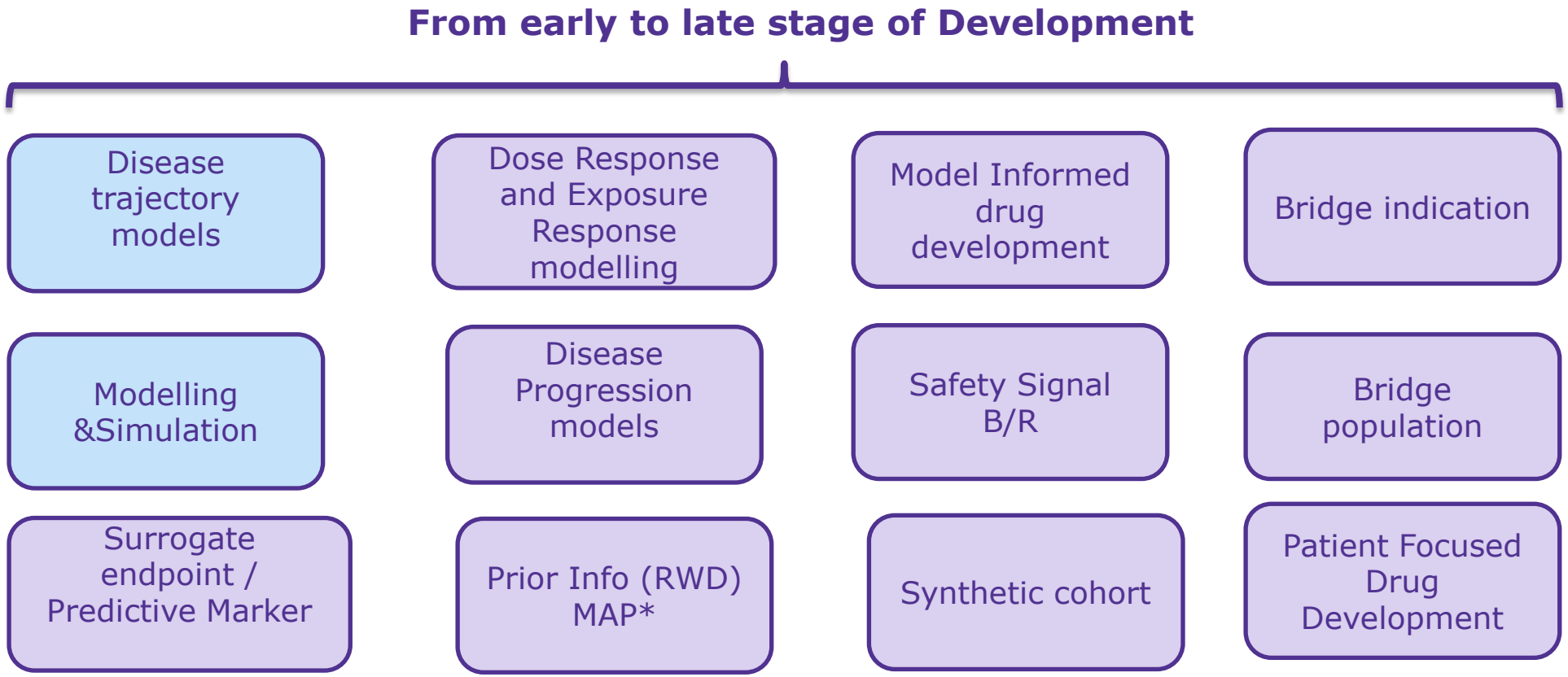


*Data Sciences includes bioinformatics, programming, software and tool development, clinical data standards, automation, and data/technology/digital strategies.

Opportunities for collaboration

- Proper quantification of **uncertainty**.
- Use of **causal inference** to answer drug development questions.
- Broad implementation of the **Estimands framework** along all stages of drug development
- Broader application of **Bayesian methods**.
- Establish **reproducible research**
- Open-source tools across drug development pipeline.

Applications: Cross collaboration between Biostatistics &PMx& other Quantitative functions



* MAP: Meta Analytic Predictive

Use cases: collaboration between Biostat and PMx at different stage of development

1. **1- Earlier stage**: New dev in Lupus- SLE (disease trajectory model)

   ->to understand time course of clinical endpoints

2. 2- **Late & LCM :** Multiple Sclerosis (Modeling & Simulation)

   ->To provide treatment guidance

1 Use case 1: How Disease Trajectory in SLE can impact CDP?

Background and Objective

➢ Drug development in Systemic Lupus Erythematosus (SLE) is challenged by low success rates, discordance in trial performance across primary endpoints, and the lack of reliable short-term outcome biomarkers of efficacy.

➢ SLE is a **multifactorial disease** in a **heterogeneous population**

➢ **Response rates for current Placebo/ SOC are high (40%–50%)**

➢ This complicates the assessment of the actual treatment effect of a new compound

➢Therefore, identification of patient characteristics is needed to define enrichment strategies for

- **Efficient POC studies (duration, population, subgroup…)**
- **Increased probability of success**

➢**Objective:**

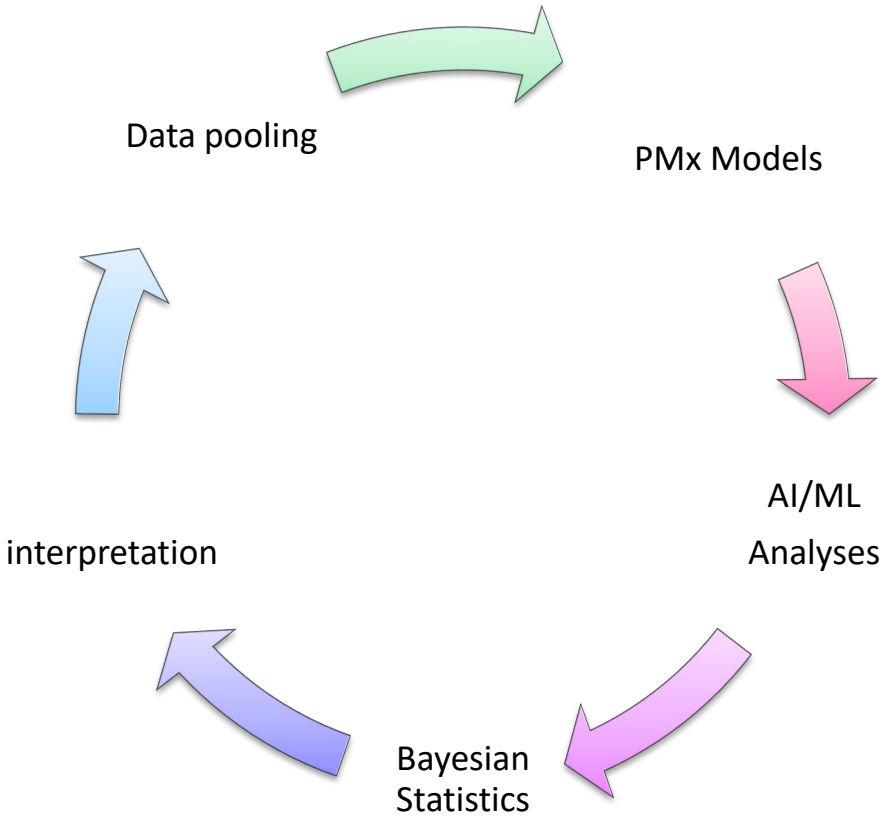
To understand the **time course of clinical endpoints** and to identify clinically **important covariates**

1 Cross-Functional Team to integrate SLE disease area knowledge

To enable multi-disciplinary **integration of disease area knowledge, pharmacometrics and statistical expertise**.

- **Data source**: Placebo/SOC Internal and external data sets (Transcelerate HTD Consortium)
- **Medical and Pharmacology input for the disease area expertise**
- Health Economics & Outcomes Research – Endpoints and competitive landscape
- **Derivation rules for complex endpoints (Component and composite endpoints)**
- **Estimands**
- **Missing pattern and imputation**
- **Statistical and PMx expertise to the modelling**
- **Interpretation of results**

1 Different Methods-Expertise involved



All the functions have to work in Symbiosis

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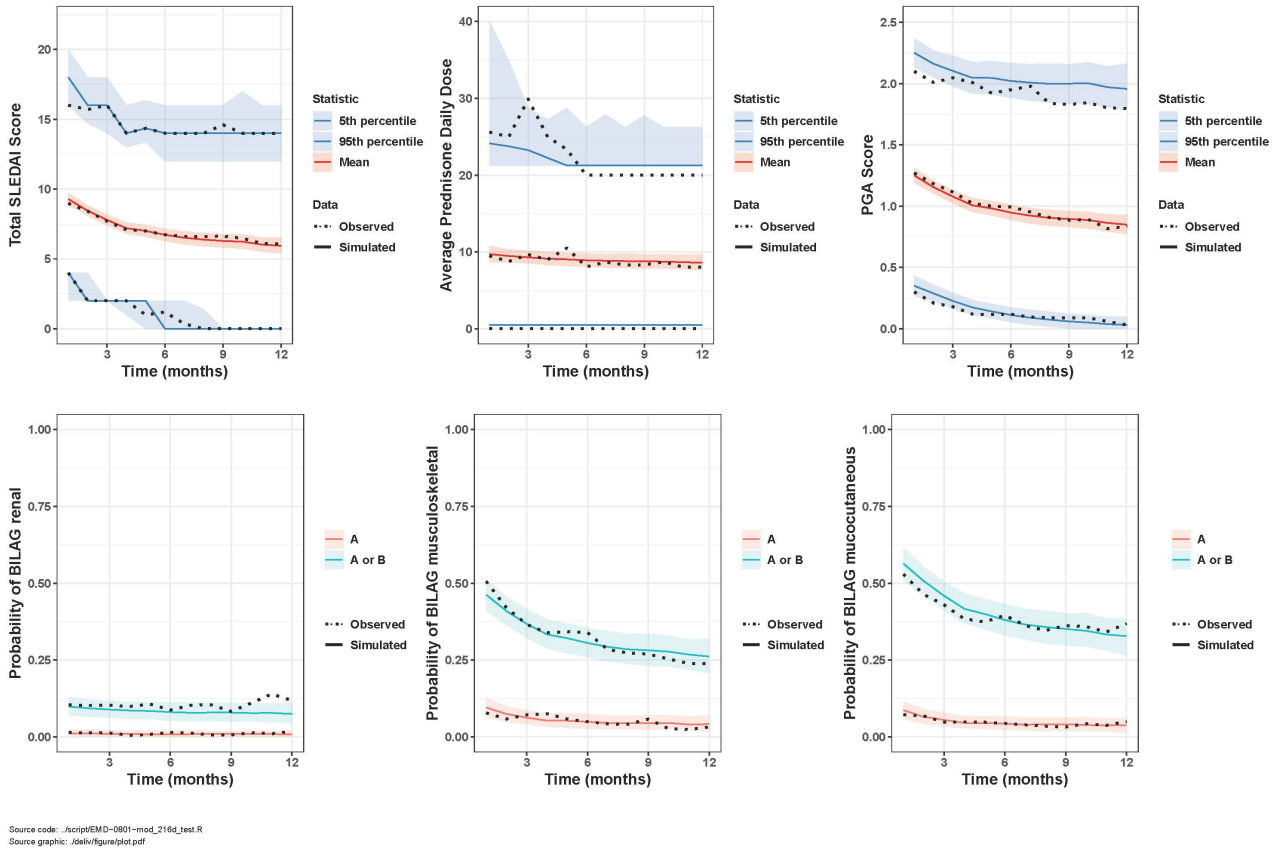
ARTICLE

Disease trajectory of SLE clinical endpoints and covariates affecting disease severity and probability of response: Analysis of pooled patient-level placebo (Standard-of-Care) data to enable model-informed drug development

Kosalaram Goteti[1] | Jonathan French[2] | Ramon Garcia[2] | Ying Li[1] | Florence Casset-Semanaz[1] | Aida Aydemir[1] | Robert Townsend[1] | Cristina Vazquez Mateo[1] | Matthew Studham[1] | Oliver Guenther[3] | Amy Kao[1] | Marc Gastonguay[2] | Pascal Girard[4] | Lisa Benincosa[1] | Karthik Venkatakrishnan[1]

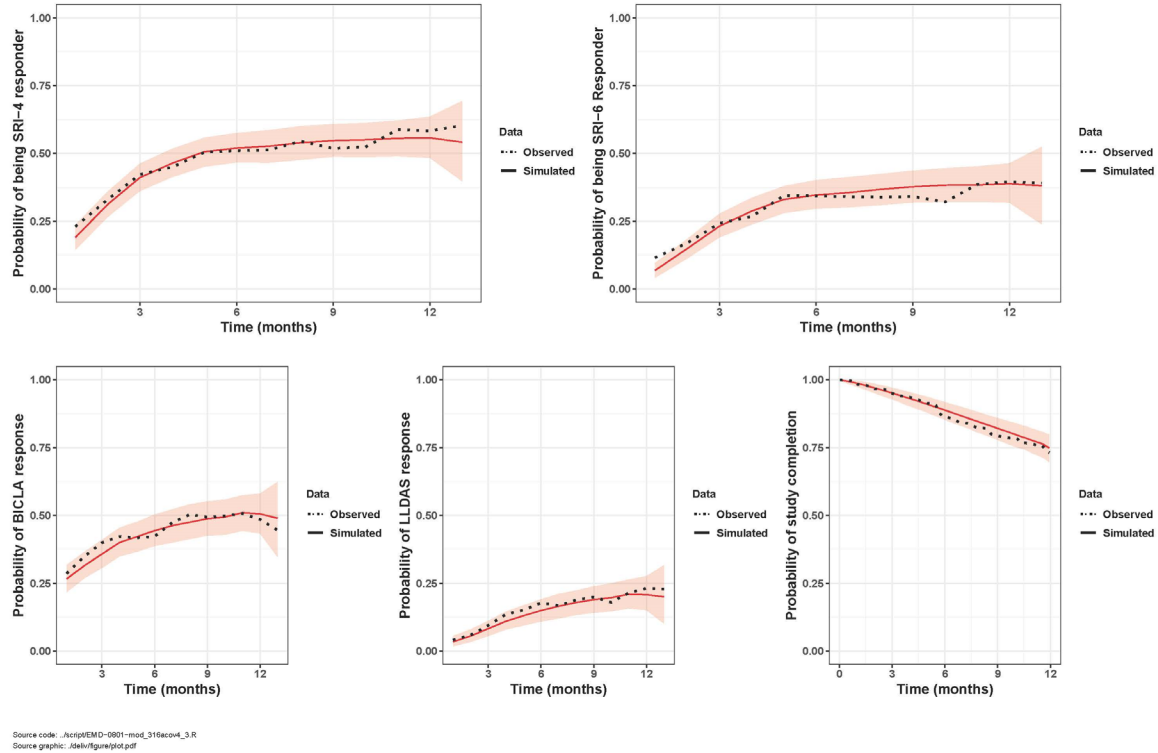
1 Longitudinal Profiles for Test Data were well described by the Final Model for component and composite

Component Scores



Source code: ../script/EMD-0801-mod_216d_test.R
Source graphic: ./deliv/figure/plot.pdf

Composite Scores



Source code: ../script/EMD-0801-mod_316acov4_3.R
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Visual predictive checks showed that latent Variable Model predicted both the Component & Composite Scores well for the median, 5th and 95th percentiles of the observed data

How might these analyses change development approach?

Results:
Across all endpoints , in prediction up to 52 w , from the final disease trajectory model, there were **covariates associated with a greater decrease in SLE disease activity and higher response to placebo+SOC.**

Across all endpoints, disease trajectory showed no difference in Asian versus non-Asian patients, supporting Asia-inclusive global SLE drug development.

- Patient enrollment strategies based on the identified covariates may improve SLE proof-of-concept trial designs to maximize success rates

- Consistency in disease trajectory in Asian versus non-Asian patients supports Asia-inclusive multiregional clinical trials, whereas the other identified covariates may inform appropriate randomization stratification factors in pivotal SLE trials.

2

Use case 2 : Multiple Sclerosis

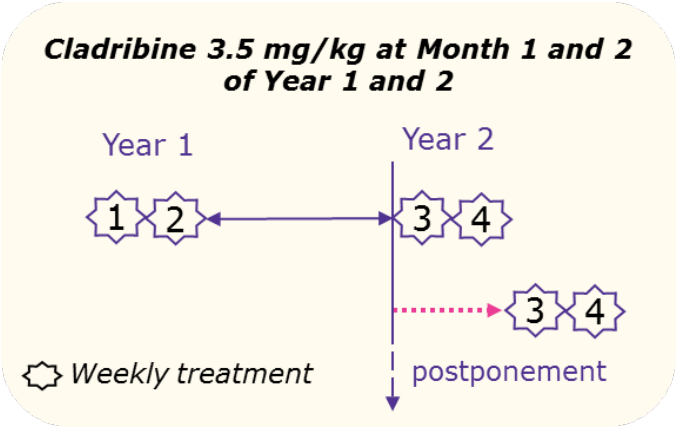
Modelling and Simulation to support Compound Treatment guidance

2 Question: how to manage the risk of lymphopenia expected due to MoA of new Treatment through different treatment guidance?

- The New Treatment -induced drop in lymphocyte counts is recovered within one year of treatment in the vast majority of patients.

- A minority of subjects having slow recovery can develop Grade 3/4 lymphopenia especially those treated when their absolute lymphocyte counts (ALC) were already at Grade 2 or worse.

Proposed Risk Minimization: treatment guidelines



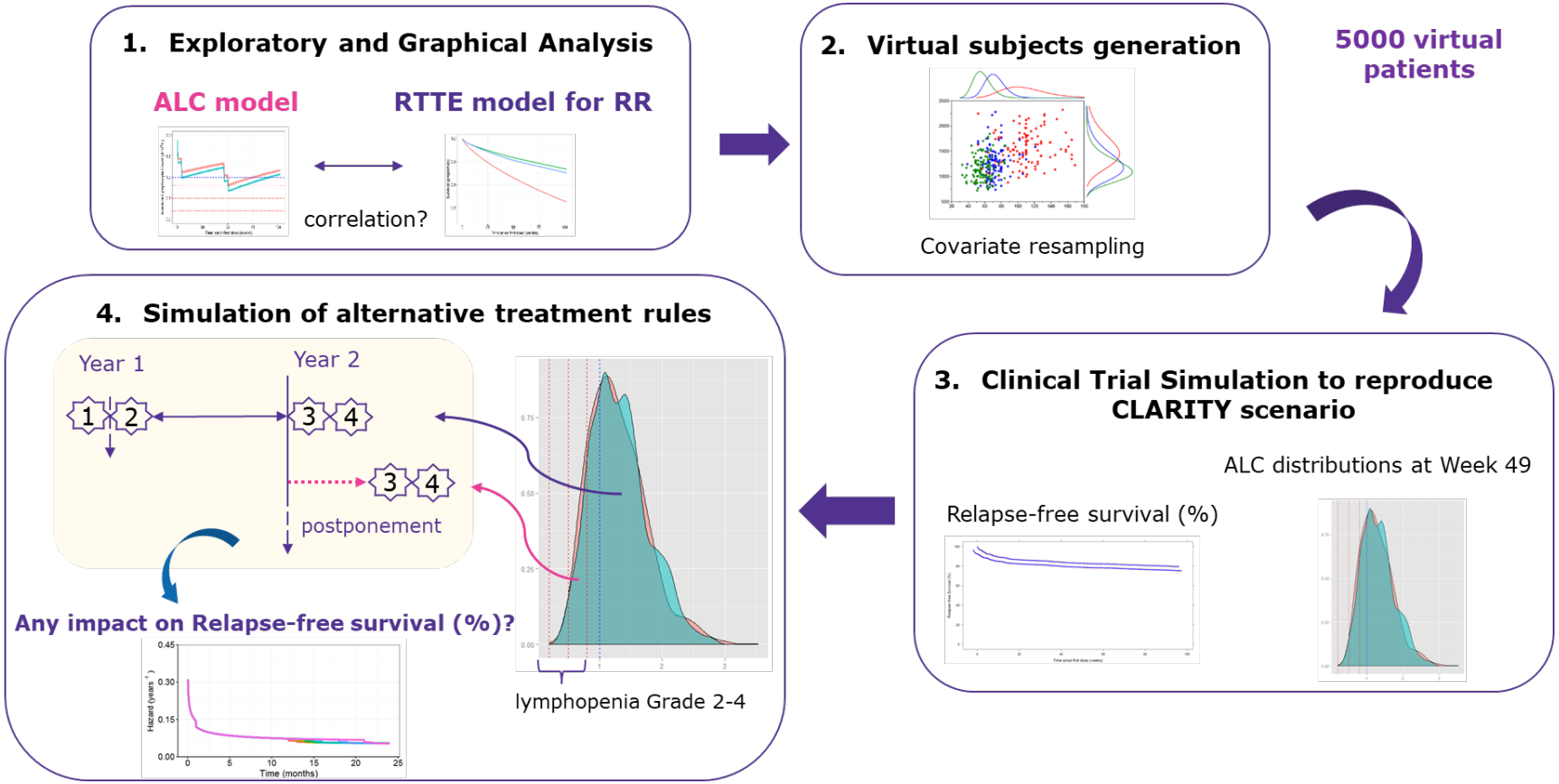
Alternative rules*:*

Treatment postponements during Year 2 allowed in blocks of 1/2/3 months in patients with lymphopenia Grade 2-4 or 3-4.

- *If, after three postponements, a patient's ALC value had not recovered to Grade 0/1, the treatment would stop*

2 Approach : Assess the impact of treatment guidelines on the occurrence of relapses through clinical trial simulations

Clinical trial **simulations** to investigate the effect of delaying year 2 treatment until ALC back to grade 1, but no longer than 6 months:



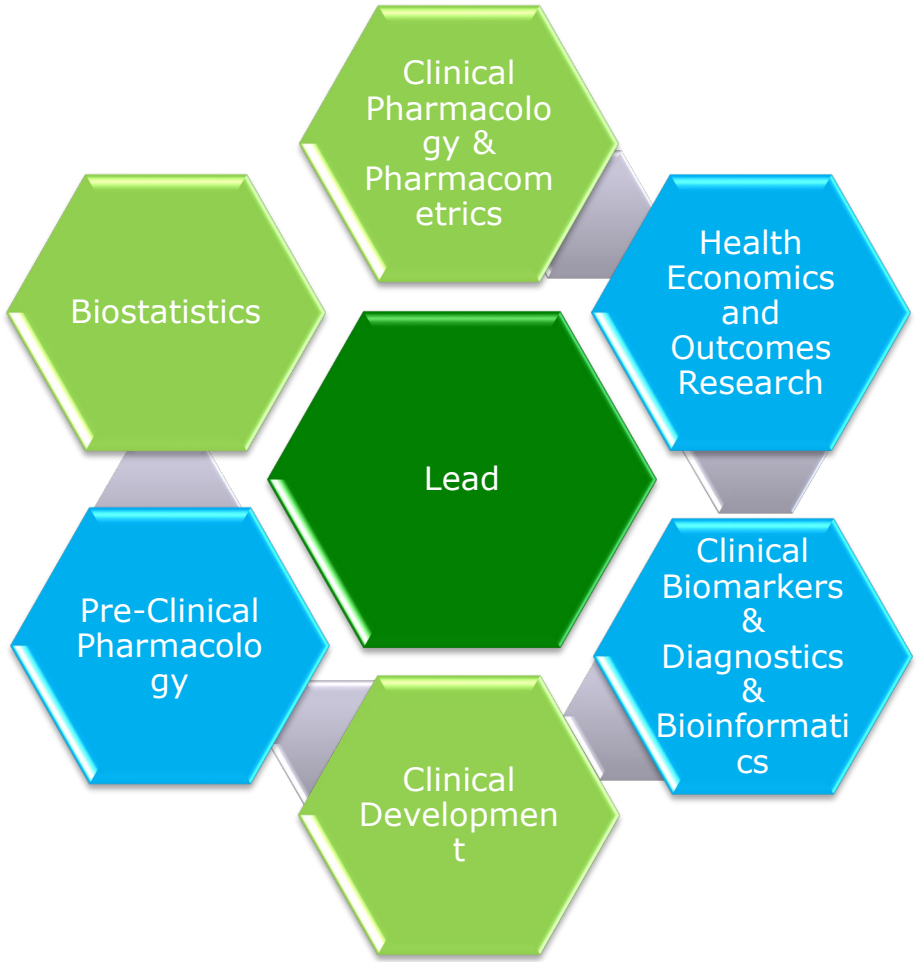
Terranova N. et al. "Effects of postponing treatment in the second year of cladribine administration: clinical trial simulation analysis of absolute lymphocyte counts and relapse rate in patients with relapsing-remitting multiple sclerosis. "Clinical pharmacokinetics 58.3 (2019): 325-333.

Results: Postponing Year 2 treatment is an appropriate risk mitigation measure

- Results were similar across considered scenarios, which implemented different postponement durations.
- 92% of virtual subjects did not require treatment postponement and < 1% discontinued due to Grade 2–4 lymphopenia at the end of the maximally permitted postponement.
- Less severe lymphopenia was observed during year 2 when a treatment algorithm was applied.
- The effect on relapse rate over 2 years was negligible.

- **Impact : Label change**

2 Cross-Functional Team to integrate the MS compound clinical data to address the research question



- Data source: internal MS Compound Clinical trials with Long term data
- Population targeted (Simulation Framework)
- Derivation rules for endpoints (relapses)
- Missing pattern and imputation
- Medical and Pharmacology input for MS expertise
- Interpretation of models and results (reproducibility)

To enable multi-disciplinary **integration of disease area knowledge, pharmacometrics, Clinical Pharmacology and statistical expertise**.

Conclusion - Some key messages

- **Collaboration** between all Quantitative Sciences disciplines is key to increase **Proba of success in Drug dev** (to manage risk for the patients and to get quicker access to the treatment for specific populations)

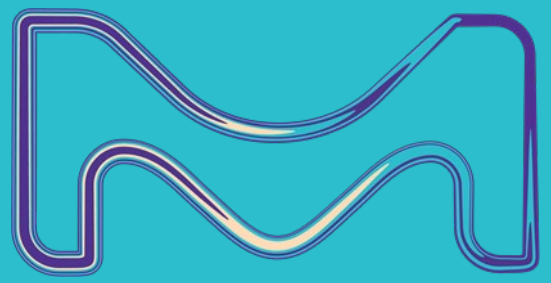
- Quantitative functions share common themes (**causal inference**, **Estimands**, **reproducibility**...) and it should help the understanding behind analyses.

- Key to share experiences/expertise to leverage data available on a **continuous** manner and to assess **which source data fit for purpose**

- **Totality of Evidence Mindset** to integrate data and iterative approaches based on partnership and collaboration, understand the language of each expertise →to foster innovation
- **Current directions**: Integrate **more AI** for indication selection/ prioritization , use of RWD , Synthetic control arm….

THANK YOU !

Acknowledgement to my colleagues :
Kosalaram Goteti; Ying Li and Nadia Terranova



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