Data space and regulatory decision making

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Statens legemiddelverk

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Outline

1. Questions
2. Data space
3. Regulatory decision making

Questions

Developer

Is there an intervention we can develop to treat such patients?

An existing intervention we could use if we knew a bit more about it?

Prescriber

What is causing this patients symptomes and how can I help him/her?

Patient/Carer

Is this something I should worry about –

Should I do something?
Should I see a physisian?

Regulator

Can this medicinal product be allowed access to the market?

Which conditions of use?

Regulatory decision making

Regulators

Are the risks outweighted by the benefit?

What are the benefits – what is the efficacy, the effect size?

- Which method was used to establish efficacy? Credible? What are the uncertainties?

What are the risks – which adverse events, frequency, severity, QoL etc..

- Which methods used to establish the safety profile? Credible? What are the uncertainties?

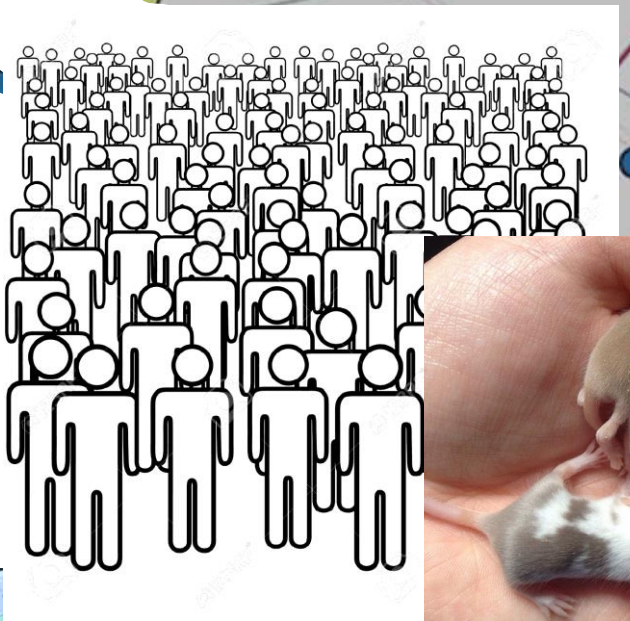
And so on…

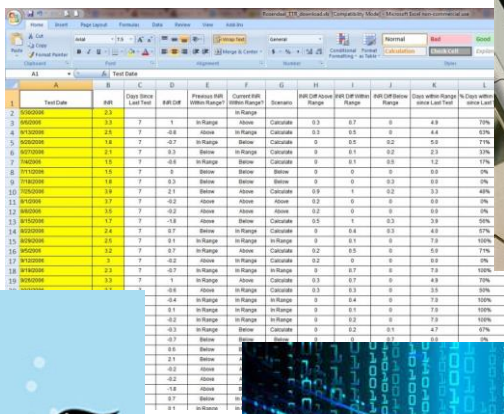
quality of drug substance and formulation,
dosing regimen,
patient information etc

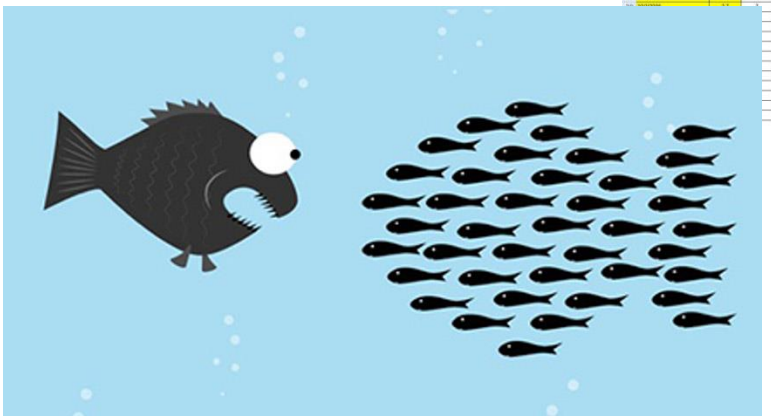
Data space

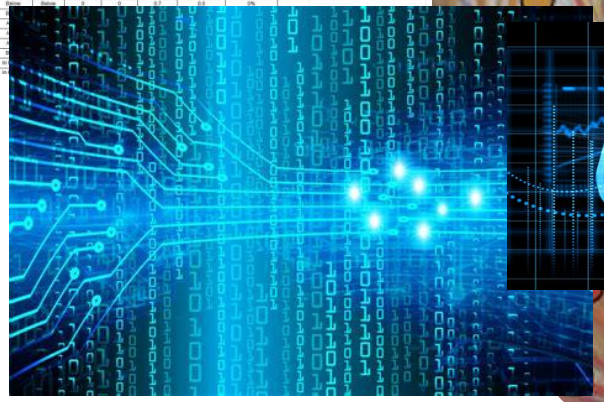
- What does data look like?

- What data do we need?
- What data can we get?
- …

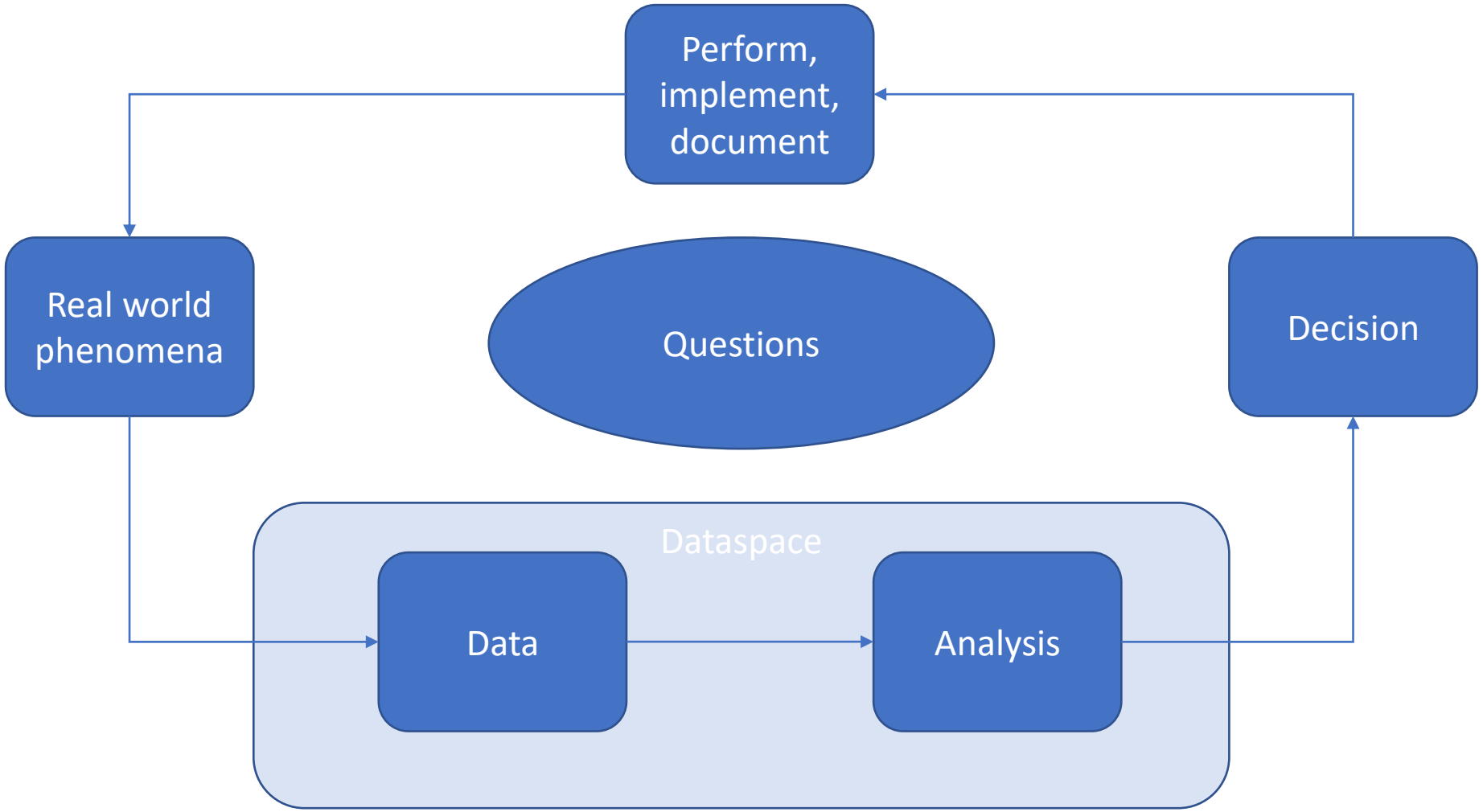




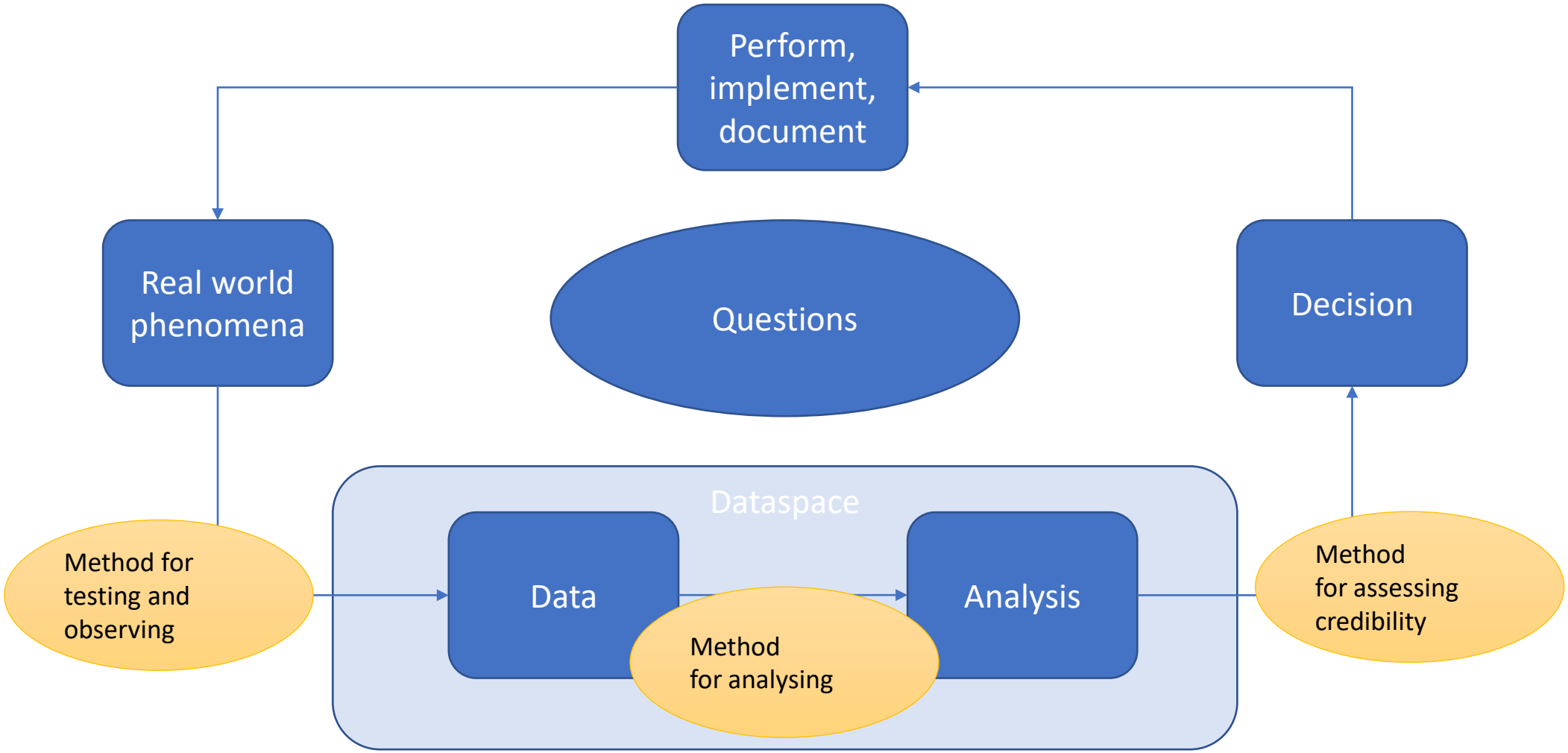




Real world phenomena

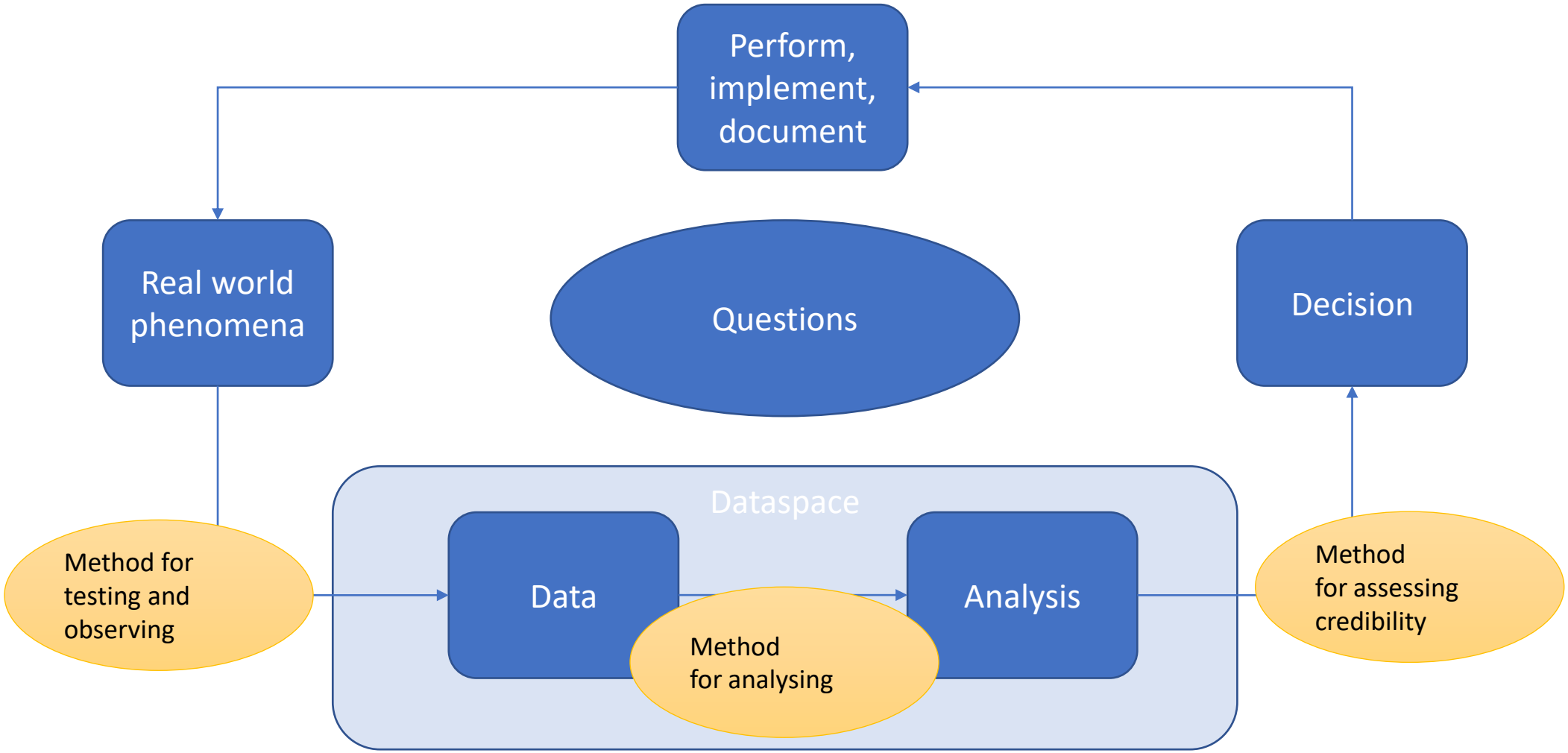


Real world phenomena



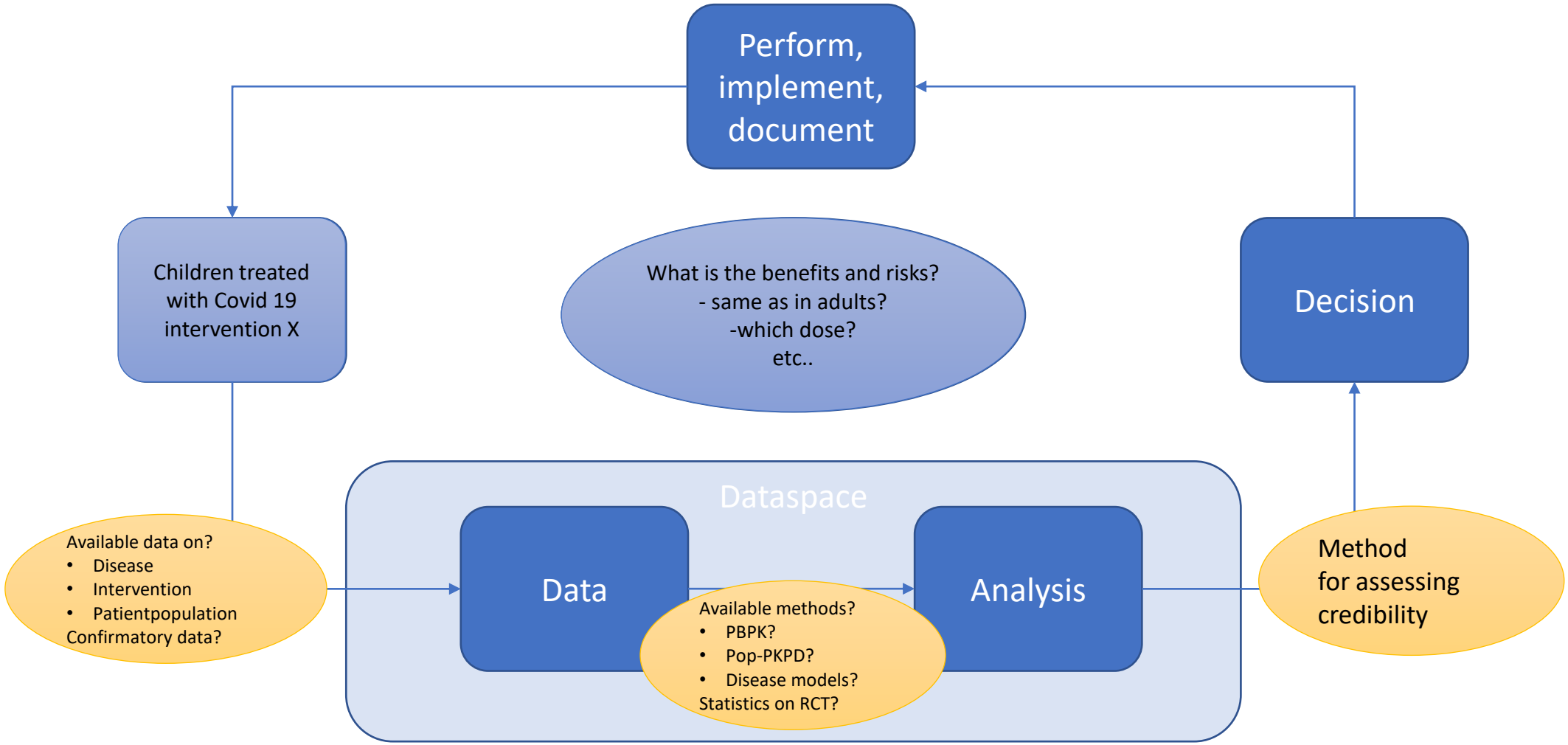
Credibility of the methods

Real world phenomena



Example

Real world phenomena



Credibility matrix

Credibility matrix	Description
Investigational product	…
Type of model	
Scientific question(s) of interest	
Context of use	
Regulatory impact	
Risk based analysis of decision consequence	
Requirements on the credibility activities	
Credibility evidence	
Model informed decision	

Ref: Skottheim Rusten and Musuamba. Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework. CPT Pharmacometrics Syst Pharmacol. 2021 Nov;10(11):1281-1296.

References on credibility assessment

Publications	Comment
Musuamba et al. Scientific and regulatory evaluation of mechanistic in silico drug and disease models in drug development: Building model credibility. CPT Pharmacometrics Syst Pharmacol. 2021 Aug;10(8):804-825.	**Mechanistic disease models, such as QSP**
Skottheim Rusten and Musuamba. Scientific and regulatory evaluation of empirical pharmacometric models: An application of the risk informed credibility assessment framework. CPT Pharmacometrics Syst Pharmacol. 2021 Nov;10(11):1281-1296.	**Empirical pharmacometric models such as pop-PKPD** Quick start tables
Kuemmel et al. Consideration of a Credibility Assessment Framework in Model-Informed Drug Development: Potential Application to Physiologically-Based Pharmacokinetic Modeling and Simulation. CPT Pharmacometrics Syst Pharmacol. 2020 Jan;9(1):21-28.	**PBPK models**
ICH. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1). 2019	Estimand framework. In a sense a credibility framework for **confirmatory RCTs** – «how we estimate what we want to know»
European Medicines Agency. Concept paper on extrapolation of efficacy and safety in medicine development. EMA/129698/2012. (2013). European Medicines Agency. Adopted reflection paper on the use of extrapolation in the development of medicines for paediatrics - Revision 1. EMA/189724/2018. (2018)	**Extrapolation** concept as a framework for using existing knowledge
The American Society of Mechanical Engineers. Assessing Credibility of Computational Modeling through Verification and Validation: Application to Medical Devices (American Society of Mechanical Engineers, New York, 2018).	A V&V standard for **medical devices** (V&V40) - introducing a risk informed credibility assessment framework
Council NR. *Assessing the Reliability of Complex Models: Mathematical and Statistical Foundations of Verification, Validation, and Uncertainty Quantification.* The National Academies Press: Washington, DC, 2012.	Same mindset on credibility activities (V&V)

In summary

Data & decisions do not exist in a vacum

Contextualization important
for understanding credibility

Which questions do we need answered
and which methods to use?

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