From Risk Assessment to Optimal Regulatory decision:

First Having the Question Right

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- From data driven to Question centric approach in decision making
- Question-driven uncertainty Quantification:

  From the « What » to the « How »

Insight from the ICH M15

Risk-based approach in model assessment

MIDD Assessment Framework (ICH M15)

Patient Risk and Regulatory Impact Assessment Framework	
Question of Interest	
Context of Use (COU)	
Consequence of wrong decision	Model Influence
Model Risk	
Model Impact	

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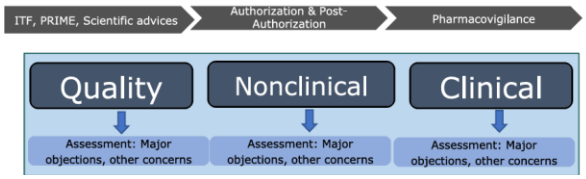
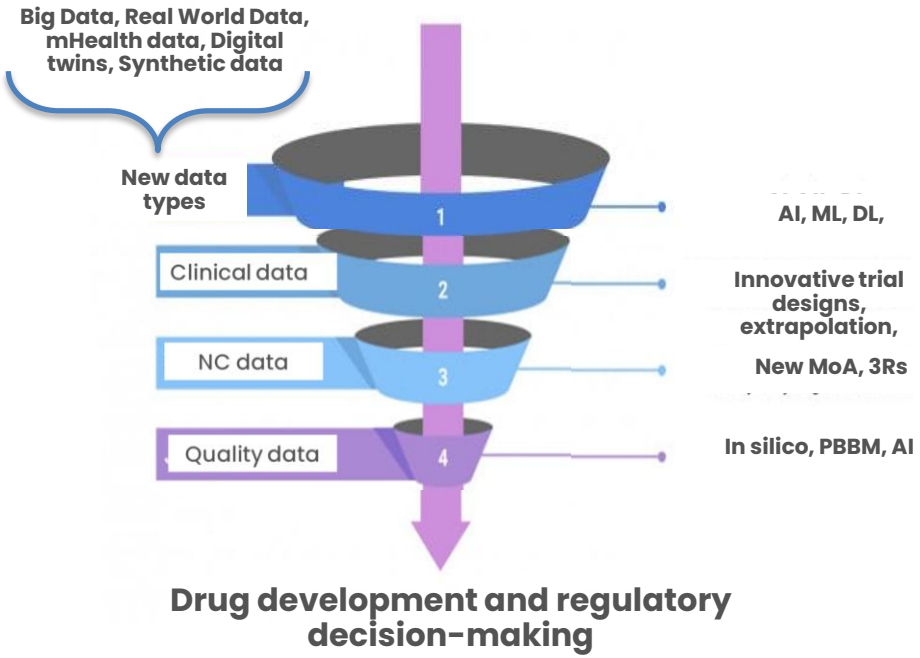
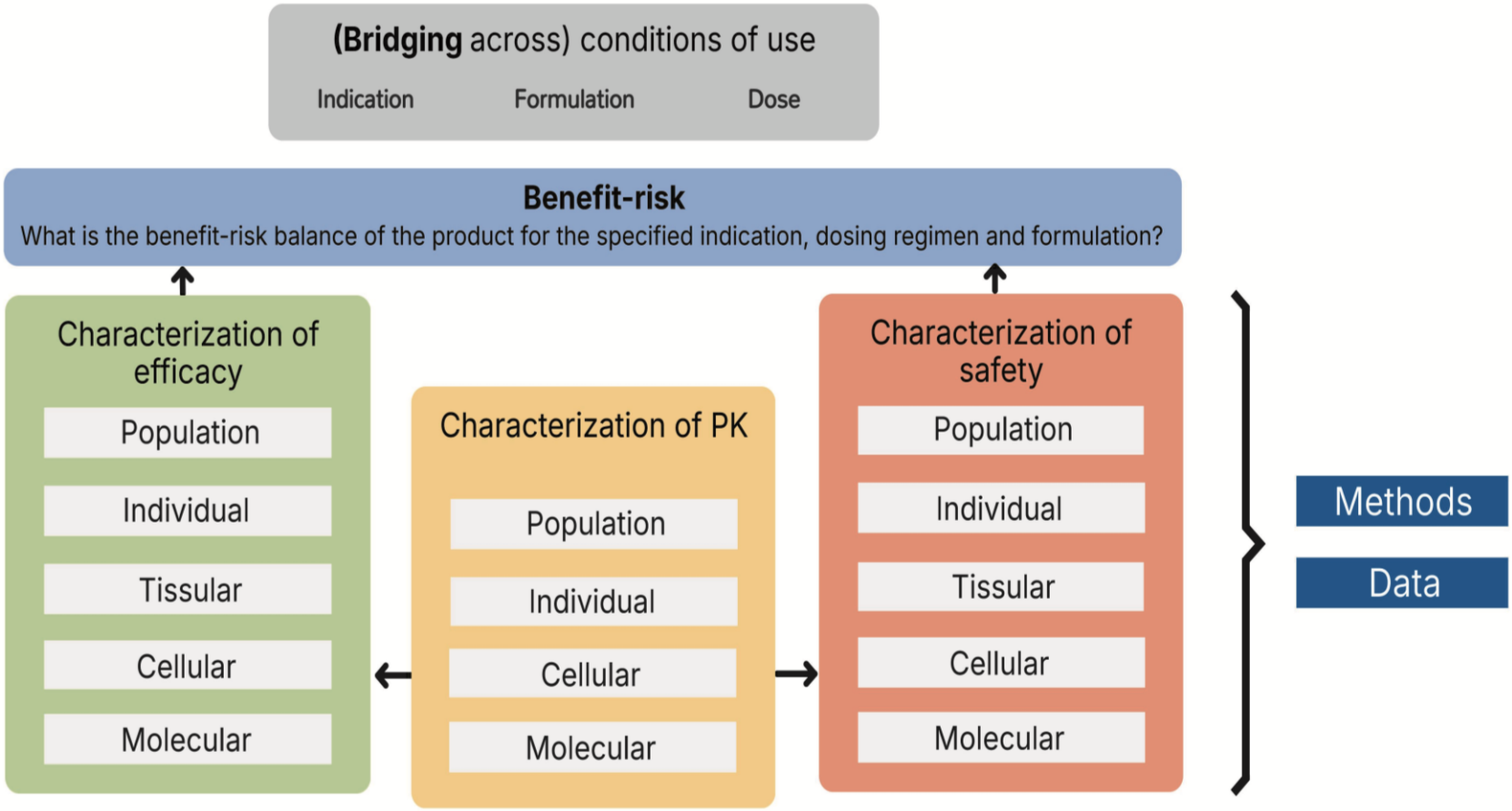
Decision-making Framework
Appropriateness of the proposed approach
Technical Criteria
Model evaluation
Final Decision (Answer to the Question of Interest)

From data-driven to Q-centric approach



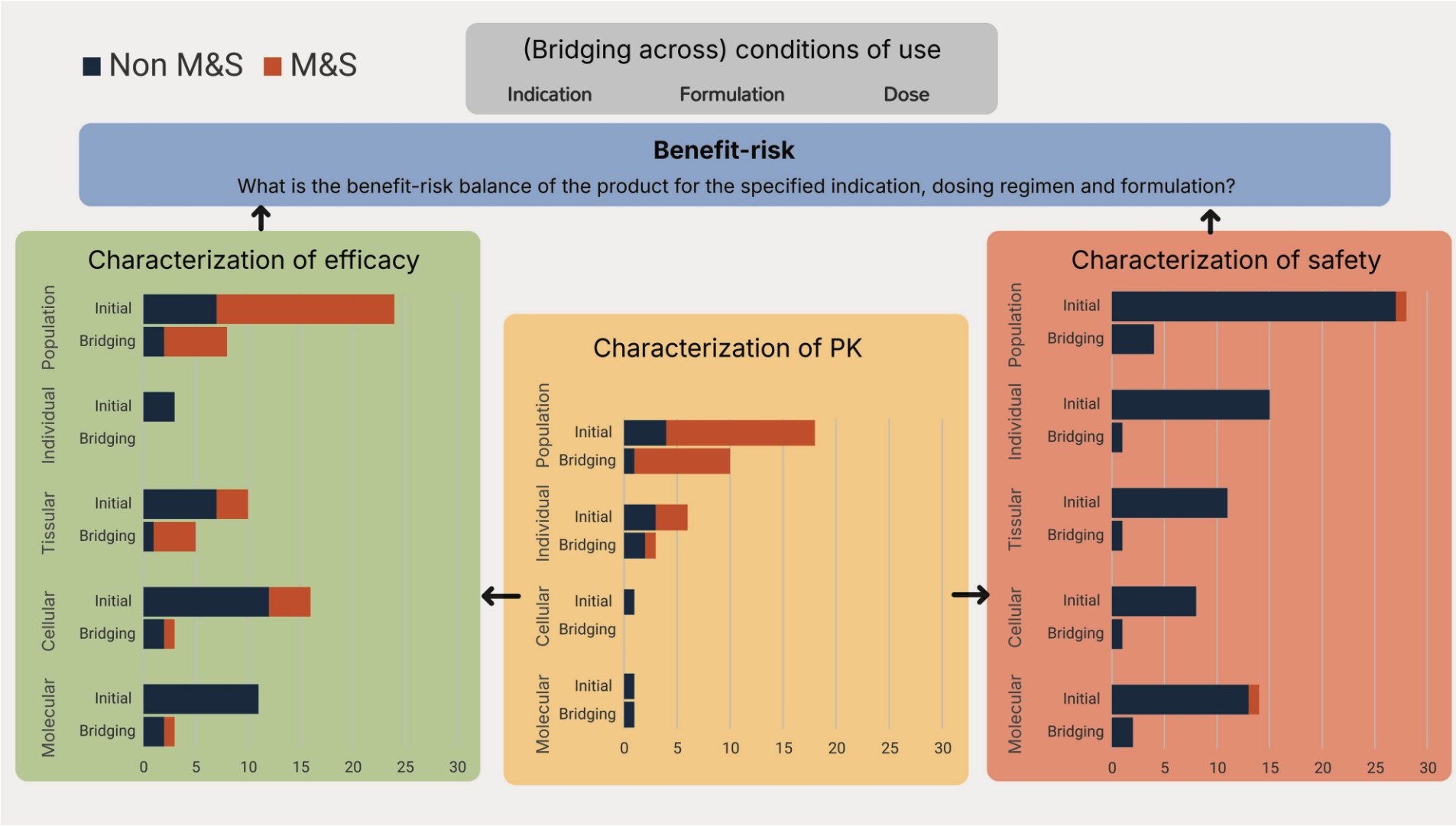


From data-driven to Q-centric approach

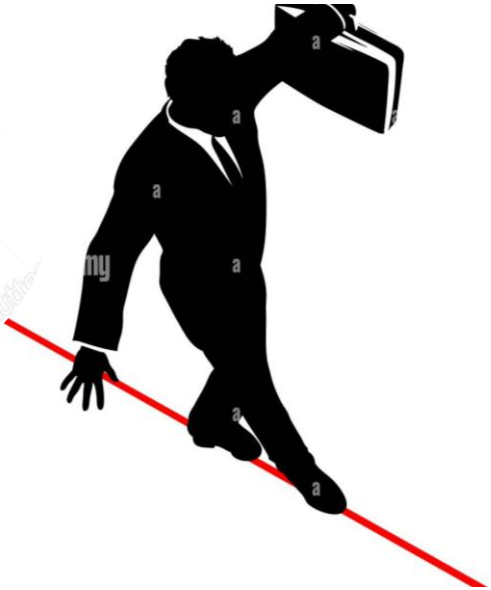


From data-driven to Q-centric approach

Example of Mabs drug development in Asthma



Question-driven uncertainty quantification



… From the « What » to the « How »

Q-driven uncertainty quantification

Credibility Assessment Framework (ICH M15)

Patient Risk and Regulatory Impact Assessment Framework	
Question of Interest	
Context of Use (COU)	
Consequence of wrong decision	Model Influence
Model Risk	
Model Impact	

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Decision-making Framework
Appropriateness of the proposed approach
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Assumptions and Uncertainty characterization/Quantificatio

Q-driven uncertainty quantification

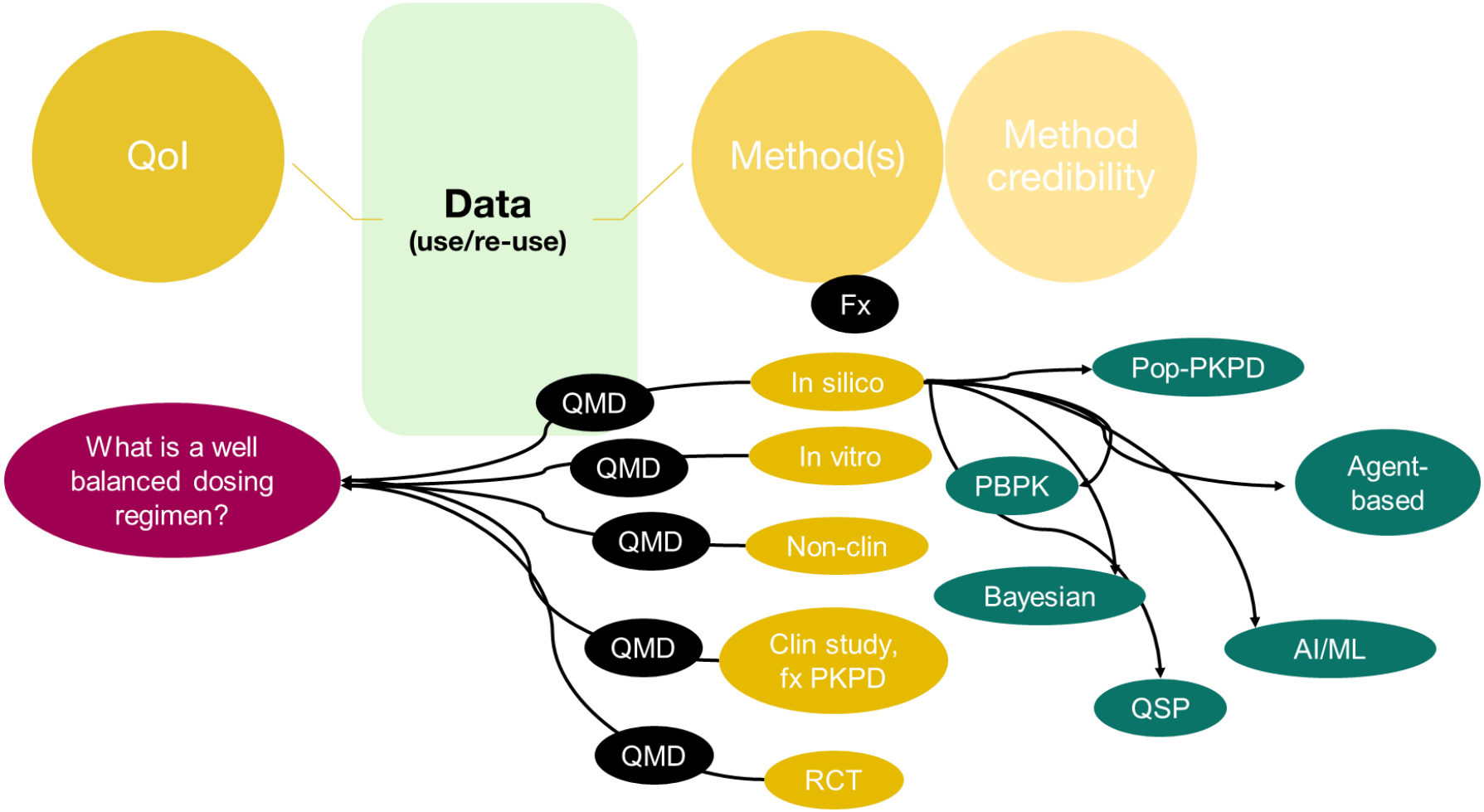
Example of Mabs drug development in Asthma

Question	Drug 1	Drug 2	Drug 3	Drug 4	Drug 5	Use of M&S
How inter-individual factors contribute to variations in PK?	popPK MA	popPK	popPK	popPK + non-M&S	popPK	1
What is the impact of comedication on PK exposure?	popPK	popPK	popPK + non-M&S	popPK	popPK	1
What is the impact of demographics on PK exposure?	dose-reponse popPK MA + non-M&S	popPK + non-M&S	popPK + non-M&S	popPK + non-M&S	Non-M&S	4/5
Which disease characteristics influence the efficacy?	Non-M&S	Non-M&S	E-R + non-M&S	E-R + non-M&S	Non-M&S	2/5
What is the PK profile in adolescent (12-18 years)?	popPK	Non-M&S	NA	Non-M&S	popPK	2/5
What is the dose-exposure response?	NA	NA	E-R	NA	PK/PD	2/5
Should the dose be flat or adjusted based on individual factors?	NA	popPK + non-M&S	NA	Non-M&S	popPK	2/5
Is the PK exposure influenced by the condition of injection?	Non-M&S	Non-M&S	Non-M&S	popPK	NA	1/5
What is the clinical efficacy of the product in adolescent (12-18 years)?	Non-M&S	Non-M&S	NA	E-R + non-M&S	NA	1/5
What is the relationship between biomarkers and clinical outcome?	Non-M&S	Non-M&S	Non-M&S	NA	PK/PD	1/5

Table 1. Examples of questions answered by M&S methods in marketing authorization application for the biologics approved for asthma treatment.

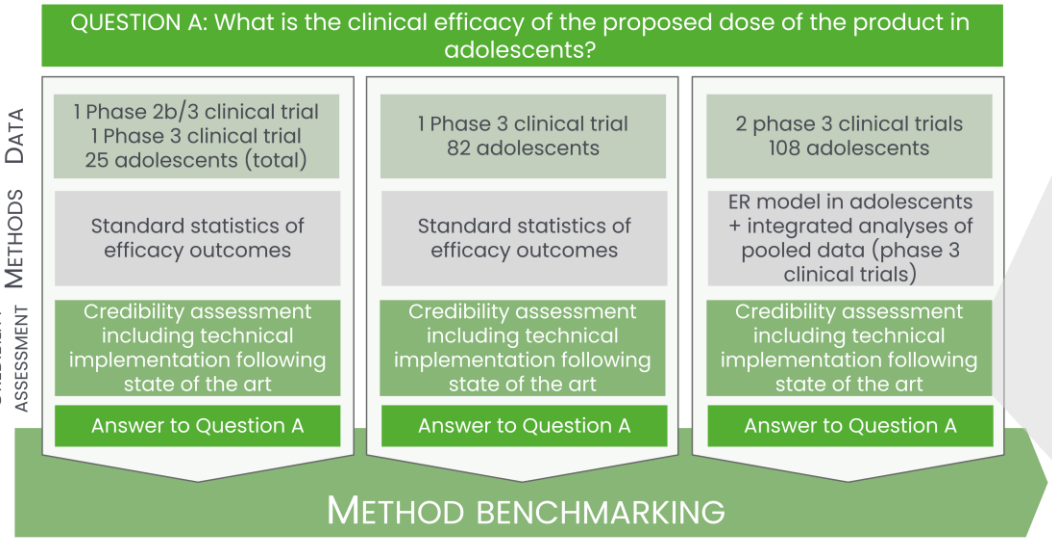
Q-driven uncertainty quantification

Need for Multidisciplinary braintorming



Q-driven uncertainty quantification

Example of Mabs drug development in Asthma



Question of Interest	What is the clinical efficacy of the proposed dose of the product in adolescents (12-17 years)?
Context of Use	Exposure-response (E-R) model informing about the clinical efficacy (i.e. exacerbation rate) of a biologic in adolescents (12 to 17 years) with asthma. The E-R model is built using 2 clinical efficacy/safety phase 3 studies conducted in adults and adolescents (~100 adolescents).
Model Influence	**Medium**: the projection of the exacerbation rate from this model was complementary of data from 2 phase 3 clinical trials performed in adults and adolescents.
Consequence of Wrong Decision	**High:** a wrong decision could lead to unregulated asthma.
Model Risk	**High:** model influence x consequence of wrong decision
Model Impact	**High:** replace a dedicated clinical trials in adolescents

Need for Multidisciplinary braintorming

Take home message

Question centric approach

…better framed questions get better answers…

Drug development and use question-driven uncertainty

There is a need for:

- A method for mapping knowledge flows
- Compatible with a process description of knowledge and assessment work
- Agnostic to and compatible with scientific domains
- That will open for increased transparency, monitoring and knowledge exhange across stakeholders, regulatory procedures and the life cycle of medicinal products

Multistakeholders and multidisciplinary collaboration is needed