

Setting the scene:

Risk-based analysis of mechanistic models

HMA/EMA workshop on mechanistic models

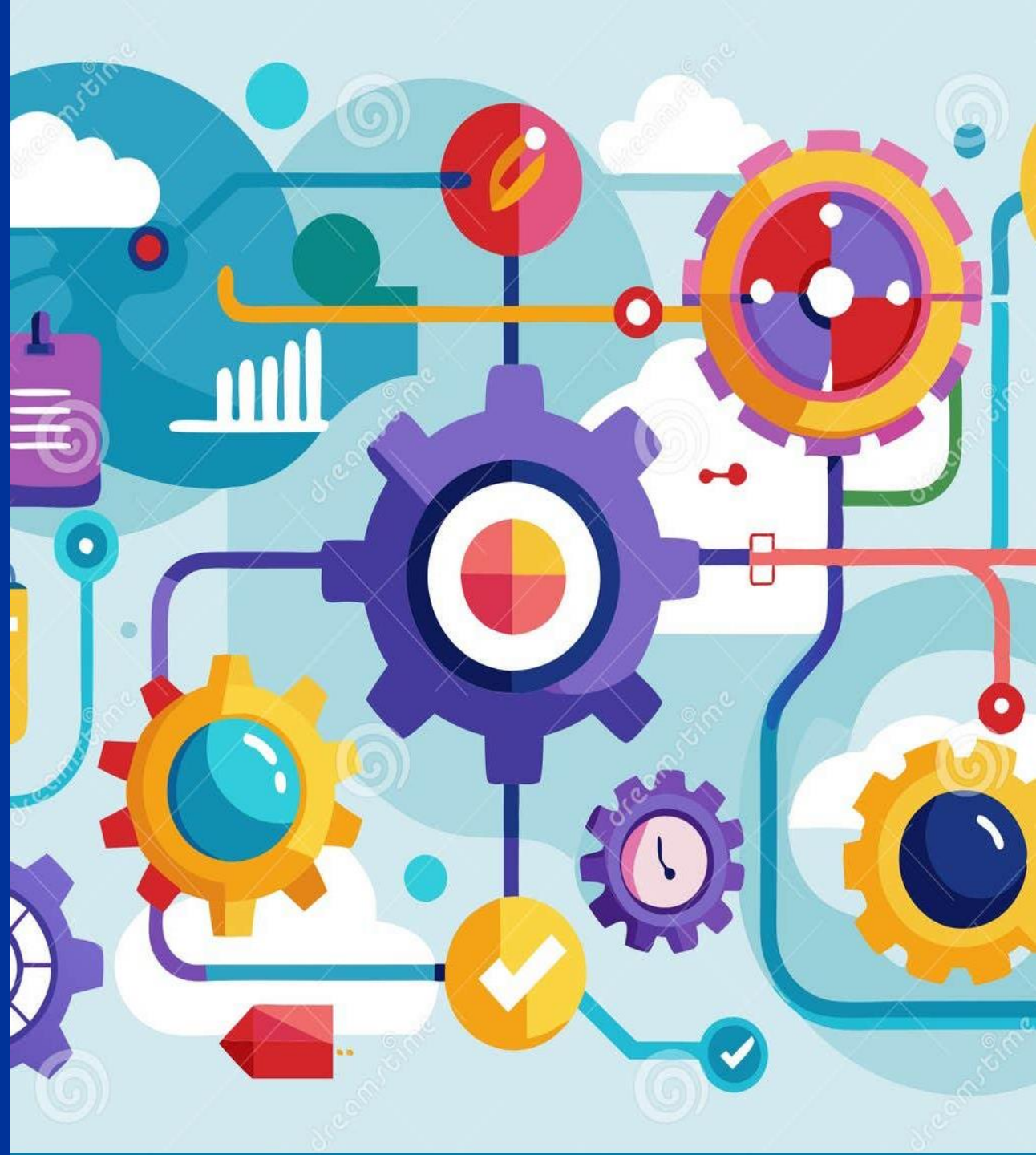
8 October 2025

Setting the scene:

Risk-based analysis of mechanistic models

HMA/EMA workshop on mechanistic models

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Wish list

1

Understand commonalities and specificities of mechanistic models

2

Identify the best paths for regulatory interactions and assessment of mechanistic models

3

Identify the current scientific gaps for regulatory assessment of mechanistic models

4

Identify the needs for guidance and preparedness for optimal assessment of mechanistic model

3

Content

1

**Background:
Value, Potential and Challenges with assessment of Mechanistic model**

2

M15 Risk-based analysis approach, EMA Qualification and Assessment of mechanistic models

3

From Risk-based to technical assessment of mechanistic models

4

Risk-based approaches and guidance for assessment of mechanistic models

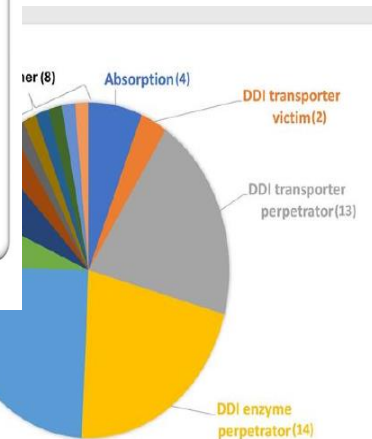
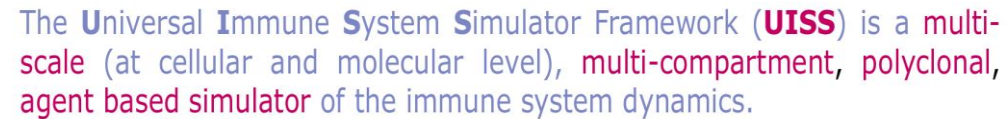
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**Background:
Value, Potential and Challenges with assessment of Mechanistic model**

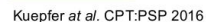
Value and Potential of Mechanistic models

- Mechanistic models such as PBPK , physiologically based biopharmaceutics models (PBBM), and quantitative systems pharmacology/toxicology (QSP/T) models are frequently and increasingly used in all phases of the drug development life cycle.
- Their importance is increasing due to their ability to integrate biopharmaceutical, physiological and pharmacological processes.

Physiologically-Based Biopharmaceutics Models (PBBM)



6 Experience with software platforms qualification for mechanistic models for agent-based modelling approaches:
For radioligand-targeting constructs, tissue exposure is a decisive outcome but it is driven by target & disease specifics usually not covered by platform qualification



Classi

Value and Potential of Mechanistic models

Session 3: Mechanistic models for the future; challenges & opportunities in the context of Model-Informed Drug Development & risk assessment

In this session applications of mechanistic models that are expected to have a high impact in future regulatory submissions will be discussed. Topics covered may include: PBPK for special populations (e.g. pregnancy, lactation, children), QSP for rare diseases, PBBM, other.

Chairs: Michael Berntgen (EMA) & Gaby Wangorsch (PEI)

Introduction by the session co-chairs **10'**

Michael Berntgen (EMA) & Gaby Wangorsch (PEI)

An industry perspective on high impact QSP and QST model applications in clinical drug development in rare diseases **20'**

Anna Sher (GSK)

Experience with software platforms qualification for mechanistic models for agent-based modelling approaches **20'**

Francesco Pappalardo (University of Catania, IT)

Panel discussion **30'**

Value and Potential of Mechanistic models

Session 3: continued

Chairs: Michael Berngten (EMA) & Gaby Wangorsch (PEI)

Opportunities for application of PBPK models in special populations and different modalities

20'

Loeckie de Zwart (J&J, o.b.o. EFPIA/EuropaBio)

The landscape of QSP modeling and Virtual Populations: From current to best practice

20'

Alexander Kulesza (o.b.o. ISoP QSP SIG)

Assessment of mechanistic models: Challenges

- **Technical criteria** for their assessment are **not always well established**
- **Multicomponent** models.
- **Different data sources** from different stages (preclinical and clinical) are combined To develop these models , leading to **multidimensional models** and consequently highly **complex mathematical** framework's able to integrate biopharmaceutical, physiological and pharmacological processes.

Assessment of mechanistic models: Challenges

16:00 Session 2: Evaluation of predictive performance of mechanistic models for regulatory decision making: acceptance criteria, performance metrics, uncertainty quantification

In this session topics related to methods and tools used for platform qualification will be addressed.

Chairs: Pieter Colin (EMA) & Robin Svensson (MPA)

A regulatory perspective on performance verification of mechanistic models - application to PBPK-based DDI predictions **20'**

Pieter Colin (EMA)

Uncertainty quantification methods for complex models used in drug development and/or regulatory approval **20'**

Andrew Hooker (CONFIRMS consortium)

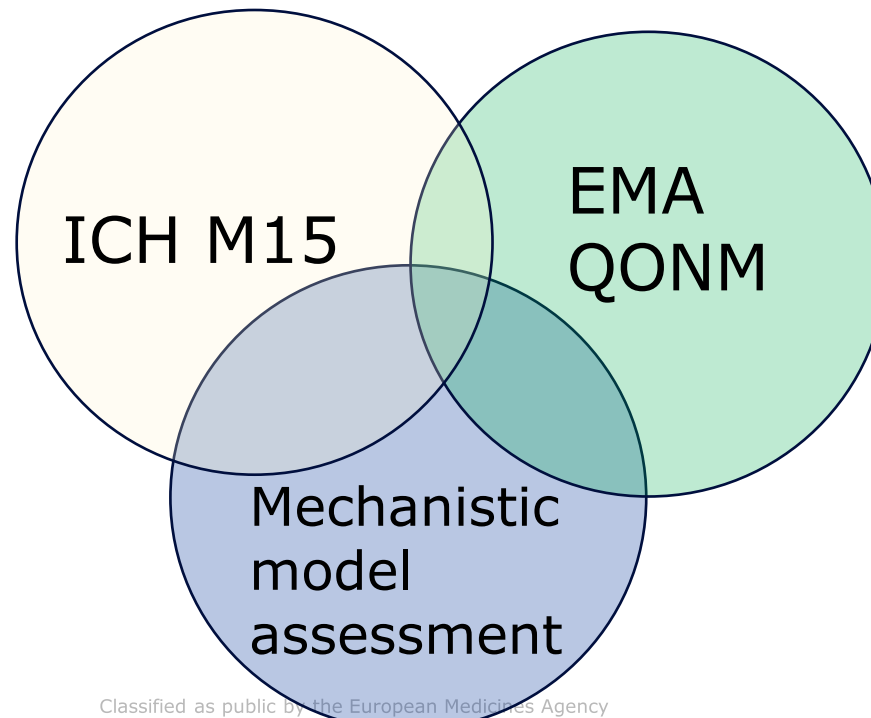
Industry collective experience and discussion from a PBPK working group on the predictive performance of mechanistic PBPK model platform for specific PBPK applications **20'**

Kunal Taskar (GSK, o.b.o. EFPIA)

Panel discussion

30'

M15 Risk-based analysis approach, EMA Qualification (procedure) and Assessment of mechanistic models



EMA Qualification of New Methodologies

QoNM supports the development, validation planning and regulatory qualification of innovative methodologies that fill a gap in evidence generation or offer clear advantages over existing approaches (e.g. feasibility, robustness, patient relevance, or efficiency). Methodologies may pertain to any phase of medicinal product development or lifecycle, including quality development, non-clinical studies, clinical trials, and post-authorisation activities.

- Methodologies should address gaps related to evidence generation or offer advantages or valid alternatives to existing approaches.
- Methodologies should be broadly available to and applicable by medicinal product developers at large. Questions related to application and/or development of novel methodologies for single medicinal product developments can be addressed as part of product-related Scientific Advice requests.
- Qualification proposals must clearly specify (a) well defined context(s) of use (CoU) linked to a well identified question in development and lifecycle of medicinal products and contributing to regulatory decision-making; the ensemble of data space, CoU and method informs a Qualification Opinion.

EMA Qualification of Novel Methodologies

Category	Examples / Context
(Bio) Marker	Prognostic/diagnostic/predictive, can be derived by application of various technologies (e.g. chemical, physical or digital measurements)
Outcome measure	Allows measurement of effects of an intervention, e.g. based on imaging, lab test, patient-/observer-reported outcomes, performance tests
Data source	Patient registries, electronic health data sources
Methodologies for data analysis and decision support	Statistical methods, modeling and simulation methods and approaches, artificial intelligence/machine learning based tools, manufacturing models
Non-clinical methodologies	Organ-on-chip, organoids, in-vitro methods, in-silico methods

Planning and assessment can follow a framework for establishing credibility of a new methodology, e.g. **outlined in the draft ICH M15 guideline for model informed drug development** and should use a risk-based assessment.

EMA Qualification of Novel Methodologies

10:30

Session 1: The qualification of mechanistic models through the EMA qualification framework and beyond.

In this session EMA wishes to interact with its stakeholders on the current landscape around the qualification of mechanistic models to support regulatory decision making. In addition, in the second part of this session, the Agency wishes to discuss with its stakeholders applications that go beyond the current framework.

Chairs: Efthymios Manolis (EMA) & Carolien Versantvoort (MEB)

EU regulatory paths to acceptance of a mechanistic model 10'

Efthymios Manolis (EMA) & Carolien Versantvoort (MEB)

Qualification of the Simcyp platform for CYP-mediated drug-drug interactions: a Certara perspective 20'

Karen Rowland Yeo (CPT Division, Certara UK)

Software Verification, Validation, and Qualification of Open Source M&S Software for Regulatory Use in Translational Model-Informed Drug Development 20'

Stephan Schaller (o.b.o. Open Systems Pharmacology Management Team)

Harmonization of PBPK platform and model qualification for regulatory assessment 20'

Viera Lukacova (SimulationsPlus)

A Pharma industry PBPK perspective on the EMA qualification framework 20'

Neil Parrot (Roche, o.b.o. EFPIA)

Panel discussion 30'

EMA Qualification of Novel Methodologies

13:30

Session 1: continued.

Chairs: Efthymios Manolis (EMA) & Carolien Versantvoort (MEB)

Holistic qualification of mechanistic models in drug development **20'**

Jan-Frederik Schlender (Novartis)

Qualification of the simcyp platform: inter-version qualification bridging **20'**

Masoud Jamei (CPT Division, Certara UK)

Considerations for qualification of Physiologically-Based Biopharmaceutics Models - Beyond the EMA framework **20'**

Xavier Pepin (SimulationsPlus)

Panel discussion **60'**

Additional Panellists:

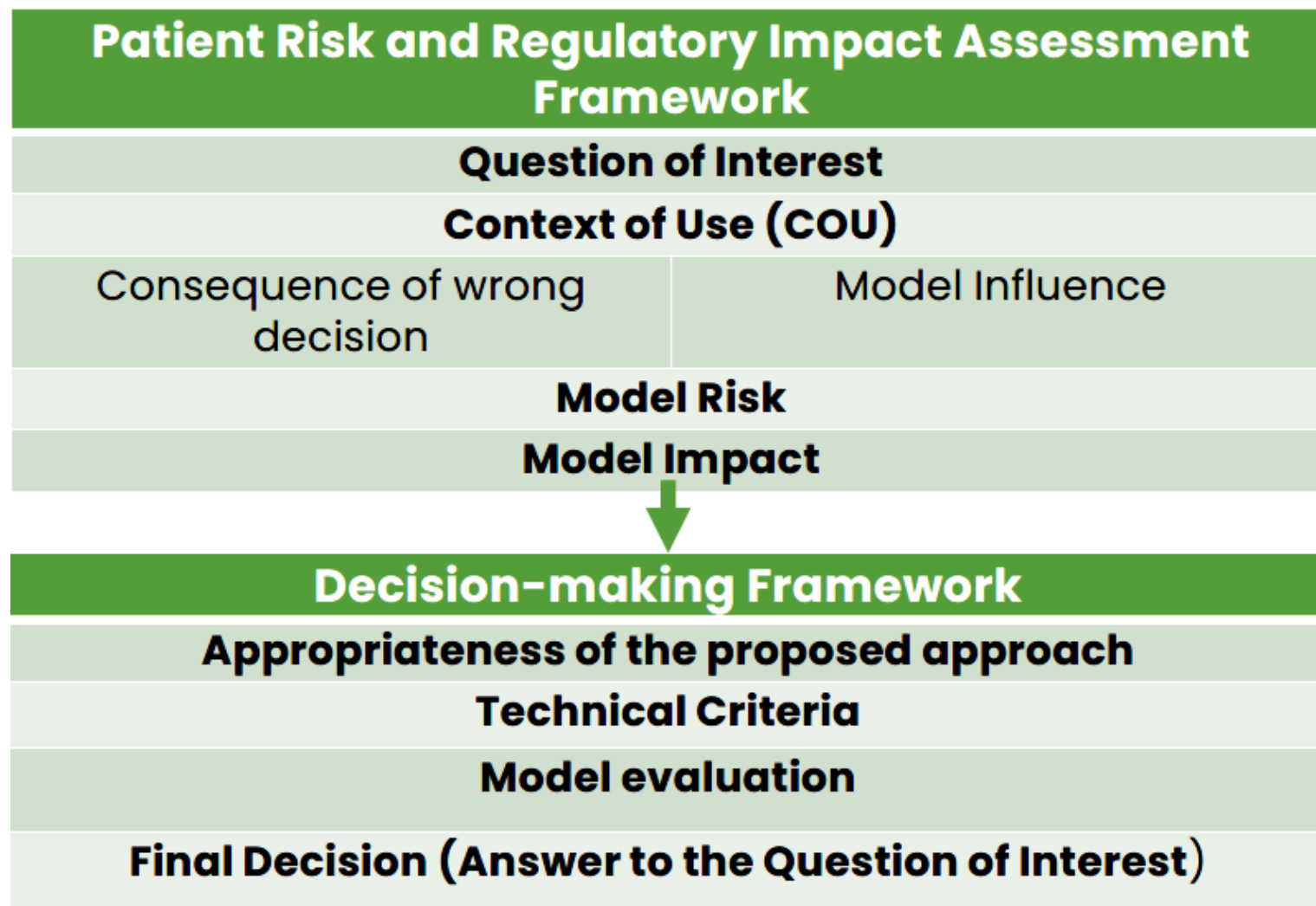
Jörg Lippert (Bayer)

Victor Mangas (AEMPS)

Scott Marshall (representative of ICH M15 WG)

Hao Zhu (FDA)

Risk-based approach for model assessment



Risk-based approach for model assessment



INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL
REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

**GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG
DEVELOPMENT**

M15

Draft version
Endorsed on 06 November 2024

Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections

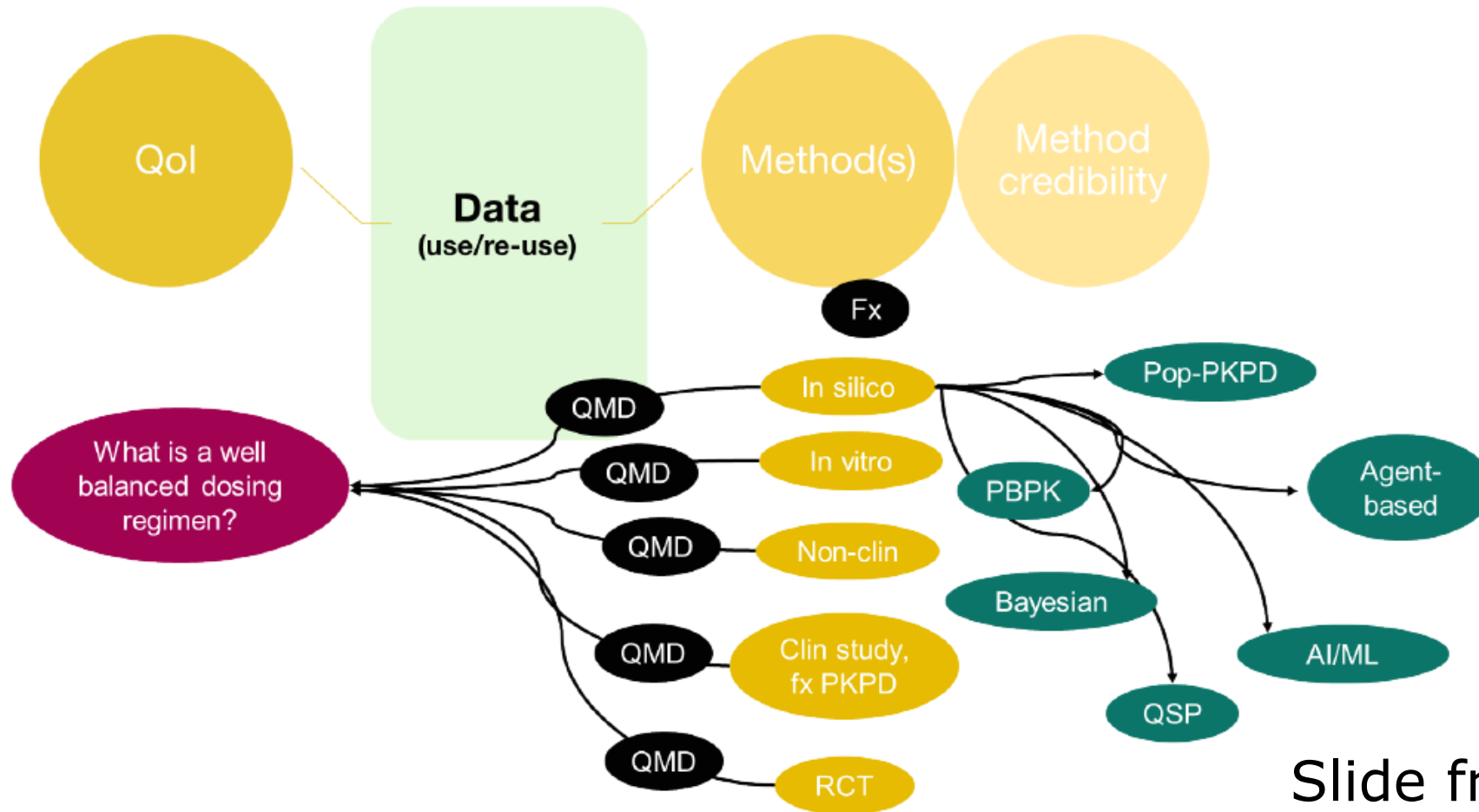
Stages	Planning and Regulatory Interaction		Implementation, Reporting, and Submission		
Sequence of Activities	Key Assessment Elements	Additional Considerations for Interaction with Regulator and to Inform Decision-Making	Model Evaluation	Model Analysis Reporting	Documentation for Regulatory Interactions and Submissions
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes¹ These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.

¹ Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

**Inform
Decision-Making**

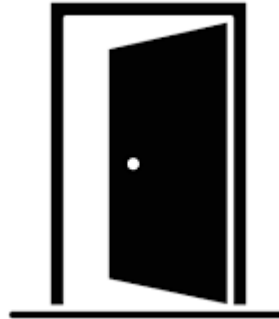
Risk-based assessment of mechanistic models



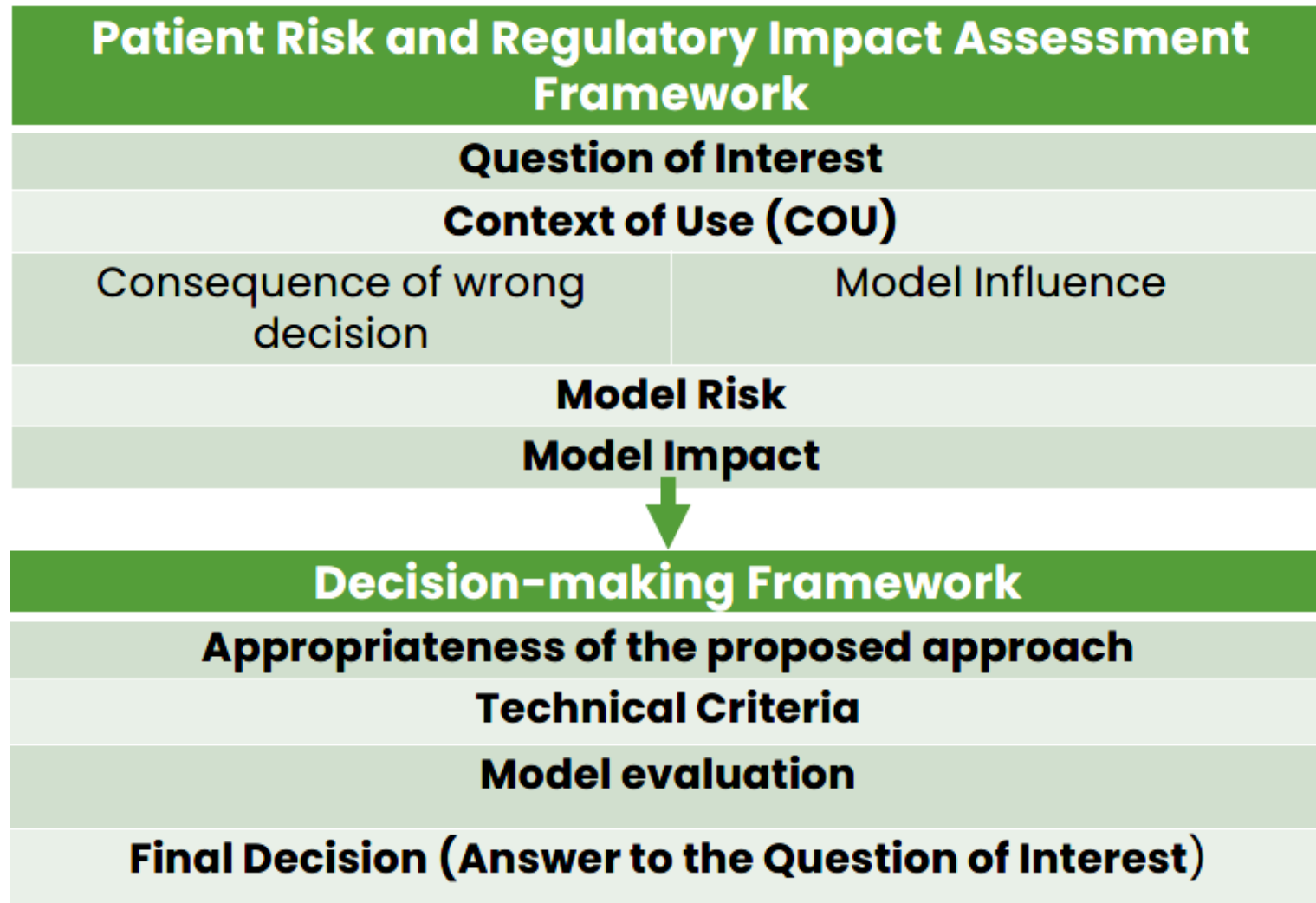
Slide from Ine Rusten

4

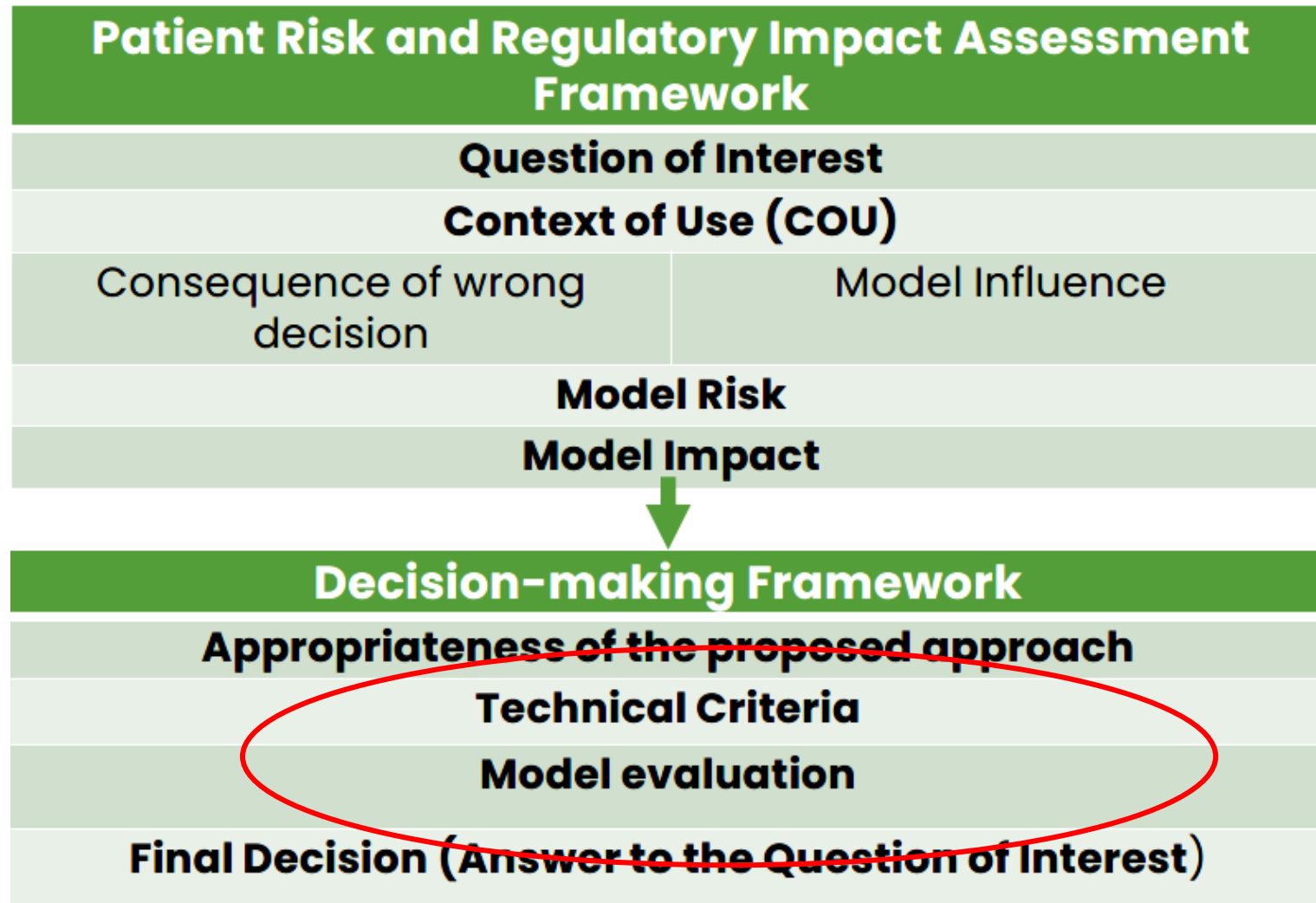
From Risk-based to technical assessment of mechanistic models



From Risk-based approach to technical assessment



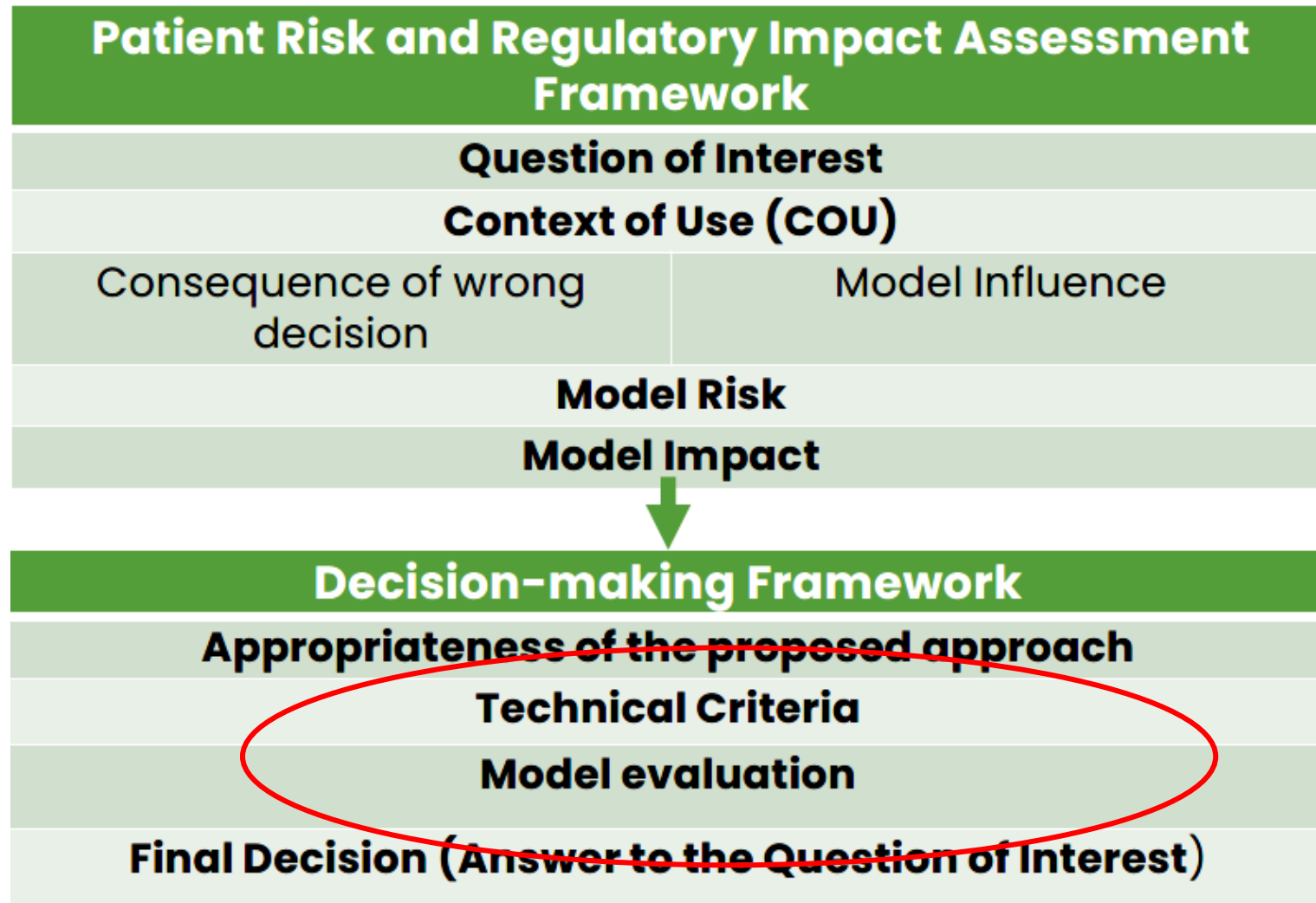
From Risk-based approach to technical assessment



From Risk-based approach to technical assessment

The following topics not to be addressed in the ICH M15 Guideline:

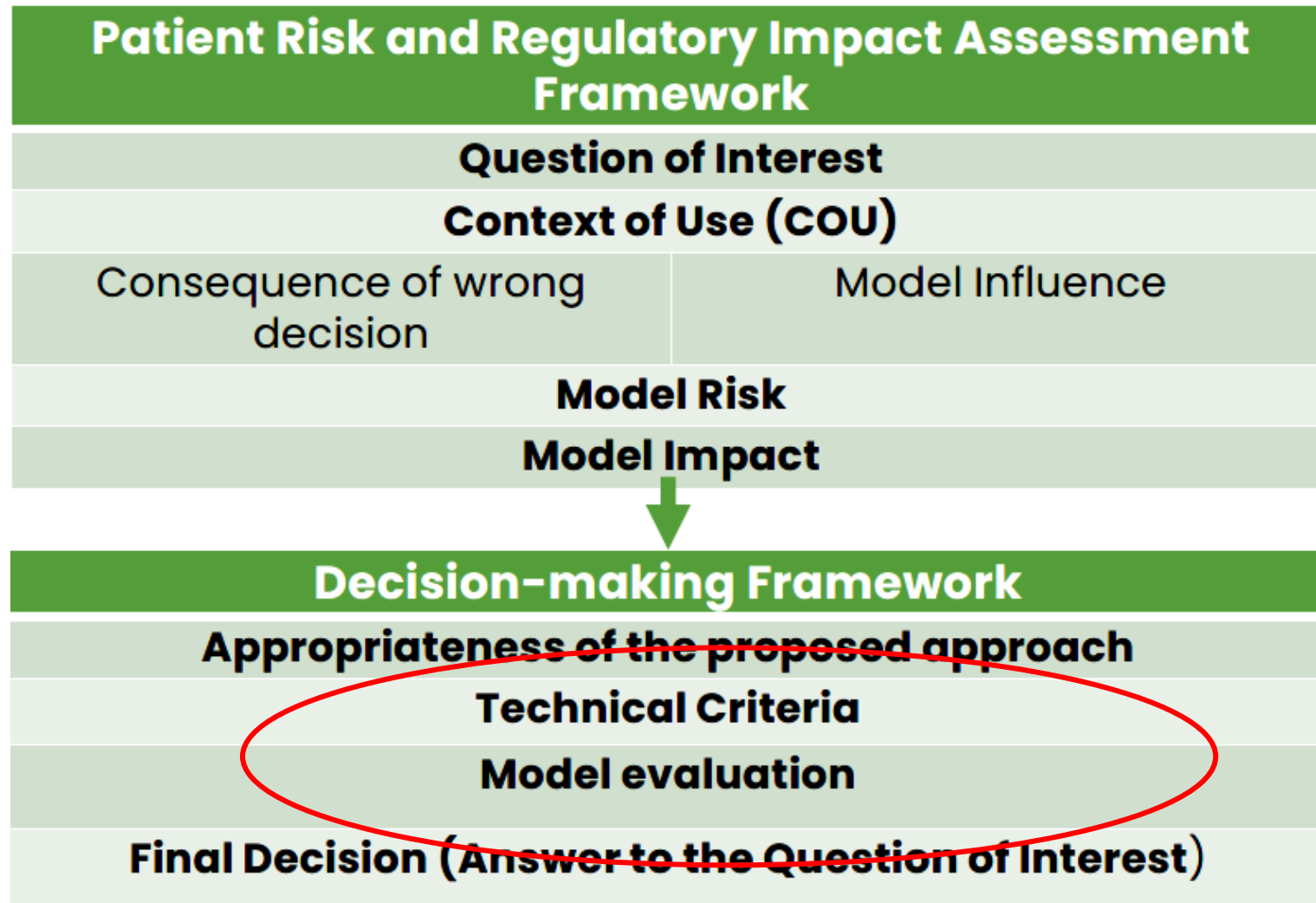
- **The specificities of different types and objectives of mechanistic models**
- Technical points to consider when assessing and their implication for regulatory decision-making based on mechanistic models
- Model structure and identifiability
- Regulatory requirement for data quality and relevance
- Uncertainty Quantification
- Virtual population generation and simulation scenarios
- Etc.



From Risk-based approach to technical assessment

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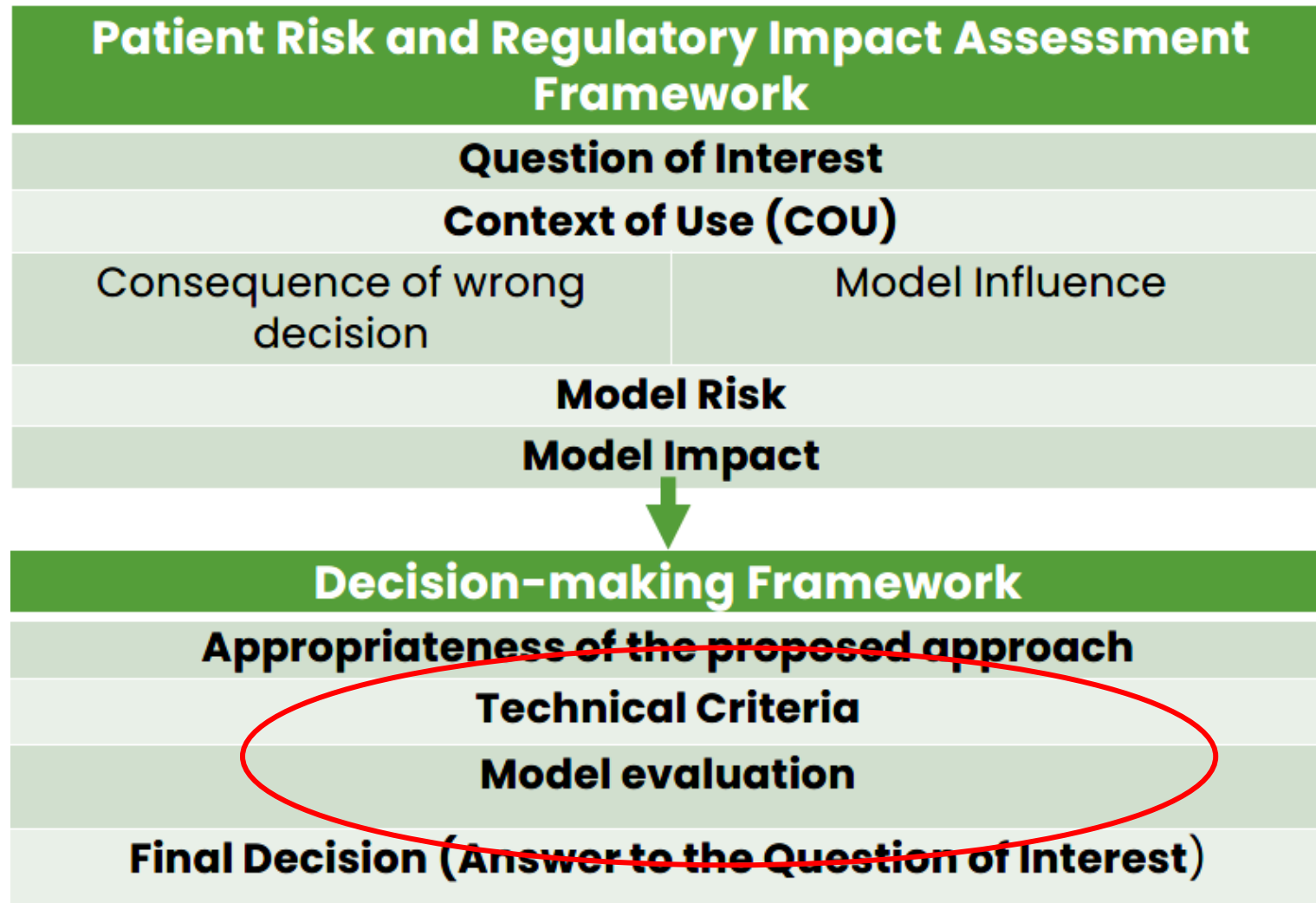
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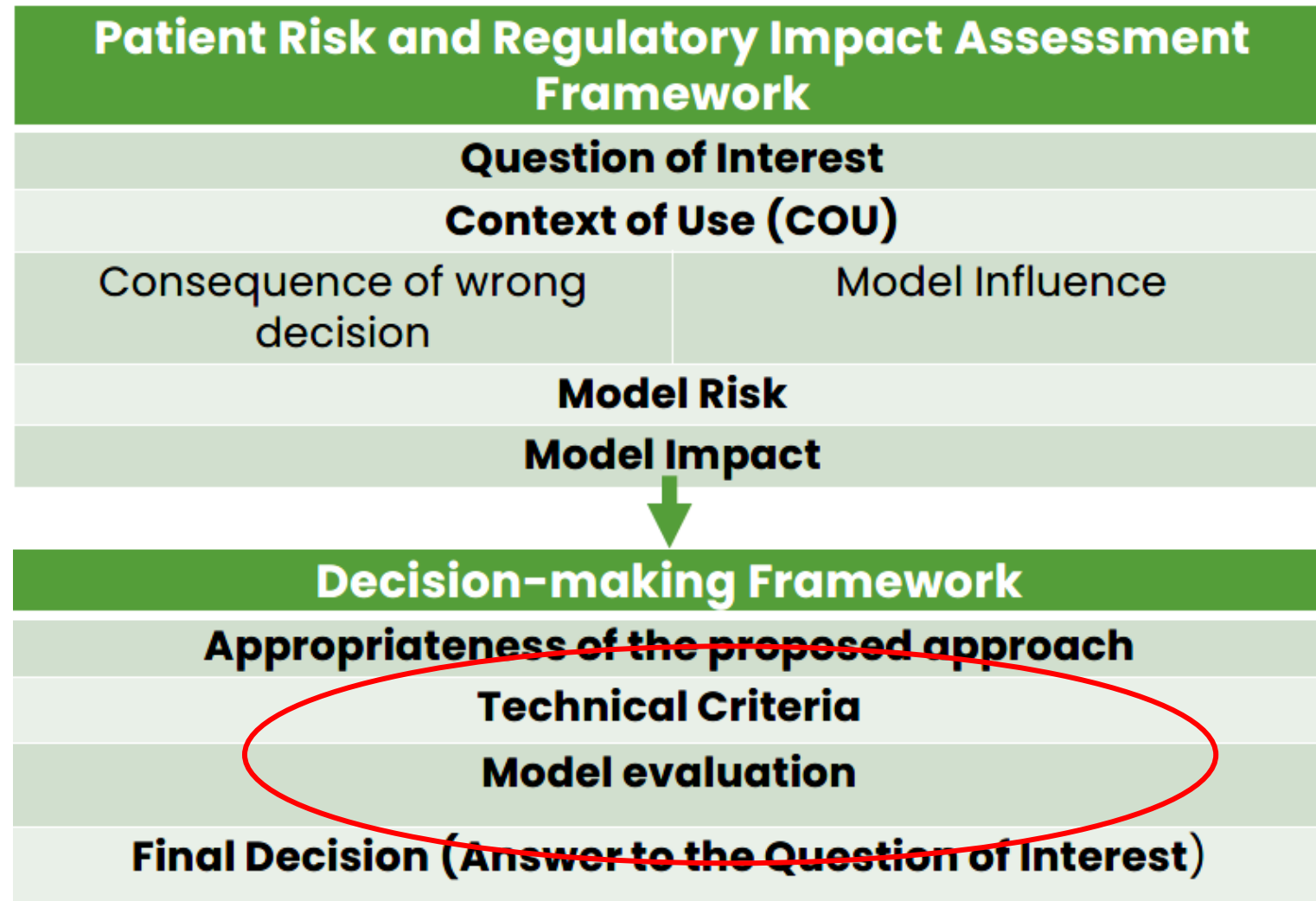
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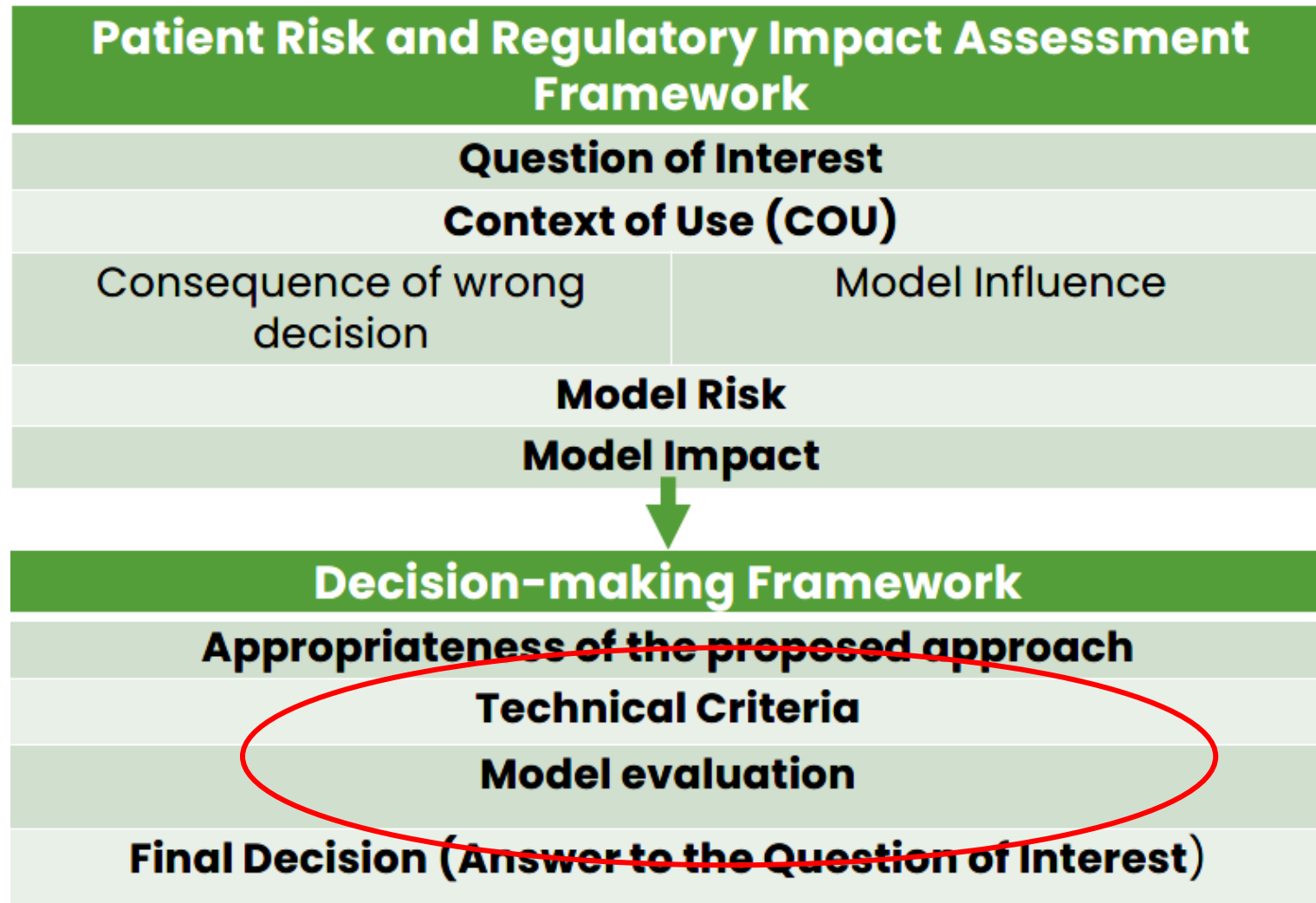
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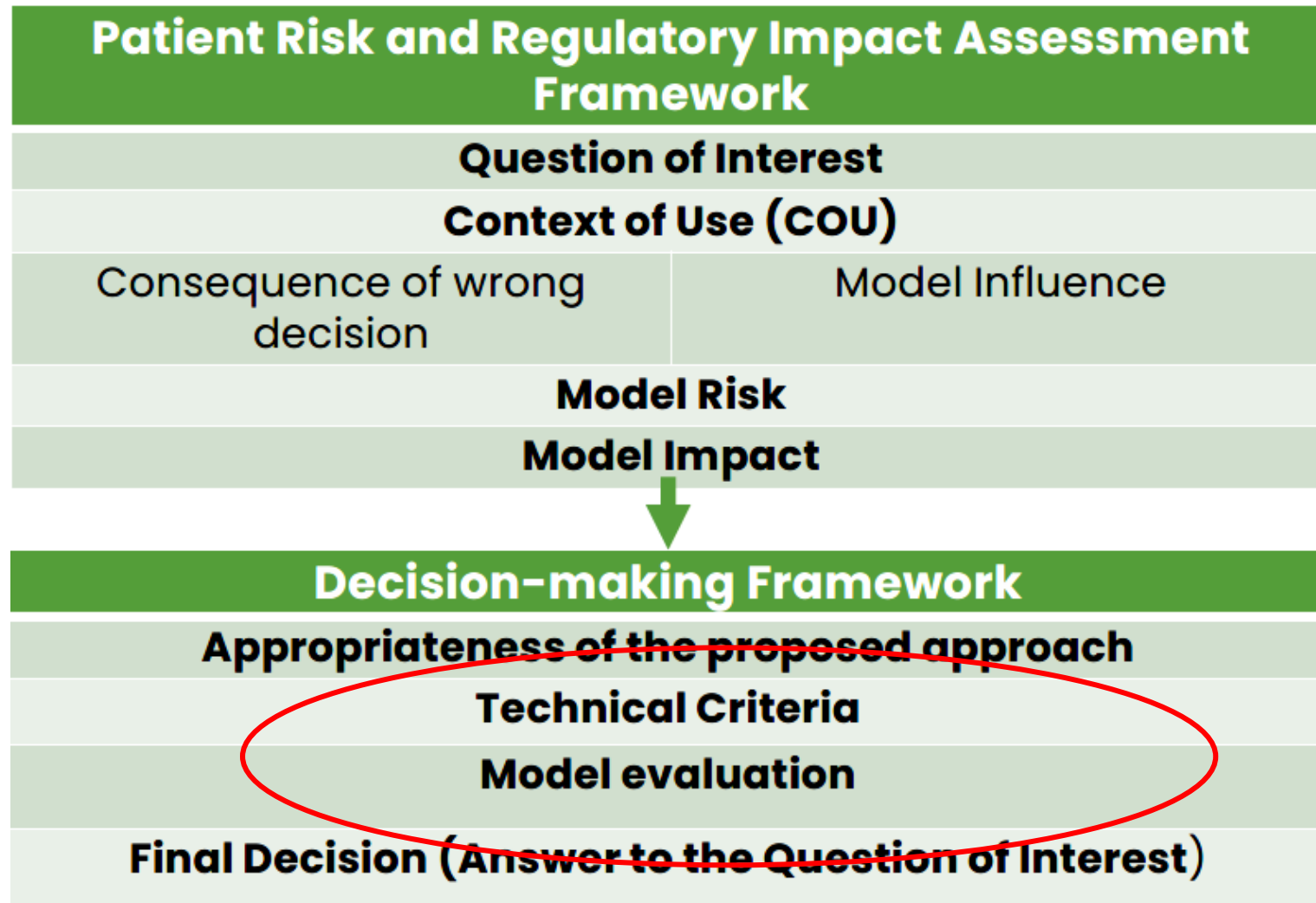
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From Risk-based approach to technical assessment

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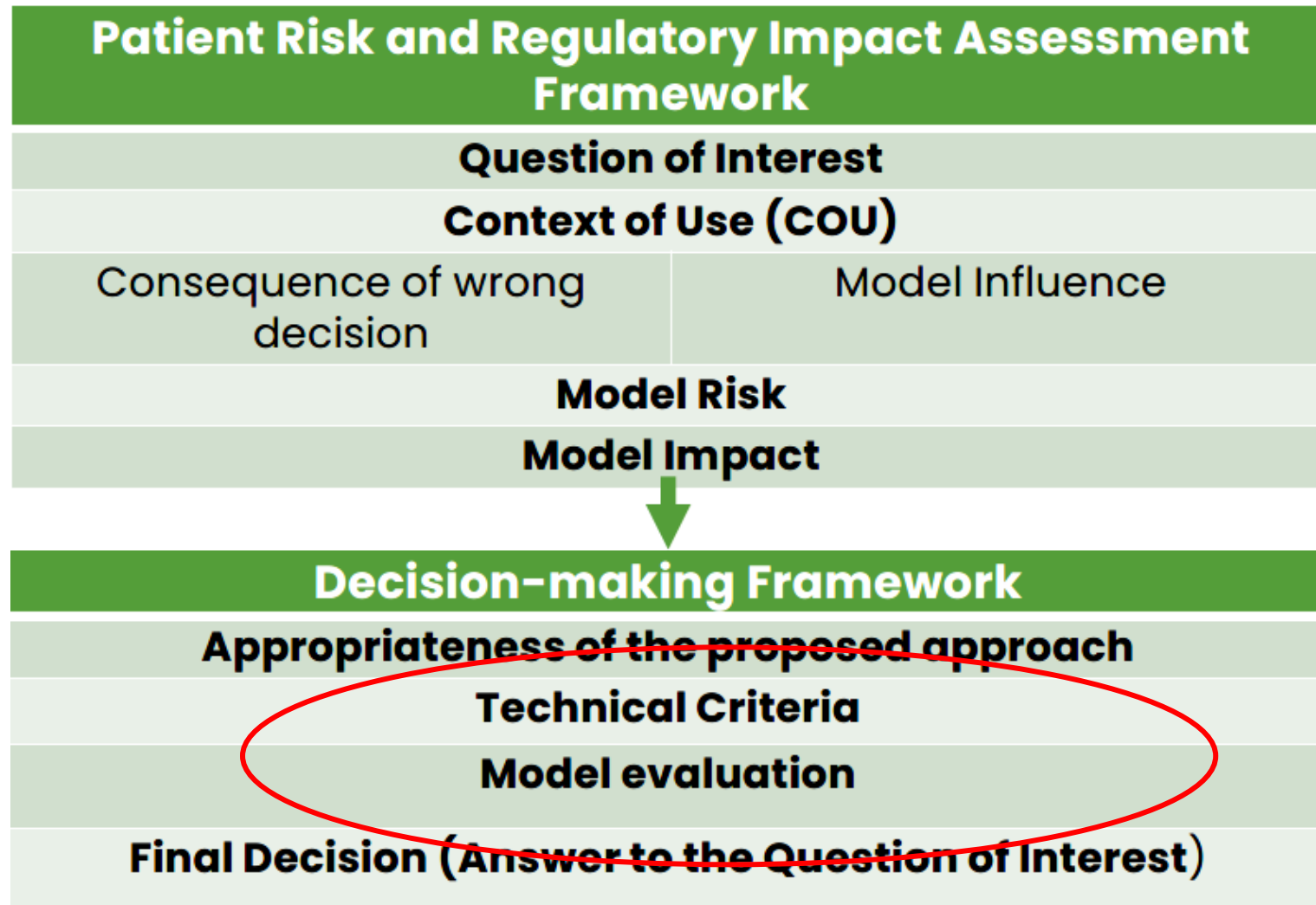
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- Etc.



Taking into account Risk and Impact assessment



Guidance for assessment of mechanistic models

30



Risk-based approaches and guidance for assessment of mechanistic models



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GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG
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Draft version
Endorsed on 06 November 2024



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 20 January 2025
2 EMA/S875/2025
3 Committee for Medicinal Products for Human Use/
4 Methodology Working Party (CHMP/MWP)

5 Concept paper on the development of a Guideline on
6 assessment and reporting of mechanistic models used in
7 the context of model informed drug development
8

Agreed by MWP	21 November 2024
Adopted by CHMP for release for consultation	20 January 2025
Start of public consultation	14 February 2025
End of consultation (deadline for comments)	31 May 2025

9
10 Comments should be provided using this [EUSurvey form](#). For any technical issues, please contact
11 the [EUSurvey Support](#).

Keywords Mechanistic Models, PBPK, QSP, PBBM, MIDD evidence

**Guideline on
assessment
and
reporting of
mechanistic
models**

Risk-based approaches and guidance for assessment of mechanistic models

13:30

Session 4: Regulatory guidance on mechanistic models, gaps & challenges in guidance documents

The aim of this session is to critically review the current EMA guidance on mechanistic models and identify areas for improvement. In addition, the Agency wishes to explore opportunities for alignment of qualification requirements at the international level and with related regulatory guidance documents (ICH M15).

Chairs: Francesca Day (EMA) & Kristin Karlsson (MPA)

Introduction by the session co-chairs

5'

Francesca Day (EMA) & Kristin Karlsson (MPA)

Guideline on assessment and reporting of mechanistic models used in the context of model informed drug development: Public comments received

20'

Flora Musuamba Tshinanu (FAMHP)

Cross-industry feedback in implementation of regulatory guidance on mechanistic models: case studies, gaps, challenges and future perspectives

20'

Pradeep Sharma (AstraZeneca, o.b.o. EFPIA/EuropaBio)

PBBM Qualification and Guidance: Key Challenges and Emerging Opportunities

20'

Claire Mackie (J&J, o.b.o. EFPIA)

Shaping the Path Forward: Advancing Mechanistic Models for Regulatory Use

20'

Hao Zhu (FDA)

Panel discussion

60'



Preparing for the next steps

~~Wish list~~ Workshop objectives

1

Hear stakeholder views on the current regulatory framework for mechanistic models.

2

Share regulatory challenges and experiences in assessing these models.

4

Identify opportunities for future mechanistic model qualification.

5

Define how the EU regulatory framework can be refined to streamline the use and assessment of mechanistic models.

Acknowledgements

Ine Rusten

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Joerg Zinserling

Andreas Kirisits

HMA/EMA workshop on mechanistic models **presenters/panelists**

Thank you

flora.musuambatshinanu@fagg-afmps.be

