ASP 2026
COMMUNITY CONFERENCE

ICH M15 and Regulatory assessment of Mechanistic models: Game changer or Business as usual?



Flora Musuamba

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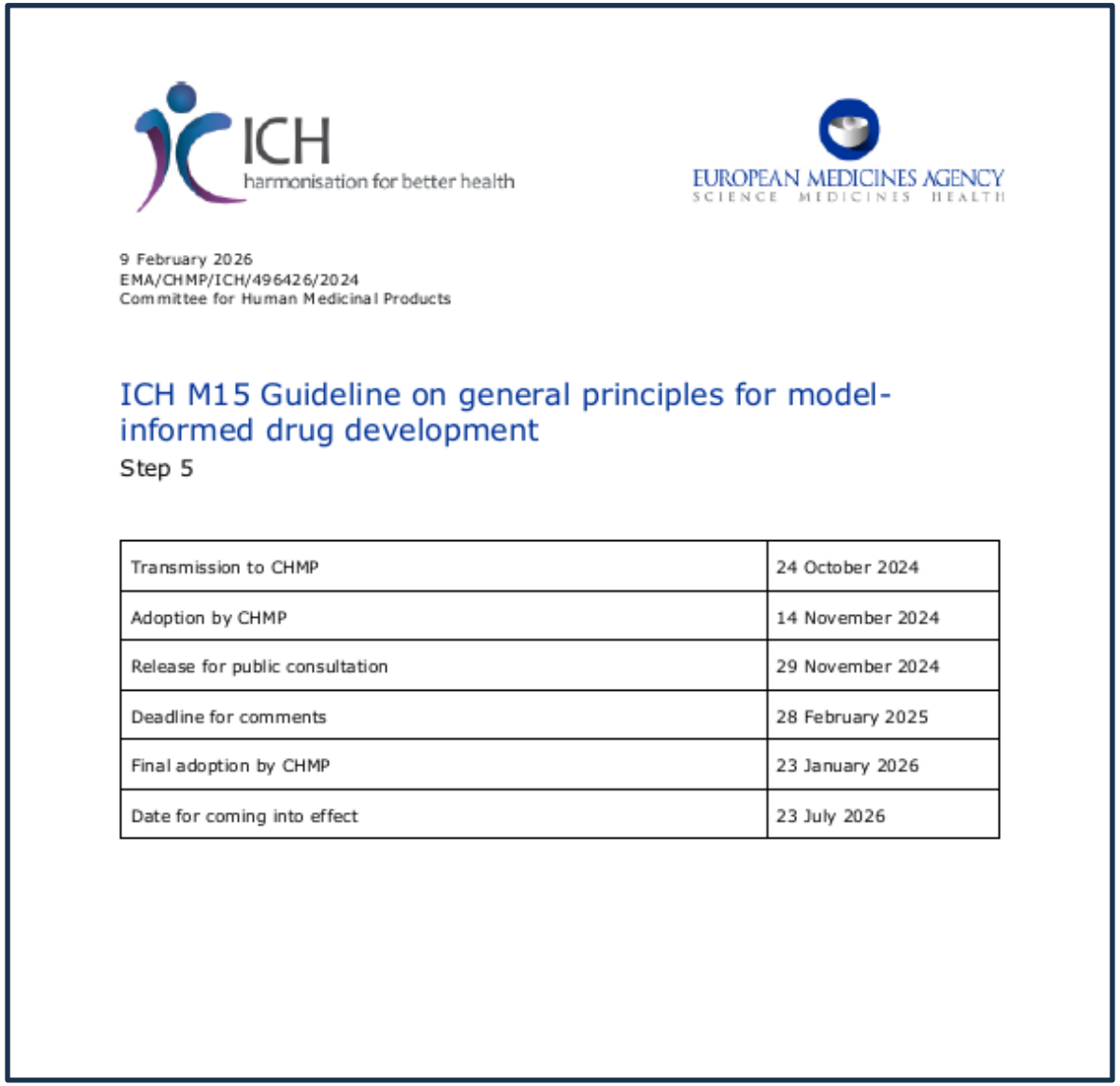
federal agency for medicines and health products

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The Journey to the Guideline

Dates	Deliverable
2019	• **Initial PhRMA Topic proposal**
2020-2022	• **Road map , Concept paper**
2022- 2024	• **ICH Step 1 – Consensus Building** • >66 2-hr Team video meetings • Three (4-5 day) F2F meetings • Two rounds of party review and a plenary review **-> Regulatory Focus**
November 2024	• ICH Step 1 Technical document signed off by topic leaders & endorsed by ICH Assembly • Step 2a -> Parties consensus on technical document • **Step 2b -> Draft Guideline adoption by Regulators (November 6th)** • Step 2 Summary Slides & Template
Q1-Q3 2025	• **Step 3 -> Regulatory Consultation & Discussion (including public consultation)** **>700 comments** **Revision of the guideline**
Jan 2026	• **Step 3 -> Signoff** • **Step 4 -> Adoption of M15 guideline**
2026	• **Implementation of the Guideline**



ICH harmonisation for better health

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

9 February 2026
EMA/CHMP/ICH/496426/2024
Committee for Human Medicinal Products

ICH M15 Guideline on general principles for model-informed drug development

Step 5

Transmission to CHMP	24 October 2024
Adoption by CHMP	14 November 2024
Release for public consultation	29 November 2024
Deadline for comments	28 February 2025
Final adoption by CHMP	23 January 2026
Date for coming into effect	23 July 2026

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Guideline Objectives and Scope

Objectives

- **To provide general recommendations for planning, model evaluation, and documentation of MIDD evidence**
- **To establish a harmonised assessment framework (including associated terminology) for MIDD evidence**
- **To facilitate a multidisciplinary understanding of MIDD and associated evidence generation**

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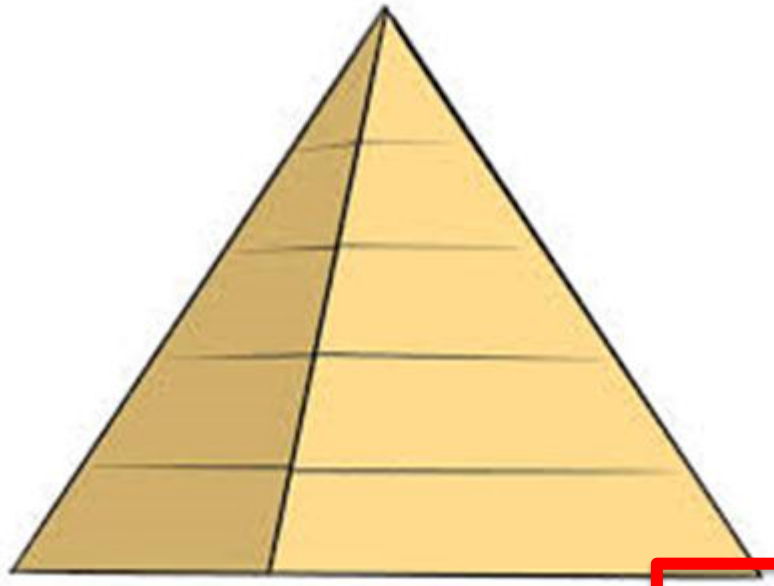
This is what is new as compared to How we were operating before M15 adoption

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MIDD Evidence for Regulatory Decision-Making

Regulatory Decision-Making



Clinical Trial Evidence

Real-world Evidence

.....

MIDD Evidence

Totality of Evidence

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GENERAL PRINCIPLES FOR MODEL-INFORMED DRUG DEVELOPMENT

M15

Harmonised Framework for Assessment of MIDD Evidence

Adapted from ICH M15 DIA2025 Presentation, Hao Zhu

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Guideline Objectives and Scope

Scope

- **Applies to both current and emerging M&S methods, approaches, and applications**
- **Focuses on assessment of MIDD evidence and provides recommendations for related regulatory interactions, reporting, and submission**
- **Does not focus on details regarding technical aspects of the model development process. Model development should be consistent with the general recommendations outlined in this Guideline.**

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Framework for Assessment of MIDD Evidence

- **Describes key concepts for assessing MIDD evidence to inform decision-making, increase transparency, and provide an understanding of the proposed MIDD strategy, its implementation, and available results with respect to provision of MIDD evidence**
- **These concepts are split into:**
  - Key Assessment Elements
  - Additional Considerations for Interaction with Regulators and to Inform Decision-making

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Outline of the Guideline

Guideline Overview in Relation to MIDD Planning and MIDD Evidence Submission

MIDD Planning[1] and Regulatory Interaction		Implementation, Reporting, and MIDD Evidence Submission[2]		
Key Assessment Elements	**Additional Considerations for Interaction with Regulators 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	• Technical Criteria for Evaluating Model and Model Outcome[3] • Appropriateness of Proposed MIDD These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation and Applicability Assessment	• Model Analysis Report(s) (MAR)	• Regulatory Documents, Including Complete Assessment Table: + Evaluation of Model(s) and Model Outcomes + Outcome of MIDD Evidence Assessment + References to All Relevant MAPs and MARs
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

Inform Decision-making

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

[1] MIDD planning refers to any timepoint when drug developers are planning MIDD activities, generally prior to availability of model outcomes relevant to the current question of interest. Planning may include internal activities; however, for the purpose of this Guideline, the focus is on consultation between drug developers and regulatory authorities.

[2] MIDD evidence submission refers to any timepoint when model outcomes are considered as MIDD evidence and submitted to regulators. This generally refers to submission for marketing applications and also includes other regulatory interactions.

[3] Model outcomes are 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.

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Framework for Assessment of MIDD Evidence: "When" ?

Guideline Overview in Relation to MIDD Planning and MIDD Evidence Submission

MIDD Planning[1] and Regulatory Interaction		Implementation, Reporting, and MIDD Evidence Submission[2]		
Key Assessment Elements	**Additional Considerations for Interaction with Regulators 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	• Technical Criteria for Evaluating Model and Model Outcome[3] • Appropriateness of Proposed MIDD These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation and Applicability Assessment	• Model Analysis Report(s) (MAR)	• Regulatory Documents, Including Complete Assessment Table: + Evaluation of Model(s) and Model Outcomes + Outcome of MIDD Evidence Assessment + References to All Relevant MAPs and MARs
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Inform Decision-making

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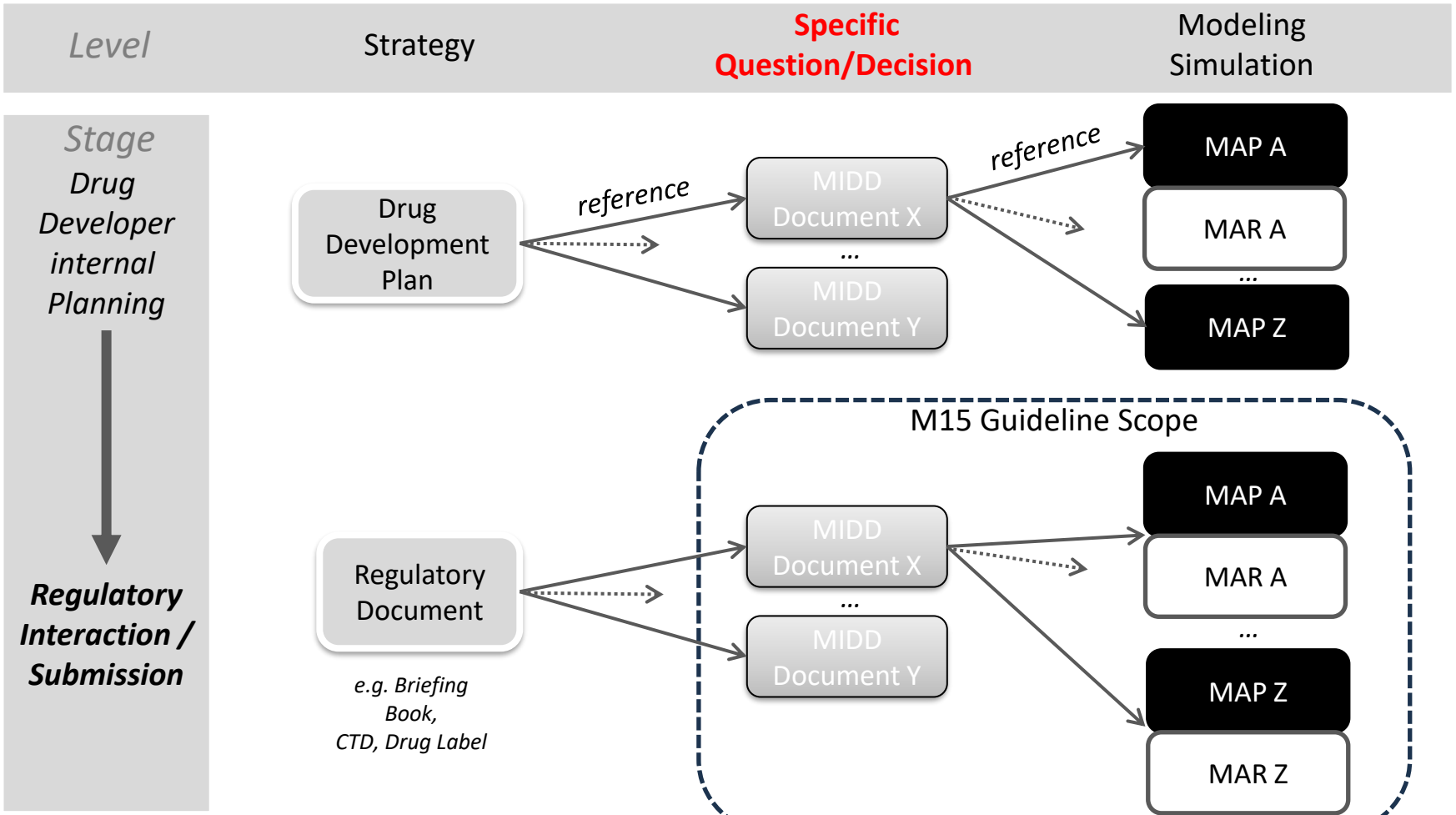
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Framework for Assessment of MIDD Evidence: "When" ?

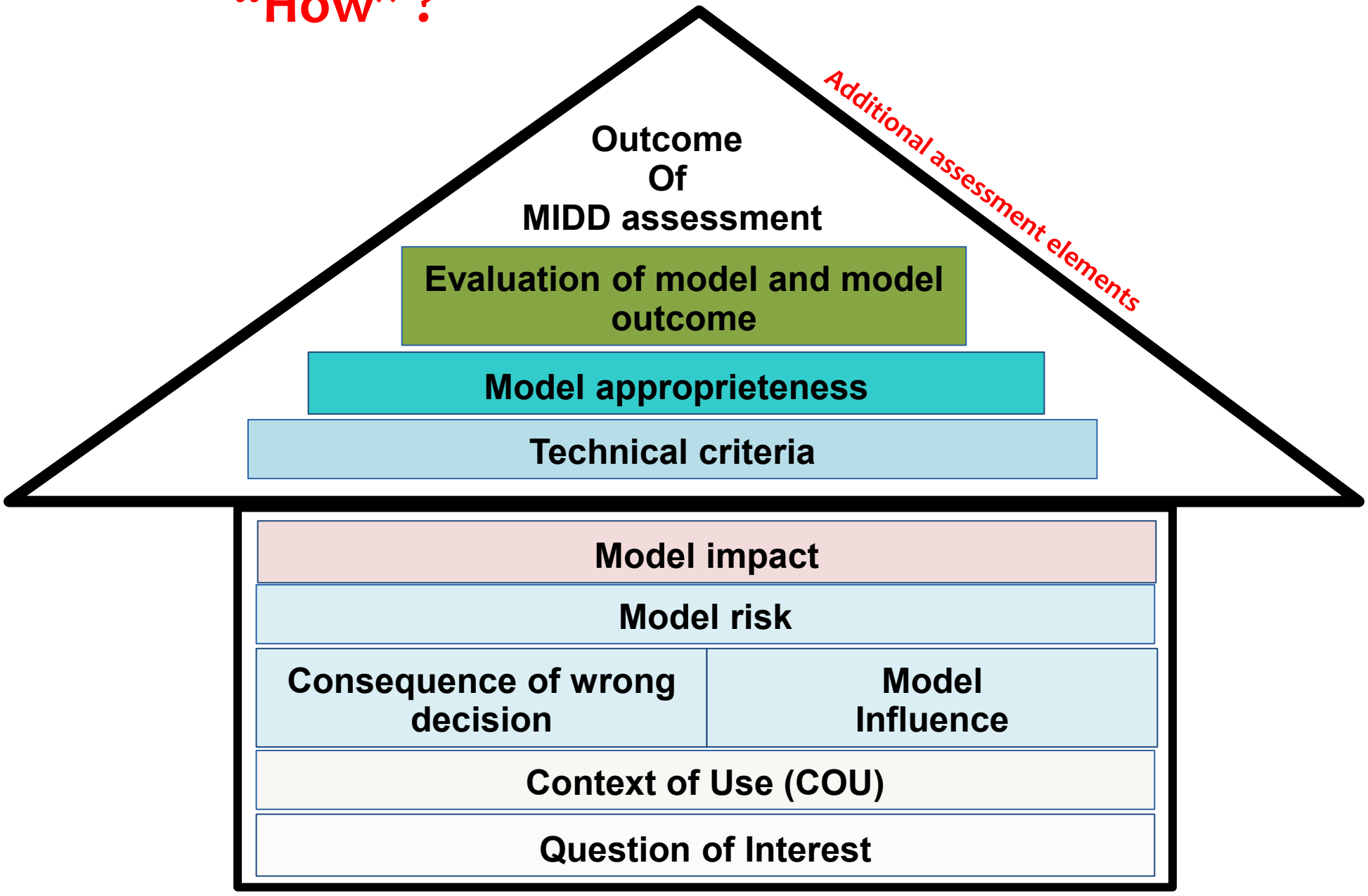


Credit: Joerg Lippert

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Framework for Assessment of MIDD Evidence:

"How" ?



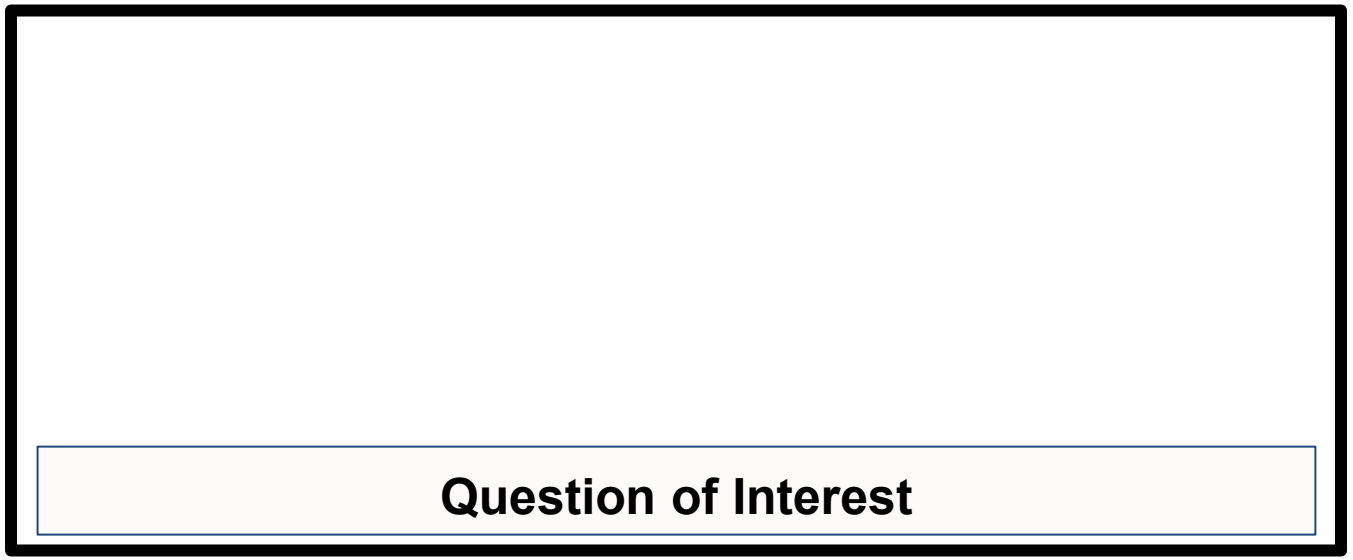
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Framework for Assessment of MIDD Evidence: "What" ?

Definition
The Question MIDD is intended to answer

Examples:

- What is the safe and effective dose for Drug X ?
- Is the proposed dose safe and effective in children of 2 to 6 years old?
- Is formulation x comparable to formulation Y in adults patients?



Key assessment assessment elements

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Framework for Assessment of MIDD Evidence: "What" ?

Definition

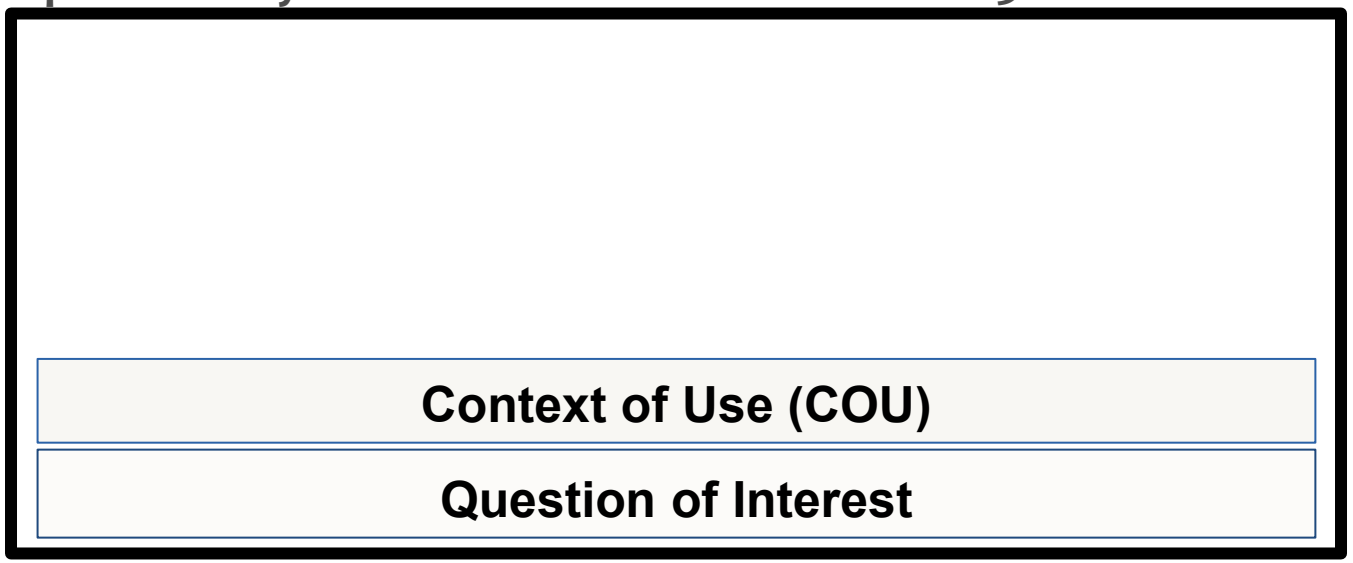
The role and scope of the model used to answer the question of interest.

Example:

QOI: What is the safe and effective dose for Drug X ?

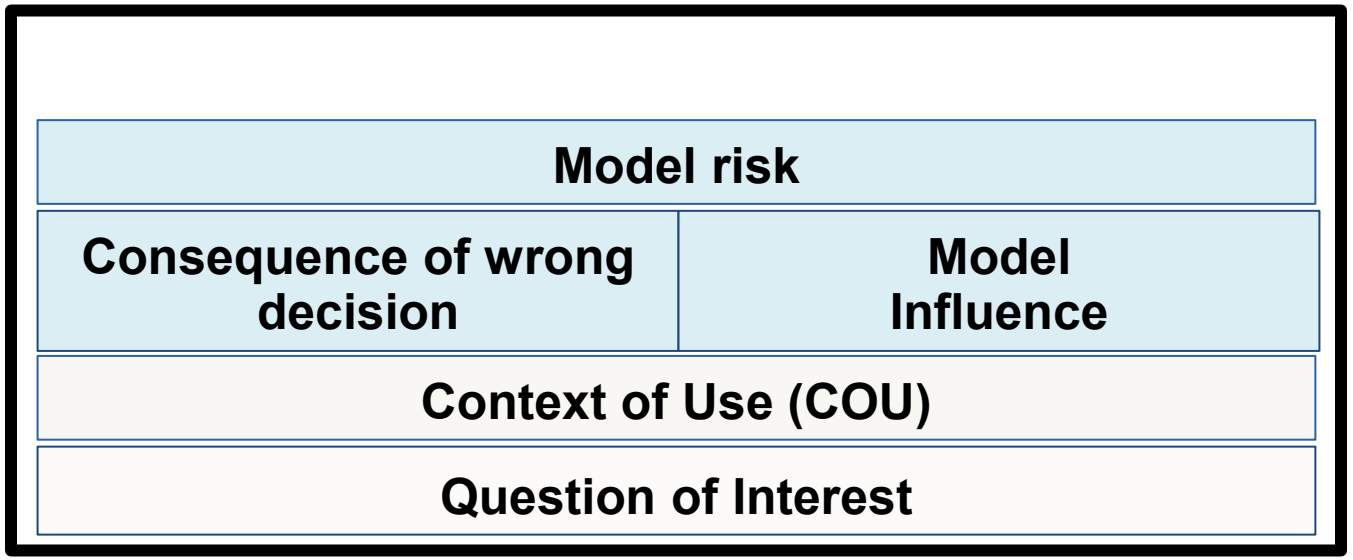
Context of use

- PBBM developed and validated using data from Phase 1 and 3 trials
- POPPK and E-R models developed and validated using data from Phase 1 and 2 trials
- Descriptive Safety data from Phase 1 and 2 trials in 3 different indications



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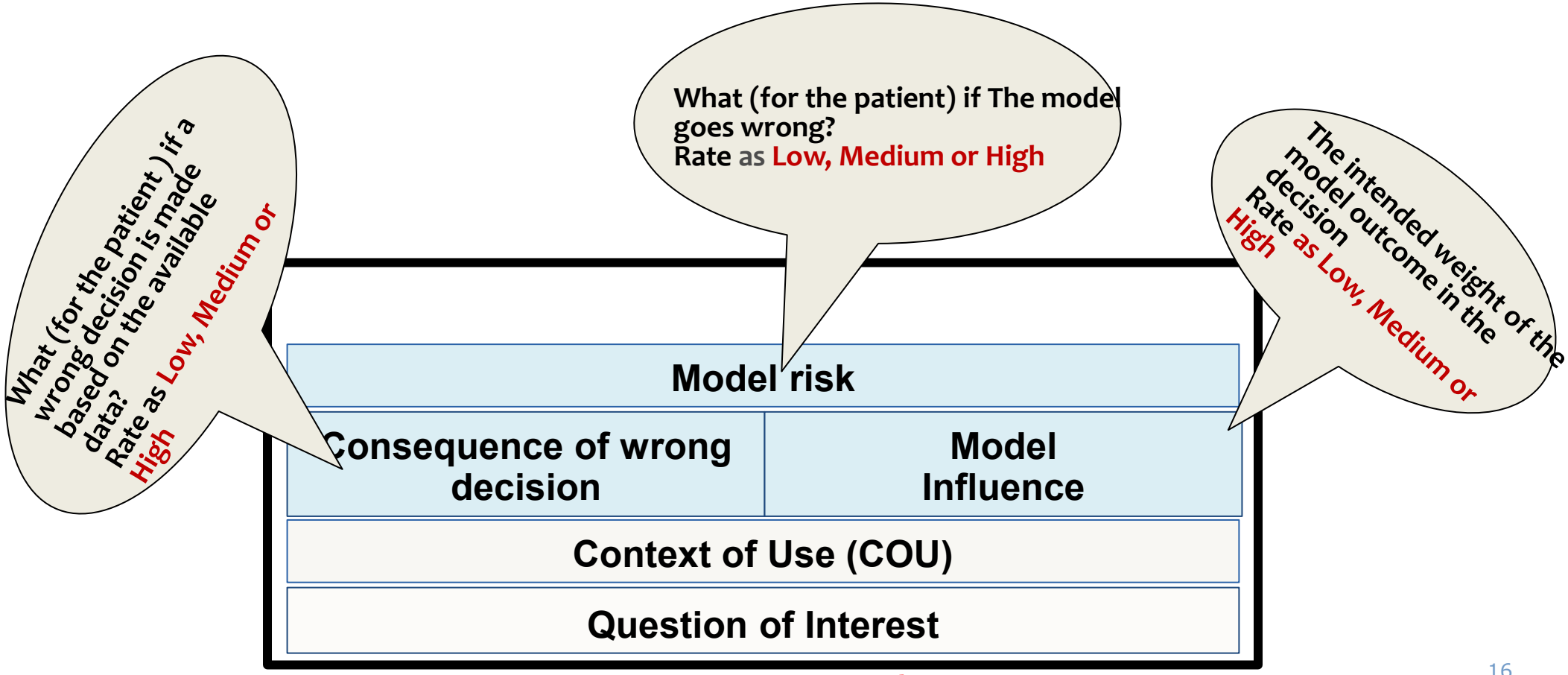
Framework for Assessment of MIDD Evidence: "What" ?



Key assessment assessment elements

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Framework for Assessment of MIDD Evidence: "What" ?



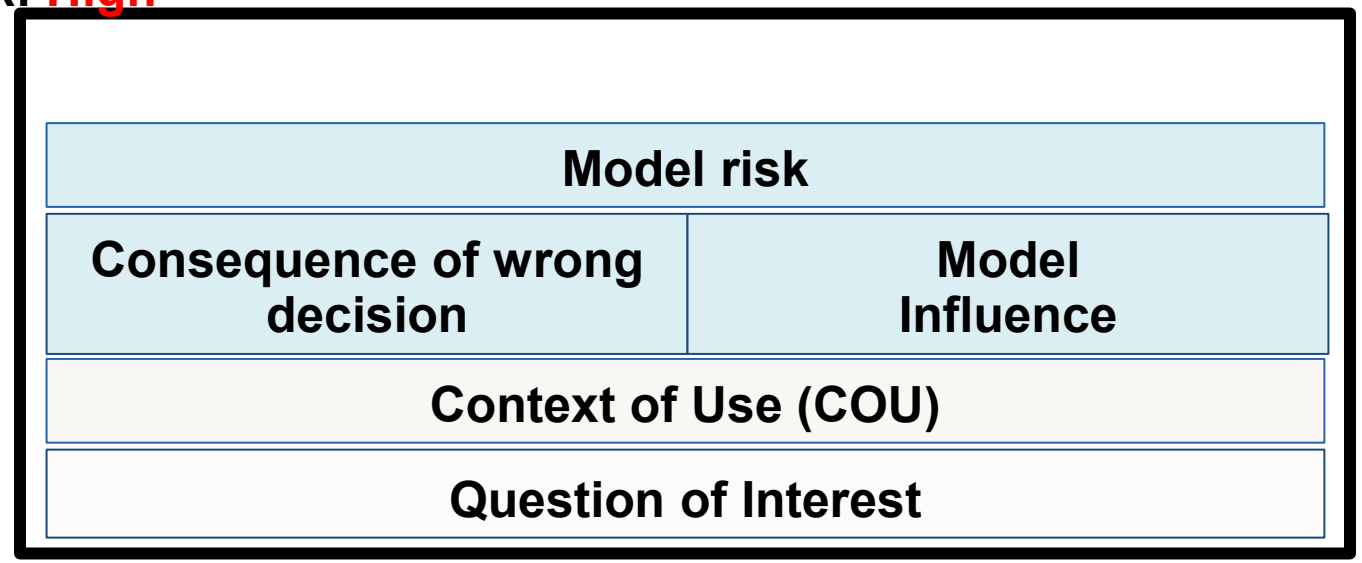
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Framework for Assessment of MIDD Evidence: "What" ?

Examples:

Paediatric indication based on an efficacy/safety data in children including a relevant number of children of 0-18 yo, with POPPK analysis on this trial data
Model Influence: Low
Consequence of wrong decision: High
Model risk: low to medium

Paediatric indication based on extrapolation of efficacy and safety based on PBPK modelling and simulation with very sparse PK data in children
Model Influence: High
Consequence of wrong decision: High
Model risk: High



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Framework for Assessment of MIDD Evidence: "What" ?

Definition

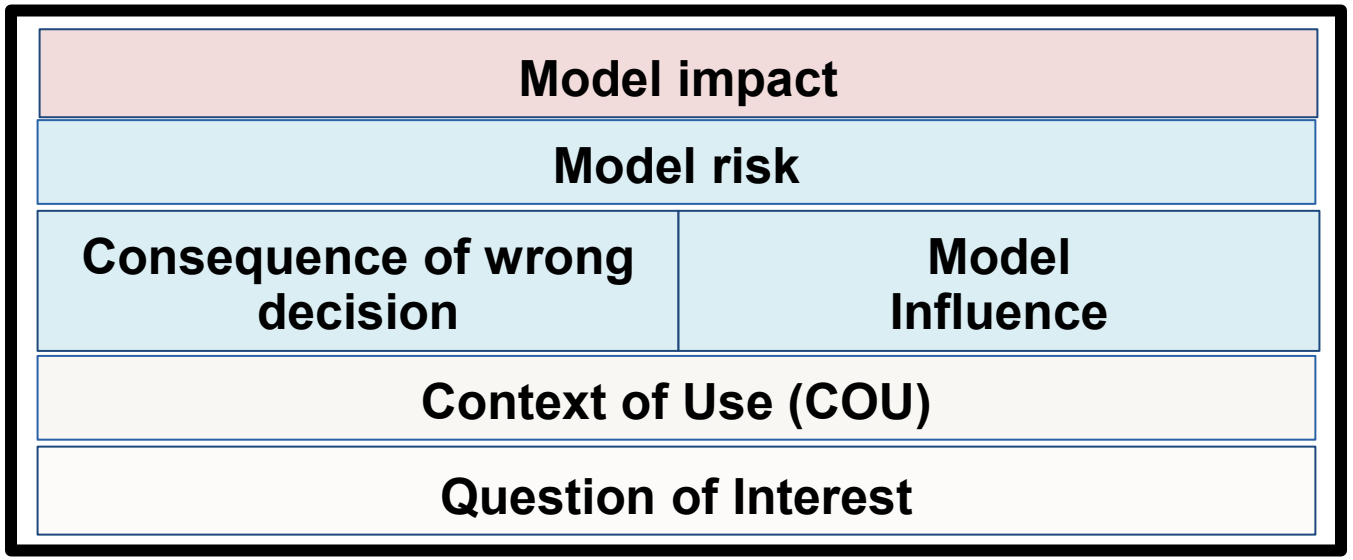
Contribution of model outcome in relation to the **regulatory expectations** and **standard.**

Rating: Low, Medium, High

Example:

Approval of an alternative dosing regimen using POPPK M&S without observed data with this dosing regimen

Model Impact: High

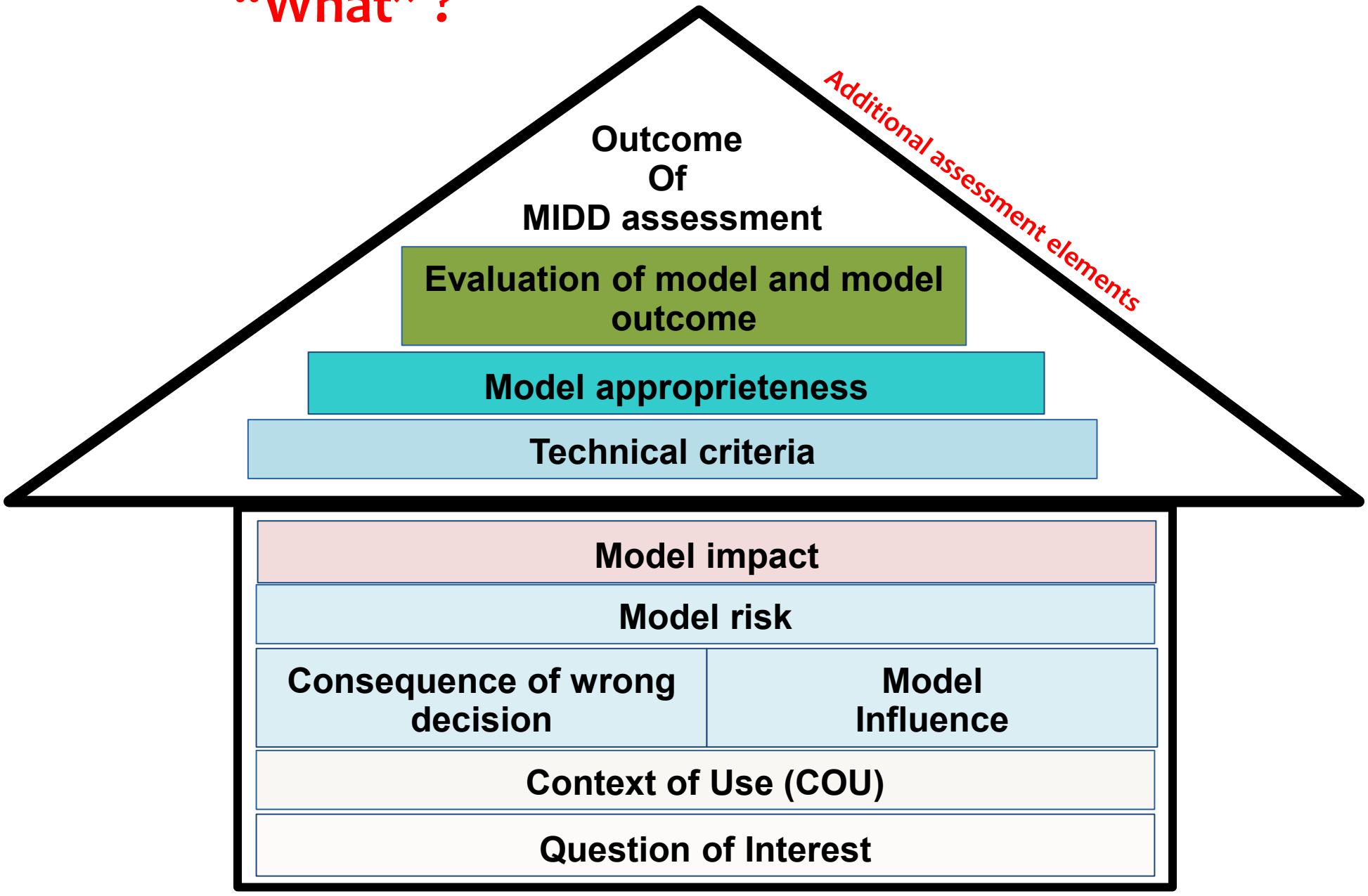


Key assessment assessment elements

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Framework for Assessment of MIDD Evidence:

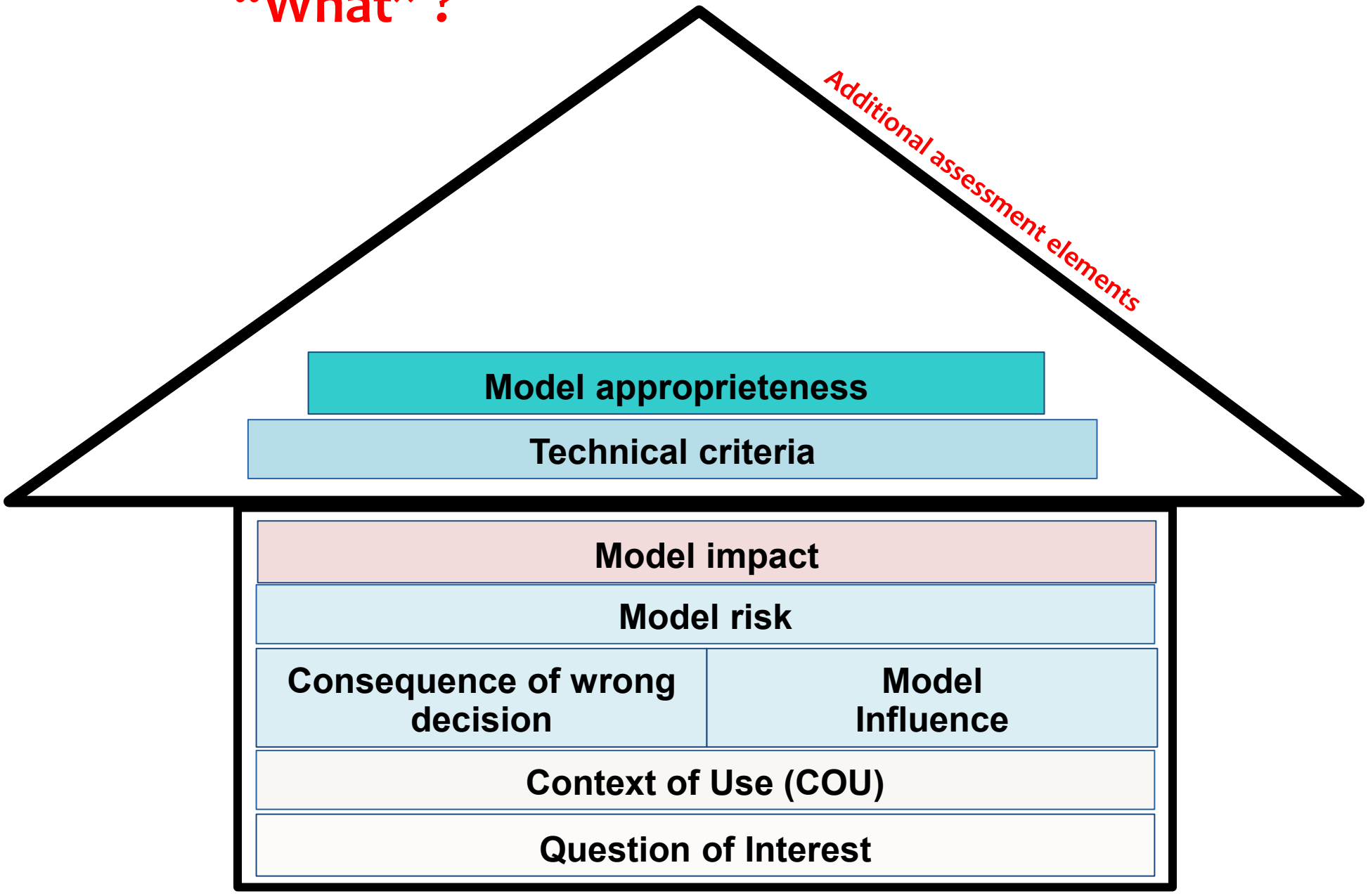
"What" ?



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Framework for Assessment of MIDD Evidence:

"What" ?



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Framework for Assessment of MIDD Evidence: "What" ?

Definition

Key criteria for **evaluating t**he ***model*** and ***model outcomes***, and that are needed to inform MIDD evidence **acceptance**,

Technical criteria

Model evaluation → **Cfr Section 3 (Verification, Validation, applicability)**

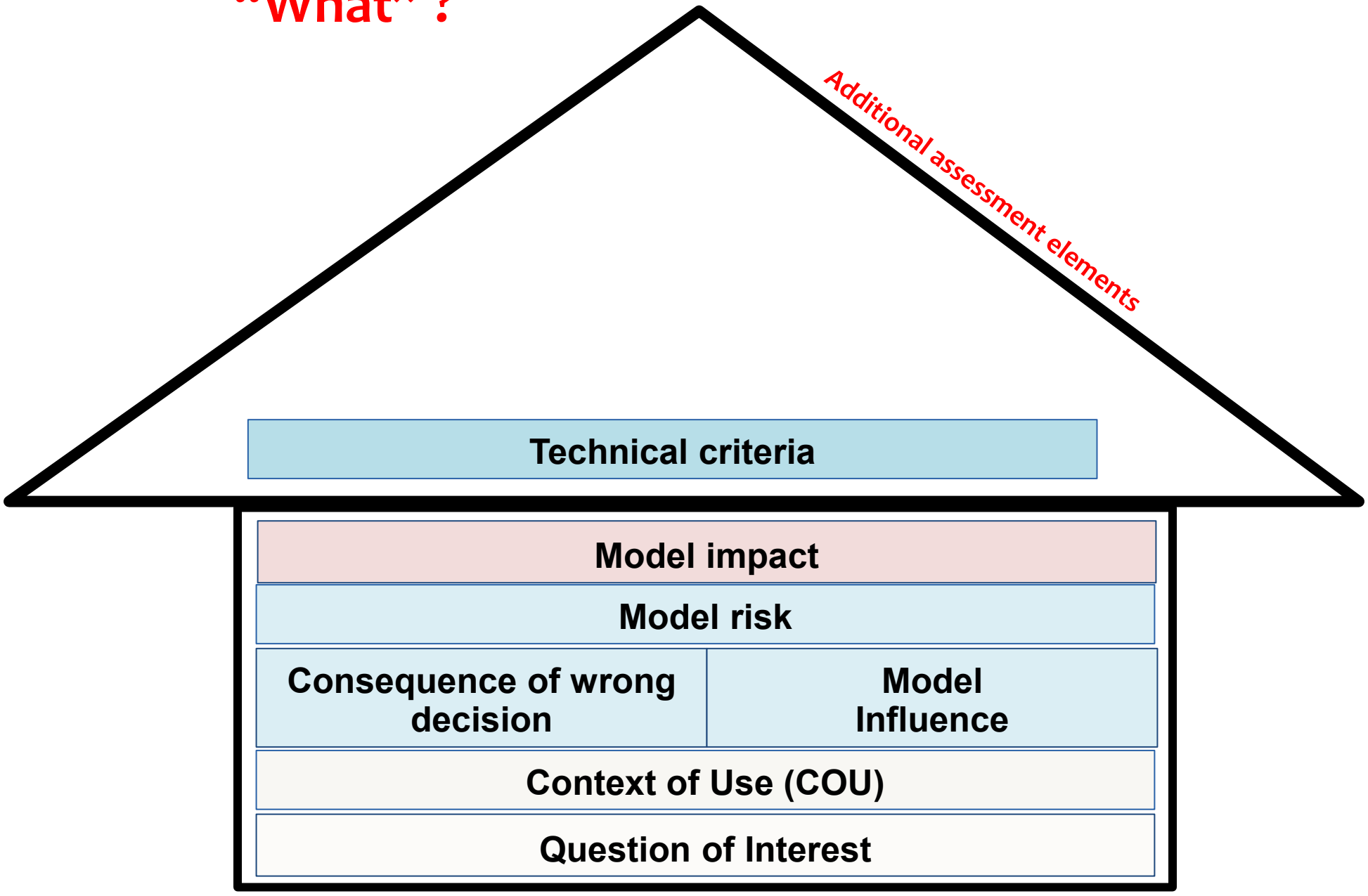
Model outcome: Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically **aligned to a question of interest**.

Drug developers should outline ***how this is commensurate with model risk***

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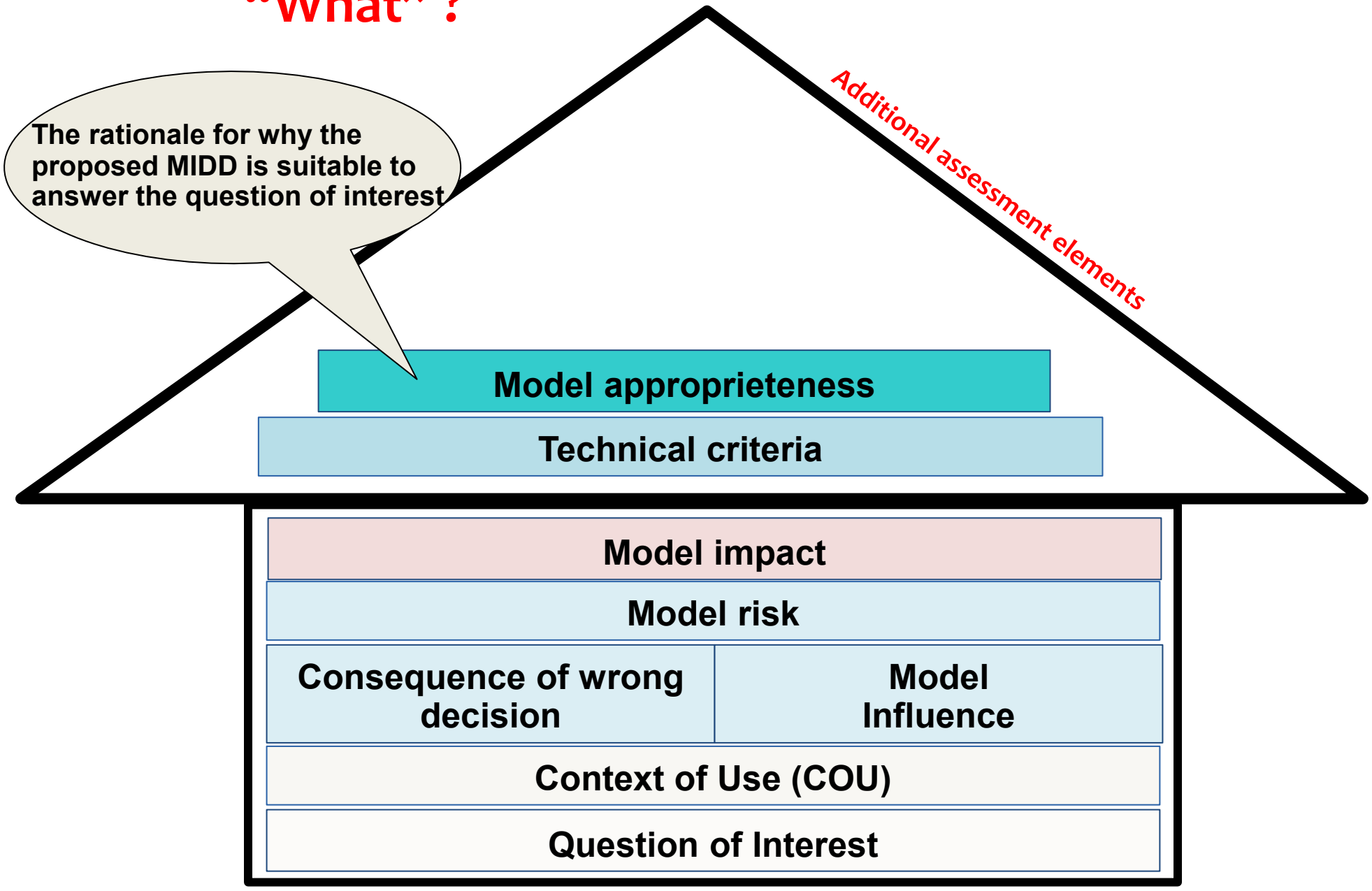
Framework for Assessment of MIDD Evidence:

"What" ?



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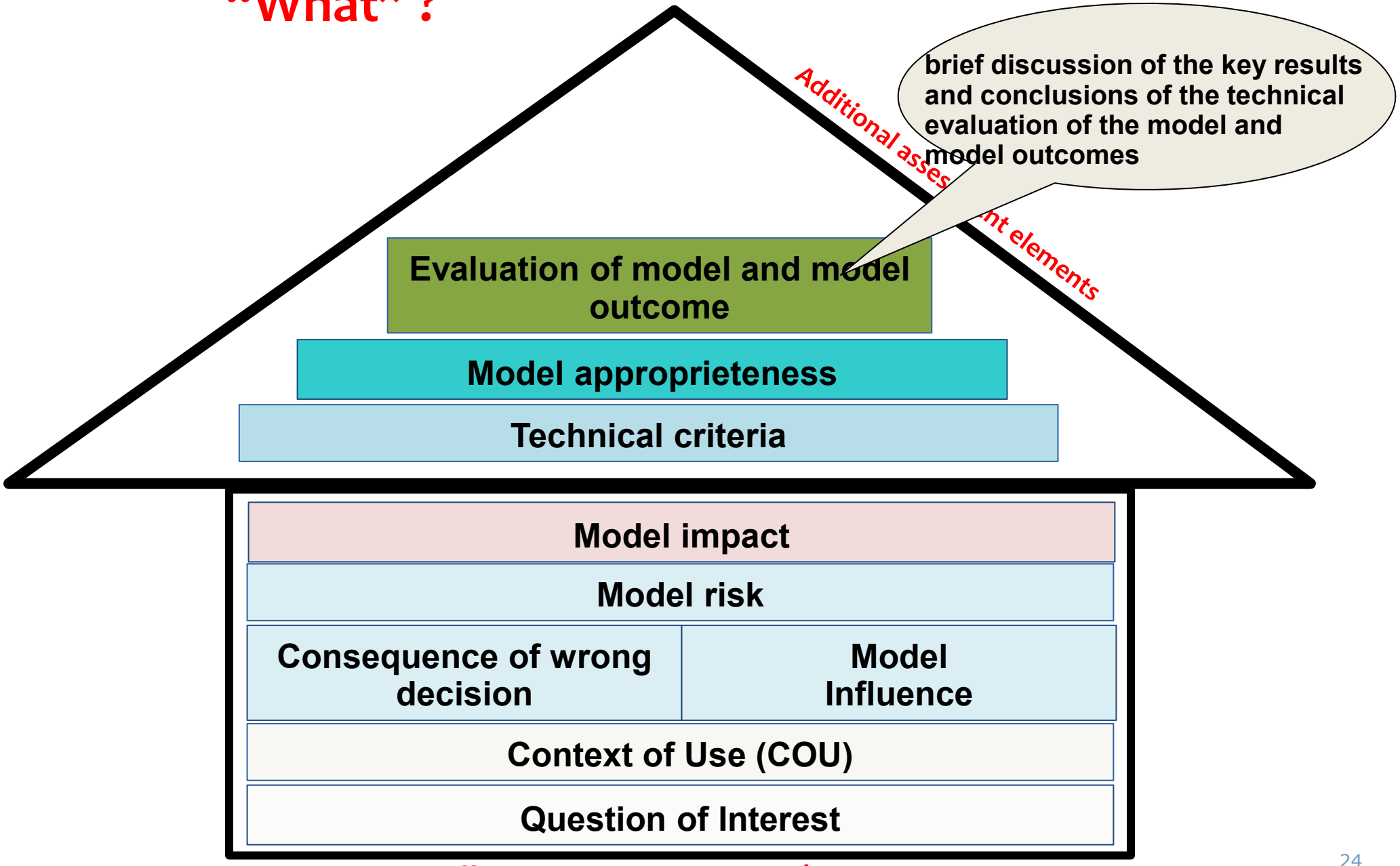
Framework for Assessment of MIDD Evidence: "What" ?



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Framework for Assessment of MIDD Evidence:

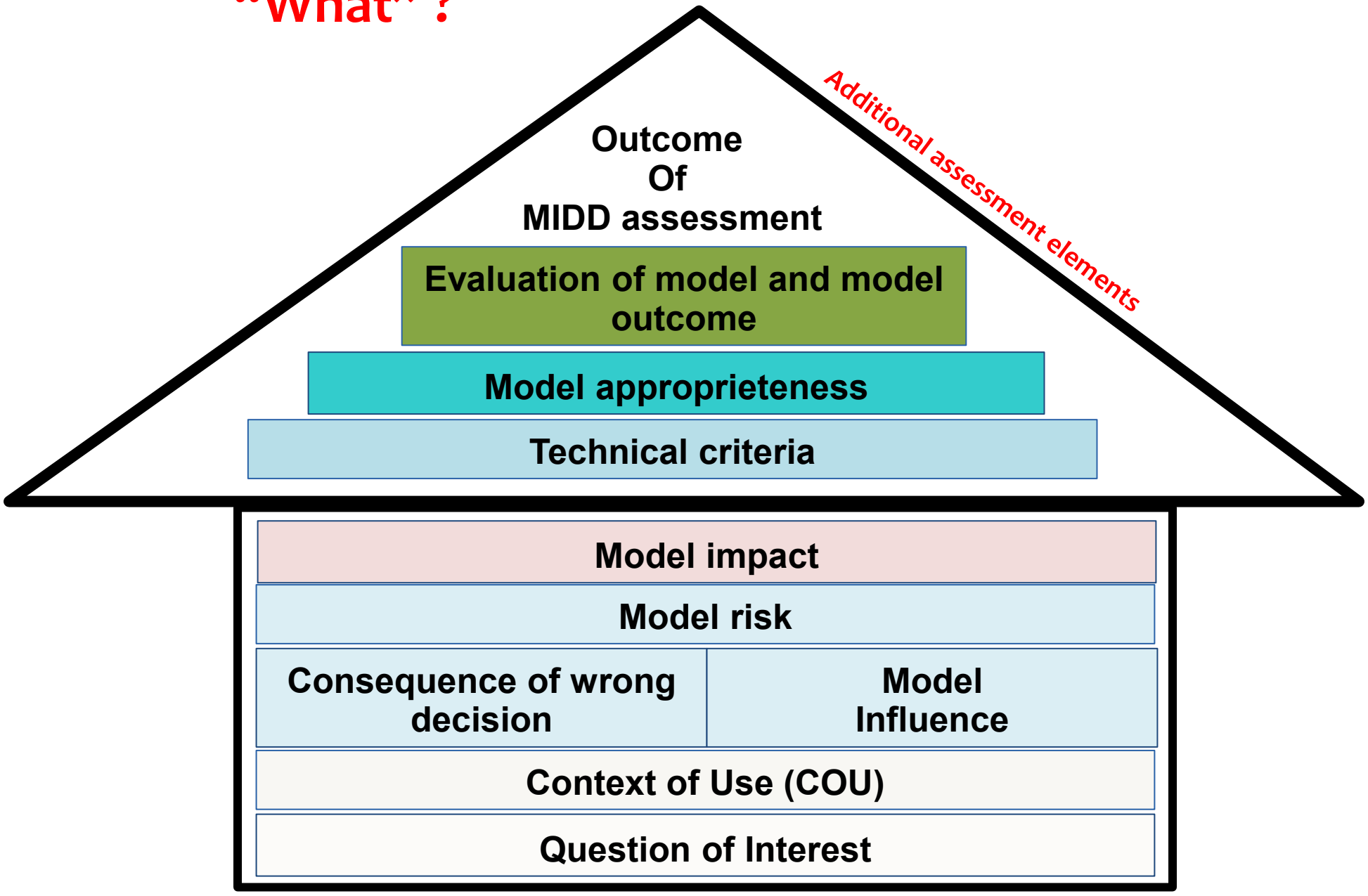
"What" ?



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Framework for Assessment of MIDD Evidence:

"What" ?



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Table for Assessment of MIDD Evidence

Item	Definition	Instruction	Entry
Key Assessment Elements Key assessment elements are expected to be included in the assessment table regardless of whether it is used at planning or submission stages.			
Question of Interest[1]	The question that MIDD is intended to answer.	Explicitly state the question of interest. This should reflect and inform multidisciplinary assessments and regulatory decision-making.	
Context of Use	The role and scope of the model(s) used to answer the question of interest.	Provide a concise, clear, and explicit description of the model, its role and scope, and the data used to build the model. In addition, discuss any additional data or evidence that will inform the answer to the question of interest.	
Model Influence	The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.	Describe the model influence; rate it as low, medium, or high; and provide a justification for the rating.	
Consequence of Wrong Decision	The potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.	Describe the consequence of a wrong decision; rate it as low, medium, or high; and provide a justification for the rating.	
Model Risk[2]	The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.	The model risk is derived by combining model influence and consequence of wrong decision. Describe the model risk; rate it as low, medium, or high; and provide a justification for the rating.	
Model Impact	The extent to which the proposed MIDD strategy varies from regulatory standards, or expectations when no regulatory standard is in place, for answering the question of interest.	Describe the model impact; rate it as low, medium, or high; and provide a justification for the rating.	

Note: This table should be used to provide concise information. Details should be provided in appropriate supportive documents (e.g., in a MAP or regulatory interaction background materials).

[1] If MIDD is planned to answer different questions of interest, it is recommended to use separate tables for each question.

[2] Model risk should be interpreted in the context of answering a specific question of interest and is not to be perceived as a risk intrinsic to MIDD or M&S.

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Table for Assessment of MIDD Evidence

Item	Definition	Instruction	Entry
Additional Considerations for Interaction with Regulators and to Inform Decision-making MIDD Planning Stage[3] The following items/rows are to be completed at the MIDD planning stage:			
Technical Criteria	Key criteria for evaluating the model and model outcomes, and that are needed to inform MIDD evidence acceptance, contributing to the answer to the question of interest.	Provide a clear and concise description of, and rationale for, the technical criteria, which are specific to the question of interest.	
Appropriateness of Proposed MIDD	The rationale for why the proposed MIDD is suitable to answer the question of interest.	Provide a brief discussion of why and how the proposed MIDD is considered appropriate for answering the question of interest, taking into account aspects of the key assessment elements and including information on how the technical criteria are suitable to ensure the appropriateness.	
MIDD Evidence Submission Stage The following items/rows are to be filled at the MIDD evidence submission stage:			
Evaluation of Model(s) and Model Outcomes	A brief discussion of the key results and conclusions of the technical evaluation[4] of the model and model outcomes.	Provide a concise summary of the technical evaluation of the model and model outcomes and describe how they fulfill the technical criteria.	
Outcome of the MIDD Evidence Assessment[5]	The multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence.	Provide a concise multidisciplinary assessment and conclusion of whether the model outcomes are considered MIDD evidence. This should integrate all of the assessment elements. Also provide a concise summary of the MIDD evidence related to the question of interest.	

Note: This table should be used to provide concise information. Details should be provided in appropriate supportive documents (e.g., in a MAP or regulatory interaction background materials).

[3] These items should also be provided at the MIDD evidence submission stage.

[4] Using the principles of model evaluation described in Section 3, with specific focus on technical criteria.

[5] "Assessment" in this context does not refer to any regulatory review activities or processes.

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EMA experience with the use of the M15 Guideline since its adoption

- **The famework and the table are increasingly used by the Sponsors to support their claims on the use of MIDD in different regulatory procedures(National advices and EMA scientific advices, CTAs, type II variations, etc.**
  - We are still in a learning curve in terms of filling the table
  - The use of the table always powerful as a communication tool

- **The famework and the table are increasingly referred to by assessors in the questions to applicants or in their answers to questions asked asked by applicants.**
  - The use of the table improves communication between sponsors and assessors
  - Drug sponsors ask and welcome feedback from assessors on the différents items in the table

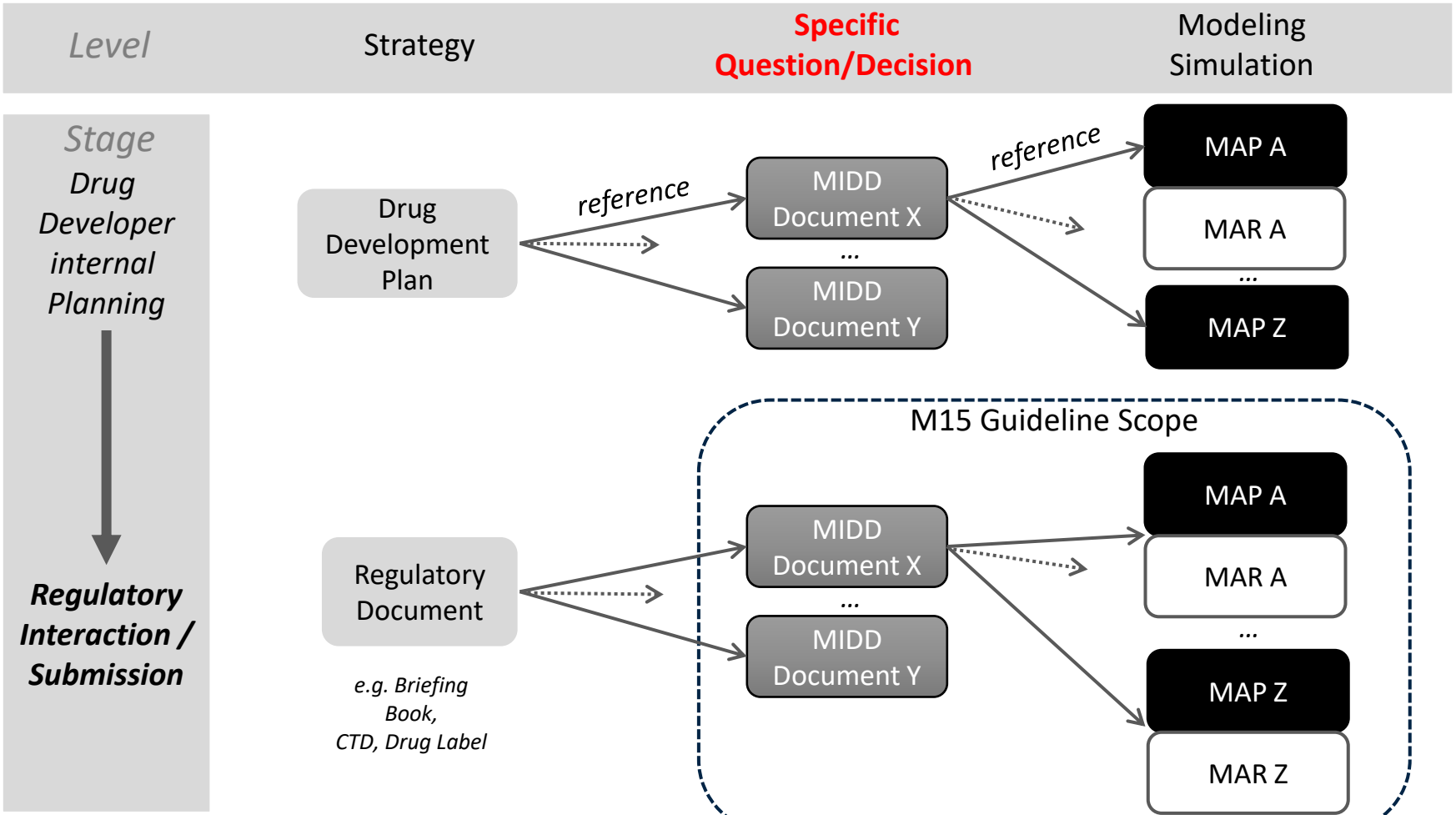
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Case example:

Use of a PBBM model to assess the Impact of the delivery device on systemic exposure

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Framework for Assessment of MIDD Evidence:



Credit: Joerg Lippert

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Case example:
Use of a PBBM model to assess the Impact of the delivery device on systemic exposure

Table for Assessment of MIDD Evidence

Item	Entry
Question of Interest	Is the auto-injector therapeutically equivalent to the vial + seringe administration in 3 autoimmune and haematologic diseases (systemic lupus erythematous (SLE), lupus nephritis (LN), and systemic sclerosis (SSc) ?
Context of Use	- **A PBBM** model is developed and validated using vial+seringe Phase 1 PK data and sparse Phase 3 PK data in LN with the AI. - A **POPPK** model is developed and validated using vial+seringe Phase 1-3 PK data - **E-R models** are proposed to describe the relationship between exposure and response (for both efficacy and safety) is established based on data from Phase 2 and 3 pre-marketing data with via + syringe in each indication - Efficacy and safety are established and the drug is approved in SLE and SS and under evaluation in LN
Model Influence	**Medium** **A justification should be provided leveraging the additional data available to inform the answer to the QOI**
Consequence of wrong desion	**Medium** **(To be assessed and justified separately for each indication based on the available efficacy and safety data)**
Model Risk	**Medium** **(derived from**
Model Impact	**High**

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Table for Assessment of MIDD Evidence

Item	Entry
Technical criteria	Key Criteria for assessment of the PBBM, the POPPK and the E-R models should be provided and justified with the medium model risk in mind
Approprieteness of the proposed MIDD	The approprieteness of the proposed proposed MIDD approach should be discussed with the medium model risk and High model impact in mind

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Take Home Message

- **The use of the MIDD assessment framework and related table is proposed as communication tool from both the sponsor and the assessors**
- **The use of the table makes it clear that the regulatory requirement for model acceptance**
- **An improvement of transparency and consistency of regulatory feedback is expected**

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Special Thank You to

The ICH M15 Expert Working Group



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Thank You!!

**Your medicines and health products,
our concern**

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