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

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

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1. Introduction

1.1. Objective of the guideline

This Guideline provides general recommendations for planning, model evaluation, and documentation of evidence derived from Model-Informed Drug Development (MIDD), hereafter "MIDD evidence."[1] It establishes a harmonized assessment framework (including associated terminology) for MIDD evidence.

1.2. Background

For the purposes of this Guideline, MIDD is defined[2] as the use of computational modeling and simulation (M&S)[3] methods that can include and integrate nonclinical data, clinical data, prior information, and knowledge (e.g., drug[4] and disease characteristics) to generate evidence. The generated MIDD evidence is used to inform drug development and decision-making by drug developers, regulatory authorities, and other stakeholders.

Early planning and inclusion of MIDD into the overall drug development plan ensures that the necessary data are generated to support MIDD strategies. Similarly, as encouraged in this Guideline, effective communication and early alignment with regulatory authorities regarding planned MIDD strategies facilitates the subsequent acceptance of MIDD evidence.

M&S methods and approaches used in MIDD strategies include, but are not limited to, population pharmacokinetics and pharmacodynamics, physiologically based pharmacokinetics and biopharmaceutics, exposure-response, model-based meta-analysis, quantitative systems pharmacology and toxicology, agent-based models, disease progression models, and artificial intelligence/machine learning. M&S methods and approaches may be used alone or in combination.

1.3. Scope of the guideline

This ICH M15 Guideline on general principles for MIDD applies to both current and emerging M&S methods, approaches, and applications. It focuses on assessment of MIDD evidence and provides recommendations for related regulatory interactions, reporting, and submission. This Guideline is intended to facilitate a multidisciplinary understanding of MIDD and associated evidence generation. It should be used in conjunction with relevant topic-specific ICH Guidelines (e.g., E4, E5, E6, E7, E9, E11, E14, E17, M12, M13, and S7B).

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[1] MIDD evidence is defined as model outcomes (see Table 1 and Appendix 3) that have been determined by application of the MIDD evidence assessment framework (see Section 2), including model evaluation, to be appropriate to inform the answer to the question of interest.

[2] It is acknowledged that MIDD is a general term with other definitions that relate to its use with respect to general drug development strategy (including trial design) and decision-making that may not require submission to regulatory authorities.

[3] While it is acknowledged that they are not always synonymous, the terms "model" or "modeling" are often used in this Guideline to represent "M&S" to improve readability and reflect commonly used terminology.

[4] For the purpose of this Guideline, the term "drug" is considered synonymous with investigational product, medicine, medicinal product, biological product, and pharmaceutical product; this includes "drugs" for which marketing authorization is sought.

Model development should be consistent with the general recommendations outlined in this Guideline in conjunction with current accepted standards and/or scientific practices for the M&S method(s). This Guideline does not focus on details regarding technical aspects of the model development process.

The Guideline should be read in conjunction with supplementary official ICH training materials.[5]

1.4. Guideline overview

This Guideline first outlines the framework for assessing MIDD evidence (Section 2), then provides an overview of the model evaluation needed (Section 3) as the basis for MIDD evidence assessment, and finally presents general recommendations for reporting and submission at both the model and MIDD evidence levels (Section 4).

An overview of the Guideline in relation to MIDD planning and MIDD evidence submission is provided in Table 1.

[5] At the time of release of this Guideline, these training materials are in development.

Table 1: 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.

2. Framework for assessment of MIDD evidence

This section describes key concepts for assessing MIDD evidence to inform decision-making. To aid in regulatory interaction and submission, a table for assessment of MIDD evidence[6] (hereafter "assessment table") is provided in Appendix 1.

Drug developers should use the assessment table as a tool for communication between drug developers and regulatory authorities, across multidisciplinary teams, to increase transparency and provide an understanding of the proposed MIDD strategy, its implementation, and available results with respect to provision of MIDD evidence. Early alignment with regulatory authorities facilitates subsequent acceptance of MIDD evidence.

Within the following subsections, definitions for each part of the assessment table are provided followed by instructions with respect to their use. An example of a completed assessment table is provided in the supplemental official ICH training materials to illustrate the concept and the thought process on how to fill out the assessment table.

2.1. Key assessment elements

The key assessment elements include question of interest, context of use, model influence, consequence of wrong decision, model risk, and model impact. Model risk and model impact are the outcome of risk and impact assessment, respectively. Model risk is the combination of model influence and consequence of wrong decision and is essential for determining the requirements for model evaluation. All key assessment elements are expected to be included in the assessment table regardless of whether it is used at the planning or submission stages. A clear understanding of these elements is considered essential for planning, evidence assessment, and communication. The key assessment elements are described in the following subsections. For each assessment element that is rated low, medium, or high, justification is always expected and essential in enabling the assessment.

2.1.1. Question of interest

The question of interest is the question that MIDD is intended to answer. The question of interest should be explicitly stated. It should reflect and inform multidisciplinary assessments and regulatory decision-making. It should be noted that the question of interest can be broader than the intended use of the model(s). It should reflect information needed for the drug development program given the development stage and/or product lifecycle status. If MIDD is planned to answer different questions of interest, it is recommended to use separate tables for each question.

2.1.2. Context of Use

The context of use should be outlined as a concise, clear, and explicit description of the role and scope of the model(s) used to answer the question of interest. It should include a description of the model, its role and scope, the data used to build the model, and any additional data or evidence that will inform the answer to the question of interest. The additional data or evidence can include evidence from clinical trials or nonclinical experiments, post-marketing, or real-world evidence that will inform the answer to the question of interest.

[6] Some concepts in this assessment framework/table have been modified from: The American Society of Mechanical Engineers (ASME). V&V 40 - Assessing Credibility of Computational Modeling Through Verification and Validation: Application to Medical Devices. ASME V&V 40-2018.

2.1.3. Model influence

Model influence is the intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.

Model influence should be described and rated as low, medium, or high, and then the rating justified. The description, rating, and justification should focus on the weight of the model outcomes in relation to the other relevant information used for answering the question of interest. The model influence rating should increase from low to medium to high as the weight of model outcomes increases.

In general, when model outcomes are the sole source to support the decision, model influence should be considered as high. If there is considerable data and evidence coming from other relevant sources, the model influence may be rated low or medium depending on the weight of the model outcomes.

2.1.4. Consequence of wrong decision

The consequence of wrong decision refers to the potential negative effect (e.g., on patient safety and/or lack of efficacy) resulting from an incorrect decision based on all available information.

Consequence of wrong decision should be described and rated as low, medium, or high, and then the rating justified.

The rating for consequence of wrong decision should take into consideration both the severity of potential negative effects as well as the likelihood that a wrong decision will result in potential negative effects. Both of these factors should be considered based on all available information at the time of regulatory interaction (e.g., nonclinical data, clinical data, prior information, and knowledge) and then combined to generate a rating for consequence of wrong decision.

2.1.5. Model risk

Model risk is 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. Model risk should be described and rated as low, medium, or high, and then the rating should be justified. The rating should increase from low to medium to high as the ratings for model influence and/or consequence of wrong decision increase. In general, if the ratings for both model influence and consequence of wrong decision are low, model risk is low. If the ratings for both are high, model risk is high. When the ratings for model influence and consequence of wrong decision differ, the model risk rating may be driven by the most influential of the two items; these considerations should be captured in the justification.

Model risk is key for determining the requirements for model evaluation and is used for MIDD planning, communication, and evidence assessment. Model evaluation should at minimum meet the current accepted standards and be commensurate with the model risk (see Section 3).

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.

2.1.6. Model impact

Model impact reflects 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.

Model impact should be described and rated as low, medium, or high, and then the rating should be justified.

The rating should increase with the degree to which the MIDD strategy varies from current regulatory standards, or expectations when no regulatory standard is in place.

Model impact is used for MIDD planning, communication, early alignment, and evidence assessment.

2.2. Additional considerations for interaction with regulators and to inform decision-making

In addition to the key assessment elements described in Section 2.1, technical criteria, appropriateness of proposed MIDD, evaluation of model(s) and model outcomes, and outcome of the MIDD evidence assessment should be included to inform decision-making related to MIDD planning and/or MIDD evidence submission and should be provided to regulators to support regulatory interactions.

Technical criteria and appropriateness of proposed MIDD can be discussed as early as the planning stage in conjunction with key assessment elements.

A summary related to evaluation of model and model outcomes should be submitted once the analysis is completed and ready for regulatory submission.

The outcome of the MIDD evidence assessment should be provided at the MIDD evidence submission stage.

2.2.1. Technical criteria

Technical criteria are key criteria for evaluating the model[7] and model outcomes, and that are needed to inform MIDD evidence acceptance, contributing to the answer to the question of interest.

A clear and concise description of and rationale for the technical criteria, which are specific to the question of interest, should be provided in the assessment table.

As part of predefining technical criteria, drug developers should outline how this is commensurate with model risk. The details of technical criteria should be provided in appropriate documents (e.g., in a model analysis plan [MAP] or regulatory interaction background materials; see Section 4).

2.2.2. Appropriateness of proposed MIDD

The appropriateness of proposed MIDD is the rationale for why the proposed MIDD is suitable to answer the question of interest.

To facilitate regulatory interaction, most importantly at the planning stage, drug developers should provide a brief discussion of why and how the proposed MIDD is considered appropriate for answering the question of interest. Drug developers are encouraged to consider aspects of the key assessment elements to provide justification for appropriateness. Information on how the technical criteria are suitable to ensure the appropriateness of the model outcomes for generating MIDD evidence should be included.

[7] General technical standards for model evaluation are addressed in Section 3.

2.2.3. Evaluation of model(s) and model outcomes

Evaluation of model(s) and model outcomes is a brief discussion of the key results and conclusions of the technical evaluation of the model and model outcomes.

To facilitate regulatory interaction at the MIDD evidence submission stage, drug developers should include a concise summary of the technical evaluation of the model and model outcomes and describe how they fulfill the technical criteria. A detailed evaluation of model and model outcomes should be provided in appropriate documents (e.g., in a model analysis report [MAR] or regulatory interaction background materials; see Appendix 2). For additional details on model evaluation, refer to Section 3.

2.2.4. Outcome of the MIDD evidence assessment

The outcome of the MIDD evidence assessment is the multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence. This should integrate all of the assessment elements and be summarized.

Once model outcomes are determined to be MIDD evidence, it should be used to answer the question of interest. A concise summary of the MIDD evidence and its use should be provided. MIDD evidence can be used in combination with other relevant information and/or evidence to answer the question of interest.

3. Model evaluation

This section provides an overview of model evaluation elements (i.e., verification, validation, and applicability assessment[8]) and related general recommendations. These elements should be used to determine the acceptability of the model(s) to answer the question of interest, forming the basis of MIDD evidence assessment to inform related decision-making (see Section 2). Model evaluation should at minimum meet the current accepted standards, if available, and/or established scientific practices associated with the specific M&S method(s) (see Section 1.3) and be commensurate with model risk (see Section 2 and Section 2.2.1).

Descriptions of model evaluation and related general recommendations in this section are intentionally presented at a high level to facilitate use across M&S methods. Adopting these recommendations ensures that appropriate actions have been taken to inform decision-making.

The elements of model evaluation are defined as follows:

- Verification activities aim to ensure user-generated codes for processing the data and conducting the analysis are error-free, equations reflecting the model assumptions and their representation in the programming language or software are correct, and calculations are accurate.
- Validation and applicability assessment (also referred to as "fit-for-purpose") activities aim to assess the model performance and robustness. These activities include assessing the adequacy and relevance of the following: the data, the model's conceptual form (e.g., overall structure and complexity), the model assumptions, the approach to model development, the graphical and numerical diagnostics, and the external validation. Validation focuses on the overall comparison of the model versus data, prior information, and knowledge, while applicability assessment focuses on the adequacy of the data and model for each intended use.

[8] Model applicability is not interchangeable with appropriateness of proposed MIDD. As described in Section 2.2.2, appropriateness assesses whether the proposed MIDD strategy is suitable, while applicability assesses whether the data and model are adequate for their intended use.

The following are general recommendations for the model evaluation elements:

Verification

- Verification of the key user-generated codes, equations, and calculations should be documented and available for review by regulatory authorities.
- Modeling activities should use a valid computerized system that is reliable, reproducible, and traceable. Documentation of appropriate software testing should be available.
- Compliance with appropriate quality assurance is expected for data management and modeling activities.

Validation and Applicability Assessment

- The relevance and appropriateness of the data to answer the question of interest should be justified. The rationale for exclusion of data should be provided and the potential for bias assessed. In general, data selection, associated transformations, and imputations should be specified, justified, and documented in the MAP and MAR.
- The model structure and parameters should be consistent with the available knowledge on drug characteristics, pharmacology, physiology, and disease pathophysiology, when relevant.
- Limitations of the data and model should be described and discussed.
- Key M&S assumptions[9] should be identified, described, and justified, and alternatives considered.
- M&S method-specific issues should be considered (e.g., selection bias for model-based meta-analysis, knowledge gaps for a mechanistic model, or overfitting for an artificial intelligence/machine learning model).
- Model robustness should be assessed to characterize the dependency on data, parameters, parameterization, assumptions, and associated uncertainty (e.g., sensitivity analysis).
- Model performance (e.g., precision and bias) should meet general technical standards associated with the specific M&S method(s) and should be assessed using graphical and numerical metrics. The metrics that relate to the question of interest and associated analysis objective(s) should be prioritized in model evaluation.
- As indicated in Section 2.2, drug developers are encouraged to gain alignment with regulatory authorities on technical criteria as part of the MIDD using the assessment table.
- External validation with independent data is encouraged in order to assess the adequacy of model performance. Depending on the question of interest, context of use, and model risk, external validation can further increase confidence and in some cases can be essential for the model's proposed application.
- Simulation methods and scenarios should be described sufficiently to enable the evaluation of their plausibility and the relevance to model applicability and should account for parameter and assumption uncertainties.

[9] M&S assumptions include but are not limited to data handling (e.g., imputation), model structure and parameters (e.g., derived or fixed based on prior information), and mathematical or statistical aspects of the model.

- Predefined MAPs covering the planned model evaluation activities and technical criteria are recommended (see Section 4.1). Changes to the planned analyses should be justified, and these should be documented in the MAR.

4. MIDD reporting and submission

This section provides recommendations on MAPs (Section 4.1), MARs (Section 4.2), and documentation for regulatory interactions and submissions (Section 4.3).

4.1. Model analysis plan (MAP)

It is recommended to pre-define[10] and document each intended model analysis in a MAP. A MAP typically includes an introduction, objectives, data, and methods, which align with the corresponding MAR sections (Appendix 2). Planned model evaluation activities and technical criteria should be described in the MAP. For regulatory interactions, providing a MAP that defines the M&S can facilitate discussions.

4.2. Model analysis report (MAR)

The results of each model analysis submitted to regulators should be documented in a MAR. Descriptions of the typical MAR sections are provided in Appendix 2. The MAR structure can be adjusted to meet the needs for reporting specific M&S methods. If a MAP was developed, it should be provided as an appendix within the associated MAR. Changes to the planned analyses should be justified and documented. M&S results should be described, and interpretation of results and model evaluation should be discussed.

4.3. Documentation for regulatory interactions and submissions

The following are general recommendations for documentation of MIDD planning as well as evidence reporting and submissions:

- The assessment table should be used as a communication tool throughout interactions with regulatory authorities during the MIDD planning stage and MIDD evidence submission stage.
- New questions of interest may emerge requiring separate assessment tables, and the associated plan could evolve as data and knowledge accumulate. Some of these iterations may require engagement with regulatory authorities to gain alignment on the MIDD planning.
- Additional documents relevant to MIDD planning or model use in the generation of MIDD evidence, such as individual MAPs or MARs, should be cross-referenced within the assessment table and other relevant regulatory documents.
- The assessment table should be included in the most appropriate section(s) of the respective regulatory documentation (e.g., regulatory interaction background materials and Common Technical Document sections) in line with the question of interest.

[10] For the purposes of this guideline, "pre-define" refers to documentation prior to accessing the data or performing the analysis, as appropriate considering the context of use.

- Additional details supporting the assessment table and not captured in the MAR(s) (e.g., when a question of interest emerges after MAR finalization and a new MAR is not produced) should be described in other relevant regulatory documents. These details may include but are not limited to the following.
    - Further descriptions of the integration of multiple models or multiple sources of evidence to answer the question of interest.
    - Additional evaluation and discussion of model(s), model outcomes, and technical criteria related to the specific to the question of interest.
- Inclusion of a summary of previously received regulatory feedback (including regulatory assessment, if possible) on the MIDD is encouraged to be provided within regulatory interaction background materials and other relevant regulatory documents.
- All documents and files supporting submitted MIDD evidence, including data used in M&S analyses, relevant coding scripts (e.g., the base and final models for population pharmacokinetics including dataset building), definition files, and other relevant electronic files used should be submitted or available for regulatory review and assessment.

APPENDIX 1 - 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.	
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,	Provide a clear and concise description of, and rationale for, the technical criteria, which are specific to the question of interest.	

Item	Definition	Instruction	Entry
	contributing to the answer 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).

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.

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.

APPENDIX 2 - Model analysis report content

This appendix provides the content typically found within a MAR, although the content and structure should be adapted to the specific M&S methodology employed. As noted in Section 4.3, a single MAR or multiple MARs can provide model outcomes to answer question(s) of interest. The sections of the MAR, especially the objectives, may align directly with particular question(s) of interest or may have a broader perspective.

When a MAR describes model outcomes intended to be MIDD evidence to support the answer to a specific question of interest, the details associated with elements of the assessment table (e.g., technical criteria, model outcomes) can be included in the MAR and cross-references to the relevant assessment table elements may be included.

Sections	Content
Executive Summary	• An overview of the rationale for the analyses • A brief summary of the data and methods • A brief summary of the results and conclusions
Introduction	• The rationale for the analyses • Relevant background information and knowledge • If applicable, a description of pre-existing analyses with reference to previously submitted reports
Objectives	The objectives of the analyses including the intended application of the model. These may align directly with particular question(s) of interest or may have a broader perspective.[1]

Data and Methods	Descriptions of the following:
	• Data sources
	  ○ Criteria and rationale with respect to source data inclusion and exclusion
	  ○ Relevant design features of studies and/or experiments
	• M&S methods, computational platforms, model development, assumptions, and strategic approaches (e.g., the sequence of development, numerical methods; see Section 2 and Section 3)
	• Approaches for model evaluation (i.e., verification, validation, and applicability assessment; see Section 3)
	• If relevant, prediction and simulation methods and scenarios
	• Detailed technical criteria for model evaluation and model outcomes[1]

Results	• Data description, including graphical and/or tabular displays, as appropriate. Data excluded during the analyses should be described along with the appropriate rationale. • The results of model development and model evaluation, with predictions and simulations (e.g., parameter estimates, related uncertainty) as graphical and/or tabular displays

Sections	Content
	• The detailed results of the assessment against the technical criteria for model evaluation and model outcomes[1] • If relevant, deviations from the MAP should be described and justified.
Discussion	Interpretation of results, including data and model adequacy, limitations of the data and model, and clinical and/or other implications, taking into account: • Deviations from the MAP • Model evaluation and model outcomes[1] (including technical criteria[1] and model applicability) • Relevant nonclinical and clinical information and knowledge, if applicable
Conclusions	The conclusions of the analyses
Appendices	Additional materials cross-referenced in the MAR, for example: • A references list covering the sources of data used for the analyses (e.g., bioanalytical reports, clinical study reports, laboratory reports, or literature) • Supplemental data descriptions and model development and evaluation results, including graphical and/or tabular displays, as appropriate • The user-generated code for the relevant model(s)

[1] When a MAR describes model outcomes intended to be MIDD evidence to support the answer to a specific question of interest, the details associated with elements of the assessment table (e.g., technical criteria, model outcomes) can be included in the MAR and cross-references to the relevant assessment table elements may be included.

APPENDIX 3 - Glossary

The following list of key terms and definitions is intended to promote consistent understanding and application of this Guideline:

Appropriateness of proposed MIDD:

The rationale for why the proposed MIDD is suitable to answer the question of interest.

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.

Context of use:

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

Evaluation of model(s) and model outcomes:

A brief discussion of the key results and conclusions of the technical evaluation of the model and model outcomes.

MIDD evidence:

Model outcomes that have been determined by application of the MIDD evidence assessment framework, including model evaluation, to be appropriate to inform the answer to the question of interest.

MIDD evidence submission stage:

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.

MIDD planning stage:

Any timepoint when drug developers are planning MIDD activities, generally prior to availability of model outcomes relevant to the 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.

Model evaluation:

Model evaluation refers to performing verification, validation, and applicability assessment of the model.

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.

Model influence:

The intended weight of the model outcomes in decision-making considering the contribution of additional data or evidence.

Model-Informed Drug Development (MIDD):

The use of computational M&S methods that can include and integrate nonclinical data, clinical data, prior information, and knowledge (e.g., drug and disease characteristics) to generate evidence to

inform drug development and decision-making by drug developers, regulatory authorities, and other stakeholders.

Model outcomes:

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. These can be assessed as MIDD evidence using the MIDD evidence assessment framework.

Model risk:

The contribution of the model outcomes to a possible wrong decision and subsequent potential undesirable consequences.

Multidisciplinary team:

A team of subject matter experts from functional areas relevant to the question of interest and context of use.

Outcome of the MIDD evidence assessment:

The multidisciplinary team's assessment and conclusion on whether the model outcomes are considered MIDD evidence. "Assessment" in this context does not refer to any regulatory review activities or processes.

Question of interest:

The question that MIDD is intended to answer.

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.

User-generated code:

Instructions written by the user of a programming language or software.

Validation and applicability assessment:

Activities that aim to assess the model performance and robustness.

Verification:

An activity that aims to ensure user-generated codes for processing the data and conducting the analysis are error-free, equations reflecting the model assumptions and their representation in the programming language or software are correct, and calculations are accurate.