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Single Day Events

***Clinical Data Standards in the Era of AI & ML* -**
Achieving Efficiency in Programming, Analysis and Submission

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From Standards to Strategy: Enabling Exposure–Response Modelling with AI under ICH M15

Enabling Model-Informed Decisions through Standardized Data in the AI Era

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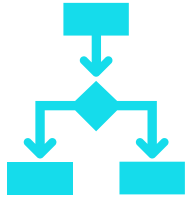
Disclaimer

The views and opinions expressed in this presentation are my own and do not necessarily reflect those to my organization . All information is presented for educational and informational purposes only .

Why this matters now

🚀AI & MIDD Momentum

📏Regulatory Expectations



🎯Predictive Decision-Making

🔒Trusted Data Foundation

Model-Informed Drug Development (MIDD)

ICH M15: Key Principles

1. Models are evaluated based on a clearly defined ***question of interest***
2. Require a well-specified ***context of use*** (decision-focused application)
3. Assess ***model influence*** relative to other evidence
4. Consider ***risk of incorrect decisions*** and associated uncertainty
5. Evaluate ***model impact*** on development and regulatory strategy
6. **Require transparent, traceable, and reproducible model inputs and outputs**

Role of Exposure–Response Modeling in MIDD

- Quantifies exposure–response variability across patients.
- Supports dose selection & benefit–risk decisions
- Links exposure to clinical endpoints (efficacy, safety, biomarkers)
- Moves beyond MTD to optimal exposure targets
- Uses regression models to predict outcomes

Current challenges in enabling model-informed analytics

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Data & Integration

Fragmented clinical, PK, and exposure data
No unified structure across key endpoints

Workflow Efficiency

Repeated re-derivation across analyses
Inconsistent exposure–response definitions

Traceability

Limited lineage from source to model
Poor transparency of model-ready inputs

Regulatory Readiness

Challenges meeting ICH M15 expectations
AI outputs not yet submission-ready

ADER: The Standardized Dataset for Model-Ready E-R Analysis

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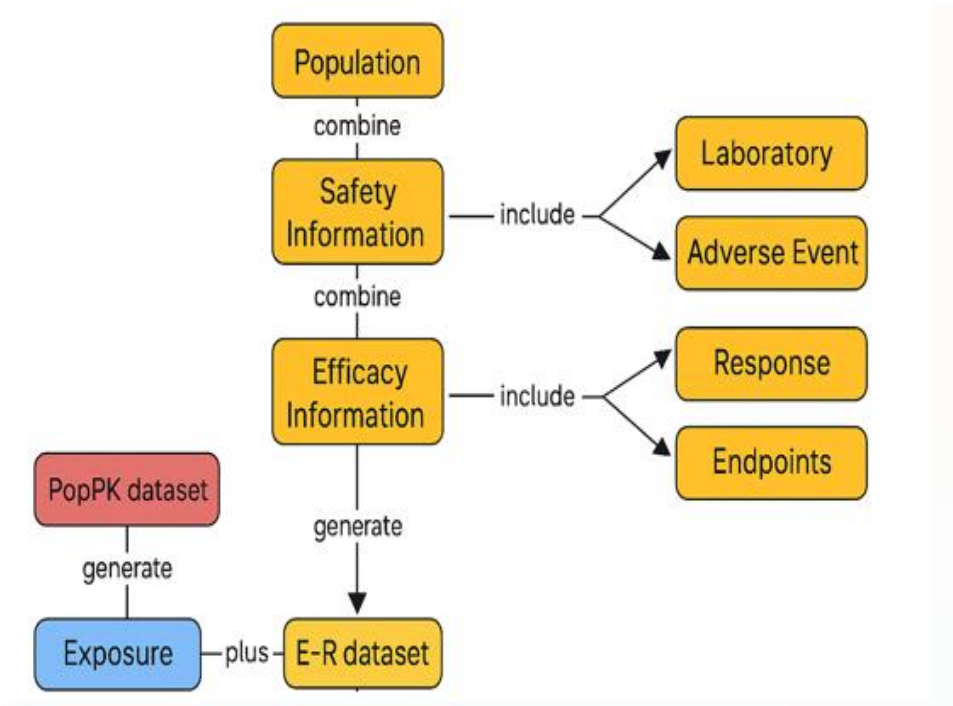
🌐 **Unified Data Source**
🔗 ADSL + ADPPK + ADAE seamlessly integrated into a single subject-level dataset

🧠 **Efficient Modeling**
⚡ Pre-linked exposure and response data enables faster, analysis-focused modeling

🔍 **Traceable & Consistent**
🏔️ Clear SDTM → ADaM → ADER flow ensures reproducibility and audit readiness

📏 **ICH M15 Aligned**
📖 Transparent, reviewable inputs supporting model-informed drug development



The Transformative Role of AI in E-R Modeling: From Data Creation to Analysis

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AI-Driven Automation of ADER Creation	1. Automated Implementation of Analysis Logic: 2. AI-Assisted Code Generation 3. Intelligent Quality Control
Enhancing E-R Analysis and Interpretation	1. Discovering Complex Relationships: 2. Identifying Key Drivers and Interactions: 3. Enabling Explainable Insights

Standards provide the foundation, AI/ML accelerates and enhances efficiency

Achieving Efficiency in ER Modeling through Standards + AI

Efficiency Gains Across Workflow

Step	Traditional Approach	AI/ML + Standards Approach
Data Standardization	Manual mapping	Automated mapping
Data Cleaning	Rule-based checks	Intelligent anomaly detection
Analysis	Predefined models	Flexible, data-driven models
Interpretation	Static outputs	Dynamic, explainable insights (SHAP)

Combining standardized data with AI transforms static workflows into efficient, scalable, and insight-driven exposure–response analysis

Phase II Case Study

Workflow

ADER integrates exposure, demographic, efficacy, and safety data into a single model-ready layer. The workflow then applies multi-task machine learning to estimate tumor response, adverse-event risk, and dose optimization opportunities.

High-level for XGBoost and SHAP

XGBoost is a gradient boosting algorithm that builds multiple decision trees sequentially to minimize prediction error.
Object function is to minimize:
$l(yi, \hat{y}i)$ → loss (error) + control the complexities hidden in the data

After each iteration :

1. Computes prediction error :
   Residual = yi - $\hat{y}i$

2. Computes the gradient :

$$g_i = \frac{\partial l(y_i, \hat{y}_i)}{\partial \hat{y}_i}$$

Measures the **rate of change** of one variable with respect to another.

3. Update the prediction by specifying the learning rate.
Prediction is done based on summation of all trees to output probability of response.

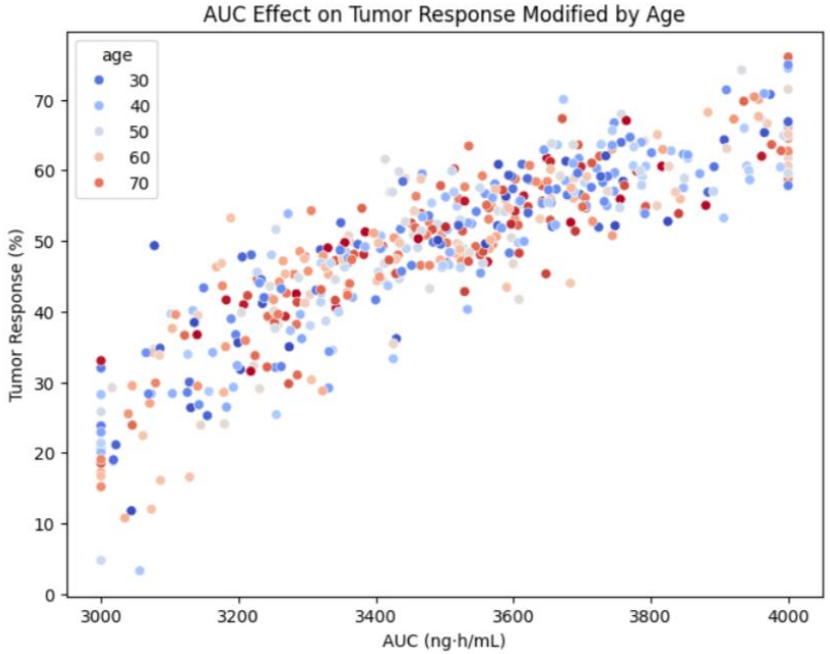
SHAP (SHapley Additive exPlanations) explains model predictions by assigning each feature a contribution using Shapley values from game theory.

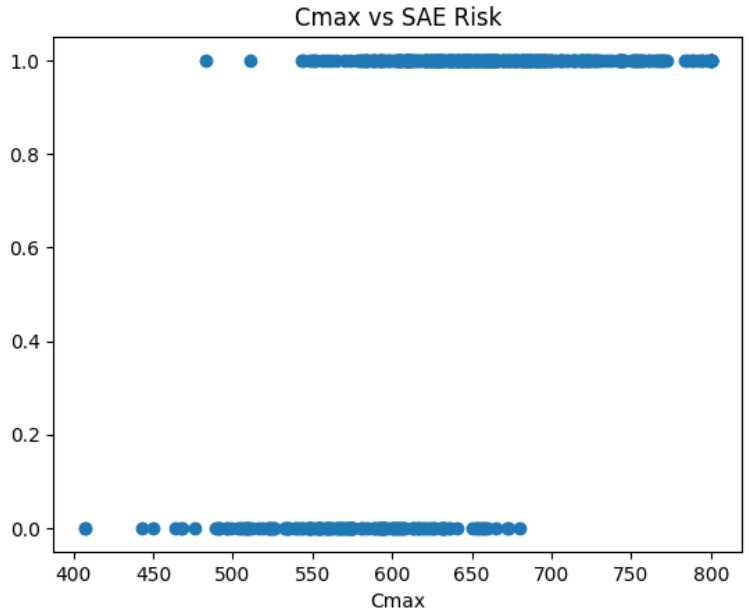
Intuition :
ϕi=average marginal contribution of feature 'i'

For feature i :
Consider all subsets "S"
Add variable 'i'
Measure change in prediction

SHAP gives you:
1. Feature importance
2. Direction of effect
3. Individual explanation
4. Detection of thresholds

Phase II Case Study Continued





Key findings :

- Nonlinear AUC–response relationship with plateau beyond ~3400–3800 (ng·h/mL)
- Age modifies exposure–response dynamics .
- Sharp increase in SAE risk above Cmax ~550 (ng/mL)
- Optimal window: AUC 3400–3800 (ng·h/mL) & Cmax <550 (ng/mL)

Benefit-Risk Optimization

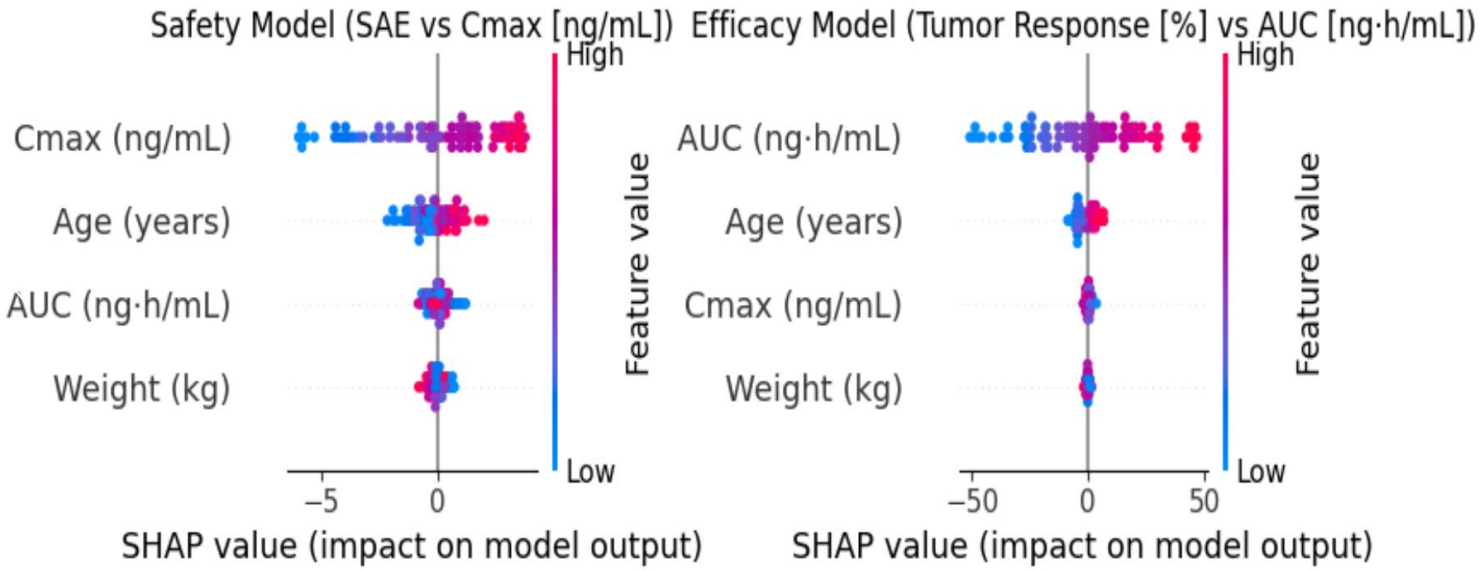
An optimal exposure range was identified (AUC: 3400–3800, Cmax <550), balancing efficacy and safety. The model correctly predicts patient safety outcomes in 84% of cases, indicating strong performance in identifying risk patterns.

Personalized Dosing : The AI model provides individualized risk predictions and suggested patient-specific exposure targets, enabling precision dosing strategies.

AUC - Area under the curve

Cmax – Maximum Concentration (highest amount of drug measured in the bloodstream or a targeted organ after administration)

Phase II Case Study Continued



Key insights:

Safety Model:

- Cmax (ng/mL) is the dominant driver of SAE risk, showing the largest impact.
- Higher Cmax values (red points) are consistently associated with increased SAE risk, confirming a strong, monotonic toxicity relationship.
- Other covariates (age, AUC, weight) show minimal contribution, indicating: Safety is primarily exposure-driven (peak concentration)with limited influence of patient characteristics

Efficacy Model:

- AUC (ng·h/mL) is the dominant driver of tumor response, showing the highest impact on model predictions.
- Increasing AUC is associated with progressively higher efficacy, confirming a strong exposure–response relationship
- Age moderately modifies response, indicating variability in treatment benefit across patient groups
- Other variables (Cmax, Cmin, weight) show minimal contribution to efficacy, reinforcing AUC as the primary determinant

SHAP = SHapley Additive exPlanations

From Standards to Strategy: Enabling E–R Modeling under ICH M15

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Role of ADER in Supporting ICH M15 Compliance
Standardized ADER dataset provides:

- Clearly defined **model inputs** (exposure, efficacy, safety)
- **Consistent and reusable data structure** across analyses
- Ensures:
  Traceability (SDTM → ADaM → ADER → Model outputs)
  Alignment between **MAP planning** and **MAR reporting**

Supports MAP (Model Analysis Plan)

- Data-driven identification of E–R relationships
- Detects nonlinear patterns & covariate effects
- Guides model structure and variable selection

Supports MAR (Model Analysis Report)

- SHAP provides interpretable model outputs .
- Explains feature contribution (AUC, Cmax, etc.)
- Enhances transparency and traceability

The future of exposure–response modeling is not replacing traditional methods with AI but integrating AI-driven insights with structured data and interpretable models to support reliable, transparent, and regulator-ready decisions.

Conclusion and Key Takeaways

Data Ingestion

Standardization is the Catalyst

Accelerated & Precise Decisions

Integration over Replacement

Regulatory Readiness

References

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THANK YOU!