Emerging Programs AI Workgroup Meeting #3

Date: 03/13/2025

Topic: Dosing/Dose Regimen Optimization

Overview and Current Issues:

The application of Artificial Intelligence (AI) and Machine Learning (ML) in clinical trials is increasingly gaining traction, particularly in the area of dose and dosing regimen optimization. This meeting, the third in the Emerging Programs workgroup series, focused on how AI-driven approaches can enhance dosing strategies by addressing key challenges such as patient variability, pharmacokinetics (PK), pharmacodynamics (PD), and exposure-response interpretation.

Traditional dose optimization methods rely heavily on expert-guided pharmacometric models, which can be complex, labor-intensive, and limited in scalability. AI offers an opportunity to improve efficiency, accuracy, and personalization in dose selection—especially through data-driven modeling, causal inference, and simulation-based scenario testing. Despite the potential, challenges remain in data variability and noise, regulatory compliance, model interpretability, integration with existing workflows, and cultural readiness within clinical development teams.

Meeting Key Points:

- **Three-Tier AI Framework:** James Lu (Genentech) emphasized a structured view of AI's role:
    - **Tool** (Level 1) – to automate manual processes like code generation and data visualization
    - **Assistant** (Level 2)– to augment and improve conventional modeling (e.g. by introducing nonlinear assumptions to better describe the data)
    - **Partner** (Level 3)– to push the boundaries of what can be predicted using deep learning and pharmacology-informed models.
- **Causal Inference and Exposure-Response:** Robust exposure-response modeling requires understanding cause-effect relationships (i.e. causal awareness). James presented how

causal diagrams are critical in understanding trial design complexities (e.g., induction vs. maintenance phases) and identifying confounding factors.

- **Integration with Pharmacological Principles:** Pharmacology-informed neural network (PINN) architectures were highlighted for their ability to encode PK/PD assumptions within neural models. This helps maintain interpretability and enables "what if" simulations (i.e. counterfactual simulation) for untested dosing regimens. Neural networks learn to improve the model as the amount of data increases and learn to obtain useful abstractions of patient data.
- **Extrapolation and Real-World Simulation:** AI models must not only learn from existing data but also extrapolate to new scenarios. Demonstrations included simulating patient responses to alternate dosing schedules not included in the original training dataset.

Case Examples presented:

Guest speaker James Lu shared several applications from Genentech illustrating AI's practical impact on dose optimization, including:

- **Casually Aware Machine Learning from Phase 3 Trials in Ulcerative Colitis**
  - A causal modeling framework using XGBoost and over 60 explanatory variables showed a clear exposure-response relationship during the induction phase. Results suggested improved remission rates with higher dosing.
- **Pharmacology-Informed Neural Network Architectures in HER2-positive Metastatic Breast Cancer**
  - A deep learning approach that combined traditional PK/PD principles with neural networks to simulate causal relationships, unseen or alternate dosing regimens and predict patient response time course in patients with HER2-positive metastatic breast cancer in patients failing treatment beforehand. Results suggested improved prediction metrics to inform personalized dosing considerations.

Challenges & Solutions to Adoption:

Challenges	Description
Data Variability and Noise	Variability in patient data and limited clinical sample sizes can affect model robustness.
Complex Biological Responses	Nonlinear, multi-factorial biological systems challenge simple model and causality assumptions.
Regulatory Hurdles	While FDA guidance is evolving, there's still a need for clear standards on AI validation.
Tooling and Integration Barriers	Lack of easy-to-use AI tools and interoperability with legacy systems impedes adoption.
Cultural and Educational Gaps	Clinical teams may lack familiarity or confidence in interpreting AI-generated insights.

Proposed Solutions:

- **Transfer Learning and Pretraining** using preclinical or historical datasets to initialize models and improve performance in small-sample settings.
- **Agentic Workflows** utilizing AI agents and large language models (LLMs) to automate data wrangling, transformation, and coding tasks.
- **Understand the Biology** by leveraging existing literature to optimize the model and improve enrichment based on a better biological understanding**.**
- **Cross-functional Education** to build trust and interpretability across pharmacologists, statisticians, and operational teams.
- **Open-source and Standardization Efforts** for model validation, data formatting, and best practices in AI application.

Perspectives:

Sponsors note opportunities for:

- Greater AI integration in dosing optimization to improve efficiency and enhance patient outcomes while ensuring regulatory compliance.
- Fully operationalizing AI use by overcoming hesitancy to change culture and practices.

Regulators comment on:

- The importance of robust validation methods and transparency in AI-driven decision-making to maintain trust and adherence to regulatory standards.

Tech/AI organizations note:

- AI can help build and optimize models and open up opportunities to combine data and different typology of models to create greater efficiency.

Future Directions:

1. **Operationalize AI Models**: Develop SOPs and decision support tools to embed AI in trial design and conduct.
2. **Personalize Dosing at Scale**: Expand neural PK/PD models for therapeutic drug monitoring and real-time adaptation.
3. **Integrate Genomic and Multi-Modal Data**: Incorporate genetics, biomarkers, and digital health data in future AI systems to enhance precision.

4. **Combine different approaches:** Use AI to bridge and combine approaches, especially in dosing, such as leveraging qualitative systems pharmacology (QSP) models with PK/PD approaches, to expand simulation capabilities.

5. **Clarify Regulatory-Grade Model Validation**: Broad co-development of AI models with regulators and publication of case studies will provide clarity and build trust.
6. **Share Knowledge and Data**: As data accumulates, AI can assist to improve models, increase applicability, and potentially overcome data gaps. CTTI will launch a dedicated webpage to house these meeting summaries, along with contributed slides, pre-reads articles, and potential future briefs or webinars for broader community access and engagement.