PharmaSUG 2024 - Paper SI-190

Navigating Success: Exploring AI-Assisted Approaches in Predicting and Evaluating Outcome of Clinical Trials and Submissions

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ABSTRACT

Moving beyond the prevalent application of Artificial Intelligence (AI) in drug discovery in pharmaceutical industry, this paper aims to underscore the broader benefits of AI in predicting and evaluating outcomes of clinical trial and regulatory submissions. With the goal of aiding sponsors to mitigate risk factors for higher success rates and foster cost-effective strategies, it provides a comprehensive brainstorm on 1) Identifying potential issues that might trigger regulatory concerns via AI modeling of historical data; 2) Evaluating clinical trials through multidimensional analysis to enable proactive early interventions that heighten probability of favorable outcomes and boost trial success rate.

The discussion extends to the strategic organizational setup and workflow to implement wide-ranging AI techniques and innovative approaches to meet the goal, underlining the cross-functional collaboration and adaptive strategies.

This paper is poised to contribute to the growing discourse on how AI assisted approaches can empower informed decision-making, optimize resource allocation, and increase profitability for sponsors with promising drug candidates, and ultimately benefit patients through receiving approved treatments earlier.

INTRODUCTION

FACTS OF SUBMISSIONS Historically, probability of overall success from Phase I clinical trials to New Drug Application (NDA)/Biologic License Application (BLA) approval hovers around 10%, while Hematology had the highest and Oncology had the lowest of the likelihood of approval. Failures occurred due to lack of clinical efficacy (40%-50%), unmanageable toxicity (30%), poor drug-like properties (10%-15%), and lack of commercial needs and poor strategic planning (10%) (Sun et al, 2022). Likewise, regulatory submissions face various risks from inadequate trial designs, data inconsistencies, or incomplete guidelines adherence lowering chances of approval· Food and Drug Administration (FDA) issues complete response letters for over 30% NDA, requesting additional data and trials, which further extends development timelines. This signifies an imperative need for predicting and evaluating trial outcomes and submission success to mitigate downstream impact to sponsors and patients.

CHALLENGE OF PREDICTIONS However, rising trial complexity from increasing data volumes, protocol intricacies, combination therapies, and expanding trial geographies etc. has made the ability to accurately anticipate trial outcomes and submission result difficult.

ADOPTING NEW METHODS FDA Modernization Act 2.0 was signed into law in late 2022. This legislation endorses cutting-edge alternatives like cell-based approaches, micro physiologic systems, and computer-driven methodologies, such as AI and machine learning. While FDA is embracing AI/ Machine Learning (ML) approaches to streamline its workflow and improve the efficiency of submission reviewing, the advent of AI in pharmaceutical industry also signifies a significant shift from conventional methods of research and analysis. These technologies offer the potential to analyze vast datasets, recognize patterns and factors, and conduct predictive analytics with a level of speed and accuracy previously unattainable. This enhanced predictive capability further allows for timely interventions, optimizing trial designs, and enhancing the success rate of clinical studies.

EXPLORING AI-ASSISTED ANALYSIS

The overarching concept is with help from AI, to analyze past submissions, previous FDA requests and existing data to identify risk factors, determine optimal areas to supplement in advance. It is imperative for companies to utilize tailored solutions to enable expeditious and streamlined clinical research.

IDENTIFYING RISK FACTORS

Table 1 proposes the categories to tackle the potential risk factors along with Agency information request (IR) examples. These risk factors can be evaluated and prioritized to align with the company's goal, ensuring that efforts are directed towards the most impactful areas.

TABLE 1. POTENTIAL RISK FACTORS ILLUSTRATION

Category	Risk Factors	Agency IR Examples
Protocol	Inadequate or flawed Protocol Design.	Requests for more details on clinical trial data and results, such as subgroup analyses, exploratory endpoint data, patient narratives, etc. These fill gaps to fully evaluate efficacy and safety.
Recruitment	Failing to demonstrate the effectiveness of a given intervention.	Requests for more patient population to have adequate statistical power.
	Potential risks associated with prolonged recruitment timelines or a surge in population for global sites.	Requests for the modification of inclusion/exclusion criteria or adjustments to population allocation for a specific site.
Analysis	Failing to adequately represent or analyze certain patient subgroups.	Requests for additional pharmacokinetic, pharmacodynamic, immunogenicity, or other biologic activity data to further characterize product performance.
	Inadequate or unclear Statistical Analysis Methodology.	Requests for clarification on statistical analysis methodologies, excludes, missing data, or questions around population and sample size to ensure appropriateness.
Quality	Non-adherence to Protocol and inconsistent Data Quality.	Requests to analyze how protocol amendments during trials may have impacted the overall results and conclusions.
	Poorly written Submission Documentation Quality.	Requests for sponsor rationale or justification for certain decisions made regarding trial design, endpoints selected, pool ability determinations between studies, etc.
	Insufficient details on manufacturing processes and product quality.	Requests for more details on manufacturing and product quality information, like the validation of analytical methods, stability data, etc.
Pre-clinical Design	Lack of comprehensive preclinical data or justification for Decisions.	Requests for more preclinical data, such as additional toxicology, pharmacology, or animal model testing to answer safety questions.
Regulatory Guidelines	Non-compliance with ever-evolving regulatory guidelines.	Requests for more details on trial monitoring, compliance, and process deficiencies for better trial evaluation.

APPROCHES OF EVALUATION

- **Protocol Design and Feasibility**

Approach: Use AI to analyze past Agency submissions and outcomes, identifying successful protocol characteristics, trends, and flag potential deficiencies; Employ AI models to analyze safety and efficacy data from clinical trials for early identification of risk signals

AI/ML Tools: Neural networks for pattern recognition in historical data.

- **Patient Population and Subgroup Analysis**

Approach: Apply AI analysis to identify confounding variables, determine optimal levels of detail for subgroup analyses; precise inclusion/exclusion criteria

AI/ML Tools: Machine learning models for data segmentation and pattern recognition.

- **Statistical Analysis Methodology**

Approach: Implement AI algorithms to analyze and optimize statistical methodologies based on past FDA submissions and feedback; identify predictive attributes in treated patients with stronger outcomes

AI/ML Tools: Machine learning algorithms for auditing statistical approaches.

- **Adherence to Protocol and Data Quality**

Approach: Implement auditing tools to automatically check for deviations and inconsistencies in trial conduct and data; profiling patients for non-adherence

AI/ML Tools: Computer vision for monitoring trial processes, NLP for analyzing trial documentation.

- **Submission Documentation Quality**

Approach: Leverage AI language models to assist in creating clear, consistent, and regulatory-compliant submission documents.

AI/ML Tools: AI language generation and processing tools.

- **Manufacturing and Product Quality Information**

Approach: Use AI predictive modeling to anticipate areas of FDA concern in manufacturing.

AI/ML Tools: Predictive analytics for smart manufacturing processes.

- **Preclinical Data and Justification for Decisions**

Approach: Utilize AI-based simulation models and ML analysis to predict commonly requested preclinical experiments.

AI/ML Tools: Simulation models and data mining algorithms.

- **Adherence to Regulatory Guidelines**

Approach: Continuously monitor and analyze regulatory updates using AI systems.

AI/ML Tools: NLP and regulatory compliance tracking algorithms.

- **Additional Strategies Consideration:**

Data Integration: Combine clinical trial data with real-world evidence (RWE) and previous submission data for a comprehensive analysis.

Continuous Monitoring: Implement real-time monitoring of clinical trial data to identify and address issues as they arise.

Stakeholder Collaboration: Facilitate communication and collaboration among stakeholders, ensuring alignment on trial objectives and methodologies.

Virtual submission: simulate potential Agency inspections and questions based on historical data.

In summary, AI/ML approaches for mining historical trial data, simulation-based analysis of trial dynamics, predictive analytics around safety/efficacy signals, and extracting insights from prior regulator communications can help evaluate trial outcomes and predict submission approvals.

ENTERPRISE SOLUTION – HUB OF OUTCOME PREDICTION AND EVALUATION (HOPE)

In addressing the imperative need for robust prediction and evaluation within the realm of clinical trials, an innovative solution arises: the creation of a centralized entity termed the Hub of Outcome Prediction and Evaluation (HOPE). This strategic initiative involves the establishment of a dynamic unit equipped with scalable and reproducible AI-assisted workflows. The primary objective is to seamlessly generate actionable risk predictions, thereby enhancing the probability of favorable trial outcomes and successful submissions.

The envisioned HOPE unit acts as a pivotal hub, harnessing the power of advanced artificial intelligence to refine and optimize the predictive capabilities crucial for navigating the intricacies of clinical trials. By leveraging scalable workflows, the solution ensures adaptability to varying trial complexities, offering a versatile platform that aligns with the evolving landscape of pharmaceutical research and development.

Through a commitment to reproducibility, the HOPE unit aims to instill confidence in the generated predictions, fostering reliability across diverse scenarios. This strategic approach not only streamlines the prediction process but also contributes to the overall efficiency of clinical trial management, facilitating informed decision-making at every phase.

In essence, HOPE stands as a beacon of innovation, providing a centralized, technologically advanced solution that propels the industry toward a future where predictive analytics and outcome evaluation are seamlessly integrated, ensuring a higher likelihood of success in clinical trial endeavors.

OBJECTIVES

Build-up an AI/ML assisted evaluation model/system to predict the trial outcomes and submission success. Identify patterns and factors from trial data associated with efficacy readouts and submission approvals.

AI is not the purpose and it's a tool.

WORKING MODEL

Here are four common models: in-house, in-source, full-service partnership, and functional service provider. Each has its advantages and considerations:

1. **In-House Model:**
    - Advantages:
        - Full control and oversight of the project.
        - Direct management of resources.
        - Seamless communication within the team.
    - Considerations:

- May require significant infrastructure and resources.
- Limited scalability for large or complex projects.
- Potential for higher costs and increased workload for internal teams.

2. **In-Source Model:**
    - Advantages:
        - Combines internal and external resources.
        - Allows for flexibility in resource allocation.
        - May leverage external expertise while maintaining control.
    - Considerations:
        - Management challenges related to dual oversight.
        - Cost implications and potential for increased complexity.

3. **Full-Service Partnership:**
    - Advantages:
        - Comprehensive support for the entire clinical trial process.
        - Streamlined communication and collaboration.
        - Use provider side of documentations and systems.
    - Considerations:
        - Close collaboration and clear communication are crucial.
        - Limited footprint for in-house resources.
        - Potential challenges in adapting to specific project requirements.

4. **Functional Service Provider:**
    - Advantages:
        - Specialized support for specific functions.
        - Allows for targeted outsourcing based on expertise.
        - Cost efficiency allowing sponsors to scale resources up or down as needed.
        - Retain internal presence and establish control through the adoption of sponsor standards.
    - Considerations:
        - Dependency on external expertise.
        - Coordination among multiple service providers.

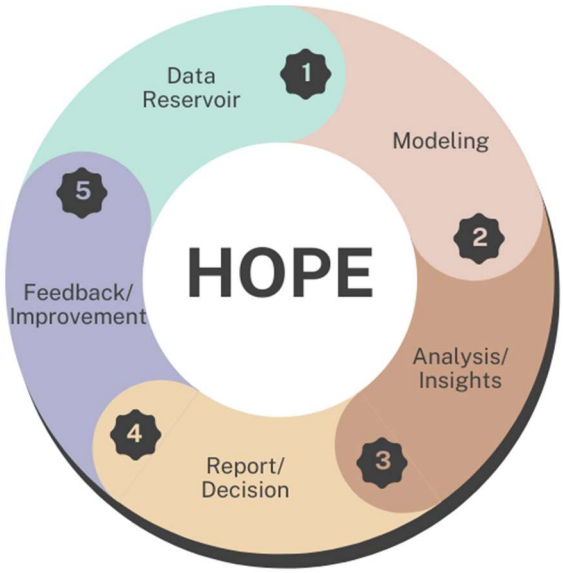
The selection of the most appropriate model hinges on considerations such as project size, complexity, internal capabilities, resource availability, and the desired level of control. Sponsors must thoroughly evaluate their needs and objectives before settling on a model. Success is contingent upon effective

communication and collaboration. Quality is determined by measurements clearly defined by the sponsor, and consistency is anticipated irrespective of the chosen model.

WORKING FLOW:

The depicted working flow is outlined in Figure 1, providing an initial draft of the comprehensive workflow life cycle. This visual representation encapsulates the fundamental steps that guide the progression of tasks and processes. For a more nuanced understanding, the subsequent five steps offer a granular breakdown, delving into intricate details to illuminate each phase of the workflow.

FIGURE 1. FULL LIFE CYCLE WORKFLOW



Step 1: Data Collection and Maintenance

- Work with enterprise data warehouse teams (i.e. IT) to collect historical data of past trials, submissions, regulatory interactions etc.
- Construct cloud-based data lake architecture for storing structured & unstructured data at scale.
- Ingest real-world data feeds like literature publications, Electronic Health Record (EHR) records, genomic databases etc. Set up systems for real-time data collection during ongoing trials.
- Implement pipeline for extracting, transforming, and loading a wide array of heterogeneous datasets.
- Data Preprocessing: Establish criteria for data quality and relevance. Clean, preprocess, and normalize data for analysis. Handle missing data and ensure data privacy and compliance.

Step 2: Prediction/Evaluation Model Development

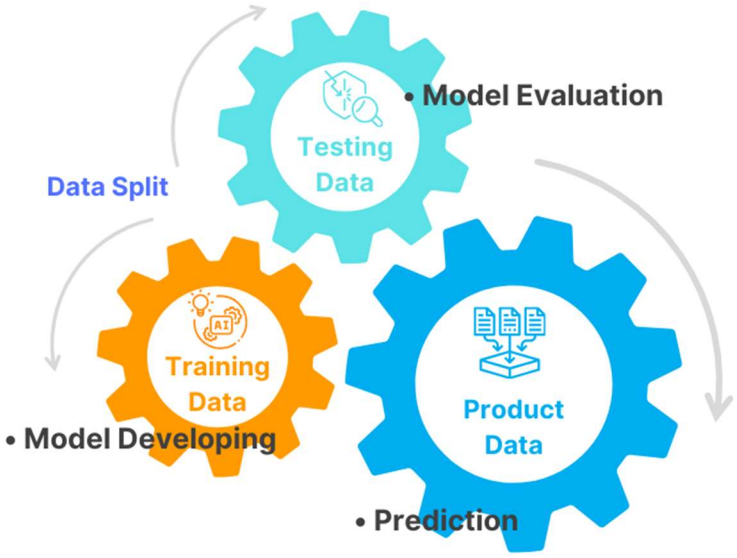
- **Identify Analytical Objectives:**

  Define specific goals and scopes (e.g., predicting trial outcomes and success probability, identifying potential submission issues).

- **Model Selection and Development:**
  - Curate Datasets
    - Comprehensive dataset curation for clinical trials and regulatory submissions
    - Profile available datasets on past clinical trials and regulatory submissions
    - Identify key attributes and outcome variables of interest for training predictive models
    - Meticulous cleaning, preprocessing, and annotation of datasets for machine learning
    - Split data into training, validation and test sets for modeling
  - Develop/select appropriate AI/ML models
    - Explore various modeling methodology/algorithm, i.e. neural networks, random forests, and regression
    - Conduct feature engineering to transform variables into optimal predictive inputs
    - Train models to predict clinical trial outcomes and submission approvals or rejections
  - Model Validation and Testing:
    - Validate models against separate datasets.
    - Test models in simulated environments.
    - Back test models/strategies to assess model reliability and effectiveness in real-world scenarios.

Workflow of Prediction/Evaluation Model Development is illustrated in Figure 2.

FIGURE 2. MACHINE LEARNING WORKFLOW



Step 3: Analysis and Insights Generation

- Conduct AI/ML analyses on collected data, using the evaluation system built up.
- Generate insights related to trial outcomes and potential submission success.
- Collaborate with clinical and regulatory experts to interpret results.
- Translate results into actionable insights.
- Collect insights/feedbacks to improve model performance

Step 4: Reporting and Decision Support

- Generate comprehensive reports detailing AI/ML findings and recommendations, with visual dashboards.
- Include risk assessments and predictive outcomes, highlight predictions and underlying drivers/variables behind the outputs.
- Support decision making, provide recommendations for trial management, resource allocation, mitigate potential risks and sharpen submission strategies.

Step 5: Continuous Improvement and Adaptation

- Collect feedback on AI/ML model performance and outcomes and update and iterate models.
- Continuously retrain and adapt models on new data from ongoing trials and submissions, and keep updated on evolving FDA guidelines, requirements, and regulatory changes
- Version control of models and evaluate updated performance vs older versions.

Additional Notes

- Ethical and compliance considerations
- Ensure patient privacy and data security all the time.
- Training and Development: Provide ongoing training for team members on latest AI/ML technologies, clinical trial methodologies, and regulatory changes.
- Stakeholder Engagement: Engage regularly with stakeholders across the organization to ensure alignment and support for the team's activities.

CONCLUSION

As this paper has explored, AI-assisted approaches for mining trial and submission history data, quantification of risk factors and modeling trial outcomes can strengthen the feasibility and reliability of trial success prediction. A dedicated working unit with focused goals and objectives may offer focused expertise, maximized data utilization, and consistent innovation and development.

"Outcomes are what count; don't let good process excuse bad results". In practice, the focus should remain steadfastly on driving tangible real-world success. Theories, plans, SOPs, and advanced methods may seem robust but not always produce positive outcomes. The true measure of effectiveness of processes lies in the actual results they deliver. This paper not only reinforces the necessity of maintaining an outcome-driven perspective, but also implicates the potential of improving the processes by looking into the possible results ahead. By continually evaluating and refining the processes, pharmaceutical companies can ensure they remain aligned with the ultimate goal of bringing effective and safe treatments to patients efficiently.

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