White Paper

Artificial Intelligence in Drug Development

Navigating emerging regulatory expectations and enhancing clinical trials.

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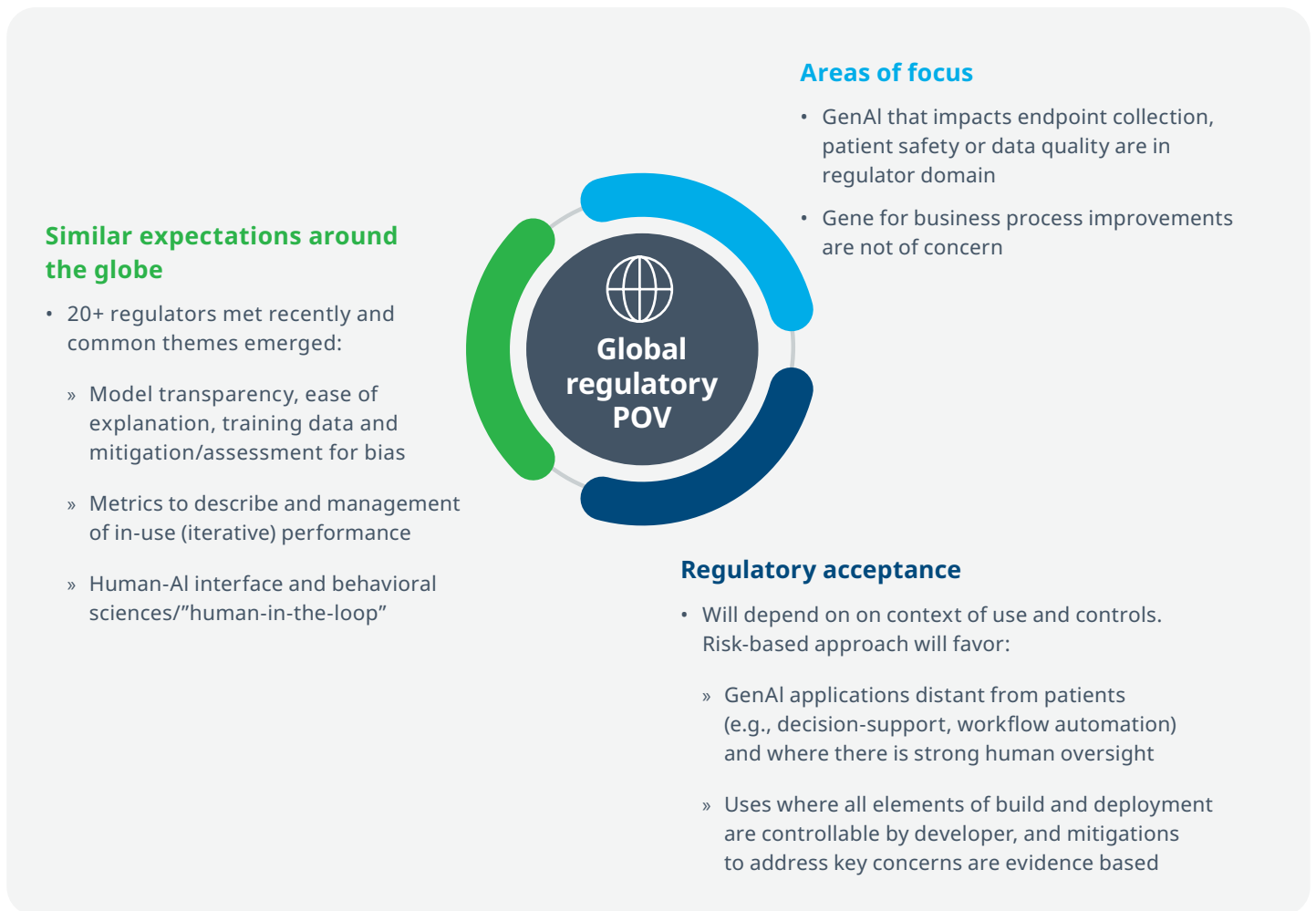
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Introduction

As the possibilities of artificial intelligence (AI) and machine learning (ML) continue to expand, drug developers are exploring ways to use these technologies within clinical trials while maintaining regulatory compliance (Figure 1). From a regulatory perspective, health authorities express openness to the use of AI/ML across a variety of applications throughout the drug development lifecycle, including clinical trials. However, they are still developing regulatory guidelines and defining the parameters necessary to ensure AI/ML usage promotes high standards of safety, quality, and explainability.

AI/ML implementation can be beneficial throughout the drug development lifecycle, from discovery to clinical research to post-marketing safety surveillance and pharmaceutical manufacturing. For sponsors looking to introduce automation during the clinical phase, the first step should be gathering insight into how to implement AI/ML to improve the efficiency, design, and effectiveness of a trial, while bringing regulatory considerations into the process. For drug development organizations hoping to use AI/ML in a clinical trial, project teams should become familiar with how other developers are using these tools to enhance their processes while prioritizing regulatory expectations and mitigating uncertainties. This paper explores some of the regulatory considerations regarding the use of AI/ML in the clinical trial setting.

Figure 1: Regulatory Views on GenAI for Clinical Development

Similar expectations around the globe

- 20+ regulators met recently and common themes emerged:
  - » Model transparency, ease of explanation, training data and mitigation/assessment for bias
  - » Metrics to describe and management of in-use (iterative) performance
  - » Human-AI interface and behavioral sciences/"human-in-the-loop"

Global regulatory POV

Areas of focus

- GenAI that impacts endpoint collection, patient safety or data quality are in regulator domain
- Gene for business process improvements are not of concern

Regulatory acceptance

- Will depend on on context of use and controls. Risk-based approach will favor:
  - » GenAI applications distant from patients (e.g., decision-support, workflow automation) and where there is strong human oversight
  - » Uses where all elements of build and deployment are controllable by developer, and mitigations to address key concerns are evidence based

Consider the regulatory climate

In hopes of inciting a collaborative discussion on how to use AI/ML safely throughout the drug development process, global health authorities have started to publish various consideration papers, discussion papers, and draft guidelines on introducing AI/ML into clinical trials. The FDA recently published a discussion paper entitled, "Using Artificial Intelligence & Machine Learning in the Development of Drug & Biological Products," in which they outlined their current understanding of potential AI/ML use cases in clinical trials and considerations for applying them.[1] Similarly, the European Medicines Agency (EMA) published a draft article entitled, "Reflection paper on the use of Artificial Intelligence (AI) in the medicinal product lifecycle," that also detailed current AI/ML uses in clinical trials.[2]

In the FDA paper, regulators posed questions to drug developers for greater insight into how organizations are using AI/ML and feedback into where they are seeking additional clarity; the EMA requested drug developer feedback on their draft as well.[1,2] While regulators acknowledge the use and promise of AI/ML in clinical trials, their priority is protecting trial participants across usage areas. As more is published about AI/ML usage in clinical trials and beyond, expect further regulatory guidance to be published. In the following sections, consider the current recommendations and best practices as advised by regulators.

Design risk-based approaches

First and foremost, drug developers should assess whether the use of AI/ML introduces specific risks into their process and could lead to potential harm for study participants. If used incorrectly, AI/ML could amplify errors and perpetuate existing biases present in underlying data sources. Proactively take measures to avoid the integration of bias into AI/ML applications and to promote AI trustworthiness.

Per the FDA's paper, "A risk management plan that considers the context of use may be applied to identify and mitigate risks. This approach helps guide the level of documentation, transparency, and explainability, with tracking and recording of key steps and decisions, including the rationale for any deviations and procedures that enable vigilant oversight and auditing."[1]

By using a risk-based approach, developers are able to monitor potential obstacles and adapt more efficiently.

The EMA also details this approach as such: "A risk-based approach for development, deployment and performance monitoring of AI/ML tools allows developers to proactively define the risks to be managed throughout the AI/ML tool lifecycle. The concept of risk includes, but is not limited to, regulatory impact."[2] By using a risk-based approach, developers are able to monitor potential obstacles and adapt more efficiently.

Develop a set of standards

According to the FDA, "An AI/ML system may exhibit limited explainability due to underlying complexity and may not be fully transparent for proprietary reasons. These concerns have resulted in a focus on developing standards for trustworthy AI that address specific characteristics in areas such as explainability, reliability, privacy, safety, security, and bias mitigation."[1] As a result, there is a notable push for AI/ML usage standards across the sector to ensure greater confidence and reliability.

In the National Institute of Standards and Technology's guidance, "U.S. Leadership in AI: A Plan for Federal Engagement in Developing Technical Standards and

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Related Tools," experts addressed key areas of focus for AI standards development, including data and knowledge, performance testing and reporting methodology, risk management, and trustworthiness.[1,3] Other organizations, including the International Organization for Standardization, are developing AI/ML standards alongside techniques to address data quality and performance.

Apply good machine learning practices

In October 2021, the FDA, Health Canada, and the UK's Medicines and Healthcare products Regulatory Agency (MHRA) opted to jointly publish, "Good Machine Learning Practice for Medical Device Development: Guiding Principles."[4] The 10 guiding principles center around developing safe, high-quality medical devices that adhere to Good Machine Learning Practices (GMLP) for their implementation of AI/ML. Some highlights from these guiding principles include:

- Adopt a total product lifecycle approach in which multidisciplinary expertise is incorporated throughout development, including an in-depth understanding of how a model is integrated into the clinical workflow.

- Include adequate representation of age, gender, sex, race, and ethnicity within the study to manage bias, improve generalizability, and provide sufficient transparency for the intended use and indications.

- Monitor deployed models for performance while managing the risk of model retraining.

The guidelines also emphasize using good software engineering and security practices and providing users with clear instructions. While these proposed principles for GMLPs were conceived for application to medical devices, it is also conceivable that the core concepts or principles could apply to other medical product areas, such as the use of AI/ML in clinical trials for drugs and biologics.

Leverage AI/ML strategically in your trial

AI/ML is used in many areas associated with the design and execution of clinical trials, including: recruitment; selection and stratification of trial participants; dose optimization; adherence and retention; site selection; data collection, management, and analysis; and clinical endpoint assessment. Consider how AI/ML could improve efficiency and effectiveness in three of these areas.

I. RECRUITMENT

AI/ML models aid significantly in patient recruitment for clinical trials. These platforms search and identify individuals that could benefit from investigational treatments by mining data, including information derived from clinical trial databases, trial announcements, social media, medical literature, registries, and electronic health records. Though these algorithms are trained on high volumes of patient data and enrollment criteria from past trials, it is important to ensure adequate representation of populations that are likely to use the drug to confirm that equitable inclusion occurred during recruitment. A great use case for such an application could be to leverage AI/ML to enrich Diversity Action Plans for clinical trials.

II. SELECTION AND STRATIFICATION OF TRIAL PARTICIPANTS

According to the FDA, AI/ML can be used to predict an individual trial participant's clinical outcome via specific qualities and metrics. Models such as these can be used to select and evaluate patients prior to randomization to help reduce variability and improve the productivity of a study. These types of predictive models can also be used in stratification. Per the FDA, "An AI/ML model could predict the probability of a serious adverse event before an investigational treatment is administered."[1] After determining whether a participant is potentially at risk for adverse events, they could be stratified and monitored based on the degree of potential risk.

III. DOSE OPTIMIZATION

In terms of dose optimization, AI/ML is also used to characterize and predict pharmacokinetic (PK) profiles following drug administration, as well as the relationship between drug exposure and response. By leveraging these models, trial designers can optimize the dosing regimen for a study and determine ideal doses for understudied populations, including rare disease patients, pediatric patients, or pregnant patients. In the field of oncology, this could prove to be quite a beneficial approach to the use of AI/ML, considering new paradigms for dose selection in cancer trials.

These are just a few of the possibilities available to developers with AI/ML programs. AI/ML is also being used to monitor and improve adherence via smartphone reminders and e-tracking, to identify the best possible sites for a clinical trial, and to analyze the diverse data sets obtained during trials.

Prepare project teams for success

Using AI/ML to supplement your clinical trial workflows yields major benefits, including enhanced patient recruitment and strategic dose optimization. To ensure you are following best practices and considering evolving regulatory expectations, stay abreast of the current and expected near-future regulatory developments to be ready to adapt your processes accordingly. New opportunities will also emerge. If there are areas where you are seeking greater guidance from regulators, consider seeking direct feedback from them to help meet your organization's needs. To use AI/ML across the clinical trial lifecycle ethically and sustainably, it is critical for developers and regulators to collaborate continuously.

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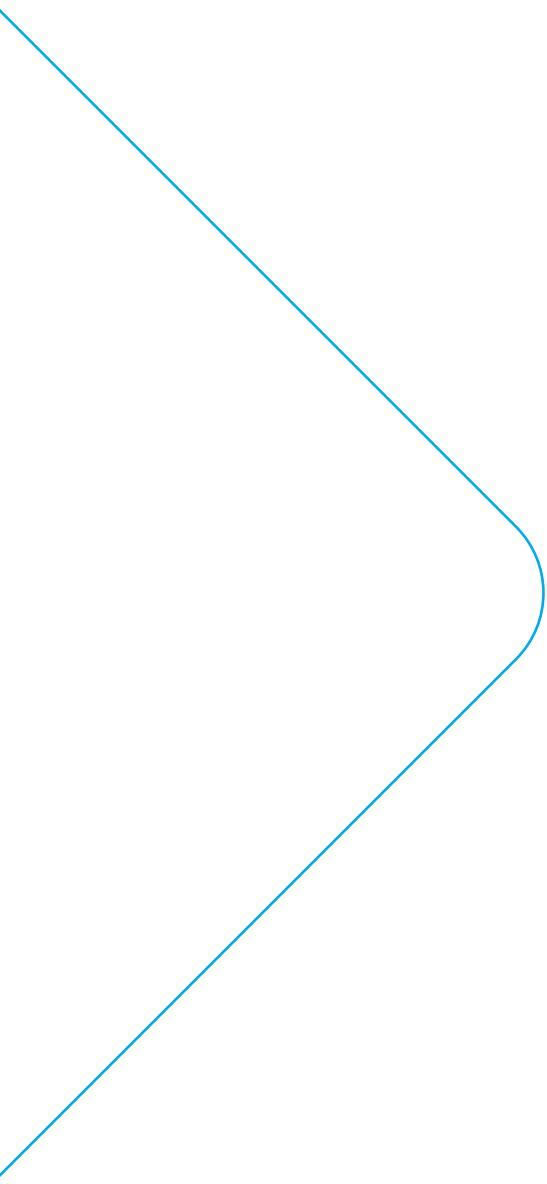
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With more than two decades of experience in Regulatory
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