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WHITE PAPER

Understanding the FDA's AI Credibility Framework and Its Implications for Clinical Outcomes Assessment

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At Signant Health, we work with pharmaceutical sponsors across the full spectrum of clinical outcomes assessment from study design through data collection, quality monitoring, and regulatory submission. As artificial intelligence (AI) becomes an increasingly integral part of how evidence is generated and evaluated in clinical trials, we believe it is important for our clients and the broader industry to understand the regulatory standards that now apply. The FDA's January 2025 draft guidance on AI credibility assessment is directly relevant to any sponsor using AI to support regulatory decision-making in the context of COA. This paper provides a practical overview of the framework and what it means for clinical development programs.

Executive summary

On January 6, 2025, the U.S. Food and Drug Administration (FDA) issued its inaugural draft guidance document addressing the use of artificial intelligence (AI) in drug and biological product development. This guidance establishes a risk-based framework for assessing AI model credibility and carries significant implications for clinical outcomes assessment (COA) methodologies in clinical trials. For sponsors engaged in electronic clinical outcomes assessment (eCOA), electronic patient-reported outcomes (ePRO), or clinician-rated outcomes, this regulatory framework warrants attention and strategic consideration. This paper examines the guidance's core principles, key requirements, and practical implications for pharmaceutical development programs.[2,3]

01 Introduction: The Regulatory Response to AI Integration in Drug Development

Current State of AI Adoption in Pharmaceutical Research

Since 2016, the FDA has reviewed more than 500 drug and biological product submissions incorporating AI components, demonstrating the rapid proliferation of AI technologies across pharmaceutical development. The application of AI in clinical trials has expanded exponentially, encompassing predictive modeling of patient outcomes, analysis of real-world data, and processing information from digital health technologies. Within the clinical outcomes assessment domain, AI applications currently include real-time flagging of incomplete patient-reported outcome (PRO) data, detection of anomalous response patterns in eCOA submissions, optimization of visit schedules based on patient engagement predictions, and natural language processing for analysis of open-text patient feedback.[2,4] AI also has application in the COA development process, for example in synthesis of sources of information to describe disease history, extraction of insights to drive conceptual model development using unstructured data sources, such as social media, and derivation of sensor-based outcome measures from large datasets. However, those applications representing operational efficiencies not impacting patient safety fall outside of the scope of the FDA draft guidance.

Regulatory Gap and the Need for Standardization

Prior to this guidance, the regulatory landscape lacked a unified framework for establishing AI model credibility for intended use cases. This absence of standardized evaluation criteria created uncertainty for sponsors regarding validation requirements and acceptance thresholds. The January 6, 2025 guidance addresses this regulatory gap by providing explicit criteria and procedural expectations for AI credibility assessment.[1]

02 Conceptual Foundation: Context of Use (COU)

Definition and Significance

The FDA's credibility framework is predicated on the concept of Context of Use (COU), defined as the specific manner in which an AI model is employed to address a particular question of interest. This foundational concept recognizes that identical AI technologies may carry substantially different regulatory implications depending on their operational deployment. For instance, an AI model that flags potentially incomplete PRO entries for site coordinator review operates within a fundamentally different context of use than a model that imputes missing endpoint data for final efficacy analysis, despite potentially utilizing similar underlying technologies.[5,1]

COU as a Determinant of Regulatory Requirements

The COU framework enables proportionate regulatory scrutiny, ensuring that validation rigor aligns with the potential impact of AI-generated outputs on regulatory decision-making. The seven-step credibility assessment process described in Section 4 begins with explicit definition of both the question of interest and the COU.[5]

03 Risk-Based Assessment Methodology

Two-Dimensional Risk Evaluation Framework

The FDA's framework evaluates AI model risk based on two independent dimensions:[2,4]

Model Influence
This dimension assesses the relative contribution of AI output to decision-making processes compared to other evidentiary sources. Evaluation considers whether the AI model serves as the sole basis for decisions or functions as one component within a broader evidence base that includes clinical trial data, nonclinical studies, or other supporting information.

Decision Consequence
This dimension evaluates the potential impact of incorrect AI model outputs. Assessment examines whether errors could affect patient safety, trial enrollment criteria, study integrity, or regulatory decision-making outcomes.

Risk Stratification and Validation Requirements

Higher-risk applications typically involve AI models making final determinations without human oversight, particularly when such determinations could affect patient safety or study validity. For clinical outcomes assessment applications, this necessitates careful consideration of AI positioning within operational workflows. Real-time data quality monitoring with mandatory human review represents a lower-risk scenario, whereas automated endpoint adjudication without oversight constitutes a potentially high-risk application requiring more extensive validation.[4]

04 The Seven-Step Credibility Assessment Process

The seven steps are as follows:[4,5]

Step 1: Define the Question of Interest

Sponsors must articulate the specific question, decision, or concern that the AI model will address. This requires precise specification of the regulatory or scientific objective.

Step 2: Define the Context of Use

Sponsors must specify what parameters will be modeled, how outputs will be utilized in decision-making processes, and whether AI serves as the sole determinant or one component within a multi-factorial evidence base.

Step 3: Assess AI Model Risk

Risk assessment must be conducted using the two-dimensional framework evaluating model influence and decision consequence.

Step 4: Develop a Credibility Assessment Plan

Sponsors must create a comprehensive validation plan addressing model design specifications, data strategy, training methodologies, performance metrics, and evaluation methods. The plan's scope and rigor must be commensurate with the assessed risk level.[2]

Step 5: Execute the Credibility Assessment Plan

Sponsors must implement all planned credibility assessment activities according to the established plan.

Step 6: Document Results

Sponsors must compile a credibility assessment report describing outcomes and confirming model credibility for the intended context of use.

Step 7: Determine Adequacy

Based on assessment results, sponsors must determine whether the model demonstrates sufficient credibility for its intended application or whether additional validation work is required.[5]

Lifecycle Mantenance Requirements

Beyond initial validation, the FDA's draft guidance explicitly accommodates continuously evolving AI models, rather than requiring them to be locked. However, the FDA identifies that the level of oversight for ongoing changes should be "commensurate with the model risk and the COU." Higher-risk models face more stringent monitoring and re-validation triggers; lower-risk models require less. Sponsors should, therefore, implement lifecycle maintenance plans incorporating continuous monitoring protocols, defined performance metrics, specified monitoring frequencies, and predetermined triggers for model retesting as systems evolve over time. This lifecycle approach recognizes that AI models are not static entities and may require periodic retraining, updating, or adjustment throughout study conduct.[4,5]

05 Implications for Pharmaceutical Development Programs

Enhanced Documentation Requirements

The guidance effectively eliminates the acceptability of "black box" AI implementations in regulatory submissions. Sponsors must be prepared to provide comprehensive documentation articulating model operational mechanisms, training methodologies, source data characteristics, and ongoing performance monitoring protocols.[5,4]

Early Regulatory Engagement

The guidance strongly encourages sponsors to engage with the FDA early in development programs when AI applications may influence regulatory decision-making. Sponsors should consider Type C meetings or pre-Investigational New Drug (IND) discussions to obtain regulatory feedback on planned AI implementations.[2]

Risk-Proportionate Validation Strategies

The risk-based framework permits variable validation intensity. Lower-risk applications may require relatively straightforward validation protocols, while high-risk applications demand extensive testing, comprehensive documentation, and rigorous ongoing monitoring.[4]

Organizational Preparedness Requirements

Implementation of this guidance necessitates organizational capabilities in several domains:

Technical Expertise

Organizations must maintain or acquire expertise in AI model development, validation methodologies, and performance monitoring.

Quality Systems

Existing quality management systems must be adapted to accomodate AI-specific validation and lifecycle management requirements.

Cross-Functional Collaboration

Successful implementation requires coordination among biostatistics, clinical operations, data management, regulatory affairs, and quality assurance functions.

Vendor Management

When AI capabilities are provided by external vendors, sponsors must ensure contractual arrangements enable access to necessary documentation and model specifications for regulatory submissions.

06 Forward-Looking Considerations

Broader Regulatory Implications

While this guidance specifically addresses drug and biological products, the underlying principles likely signal the FDA's overarching approach to AI across all clinical trial technologies. The risk-based, context-driven methodology aligns with regulatory frameworks in other domains and may likely anticipate similar requirements for medical devices and diagnostics incorporating AI capabilities.[2]

Industry Best Practices Evolution

The guidance codifies principles that forward-thinking organizations have already begun implementing. The emphasis on transparency, appropriate safeguards, and ongoing oversight aligns with emerging industry consensus regarding responsible AI deployment. Organizations that have proactively adopted such practices will be better positioned to meet regulatory expectations.

International Regulatory Harmonization

As regulatory agencies worldwide develop AI frameworks, opportunities for international harmonization may emerge. Sponsors conducting global clinical development programs should monitor evolving guidance from the European Medicines Agency (EMA), Japan's Pharmaceuticals and Medical Devices Agency (PMDA), and other major regulatory authorities to identify areas of alignment and divergence.

07 Conclusion

The FDA's January 6, 2025 draft guidance represents a significant milestone in the regulatory oversight of AI applications in pharmaceutical development. The risk-based credibility assessment framework provides much-needed clarity regarding validation expectations while maintaining sufficient flexibility to accommodate diverse AI applications and evolving technologies.

The guidance reinforces that technology should enhance, not replace, clinical and scientific rigor. AI has substantial potential to improve trial efficiency and data quality, but only when implemented with appropriate safeguards, transparency, and oversight. Organizations must now translate these expectations into operational capabilities.

The FDA accepted public comments on this draft guidance through April 7, 2025.

Signant Health is committed to supporting sponsors in navigating this evolving regulatory landscape. Our approach to COA development and implementation is grounded in scientific rigor, regulatory transparency, and a deep understanding of how evidence quality affects the decisions that matter most. We will continue to monitor the FDA's AI guidance as it progresses from draft to final form and share our perspective as the framework develops.

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