164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2026-N-4390]

AI-Enabled Optimization of Early-Phase Clinical Trials Pilot Program; Request for Information

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice; request for information.

SUMMARY: The Food and Drug Administration (FDA or the Agency) is issuing this request for information to solicit input on a proposed pilot program to assess how artificial intelligence (AI)-enabled technologies can improve efficiency, speed, and quality of decision-making in early phase clinical trials. Early-phase clinical trials represent a critical bottleneck in drug development, often characterized by high uncertainty, limited patient populations, and inefficient decision-making processes. This pilot program aims to explore how advances in AI and data science can improve trial efficiency, enhance safety monitoring, facilitate dose selection decisions, and enable more informed early go/no-go decisions (e.g., a regulatory decision as to whether a Phase 1 study may proceed) while maintaining FDA's rigorous scientific and regulatory standards and promoting trustworthy AI systems. The pilot program will be guided by principles aligned with the National Institute of Standards and Technology (NIST) AI Risk Management Framework (AI RMF).

DATES: Either electronic or written comments must be received by [INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. The https://www.regulations.gov electronic filing system will accept comments until 11:59 p.m. Eastern Time at the end of [INSERT

DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are received on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand Delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.
- For written/paper comments submitted to the Dockets Management Staff, FDA

will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2026-N-4390 for "AI-Enabled Optimization of Early-Phase Clinical Trials Pilot Program; Request for Information." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions —To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the

information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Mallika Mundkur, Deputy Chief Medical Officer, Office of the Commissioner, Food and Drug Administration, 10903 New Hampshire Ave., Silver Spring, MD 20993, 301-796-8800.

SUPPLEMENTARY INFORMATION:

I. Background

This request for information provides an opportunity for interested parties and the public to share their input on a proposed pilot program to assess how AI-enabled technologies can improve efficiency, speed, and quality of decision-making in early phase clinical trials.

A. Challenges

Early-phase trials face:

- Uncertainty in dosing, safety, and efficacy
- Limited patient populations
- Inefficient progression decisions
- Long timelines and high resource demands

B. Potential of AI[1]

[1] 15 U.S.C. 9401(3) (also cited in FDA's Draft Guidance for Industry on Considerations for the Use of AI to Support Regulatory Decision-Making for Drugs and Biological Products):

AI may:

- Improve patient recruitment
- Optimize dose escalation
- Enhance safety monitoring
- Enable adaptive designs
- Support earlier Phase 1 to 2 decisions
- Improve biomarker assessment
- Improve biomarker-based patient selection/stratification
- Validate endpoints

C. Trustworthy AI

- FDA supports AI use by external sponsors/investigators aligned with NIST AI RMF[2] principles: valid, safe, secure, accountable, explainable, privacy-protective, and fair.
- FDA will apply considerations previously outlined in draft guidance regarding the use of AI to support regulatory decision-making.[3]

D. Industry Alignment

- Industry practices include AI governance, assurance, and risk management frameworks. FDA aims to enhance the use of AI by industry in the conduct of clinical trials in line with such practices.

E. Pilot Program

The term "artificial intelligence" means a machine-based system that can, for a given set of human-defined objectives, make predictions, recommendations or decisions influencing real or virtual environments. Artificial intelligence systems use machine and human-based inputs to-
(A) perceive real and virtual environments;
(B) abstract such perceptions into models through analysis in an automated manner; and
(C) use model inference to formulate options for information or action.

[2] The NIST AI RMF is available at https://www.nist.gov/itl/ai-risk-management-framework.
[3] Considerations for the Use of Artificial Intelligence To Support Regulatory Decision-Making for Drug and Biological Products available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-use-artificial-intelligence-support-regulatory-decision-making-drug-and-biological.

- The pilot will involve the recruitment of sponsors that are currently or will be pursuing early phase clinical trials through product applications submitted to the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, and the Oncology Center of Excellence.
- The pilot will be coordinated by the Deputy Chief Medical Officer within the Office of the Commissioner.

II. Expanded Considerations for Pilot Development

FDA seeks input on the questions below. To help FDA review comments efficiently, please identify the question to which you are responding by its associated category and number. If you are responding to more than one question, please identify each question to which you are responding, and categorize each response by question.

A. Pilot Program Design and Implementation

FDA seeks input on how to structure the pilot to maximize learning, feasibility, and impact:

1. Scope and Focus
    a. Which trial types or trial issues might benefit most from the application of AI (e.g., first-in-human, oncology dose escalation, rare disease trials)?
    b. Should the pilot target specific therapeutic areas or remain broadly applicable?
    c. Should priority be given to specific AI use cases (e.g., recruitment, safety monitoring)? If so, which?
2. Participant Selection
    a. What criteria should FDA use to select sponsors, trials, or technologies?
    b. How can the pilot ensure representation across organization size, capability, and therapeutic areas?
3. Collaboration Models

a. What partnerships (e.g., sponsor–tech vendor–academic–FDA) are most effective?
b. How can FDA facilitate pre-competitive collaboration and knowledge sharing?
c. What role should patient groups and investigators play in AI governance?

4. Operational Structure
   a. What support (e.g., regulatory engagement, technical guidance) should FDA provide?
   b. What infrastructure is needed (e.g., secure data environments, shared tools)?
   c. How can the pilot accommodate varying levels of AI maturity across participants?
5. Timeline and Milestones
   a. What is an appropriate duration for the pilot?
   b. What interim milestones or checkpoints should be included (e.g., enrollment, safety review, interim analyses)?
   c. How should FDA balance rapid insights with rigorous evaluation?
6. Knowledge Sharing
   a. How should lessons learned be captured and disseminated?
   b. What mechanisms can promote transparency while protecting proprietary information?

B. Evaluation Metrics and Success Criteria

FDA seeks input on appropriate metrics and approaches to evaluate the pilot program, including:

1. Trial Efficiency and Speed
   a. How should improvements in trial efficiency be measured (e.g., time to initiation, enrollment, or completion)?
   b. What metrics should be used to assess reductions in time from Phase 1 completion to Phase 2 initiation?

c. How can improvements in participant screening, recruitment efficiency, and participant retention be quantified?

2. Decision Quality
    a. How can the quality and timeliness of go/no-go decisions be evaluated (both FDA regulatory decisions and sponsor-internal decision points)?
    b. What methods can assess concordance between AI-supported and traditional decision-making?
    c. How should reductions in late-stage trial failures attributable to improved early-phase decisions be measured?
3. Participant Safety and Data Integrity
    a. What metrics should be used to evaluate the detection and response time for safety signals?
    b. How should the impact of AI on adverse event rates or protocol deviations be assessed?
    c. What measures can assess improvements in data completeness, accuracy, and consistency?
4. AI System Performance
    a. What metrics are most appropriate for evaluating AI model accuracy, robustness, and generalizability?
    b. How should AI system stability over time be measured, including detection and mitigation of model drift?
    c. How can performance be evaluated across different patient populations, trial sites, and therapeutic areas?
5. Trustworthiness (Aligned with NIST AI RMF)
    a. What evidence should demonstrate that AI systems are valid and reliable in clinical trial contexts?

b. How should safety and risk mitigation associated with AI systems be evaluated?

c. What metrics can assess transparency and explainability for different stakeholders, and are there metrics available that would be applicable to both sponsor-developed and proprietary systems?

d. How should privacy protections and data governance practices be evaluated?

e. What approaches should be used to assess fairness across demographic and clinical subgroups?

6. Comparative Evaluation

a. What comparators are most appropriate (e.g., historical controls, concurrent non-AI trials, simulation studies)?

b. How should differences in trial design, complexity, or therapeutic area be accounted for in comparisons?

7. Qualitative Outcomes

a. How can stakeholder trust in AI-enabled trial approaches be assessed (e.g., investigators, participants, regulators)?

b. What methods can evaluate usability and integration into clinical workflows?

c. How should perceived value, scalability, and operational feasibility be measured?

Grace R. Graham,

Deputy Commissioner for Policy, Legislation, and International Affairs.

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