PREMIER TRANSFORMING HEALTHCARE TOGETHER®

January 19, 2024

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Submitted electronically to: http://www.regulations.gov

RE: Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop; Request for Comments (FDA-2023-N-4489-0001)

Dear Dr. Califf:

Premier Inc. appreciates the opportunity to submit comments to the Food and Drug Administration (FDA)Center for Drug Evaluation and Research (CDER) regarding the comment solicitation *Enhancing Adoption of Innovative Clinical Trial Approaches; Public Workshop.* This workshop presents CDER with the opportunity to reduce barriers to innovation in clinical trials, build resiliency in the drug supply chain and eliminate regulatory gaps and procedural pitfalls at a commensurate pace with evolving artificial intelligence (AI) and machine learning (ML) technology.

Premier supports CDER's efforts as a positive step towards recognizing the ways in which technology can be leveraged to reduce costs, improve data quality and access, expedite administrative processes and advance health equity. Specifically, Premier applauds CDER's efforts to incorporate emerging technologies into drug development, as well as to identify and resolve barriers to innovation. In our comments, Premier recommends that CDER address the following:

- Clarifying applicability of anti-kickback statute in certain situations that may arise in innovative trial designs and recruitment processes;
- Clearly specifying a minimum cybersecurity standard for the transmission and storage of participant health data using digital health technology;
- Issuing clear guidance on patient consent and data-sharing requirements in clinical trials, particularly with the rise of promising technology applications for real-world data in decentralized clinical trials and synthetic control arms;
- Taking steps to capture, monitor and manage pre-specification activities in drug development; and
- Affirming that Pre-Approval Information Exchange (PIE), which allows trial sponsors to proactively communicate to payors certain information about products in development to expediate coverage upon product approval, is applicable in the case of decentralized clinical trials.

Our detailed recommendations are included below.

I. BACKGROUND ON PREMIER INC.

Premier is a leading healthcare improvement company, uniting an alliance of more than 4,350 U.S. hospitals and health systems and approximately 300,000 continuum of care providers to transform healthcare. With integrated data and analytics, collaboratives, supply chain solutions, consulting and other services, Premier enables better care and outcomes at a lower cost. Premier's sophisticated technology systems contain robust data gleaned from nearly half of U.S. hospital discharges, 812 million hospital outpatient and clinic encounters and 131 million physician office visits. Premier is a data-driven organization with a 360-degree view of the supply chain, working with more than 1,400 manufacturers to source the highest quality and

most cost-effective products and services. Premier's work is closely aligned with healthcare providers, who drive the product and service contracting decisions using a data driven approach to remove biases in product sourcing and contracting and assure access to the highest quality products. In addition, Premier operates the nation's largest population health collaborative, having worked with more than 200 accountable care organizations (ACOs).

A Malcolm Baldrige National Quality Award recipient, Premier plays a critical role in the rapidly evolving healthcare industry, collaborating with healthcare providers, manufacturers, distributors, government and other entities to co-develop long-term innovations that reinvent and improve the way care is delivered to patients nationwide. Headquartered in Charlotte, North Carolina, Premier is passionate about transforming American healthcare.

Premier is already leveraging AI to move the needle to modernize the clinical trial process. Premier's PINC AI™ Applied Sciences (PAS) is a trusted leader in accelerating healthcare improvement through services, data, and scalable solutions, spanning the continuum of care and enabling sustainable innovation and rigorous research. These services and real-world data are valuable resources for the pharmaceutical, device and diagnostic industries, academia, federal and national healthcare agencies, as well as hospitals and health systems. Since 2000, PAS researchers have produced more than 1,000 publications which appear in 264 scholarly, peer-reviewed journals, covering a wide variety of topics such as population-based analyses of drugs, devices, treatments, disease states, epidemiology, resource utilization, healthcare economics and clinical outcomes.

Premier's detailed feedback, based on our depth of experience in using AI in healthcare, is included below.

II. APPLICATIONS OF ARTIFICIAL INTELLIGENCE IN PHARMACEUTICAL MANUFACTURING

Premier sees potential for AI to transform three key segments of the drug manufacturing process: supply chain visibility, advanced process control and quality monitoring.

Supply chain visibility. Premier believes the application of AI can advance national security by helping build a more efficient and resilient healthcare supply chain. Specifically, AI can enable better demand forecasting for products and services, such as drug components, through analysis of historical and emerging clinical and patient data. As the COVID-19 pandemic demonstrated, the ability to understand and react to shortages poses a critical challenge to healthcare providers; AI enables better planning and response time to national or regional emergencies. AI can drive better inventory management by automating the monitoring and replenishment of inventory levels. Healthcare providers can leverage AI to better manage suppliers through faster more efficient contracting processes and by monitoring of supplier key performance metrics. As Premier works to combat drug shortages, the most effective remedies begin with supply chain visibility and reliable predictions that allow manufacturers to plan for and respond to shortages or disruptions – this crucial element of the drug manufacturing process presents a key value-add opportunity for AI technology.

Advanced process control. Another significant value-add for AI in the drug manufacturing process is in the development and optimization of advanced process control systems (APCs). Process controls typically regulate conditions during the manufacturing process, such as temperature, pressure, feedback and speed. However, a recent report found that industrial process controls are overwhelmingly still manually regulated, and less than 10 percent of automated APCs are active, optimized and achieving the desired objective. These technologies are now ready to transform drug manufacturing on a commercial scale; however, challenges still remain to widespread adoption. Premier strongly believes that the FDA should issue clear guidance that supports the industry-wide transition to AI-powered APCs. Such technologies offer drug manufacturers the opportunity to assess the entire set of input variables and the effect of each on system performance and product quality, automating plant-wide optimization. This application of AI technology can transform the physical manufacturing of drugs and pharmaceuticals, leading to cost-savings and increased resiliency, transparency and safety in the drug supply chain.

Quality monitoring. AI can also provide value-add to drug manufacturing in the field of quality monitoring and reporting. Current good manufacturing processes (cGMPs) provide an immense volume of data from imagers and sensors that, if processed and analyzed more quickly and efficiently, could transform approaches to safety and quality control. AI models trained on this data can be used to predict malfunctions or adverse events. AI can also perform advanced quality control and inspection tasks, using data feeds to quickly identify and correct product defects or catch quality issues with products on the manufacturing line. Taken together, these capabilities can improve both the accuracy and speed of inspections and quality control, helping companies to reliably meet regulatory requirements and avoid costly delays that disrupt the drug supply chain. These proactive measures can also help avoid downstream quality manufacturing issues that result in shortages and impact patient care.

Synthetic control arms in clinical trials. Premier anticipates one specific question to arise at the intersection of patient privacy and digital innovation. Given the availability of quality real-world data (RWD) through electronic health records, claims data, home health devices and other sources, synthetic control arms may soon become standard practice in many clinical trials. Synthetic control arms can increase the power of trial populations by eliminating the need for a control population and can help increase trial enrollment by easing patient fears that they will receive a placebo. The FDA has already recognized the value of RWD to support development of drugs and biologics. In order to uphold that commitment and continue to advance the use of RWD in clinical trials, CDER should devote time at any convening to enabling this crucial innovation and discussing how to move its adoption forward.

III. COMMENTS ON MAJOR BARRIERS TO INNOVATION

As CDER has identified, a number of barriers may prevent stakeholders across the pharmaceutical value chain from fully embracing the innovations described above. Across the issues raised by CDER, Premier's unique visibility into the uses of AI in healthcare and clinical trials has informed insights into which reassurances would best enable researchers, technologists and pharmaceutical manufacturers to embrace innovative uses of AI/ML and RWE, as well as novel decentralized clinical trial designs that take advantage of the data available from DHTs.

Regulatory and Compliance Considerations

Premier has identified several key areas where the FDA could offer regulatory clarity to accelerate the pace of innovation and the use of AI/ML technology in drug development.

Kickbacks and AI Technology: Premier believes that the FDA has the opportunity to issue clarification on how anti-kickback statute will be applied to the use of AI technology in drug development, particularly in the identification and recruitment of clinical trial participants, in the following contexts:

- When patients are referred to local healthcare providers on a fee-for-service basis under the process described in this draft guidance, it raises the question of whether this represents a "kickback" for physicians who identify and enroll patients from their clinic in trials. Of course, the availability and involvement of non-trial providers is essential to protecting patient safety and ensuring participants receive medical attention as necessary, as the FDA notes in this draft guidance. Premier urges the FDA to clarify that this interaction would not be viewed as a violation of anti-kickback statute.

- In the context of clinical trials and drug development, the provision of digital health technologies to trial participants could be construed as a kickback or a violation of the "Civil Monetary Penalties Law" or the "False Claims Act." Legislation addressing the provision of digital health technologies to patients in order to promote geographic or socioeconomic diversity has included an explicit safe harbor from anti-kickback statute provision prosecution. Premier recommends that the FDA include language clarifying this exception in its final guidance.

- Decentralized clinical trial designs may promote the use of synthetic control arms and explore the potential value of synthetic data in trial design and innovation. Within this context, Premier requests clarification about whether payment-per-patient or data point would violate anti-kickback statutes. Premier strongly recommends that the FDA provide a clearly defined exception for this use of data science and cutting-edge healthcare technology to safely develop new drugs through a more cost-effective and efficient process.

In each of these scenarios, innovation in trial design and execution with demonstrably positive effects may be hindered by a conservative interpretation of existing statutes. These uses of AI technology to enhance clinical trial diversity, reduce prohibitive costs, and accelerate the development of crucial new drugs and devices do not conflict with the spirit of anti-kickback statutes, but uncertainty is anathema to innovation. The FDA should clarify the applicability of relevant statutes and, where necessary, include explicit safe harbor exceptions for these critical interests.

Protecting Patient Data: The baseline standards currently proposed by the FDA to govern data storage and cybersecurity are inadequate to ensure patient data is protected and secure. The provisions of 21 CFR part 11 are valuable to ensure the integrity and validity of patient records, but do not adequately establish best practices for confidentiality, privacy or cybersecurity. These crucial components of patient protection should not be left up to trial administrators to determine. Premier strongly recommends that the FDA provide guidance on key cybersecurity concerns arising during decentralized clinical trial design and execution:

- **Cybersecurity**: The FDA should lay out a minimum cybersecurity standard for the transmission and storage of participant health data on or using digital health technology. In addition to the standards for authentication and access control contained in 21 CFR part 11, these standards should include a requirement for end-to-end encryption for data-in-transit and encryption standards for data-at-rest. The FDA could even consider bolstering the access control requirements of 21 CFR part 11 to include a zero-trust architecture mandate. The FDA should also require that all data collected during a decentralized clinical trial should be stored in a secure centralized repository to mitigate cybersecurity and privacy risk. Administrators of a decentralized clinical trial should also be required to develop a cybersecurity plan that covers each of the digital health technologies that will access patient health information during the trial.

By clarifying and bolstering these standards, the FDA can ensure that the privacy and confidentiality of participant health data is prioritized even as trial administrators explore which models and digital health technologies best facilitate decentralization. Premier expects a period of innovation in trial design as decentralized clinical trials become the norm, and the FDA should take care to ensure participant privacy is not an unintended casualty of digitization.

Data Sharing: If the FDA intends to build on its domain-specific expertise in data science, informatics, statistics and mathematics to help ensure the appropriate application of AI technology in the context of digital health technologies used for drug development, Premier has the following comments:

- ***When appropriate, Premier suggests a requirement for structured communication layers such as Predictive Model Markup Language (PMML)***. This would allow for system interoperability in a fashion similar to FHIR.

- ***The FDA should provide open-source client libraries in Python, R, or other important languages***. Python and R are important data science tools, and a client library would allow researchers to interact directly with the data elements in the fashion the FDA intends them to be used rather than each vendor making their own access decisions. In addition, it is essential for FDA to provide support (ideally financial and at a minimum technical) to vendors who create these libraries.

- ***The FDA should consider a federally hosted private cloud for communicating with clinical trial sponsors***. This would facilitate health information exchange (HIE) activity and can be used to train and evaluate the data.

Data Standards: Premier understands the importance of data standards, responsible data use and data privacy in the development and deployment of AI technology. Data standards should specifically focus on objective assessment of potential sources of bias or inaccuracy introduced through poor dataset construction, cleaning or use. These may include, but are not limited to, appropriately representative datasets, bias in data collection (e.g., subjectivity in clinical reports) or introduced by instrument performance or sensitivity (e.g., pulse oximetry devices producing inaccurate measurements of blood oxygen levels in patients with darker skin), bias introduced during curation (e.g., datasets with systemically introduced nulls and their correlation, such as failure to pursue treatment due to lack of ability to pay), and training and test data that is appropriately applicable to various patient subpopulations (e.g., data that sufficiently represents symptoms or characteristics of a condition for each age/gender/race of patient that the tool will be used to treat). Premier also supports the establishment of guidelines for proper data collection, storage and use that sufficiently protect patient rights and safety. This is particularly important given the sensitivity of health data.

Collectively, these are highly relevant regulatory concerns that introduce enough uncertainty to limit the adoption of innovative methods. CDER should take the opportunity to address these questions at its upcoming public workshop.

Patient-Focused Trial Design and Recruitment Innovations

CDER should focus on establishing proper informed consent for the use of RWD for a synthetic control arm. Premier requests clarification on the following topics:

- **Consent Procedure**: Premier requests clear guidance from the FDA on the process for properly gathering consent from patients for the use of their RWD to construct a synthetic control arm. As one premise of decentralized clinical trials is the ability to gather data from a wide or disparate patient population, the incorporation of RWD should be included in the FDA's guidance around collecting and managing data during decentralized clinical trials.

- **HIPAA Consent Waivers**: Premier urges the FDA to issue clear guidance for the use of HIPAA consent waivers to incorporate RWD into clinical trials. Specifically, the HIPAA Privacy Rule waivers that may be granted under 45 CFR section 164.512 for the purposes of "recruitment" may be essential to identifying and recruiting patients across the country for a decentralized clinical trial. However, Premier would like the FDA to clarify whether this same process is sufficient to include de-identified patient data in a synthetic control arm for a trial. Premier acknowledges that the FDA's requirements for informed consent for participation in clinical trials under 21 CFR 50.20 are separate from HIPAA Privacy Rule waivers; however, Premier believes the FDA can and should clarify whether trials incorporating HIPAA waivers into recruitment or for a synthetic control arm will be in compliance with FDA requirements.

- **De-identified Data**: If the FDA believes that the HIPAA consent waiver process is not sufficient to include RWD in a synthetic control arm, Premier requests clarification about the recommended procedure to re-identify and obtain consent from all patients selected for the control arm.

CDER and the FDA should address the aforementioned questions in both its workshop on AI innovation and through future guidance in order to facilitate the effective design and administration of decentralized clinical trials, including those with synthetic control arms. Patient privacy and informed consent are crucial components of clinical trials, and it is critical that the FDA pre-empt questions that will arise from the incorporation of digital health technology and RWD into decentralized trial models.

Infrastructure and Organizational Considerations

Premier believes that human involvement in AI/ML should begin with workforce training and meet three key standards.

Workforce Training: Premier believes technology can work alongside and learn from healthcare professionals, but current technology will not and should not replace the healthcare workforce. Premier would reiterate the importance of comprehensive risk assessments, recommended use and trainings that combat automation bias and incorporate human decision-making into the use of AI technology in healthcare.

- **Risk Assessments**: The risks and safety concerns around AI technology are unique to each use case, and Premier supports the requirement of a risk assessment and mitigation plan specific to the level of risk associated with the use case. For example, the use of AI systems to identify potential patients involves different concerns, such as privacy and confidentiality, and carries a different level of risk than the use of AI to develop a dosing regimen for a trial.

- **Recommended Use**: Premier also supports the development of standardized intended use certifications or reporting requirements for AI technologies, which would prevent new systems from producing harmful outcomes due to use outside of the technology's design. Whether the intended use of a technology is ongoing safety and quality monitoring, digital endpoint analysis, trial design, or patient identification, the training protocol and appropriate data set will have several key differences. Therefore, it is crucial that drug developers know the intended context, such as condition, applicability and use case, of each AI system.

- **Automation Bias & Workforce Enablement**: Finally, Premier acknowledges the risks of automation bias and fully automated decision-making processes. To reduce these risks, promote trust in AI technologies used in drug development and achieve the goal of supporting the healthcare and life sciences workforce through AI, Premier recommends that federal workforce training programs provide comprehensive AI literacy training for the healthcare and drug development workforce. These workers deal with high volumes of incredibly nuanced data, research, and instructions – a growing percentage of which may be supplied by AI.

  Premier believes that watermarking, a form of provenance system for AI-generated content or recommendations, is a crucial process to enable traceability and auditability for AI involvement in drug development. Watermarking or provenance data/systems for AI-generated content were a component of the voluntary commitments recently announced by the White House. Premier generally supports the development of similar metrics for scientific research or clinical decision support recommendations produced by AI technology. It is important that patients, scientists, and medical professionals understand when decisions or recommendations are made by AI so they can consciously respond and evaluate the new information accordingly.

  Specifically, watermarking is one potential strategy to combat automation bias, a risk especially pertinent to the use of AI technology in healthcare. Automation bias refers to human over-reliance on suggestions made by automated technology, such as an AI device. This tendency is often amplified in high-pressure settings that require a rapid decision. The issue of automation bias in a healthcare setting is discussed at length by the FDA in guidance on determining if a clinical decision support tool should be considered a medical device. Premier suggests that future guidance or standards for the use of AI should consider automation bias in risk assessments and implementation practices, such as workforce education and institutional controls, to minimize the potential harm that automation bias could have on patients and vulnerable populations, including to mitigate any potential risk of AI used in unintended settings or built on biased datasets.

By ensuring our healthcare workers understand how to evaluate the most appropriate AI use cases and appropriate procedures for evaluating the accuracy or validity of AI recommendations, we can maximize

the advisory benefit of AI while mitigating the risk to patients. Additionally, clear, risk-based guidance on which uses of AI technology in healthcare require human review and decision-making, similar to the principles discussed in section five of the OSTP's AI Bill of Rights, is essential.

IV. CHALLENGES OF IMPLEMENTING AND SCALING AI IN CLINICAL TRIALS

One of the biggest challenges facing the FDA and stakeholders in the pharmaceutical supply chain is scaling the use of innovative AI technologies and approaches into standard practice. This task is particularly exacerbated by self-learning AI models. In recent years, the FDA has taken important steps to consider how AI/ML-driven medical devices should be treated during the clinical trial and approval process. The resulting guidance and action plan introduced a new strategy for handling the evolving nature of AI algorithms in Software as a Medical Device (SaMD). One core component of this model involves outlining SaMD Pre-specifications (SPS), a collection of potential changes that the device manufacturer intends to incorporate into the device over its lifetime. Types of pre-specifications include retraining for performance improvement, new data acquisition systems, and changes related to the intended use. While this discussion draft specifically asks about how SPS can be managed within drug development, the corollary Algorithm Change Protocol (ACP) – which details how changes in the SPS will be performed and validated – provides an equally important guide to navigating evolving algorithms in drug development. Premier has identified the following opportunities to capture, monitor and manage SPS activities in drug development:

- **Pre-specification**: Premier suggests that the FDA can use this model to acknowledge and address the evolving nature of algorithms, but any application of this model to drug development must first acknowledge that the AI/ML systems used are not SaMD and are not themselves subject to approval. It is necessary to adjust the purpose of Pre-Specification reporting and logging from approval to the appropriate drug development use case. For the use cases highlighted in this discussion draft, Premier suggests that three principles can guide management:

    - **Predictability**: Pre-specification activities should be predictable. Changes to intended use or the introduction of new data acquisition systems should be done outside of the finite period of a clinical trial use case. For example, if an AI system is being used to identify trial participants or to optimize a dosing regimen, the trial administrators should be able to predict the timeline for an update or new feature to ensure consistency across the trial. Premier suggests that all developer-driven updates detailed in Pre-Specification should be implemented on a publicly available timeline that allows trial administrators to build in consistency across the use of the tool, with the goal of ensuring that the use of different AI tools does not introduce variability into trial procedure. For Pre-specification activities driven by a continuously adaptive algorithm, such as the incorporation of new data for retraining or enhancement, the process used should be predictable, consistent and technically explainable to trial administrators.

    - **Reliability**: Pre-specification activities should not affect the reliability of an AI tool. Elsewhere in these comments, Premier has argued the importance of ongoing disparity testing and evaluation. Pre-specification activities should be no exception. Premier supports the implementation of a standardized format for reportable, continuous model evaluation to ensure that the overall accuracy and reliability of the AI system does not change after any update, either developer-driven or as the result of an adaptive algorithm. This could take the form of regular tests or a method to flag irregular results, either of which would provide indicators that a pre-specification activity fundamentally changed the AI system.

    - **Attributability**: Premier believes that the recommendations above should be logged and tracked. Any form of update to the AL/ML system should be recorded in a log available to drug developers currently using the system, should be attributable to either a developer update or continually adaptive algorithm feature, and should be trackable over time.

- **Algorithm Change Protocol**: The Algorithm Change Protocol (ACP), as described in this FDA presentation, provides a roadmap to implementing the principles outlined above. Premier urges the FDA to issue guidance on a similar procedure that AI/ML technologies designed for use in drug development would provide to trial administrators. As the FDA cannot directly regulate the technologies used as a resource by drug developers, Premier suggests that they instead establish minimum reporting standards for sponsors based on the information above, which must be provided to the FDA as part of pre- and post-trial submissions. These could detail the information that trial administrators and drug developers should require from the AI tools they use, as well as require pre-specification plans and ACPs for the technology used to ensure those standards will be met.

V. COORDINATING INNOVATIVE APPROACHES

Premier also strongly urges the FDA to concurrently finalize and issue other coordinating final guidance in a timely and harmonized manner to allow researchers to efficiently move forward without the dampening effect that pending or uncertain regulation can have on innovation. For example, the FDA recently missed a congressionally mandated deadline of December 29, 2023 to issue or revise guidance for how and when drug developers must submit diversity action plans for clinical trial research. Further, Premier recommends that the FDA clarify opportunities to engage with the agency should implementation questions or concerns arise.

To further promote innovation and expedite patient access to novel therapeutics, ***Premier recommends that the FDA affirm that Pre-Approval Information Exchange (PIE), which allows trial sponsors to proactively communicate to payors certain information about products in development to expediate coverage upon product approval, is applicable in the case of decentralized clinical trials.*** Legal protection for such communications was afforded under the Consolidated Appropriations Act of 2023, and PIE has proven valuable for ensuring that all stakeholders in the drug, biological and device development process have the information they need to improve patient access to novel therapeutics.

VI. CONCLUSION

Premier appreciates the opportunity to suggest priorities for CDER's upcoming public workshop and ongoing efforts to develop guidance for the use of emerging technologies and innovative approaches to pharmaceutical development. If you have any questions regarding our comments, or if Premier can serve as a resource on these issues to the Administration in its policy development, please contact Mason Ingram, Director of Payer Policy, at Mason_Ingram@premierinc.com or 334.318.5016.

Sincerely,

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Premier Inc.