July 28, 2023

Robert M. Califf, M.D.
Commissioner
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852
Attention: FDA-2022-D-2870-0002

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

Re: Draft Guidance: Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders (Docket Number: FDA-2022-D-2870-0002)

Dear Dr. Califf:

Premier Inc. appreciates the opportunity to submit comments to the Food and Drug Administration (FDA) regarding the draft guidance titled *Decentralized Clinical Trials for Drugs, Biological Products, and Devices Guidance for Industry, Investigators, and Other Stakeholders (FDA-2022-D-2870-0002).* As described, this draft guidance will provide much-needed clarity into the implementation of decentralized and hybrid clinical trials, spurring innovation in clinical trials for drugs, biologicals and medical devices.

Premier supports the new draft guidance as a positive step towards recognizing the ways in which technology can be leveraged to reduce costs, expedite processes and improve diversity in clinical trials. Specifically, Premier applauds the FDA's efforts to expand clinical trial access for patients and provide clarity for clinical trial innovators.

In our comments Premier urges FDA to expeditiously finalize the draft guidance, along with all related regulatory and subregulatory guidelines, to ensure that federal requirements for decentralized clinical trials are fully harmonized. Further, Premier recommends that the FDA consider the following when finalizing this guidance:

- Finalize the draft guidance as expeditiously as possible, but no later than six months after the close of the comment period, and ensure harmonization with all related regulatory and subregulatory guidelines affecting the design and implementation of decentralized clinical trials;
- Affirm that Pre-Approval Information Exchange (PIE), which allows trial sponsors to proactively communicate to payors certain information about products in development to expedite coverage upon product approval, is applicable in the case of decentralized clinical trials;
- Clarify that, unless otherwise noted, all applicable standards for in-person clinical trial procedures remains the same in decentralized trials;
- Specify expectations for data standards in decentralized clinical trials, including for potential novel digitally-collected data;
- Affirm requirements for a physical trial hub, even in a decentralized clinical trial design;
- Clarify requirements for handling and administering investigational products, which may differ from standards that would be followed in an in-person clinical trial;
- Clarify applicability of anti-kickback statute in certain situations that may arise in innovative trial designs and recruitment processes;
- Clearly specify a minimum cybersecurity standard for the transmission and storage of participant health data on or using digital health technology;
- Provide clear guardrails for technology innovators who are looking to leverage big data, artificial intelligence and/or machine learning tools; and

- Ensure clear expectations for requiring consent when using patient data.

Our detailed recommendations are included below.

I.   BACKGROUND ON PREMIER INC.

Premier is a leading healthcare improvement company and national supply chain leader, uniting an alliance of 4,400 hospitals and health systems and approximately 250,000 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).

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.

In addition, PAS has assembled a HIPAA-compliant database containing more than one billion data points representing 25 percent of U.S. hospital inpatient and outpatient discharges drawn from a geographically diverse collection of more than 1,300 U.S. sites over the past twenty years. This database enables Premier to develop new, more efficient ways to identify the necessary patient population for a trial, as well as to develop synthetic control arms for clinical trials. A synthetic control arm is one made up entirely of existing patient data from a representative population, rather than a control group made up of randomly selected trial participants. This is data that can be tokenized to other data sets and/or clinical trial patients to allow increased visibility to patient history as well as post study follow up. Additionally, Premier's unique relationship with member sites allows Premier to foster partnerships between hospital locations and trial administrators through a hybrid clinical trial design.

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.

II.   ESTABLISHING THE VALUE OF DECENTRALIZED CLINICAL TRIALS

Premier strongly believes that hybrid and decentralized trials are critical to the modernization and simplification of the clinical trial and approval process for pharmaceuticals, biological products and medical devices. Decentralized clinical trials (hereafter used to refer to decentralized and hybrid clinical trials unless otherwise specified) hold the potential for groundbreaking benefits to researchers, developers and patients.

Cost: Decentralized clinical trials may greatly reduce the cost of designing and running clinical trials, incentivizing innovation, accelerating the pipeline for new biopharmaceutical and medical devices, and expanding FDA-approved indications to get to the patients who need them. One of the biggest expenses in clinical trials is the time it takes to identify and recruit a large enough cohort of willing participants who are able to travel to the trial location. Some 80 percent of clinical trials face costly delays based on challenges with recruitment – the ability to run decentralized trials from patient homes or different clinical locations will make it easier and less expensive to administer trials. In addition to recruitment costs, administrative staff costs and site monitoring and retention costs could also be reduced through a decentralized approach to trials, substantially reducing overall research and development (R&D) costs for these products.

Patient Access and Trial Diversity: Traditional clinical trials pose significant financial and logistical challenges to potential participants, many of which make it difficult for the trial to recruit a diverse patient population. As a result, trial data may not be representative of a device or drug's efficacy across all patient populations. Trial site location may be a barrier to trial enrollment for patients from rural areas or from a low socioeconomic background, for example, due to the burden of travel, lodging for family or caretakers and other expenses. Efforts to recruit a more diverse patient population for trials will be significantly bolstered by the widespread adoption of decentralized clinical trials by bringing the studies into the communities where more patients are.

Accelerating the Trial Process: Decentralized clinical trials have the potential to accelerate trial design and administration, shortening the lengthy FDA approval process for new drugs and devices, as well as expanded indications. Decentralized trials allow developers and researchers to design, recruit for and run trials in a more efficient and timely manner and provide researchers new opportunities to get the precise data necessary for the FDA approval. It also activates new research study sites that have the capacity and interest to conduct clinical trials but previously were not ideal due to geographical constraints, thereby furthering geographical diversity alongside participant diversity.

Given the strong positive impact that this guidance will have on the clinical trial process and the development of innovations with transformative value to patients, ***Premier urges the FDA to act quickly to finalize this draft guidance to provide necessary regulatory clarity to the parties involved in the design and administration of clinical trials.*** There should be no delay in the update and finalization of this draft guidance; Congress clearly expressed intent to drive the development and feasibility of decentralized clinical trials with its directives to the FDA in the Food and Drug Omnibus Reform Act of 2022. ***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.*** Further, Premier recommends that the FDA clarify opportunities to engage with the agency should implementation questions or concerns arise.

Additionally, 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.

III.   RECOMMENDATIONS FOR PROCEDURAL STANDARDS

Premier appreciates the flexibility afforded to trial personnel in this draft guidance; we have also identified several areas of trial procedure where the FDA can offer valuable clarification. While this draft guidance draws many parallels and makes repeated reference to standards and procedures that remain the same

across on-site and decentralized clinical trials, ***Premier urges the FDA to explicitly clarify that, unless otherwise noted, all applicable standards for clinical trial procedure remains the same in decentralized trials.*** It is crucial that clinical trials continue to produce the same quality of data and achieve the same standard of validity. To further that end, the FDA should do everything possible to instill trust and ensure quality. Premier believes additional clarification would be helpful in the following areas:

- **Data Quality**: ***Premier recommends that the FDA clarify that all the same data standards found in Good Clinical Practice (GCP) guidance comprising FDA E6 should apply to every decentralized clinical trial.*** Data must meet the same standard for both on-site and decentralized clinical trials, so it would be advantageous for the FDA to clarify this explicitly in its guidance to reduce the possibility of poor practices. ***Premier also recommends that the FDA consider situations where current GCP standards may not be applicable and issue clear guidance about acceptable practices.*** For example, when digital health technologies are used to collect patient data during trials, the FDA should ensure that investigators have certified that the device used during the trial will collect data of sufficient quality and precision to accurately assess the efficacy of the investigation product (IP). The FDA has already issued draft guidance addressing some of these concerns, but Premier requests that the FDA finalize and harmonize that guidance with this guidance to eliminate uncertainty. Additionally, digital health technologies have the capacity to incorporate environmental data, such as air pollution, or various digital biomarkers into novel digital endpoints, in contrast with traditional digital endpoints such as heart rate. ***The FDA should clarify which components of current data standards apply to the collection and incorporation of such novel data elements into trial submissions and offer guidance where necessary.***

- **Procedures**: Premier has also identified potential confusion around requirements for training or monitoring patients on or during the delivery of IP during the trial. Patients in on-site trials must be under observation during the delivery of IP. Premier recommends that the FDA make it explicitly clear that patients may be trained in or monitored during the delivery of IP in a fully virtual manner in such cases that the risk to the patient, size of the trial or cost of in-person training or monitoring would be prohibitive or present a non-insignificant burden to trial personnel or participants. This would specify that not only can regular check-ins, progress monitoring and data collection take place in a remote or virtual setting, but actual trial procedures as well. While stakeholders may assume that the above is acceptable procedure from the draft guidance, Premier recommends that FDA explicitly state that it is permissible conduct that IP delivery and management components of the trial be performed remotely. Given the context above, Premier also recommends that the FDA clarify how deviations from or violations of trial procedure should be defined in a decentralized setting. This clarification should extend to the threshold where a patient's results or data should be invalidated. Given that patients may not be under in-person supervision from trial personnel as they would be during an on-site trial, minor or potentially immaterial deviations from trial procedures may occur. ***In order to avoid confusion, FDA should clarify how trial personnel should treat these deviations and at what point a patient's data should be considered unacceptable for the trial.***

- **Physical Trial Hub**: Premier recommends that the FDA specify that even fully decentralized clinical trials require the designation and maintenance of a physical trial hub location, where IP will be handled and data will be managed. Even though this site may not physically host the trial itself, a physical hub is necessary to maintain appropriate controls on participant data and trial materials. The advantages of maintaining the experience, expertise and resources of health systems and research hospitals in the operation of clinical trials, both for patient safety and trial success, cannot be understated.

- **Investigational Products in a DCT**: While Premier appreciates the FDA's guidance regarding the use of a product's safety profile in its determination of whether the IP is appropriate for administration outside of a clinical trial site, Premier recommends incorporating FDA's Guidance

for Industry *Investigator Responsibilities - Protecting the Rights, Safety, and Welfare of Study Subjects* (Oct 2009) as a reference to this section to assist other sponsors and investigators in developing protocols for DCTs that provide reasonable medical care and access to an appropriate level of care.

Finally, Premier requests clarification on how anti-kickback statute will be applied to decentralized clinical trials 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.

- As described in Section C, 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 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.

IV.   RECOMMENDATIONS FOR TECHNOLOGY STANDARDS

While decentralized clinical trials reduce some of the administrative burden and logistical challenges that may be prohibitive to participation for some patients, these new opportunities for patients to take advantage of clinical trials must not come at the expense of privacy. Decentralized clinical trial models rely heavily on digital health technologies and data sharing - in both regards, the current draft guidance does not provide enough clarity on either minimum or best practice cybersecurity and privacy standards.

General Recommendations: The baseline standards in Section I 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.

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, the FDA should include guidance on 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.

The FDA should address the aforementioned questions in its final 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.

Use of Artificial Intelligence and Machine Learning in Clinical Trials: Premier anticipates that artificial intelligence (AI) and machine learning (ML) methods will soon be incorporated into decentralized clinical trials, raising several questions about procedure. The FDA has the opportunity to incorporate guidance around the use of AI/ML in decentralized clinical trials into final guidance, pre-empting impending regulatory uncertainty and governing the deployment of emerging technologies in a responsible, patient-centered manner. The potential uses of AI to facilitate decentralized clinical trials include:

- **Generating Synthetic Data**: AI, once trained on RWD, has the capability to generate synthetic data and patient profiles that share characteristics with the target patient population for a clinical trial. This synthetic data can be used to simulate clinical trials in order to optimize trial designs, model the possible effects or range of results of a novel intervention, and predict the statistical significance and magnitude of effects or biases. Ultimately, synthetic patient data can help optimize trial design, improve safety and reduce cost for decentralized clinical trials.

- **Identifying Trial Participants**: One of the biggest challenges facing health systems that seek to participate in or enroll patients in clinical trials is identifying and enrolling patients in a timely manner. Delays in meeting trial enrollment targets and timelines can increase the cost of the trial. AI tools have the ability to analyze the extensive universe of data available to healthcare systems in order to identify patients that may be a match for clinical trials that are currently recruiting. This application of natural language processing systems can make developing new drugs less expensive and more efficient.

The FDA should consider the benefits and risks of these uses of AI in decentralized clinical trials, as well as other emerging applications. Premier has developed a series of recommendations for the responsible use of AI in healthcare, centering the principles of transparency and trust, risk and safety, and data use and privacy.

- **Promoting Transparency**: Trust – among patients, providers, payors and suppliers – is critical to the development and deployment of AI tools in healthcare settings. In order to earn trust, AI tools must have an established standard of transparency. Recent policy proposals, including those proffered by the Office of the National Coordinator for Health Information Technology (ONC), suggest transparency can be achieved through a "nutrition label" model. This approach seeks to demystify the black box of an AI algorithm by listing the sources and classes of data used to train the algorithm and/or used as an input. Unfortunately, some versions of the "nutrition label" approach to AI transparency fail to acknowledge that when an AI tool is trained on a large, complex dataset, and is by design intended to evolve and learn, the initial static inputs captured by a label would not provide accurate insights into an ever-changing AI tool. Further, overly intrusive disclosure requirements, around either data inputs or algorithmic processes, that would force AI developers to publicly disclose their intellectual property or proprietary technology may stifle innovation. Premier recommends that AI technology in healthcare should be held to a standardized, outcomes-focused set of metrics, such as accuracy, bias, false positives, inference risks, recommended use, and other similarly well-defined values. Outcomes, rather than inputs, are where AI technologies hold potential to drive health or harm. Thus, Premier believes it is essential to focus transparency efforts on the accuracy, reliability and overall appropriateness of AI technology outputs in healthcare to ensure that the evolving tool does not produce harm.

- **Mitigating Risks**: It is important to acknowledge potential concerns around biased or discriminatory outcomes resulting from the use of AI tools in healthcare, as well as potential concerns around patient safety. Fortunately, there are several best practices that Premier and others at the forefront of technology are already following to mitigate these risks. First, we reiterate Premier's recommendation for a "model card" style assessment of AI technologies' performance, which would provide a standardized way to hold AI developers and vendors responsible for monitoring for any biased outcomes. Model card-style reporting could incorporate results from disparity testing, as recommended in the OSTP AI Bill of Rights, both before and after technology

deployment. Premier also supports the development of a standardized risk assessment, drawing on the extensive groundwork already laid by the National Institute of Standards and Technology (NIST) in the AI Risk Management Framework. An AI Risk Assessment should identify potential risks that the AI tool could introduce, potential mitigation strategies, detailed explanations of recommended uses for the tool, and risks that could arise should the tool be used inappropriately. Premier also suggests the adoption of a nuanced approach to risk level classification for the use of AI tools in healthcare. While there are some clinical applications of AI technology that could be considered high-risk, it is certainly true that not all healthcare use cases carry the same level of risk. For example, the use of AI technology to identify participants for a clinical trial would carry a significantly lower risk than the use of synthetic patient data to determine whether a trial design is safe.

- **Data Standards**: Finally, 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.

The FDA should use this opportunity to develop guidance on the use of AI in decentralized clinical trials and prevent potentially unsafe uses of emerging technologies in trial design and administration.

V. CONCLUSION

Premier appreciates the opportunity to comment on the FDA's draft guidance for decentralized clinical trials, and we reiterate a few keys points from our response:

- **Clarity**: Premier encourages the FDA to provide clear guidance on potential points of confusion that will encourage investigators to take advantage of the benefits of decentralized clinical trials.

- **Innovation**: Premier encourages the FDA to give investigators the chance to innovate and take advantage of new technological capabilities in trial design and execution, such as synthetic control arms and AI technology.

- **Timeliness**: Premier urges the FDA to move quickly to finalize guidance so as not to inhibit the adoption of decentralized models for clinical trials.

- **Consistency**: Premier believes that there are well-tested and clear guidelines about nearly every element of clinical trial design and execution, and that, wherever possible, the FDA should explicitly extend these same guidelines (e.g., guidelines for data quality, procedure, investigators) to decentralized clinical trials to ensure quality and reduce uncertainty.

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,

Soumi Saha, PharmD, JD
Senior Vice President of Government Affairs
Premier Inc.