ISPOR
The professional society for health economics and outcomes research

Improving healthcare decisions

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Docket Number: FDA-2024-D-2052-0002

Dear FDA:

ISPOR – the professional society for health economics and outcomes research - is pleased to respond on behalf of its membership to your consultation entitled "Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice; Draft Guidance for Industry."

ISPOR is a scientific and educational society with many of its members engaged in evaluating health technologies, including pharmaceuticals, medical devices, and other interventions. We have a large membership living and working in 110 countries globally, across a range of disciplines, including health economics, epidemiology, public health, pharmaceutical administration, psychology, statistics, medicine, and more, from a variety of stakeholder perspectives, such as the life sciences industry, academia, research organizations, payers, patient groups, government, and health technology assessment bodies. The research and educational offerings presented at our conferences and in our journals are relevant to many of the issues and questions raised in this request for information.

The response to this consultation was led by the ISPOR Science Office. Comments were solicited from ISPOR's most senior advisory body, the Health Science Policy Council, the ISPOR Institutional Council, Real-World Evidence Steering Committee, Real-World Evidence Special Interest Group, and the Statistical Methods in Health Economics and Outcomes Research Special Interest Group. The attached document provides a summary based on their comments. We hope they prove useful.

ISPOR would be happy to answer any questions about our response, to serve as a partner, or to participate in any follow-up consultations on the relevant program items mentioned within the report.

Sincerely,

Robert Abbott
CEO & Executive Director
ISPOR

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Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice; Draft Guidance for Industry

ISPOR – the professional society for health economics and outcomes research commends the US Food and Drug Administration on their guideline for integrating randomized controlled trials (RCTs) for drug and biological products into routine clinical practice. Of particular interest to ISPOR, the guidance serves as a good starting point on the use of real-world data (RWD) in RCTs. We have several suggested improvements. Practice-based trials also hold the promise of making it easier to enroll diverse populations in healthcare settings that they already know and trust. This is strongly consistent with ISPOR's goals of addressing healthcare accessibility and equity.

Other Data Sources and Data Tokenization

The guidance often refers to electronic health records (EHRs) when referring to the use of RWD in clinical trials. However, other types of anonymous patient data, such as claims data, can also be connected to clinical trial data using tokenization and other linkage techniques to create a comprehensive dataset. Tokenization involves generating a unique, encrypted identifier (or token) for each patient, which can be used to link their data across different sources without revealing their identity. This method ensures patient privacy while allowing researchers to track and analyze patient outcomes over time. It allows the collection of data over a variety of sources such as EHR, claims, lab data, wearables, and genomic data, linking them to data which is collected in clinical trials or through patient reported outcomes. This approach enhances the quality and completeness of the data, facilitating more accurate and meaningful research outcomes. We suggest the FDA more prominently mention non-EHR sources of RWD and support tokenization as a technological tool to enable data linkage.

Feasibility and Data Quality

The feasibility of implementing this guidance and of conducting studies integrated into routine clinical practice present a significant challenge, particularly in validation and operational execution. While the guidance suggests leveraging EHRs and simplified eligibility criteria, it assumes a level of standardization in clinical documentation and testing that is often absent, especially in under-resourced settings. Additionally, variability in data quality, arising from differing clinical practices, incomplete records, and inconsistent documentation, poses a challenge to ensuring reliable and valid trial outcomes. The integration of clinical outcome assessments (COAs) and the reliance on external medical records further introduce logistical and legal hurdles, such as ensuring access to and the accuracy of data across decentralized sites. This approach risks variability in data quality and patient safety, which could undermine the reliability of trial outcomes. Inspection processes focus on compliance and safety but do not provide clear strategies to ensure the best practice standards for regulatory reviews. Feasibility assessments, although briefly mentioned, are not given the prominence they require. It is essential that feasibility assessment becomes a requirement for these trials, as the absence of a feasibility assessment increases the risk of stopping studies midstream due to unmet data requirements or unforeseen logistical barriers. The section "Choosing Suitable Investigational Drugs" (lines 311–337) complements the focus on feasibility by recommending FDA-approved drugs with established safety profiles. This pragmatic approach enhances feasibility by reducing risks and aligning with the realities of routine clinical practice. The inclusion of selective safety data collection, such as monitoring serious adverse events, is a strength that streamlines processes while maintaining safety oversight. However, the guidance lacks strategies for addressing practical feasibility challenges, such as the titration of drugs with narrow therapeutic windows, complex administration protocols, or specialized storage needs, which pose complexities to administering a trial in practice-based settings. Moreover, the exclusion of unapproved drugs with less-defined safety profiles, though ensuring safety, may pose obstacles in areas like rare diseases. A framework for safely incorporating such drugs under controlled conditions would balance feasibility with scientific advancement.

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Informed Consent

The FDA's emphasis on informed consent is commendable but lacks practical depth. Simplifying consent materials is imperative to ensure participants fully understand their roles and risks. While embedding forms in EHRs is a promising integration step, the forms must be designed for clarity, using plain language and multimedia tools to cater to diverse literacy levels. There is also a need for dynamic consent models. As trials evolve, participants should have opportunities to modify or withdraw consent in alignment with changes in protocol, ensuring ongoing engagement and respect for autonomy—an aspect underexplored in the FDA's guidance. Also, in cases where the subject wishes to withdraw from active participation in the trial, s/he should be given an option for their RWD to still be used. While those RWD might, in many cases, represent a fraction of all data that would have otherwise been collected, they may be of secondary use to FDA as well as sponsors.

The guidance document lacks measures to mitigate coercion risks inherent in real-world clinical settings. Recommendations involve trained neutral third-party counselors to ensure voluntary and informed participation, particularly addressing the power dynamics between patients and their healthcare providers. Also, the FDA's reliance on digital consent methods may alienate populations with limited access or digital literacy. Offering alternative methods, such as verbal or paper-based consent and in the native languages of the populations served, is essential for equitable participation.

A greater emphasis is needed surrounding data privacy and transparency. Detailed disclosures on data handling, including encryption methods, sharing policies, and participant rights are necessary components of informed consent. Regular updates to participants during and after the trial would also foster trust and address growing concerns about data security. Additionally, the draft guidance lacks specific monitoring and accountability mechanisms for informed consent. Routine audits and mandatory staff training should be standard to ensure compliance with ethical standards.

Lastly, decentralized trials, a growing trend has been omitted in detail by the guidance but are particularly relevant considering that multiple health systems and/or practices may be involved in the trial, and much of participant's data may be collected remotely. We suggest leveraging secure telehealth platforms for remote consent and ensuring technical support for participants. By adapting to the realities of decentralized and virtual settings, the industry can align with participant needs and emerging practices.

We also noted a few areas of the guidance where practical examples would support effective implementation. Without these actionable examples, sponsors and investigators may struggle to operationalize the guidance, particularly in complex trials involving unapproved drugs or diverse patient populations. Specifically:

1) The guidance suggests using EHRs to capture trial data (lines 103–108) but does not provide concrete examples of how to standardize EHR systems across diverse healthcare settings or address challenges like data interoperability.
2) Similarly, while it highlights the potential role of local healthcare providers (HCPs) in performing trial-related tasks (lines 210–222), it fails to offer specific examples and strategies for training or engaging these providers, especially in resource-limited settings. If local HCPs perform certain trial tasks with minimal training or limited protocol knowledge, this practice may introduce variability in data quality and pose risks to patient safety.
3) The use of a quality-by-design (QbD) approach is mentioned to simplify trial designs (lines 247–252) but does not include practical case study examples or templates to illustrate how sponsors can balance trial rigor with the flexibility required in clinical practice.
4) The section "Identifying the Trial Population" (lines 275-293) lacks detailed guidance on addressing scenarios where essential eligibility data are either not routinely collected or are incomplete in real-world clinical practice, which is especially pertinent for trials conducted in under-resourced settings.

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This section too, would be enhanced by case examples.

Overall, the US FDA's draft guidance, *Integrating Randomized Controlled Trials for Drug and Biological Products Into Routine Clinical Practice*, provides a promising framework for integrating clinical trials into routine care and we look forward to seeing the final version. We acknowledge ISPOR members Massoud Toussi, Tuhin James Paul, Kejsi Begaj, and Sarah-Jane Cashmore for their assistance in assembling these comments, as well as ISPOR staff Laura Pizzi, Kelly Lenahan, and Madeline Shipley.