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The High Five:

Key Regulatory Topics for Drug Development in 2024

Master protocols in clinical trial design, patient outcomes in oncology, advancements of new modalities, use of AI/ML and digitizing clinical trials.

Clinical trial sponsors recognize the need to evolve their businesses to better address varying patient needs with scientific and technological innovations that are transforming clinical research. As practices change, sponsors also must keep track of evolving regulations intended to guide innovation.

Below, we discuss five noteworthy regulatory topics to closely monitor in 2024 and afterward.

CLINICAL TRIAL INNOVATION

To support shifts in clinical trial design and models to match complex scientific innovation quickly and efficiently, the FDA released draft guidance on the use of master protocols in December 2023. Master protocols allow multiple trials to share control arms, protocol elements, execution and outcomes oversight, etc., to extract more collective insights from research efforts in a timely manner.

There are multiple trial types that could leverage a master protocol, including umbrella trials to evaluate multiple treatments in parallel for a single disease and basket trials to examine a single product for multiple diseases. As such, regulatory guidance is shaping trial design approaches for sponsors, clinical research organizations and study teams alike.

For continued discussion, the FDA has scheduled two workshops in March 2024 to inform best practices for innovative clinical trial design and implementation.

EU-BASED DRUG DEVELOPMENT

There are several notable regulatory updates meant to heighten interest in planning and conducting clinical trials in Europe and to strengthen harmonization within drug development processes among European Union member countries.

For one, the EMA's Clinical Trial Regulation 536/2014, which intends to provide a single application submissions process across all EU member states through its Clinical Trial Information System portal, has been in effect for more than two years. The CTR completely overhauls processes and requirements. Initial stages of implementation have presented some challenges and opportunities, and the EMA has taken steps to foster communication and clarity to sponsors and CROs.

Sponsors need to closely follow evolving EMA transparency guidelines meant to enhance public understanding of trial updates. The last guideline revisions were published in October 2023, and experts anticipate an updated version later this year.

Building on the EU CTR, Accelerating Clinical Trials is a joint initiative of the European Commission, EMA, the Heads of Medicines Agencies. It aims to transform how clinical trials are designed and managed to deliver more impactful research that benefits patients across Europe by enabling seamless cross-border collaboration among sponsors, regulators, ethnics committees, etc. and leveraging tech-enabled advancements and other forms of support to optimize processes.

The ACT EU Workplan for 2023-2026 notes priority areas of action, including:

- Effective implementation of the CTR.
- Creation of a regulatory-specific helpdesk for non-commercial trial sponsors who are conducting multi-country trials and a scientific advice pilot program to offer guidance to all sponsors for trial and marketing authorization applications.
- Developing a multi-stakeholder platform advisory group of trial stakeholders and regulators to discuss how to improve the R&D environment in Europe for patients.
- Regulator support of the start, continuity and completion of trials during public health emergencies.

ONCOLOGY DRUG DEVELOPMENT

Regulatory support and guidance for patient-centered oncology drug development is undeniable. In 2023, the FDA's Oncology Center of Excellence approved 83 cancer therapies, including 11 approvals of seven different treatments and biologics for pediatric patients.

In advancing viable cancer therapies forward, the FDA's Oncology CoE has more than 30 dedicated initiatives to improve health outcomes for patients with cancer, including the following which were initiated in 2023:

- **Project ASIATICA** is designed to enhance diversity and bring focus to Asian Americans with cancers, a population that is under-represented in oncology clinical trials, with collaboration among policy makers, sponsors, advocacy groups and more
- **Project Endpoint** aims to develop oncology drug endpoints to advance the understanding of early novel endpoints that could improve patient outcomes.
- **Project Pragmatica** is one of the FDA's efforts to help modernize evidence generation, supporting stakeholders exploring the use of pragmatic trial design with integration of trial elements into real-world clinical practice for approved oncology therapies. In 2023, the CoE worked with the National Cancer Institute to develop the Pragmatica-Lung study, a randomized Phase 3 trial of a two-drug combination in lung cancer, to streamline eligibility criteria and safe data collection and create more inclusive recruitment.

As trial sponsors fine tune their early phase development programs, the CoE's Project Optimus initiative continues to be top of mind as they work with CROs to shift the dosing paradigm in cancer care to prioritize patient tolerability alongside efficacy earlier in trial phases. Also, Project FrontRunner is designed to encourage oncology sponsors to gauge when to potentially first develop and seek approval of new cancer therapies for advanced disease in an earlier clinical setting.

ADVANCEMENTS IN NEW MODALITIES

Currently, there is vast investment in radiopharmaceuticals, radioactive agents used to diagnose medical conditions and treat certain diseases, including various types of cancer. Already instrumental in imaging, they are used in millions of U.S. nuclear medicine procedures, and analysts are reporting a compound market growth rate of 10.2% a year.

Integrating these agents into clinical evaluation and use requires specialized knowledge to protect both patients and providers, as well as adherence to FDA best practices for clinical trial design and International Atomic Energy Agency guidance for safe handling of these materials. Researchers need to be able to characterize the behavior of an investigational radiopharmaceutical and understand its suitability and safety for healthy volunteers and patients under study. After the IAEA's 2023 International Symposium on Trends in Radiopharmaceuticals, several position statements outlining best practices for regulating the safe use of these agents were published. A position paper published in the EJNMMI Radiopharmacy and Chemistry journal in January 2024 notes that regulations are needed to account for, "the impact of the variable complexity of radiopharmaceutical preparation, personnel requirements, manufacturing practices and quality assurance, regulatory authority interfaces, communication and training, as well as marketing authorization procedures to ensure availability of radiopharmaceuticals."

Similarly, guidelines are expanding in cell and gene therapy,

most recently with the FDA releasing guidance for genome editing and the development of chimeric antigen receptor T cell (CAR-T) therapies in January. The FDA also established the Office of Therapeutic Products in 2023 to add employees to address the extensive growth of these novel treatments with increased review capacity and CAGT expertise.

In February 2024, the FDA announced the Collaboration on Gene Therapies Global Pilot (CoGenT Global) in which the World Health Organization and member countries of the International Council for Harmonization will concurrently review gene therapy applications. The intent is to decrease costs and speed development of therapies that treat rare diseases.

USE OF AI/ML IN CLINICAL TRIALS

From trial protocol optimization to drug repurposing and customized patient recruitment, research and development artificial intelligence and machine learning engineers are continuously building evidence-based use cases for how AI/ML-driven solutions can improve clinical trials. In 2021 alone, 132 drug and biologic applications for regulatory approval by the FDA included AI/ML components.

However, as with any evolving tech-enabled solution, there are considerations that industry stakeholders need to keep in mind when integrating AI/ML-driven approaches into clinical trials. To initiate industry dialogue regarding potential opportunities and concerns associated with AI/ML in drug development, the FDA released a discussion paper in May 2023, which reviews the need for risk-based approaches to monitor and oversee its use in product development. The FDA asks industry experts to provide feedback to ensure an open and ongoing discussion on how to collectively ensure AI/ML models are reliable and free of risks (e.g., biases in data used to train ML algorithms). Similarly, in July 2023, the European Medicines Agency published a draft reflection paper to open dialogue, as part of its Heads of Medicines Agencies Big Data Steering Group Big Data Workplan 2022-2025, which aims to further develop the EMA's preparedness and capabilities in data-driven regulation.

Both papers emphasize the need for human involvement when planning for AI/ML use in trials. Integrating data science expertise into the broader study team is key to ensuring AI/ML techniques are applied appropriately within the fuller process by leveraging experience to identify patterns, augment approaches and extract meaningful insights for successful trial activities.

With ongoing stakeholder feedback and knowledge sharing, it is possible the FDA and EMA may provide more formal regulatory guidance on the use of AI/ML to support safe and effective drug development.

DIGITIZING CLINICAL TRIALS

In May 2023, ICH issued the draft Good Clinical Practice E6 R3 guidance to shift the focus from a process-based approach to one based on principles specific to conducting ethical trial design and quality management. Though it supports the use of digital health technologies and decentralized solutions to improve trial efficiency and success, the R3 guidance prioritizes the importance of placing value on patient needs and preferences by designing trials with patients in mind and ensuring data is protected.

Since sponsors have ultimate responsibility for trials, it is critical to help investigators and their teams adhere to evolving GCP and regulatory guidance while giving participants flexibility in how they participate. This includes trial strategies with well-defined roles and responsibilities, especially regarding data flow and management through decentralized trial solutions and digital health technologies.

Staying on top of multiple evolving regulatory requirements worldwide is no easy feat for sponsors, especially as trials increasingly expand across countries and incorporate advanced technologies. However, close monitoring of critical regulatory updates will help sponsors maintain agile strategies and leverage regulator support of innovative approaches to ensure much-needed therapies reach patients in need with quality and timeliness. **CP**

With more than two decades of experience in Regulatory Affairs in the biopharmaceutical industry, Dr. Brady regularly advises R&D leadership and project teams on global drug development strategies, emerging technologies and the changing regulatory landscape and policies to help inform strategies and decision-making.