White Paper

Transforming Cancer Treatment

Impact of FDA Project FrontRunner on oncology drug development

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Introduction

In the ongoing battle against cancer, the opportunity to access promising investigational therapies as early as possible can have a profound impact on patient outcomes. By shifting drug development into earlier stages of treatment, the FDA's Project FrontRunner initiative seeks to accelerate the timeline, ensuring patients receive potentially beneficial treatments sooner.

This whitepaper explores the FDA's efforts to encourage earlier studies, highlighting their potential to sharpen our understanding of a treatment's effects, improve comparisons to standard care, and reduce the time it takes to bring effective new therapies to the clinic. We'll also look at what it takes to design robust randomized controlled trials (RCTs) that generate the high-quality evidence regulators expect, and illustrate these principles through a case study.

In addition, we'll consider practical guidance on engaging with the FDA early in the development process, leveraging accelerated approval pathways, and taking advantage of evolving guidance so that patients can benefit more quickly from groundbreaking treatments.

Incorporating FDA initiatives into early-phase trial design

It's important to understand how emerging FDA initiatives—such as Project Optimus for dose optimization guidance and Project FrontRunner for guidance on seeking earlier approvals for oncology therapies—inform early clinical trial strategies. These initiatives encourage a more structured approach to determining the right dose and selecting the best patient population to evaluate earlier in the treatment continuum.

A common starting point in early-phase oncology development is dose escalation. While the traditional 3+3 design is still seen, more sponsors are turning to Bayesian Optimal Interval (BOIN) or Bayesian Logistic Regression Model (BLRM) methodologies to find a recommended Phase II dose more efficiently. After identifying this "working dose," the next step is often to conduct dose expansion cohorts. These cohorts help confirm efficacy signals in specific tumor types and refine the therapy's risk-benefit profile. Once a favorable indication arises, sponsors can leverage Project FrontRunner principles to consider evaluating the therapy in earlier lines of treatment.

The broader context: FDA's Oncology Center of Excellence

Project Frontrunner is one of over 30 initiatives spearheaded by the FDA's Oncology Center of Excellence (OCE). These programs share a unified goal: to advance patient-centered regulatory decision-making through innovation and collaboration. Highlights include:

- **Diversity in clinical trials:** Encouraging inclusive enrollment to ensure therapies are effective across diverse populations.
- **Dose optimization:** Refining dosing strategies to balance efficacy and safety.
- **Real-world evidence integration:** Leveraging data from real-world settings to contextualize trial results and support regulatory submissions.

These initiatives reflect the FDA's commitment to fostering innovation while maintaining rigorous safety and efficacy standards.

The purpose of Project FrontRunner

Project FrontRunner challenges the traditional drug development model, which historically introduced new oncology therapies in late-stage treatment settings—often for patients who had run out of other options. Instead, this initiative shifts the focus to earlier lines of therapy, particularly in advanced or metastatic diseases. The goal is to provide patients with earlier access to innovative treatments, generate robust clinical evidence to support benefit-risk assessments, and promote collaborative innovation by encouraging sponsors to

work closely with regulators and stakeholders. By enabling drug developers to pursue early-phase trials in advanced settings, the FDA aims to reimagine the pathway for oncology treatments, improving healthcare outcomes.

Key elements of Project FrontRunner

RANDOMIZED CONTROLLED TRIALS (RCTS)

The FDA's Project FrontRunner aims to improve the evidence base for novel cancer therapies by promoting the use of randomized controlled trials (RCTs) in early line settings rather than traditional single-arm trials in later line patient populations who usually have exhausted available therapies. Unlike a later line setting, the early line population has a relatively larger pool and standard of care (SOC) available as a control, which makes RCT more feasible and practical. As recommended in the 2023 FDA draft guidance "Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics" there are two pathways for integrating RCTs into oncology drug development, both intended to support accelerated approval regulatory pathways:

- Two trial approach: One trial focuses on early endpoints, such as response rates, while the second addresses long-term outcomes like progression-free survival (PFS) or overall survival (OS).
- Single trial design: Combines interim analysis of early endpoints to support accelerated approval with continuing monitoring for longer-term benefits as final analysis, streamlining to a full approval.

This represents a paradigm shift for sponsors, who must now prioritize robust trial designs to align with these evolving regulatory expectations.

NON-CURATIVE SETTINGS

The FDA's initial focus for Project FrontRunner is on advanced/metastatic diseases where treatment is not expected to be curative. FDA has defined such non-curative settings in the 2022 guidance "Cancer Clinical Trial Eligibility Criteria: Available Therapy in Non-Curative Settings." To initiate an early clinical study in such a setting for a novel therapy with limited clinical experience, FDA emphasizes fully informed patient consent and rigorous nonclinical data to ensure patients understand the potential risks and benefits while enabling sponsors to gather valuable insights that inform future development.

HOW TO EXCERCISE ADVANCED TRIAL DESIGNS WITH PROJECT FRONTRUNNER

Adaptive designs and master protocols are becoming more important, allowing studies to evolve as data comes in:

- Adaptive design: Seamlessly transfer the safety dose finding from the later line populations to the early line population at early development stage (e.g., dose expansion portion).
- Master protocol (basket or umbrella or hybrid): Later and early lines of multiple tumor types and/or multiple novel regimens (mono and/or combo) with SOC controls

By answering multiple questions within a single trial, these methods speed up decision-making, make it easier to enroll the right patients, and ultimately generate stronger evidence in less time.

Figure 1: Incorporating dose optimization into early phase oncology studies

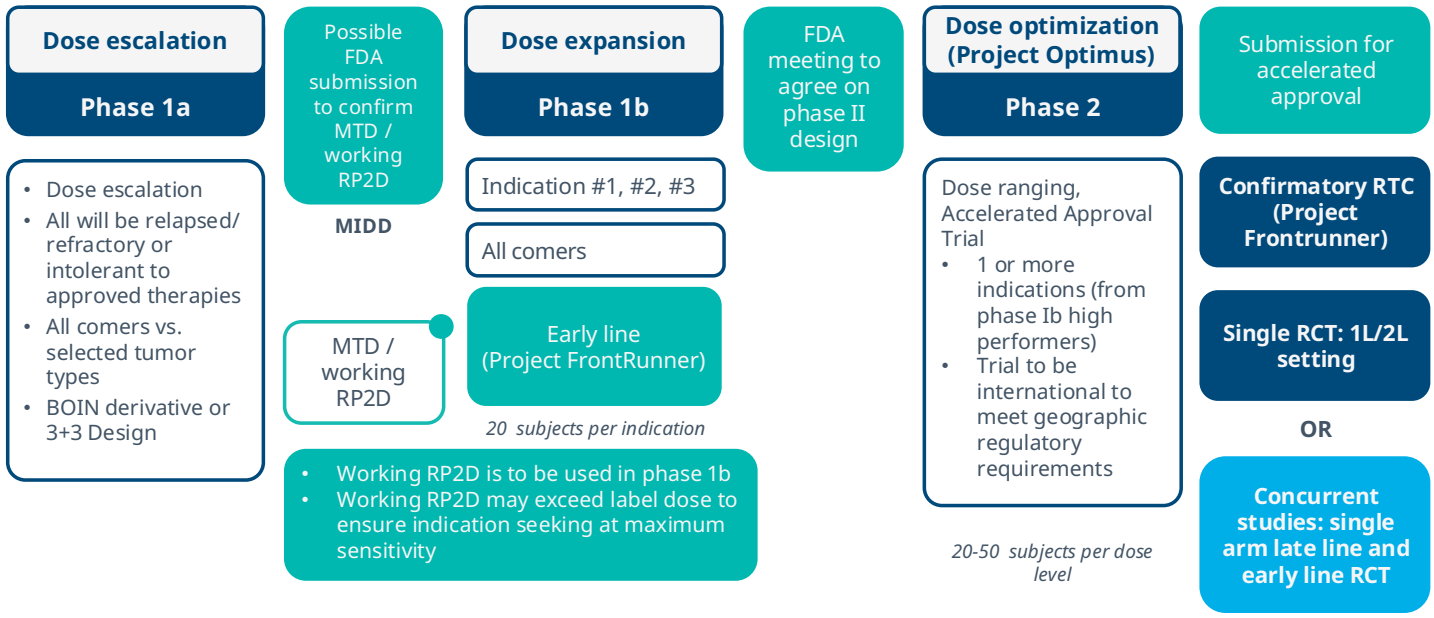
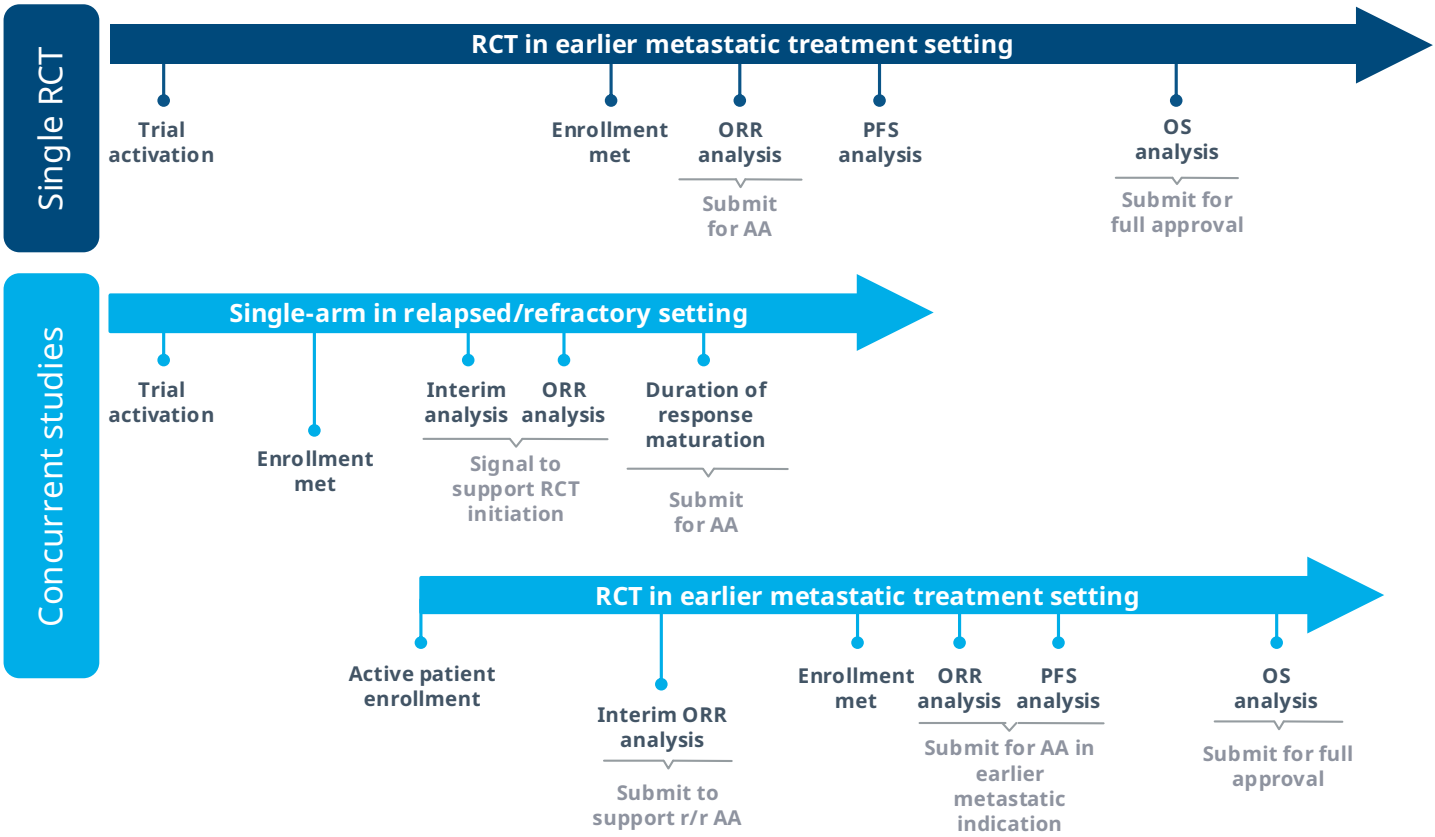


Figure 2: Strategies to earlier metastatic setting approval



Project FrontRunner outlines two general paths toward early-line evaluation:

1. **Single RCT approach**

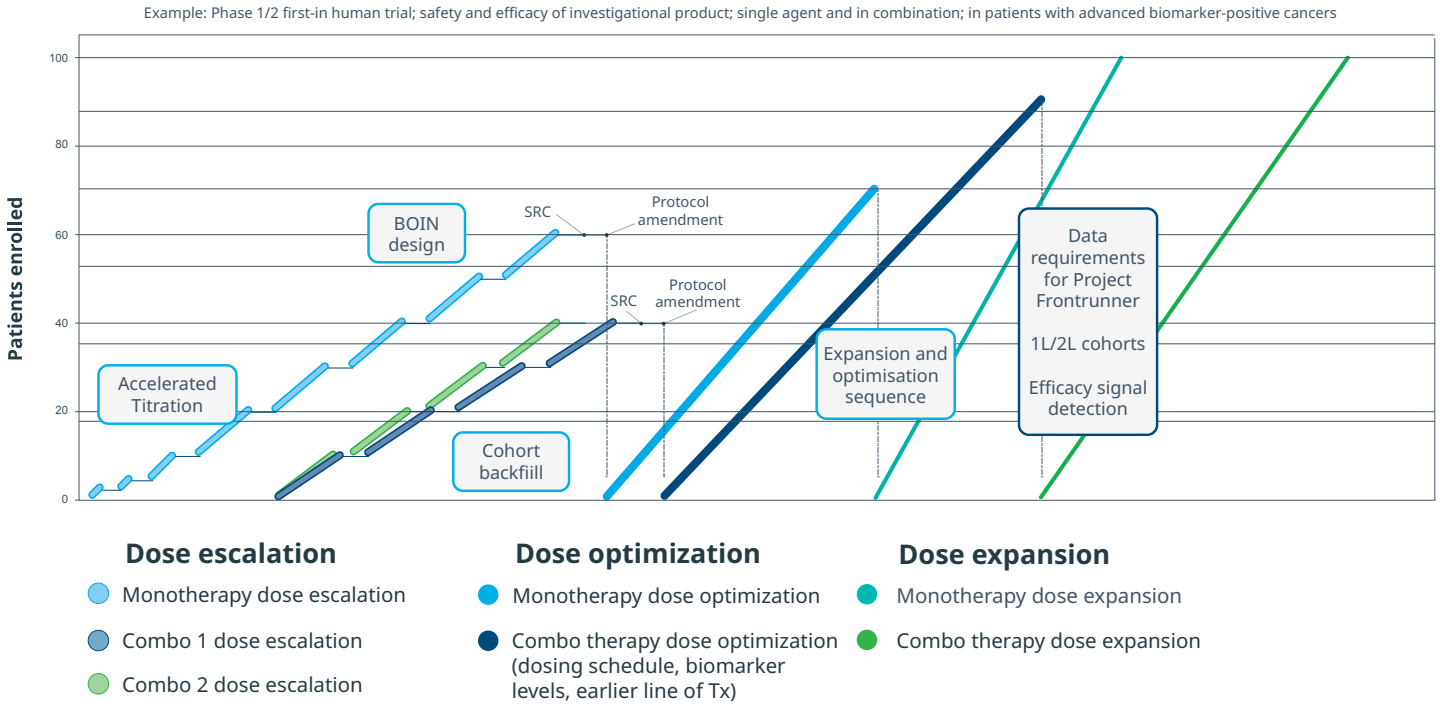
   In this scenario, a single RCT compares the new agent with standard of care in a first- or second-line setting. An interim analysis based on an early endpoint, such as overall response rate (ORR), may allow for accelerated approval if predefined thresholds are met. This design then continues to assess progression-free survival (PFS) and overall survival (OS) for full approval.

2. **Sequential studies approach**

   Another option involves initiating a single-arm, late-line study with interim ORR analysis, while concurrently starting an early-line RTC. If the late-line setting shows promising results, the concurrent early-line trial is already underway, potentially accelerating the path to earlier market access. This approach can generate data across the treatment spectrum, enhancing both safety and efficacy insights and increasing the likelihood of optimizing dose and patient selection.

As early-phase studies progress, enrollment sizes and timelines vary depending on the therapy's performance and the statistical rigor required. Dose-escalation cohorts may enroll 20–30 patients, while optimization cohorts typically enroll about 20 patients per dose. Expansion cohorts often include 20–30 patients per indication. For larger, randomized early-line studies, sample sizes depend on the target ORR, desired confidence intervals, and the underlying hypotheses.

Figure 3



By integrating these evolving strategies—dose escalation, optimization, and expansion—sponsors can position themselves to seamlessly transition into earlier-line trials aligned with Project FrontRunner principles. IQVIA has already supported sponsors in navigating these pathways, providing the strategic insight and operational capabilities needed to design and execute studies that advance promising therapies into more favorable positions in the treatment landscape.

HCC Project Frontrunner case study

A Chinese biotech company sought to bring a novel bispecific antibody for hepatocellular carcinoma (HCC) into the first-line treatment setting—an ambitious goal, considering that new oncology therapies are often introduced only after standard treatments have failed. Initial data from late-line patients in China showed promising response rates of about 40–45%, inspiring the sponsor to pursue a more accelerated strategy aligned with the FDA's Project FrontRunner principles.

Eager to advance their promising candidate into earlier stages of treatment, the sponsor turned to IQVIA's Oncology Center of Excellence, Regulatory Affairs, and Drug Development teams. Together, they formulated a comprehensive plan that would resonate with FDA guidance and support fast decision-making:

- **Regulatory and strategic guidance:** IQVIA offered insights into the U.S. regulatory landscape, advising the sponsor on how to leverage their late-line results to build a case for earlier-line evaluation.
- **Study design and endpoint selection:** The team worked closely with the sponsor to identify the right patient population, refine dose optimization strategies, and establish meaningful endpoints that would align with Project FrontRunner goals.
- **Submission preparation:** Drawing on IQVIA's experience, the sponsor developed a robust FDA briefing package, incorporating all the recommendations—from trial design to regulatory strategy—into a cohesive submission.

With IQVIA's guidance, the sponsor successfully moved their candidate into earlier development phases, setting the stage for potentially faster patient access to a groundbreaking therapy. As the FDA evaluates their submission, this collaboration highlights the power of strategic planning, tailored regulatory guidance, and innovative study design to drive progress in oncology. By shifting away from traditional late-line approaches and adopting Project FrontRunner's principles, sponsors have the opportunity to transform the cancer treatment landscape and deliver life-changing therapies to patients more quickly.

The need for flexible, efficient clinical trial frameworks

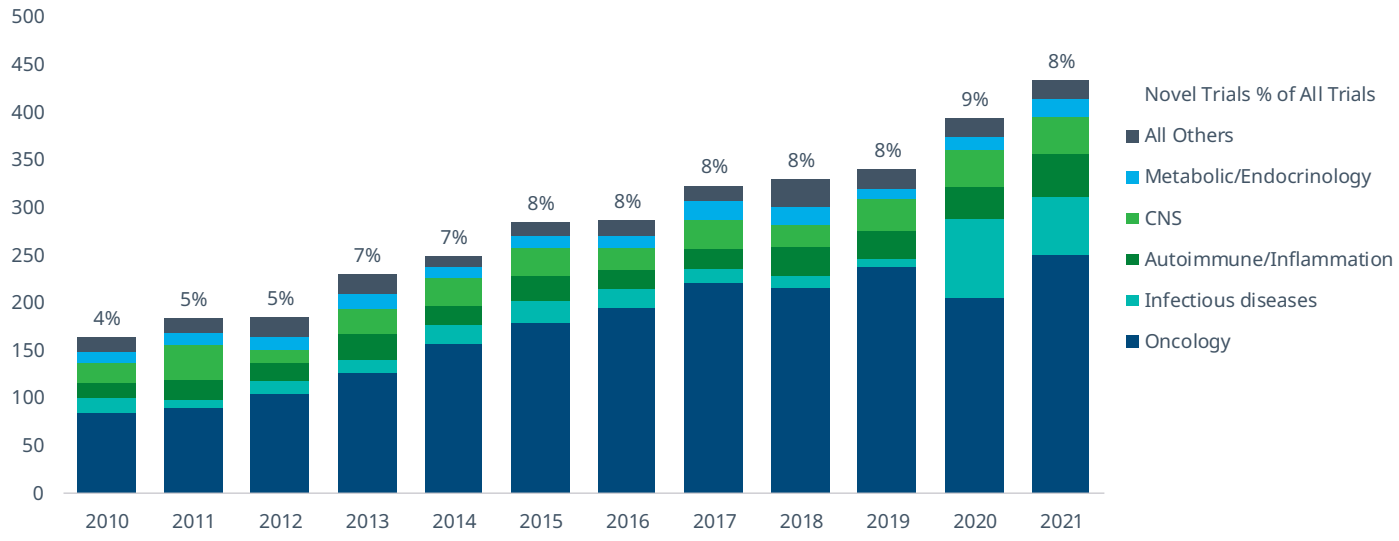
Over the past several years, regulatory bodies have begun to embrace novel trial methodologies—particularly adaptive designs and master protocols—to streamline and enhance the drug development process. Adaptive designs allow for real-time modifications to trial parameters based on emerging data, while master protocols (often basket trials in oncology) enable the simultaneous exploration of multiple tumor types within a single study framework.

Industry data through 2021 show that although the percentage of trials classified as "novel" (i.e., adaptive or master protocol designs) has remained stable, the total number of such trials has grown significantly. This trend held steady even as the COVID-19 pandemic drove a surge of master protocols and adaptive designs in respiratory research. Rather than receding after the initial crisis, these innovative approaches have continued to gain traction. In early-phase oncology specifically, it is now relatively uncommon to see a study that isn't employing some form of adaptive design, a master protocol, or both.

This shift highlights the growing importance of flexible, efficient trial frameworks, which align seamlessly closely with initiatives such as Project FrontRunner. Embracing these approaches in oncology development enables sponsors to deliver promising therapies to patients more quickly, meet regulatory standards, and streamline the approval process.

"With IQVIA's guidance, the sponsor successfully moved their candidate into earlier development phases, setting the stage for potentially faster patient access to a groundbreaking therapy."

Figure 4



Looking ahead

Project FrontRunner holds immense promise, but it comes with challenges. One significant issue is achieving regulatory alignment across international agencies, especially in global trials where regional requirements can differ significantly. Sponsors must carefully navigate these complexities to ensure broad trial feasibility.

Funding large-scale trials based on early-phase data also poses difficulties. Sponsors need to work closely with regulatory authorities early in the process and clearly articulate their development plans to gain investor confidence and secure necessary resources.
Another important challenge is conducting trials in the early line setting for a novel drug as a monotherapy (rather than SOC add-on) with no or limited clinical safety and efficacy experience of the novel drugs.

In addition, another obstacle to overcome is finding consenting patients to participate with a novel therapy in the first line setting when the treatment is unproven. If dose optimization is included in a Project FrontRunner randomized controlled study, that is an additional educational component for the investigator to properly educate the patient on a possible lower effective dose that will be evaluated in the first line setting.

However, even with these challenges, Project FrontRunner stands out as an opportunity in oncology, and it is expected that more examples and case studies will emerge as Project FrontRunner approaches are adopted and implemented in oncology drug development. By focusing on providing earlier access to innovative therapies, it has the power to:

- Transform the standard of care for cancer patients
- Accelerate the timeline for drug development and approval
- Foster a collaborative ecosystem among sponsors, regulators, and stakeholders

IQVIA's deep expertise in navigating these complex processes makes it an invaluable partner for sponsors looking to maximize the potential of Project Frontrunner. As more data emerges and successful case studies are published, the adoption of this initiative is likely to increase, cementing its role in the future of oncology.

The initiative's alignment with innovative trial designs and regulatory priorities opens the door to faster, more effective cancer treatments. For sponsors, patients, and the broader healthcare community, this marks a meaningful step forward in the fight against cancer.

About the authors

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Hodge has 30 years of drug development experience in oncology. Prior to joining IQVIA, he worked at GSK for more than 16 years in various roles and led the early clinical development of 10 molecules from first in human to proof of concept. While at GSK, Hodge was involved in 10 investigational new drugs and 5 new drug applications. He has published more than 100 abstracts and papers in peer-reviewed journals and at international meetings in the field of oncology. Hodge has extensive experience in the development of small molecule tyrosine kinase inhibitors, biologics, novel chemotherapeutics and immuno-oncology therapies. He also leads IQVIA's dose optimization working group in oncology. Hodge received both his master and bachelor of science degrees in medical microbiology and bacteriology from Virginia Tech in Blacksburg, Virginia.

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With more than 20 years of experience in regulatory affairs in the biopharmaceutical industry, 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.

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Chen is responsible for creating integrated development strategies and solutions for pharmaceutical products across multiple therapeutic areas through preclinical, clinical, regulatory and commercial phases. He has more than 20 years of experience working with the FDA and has comprehensive understanding of regulatory science requirements for FDA approval of new drugs/biologics. Chen received his medical degree from Beijing Medical University in Beijing, China, and his doctorate in pharmacology and toxicology from the University of California, Davis. He completed his fellowship in clinical pharmacology Stanford Medicine in Stanford, California.

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Cameron has more than 14 years of experience consulting worldwide with biopharmaceutical organizations. This experience extends to working with a broad range of stakeholders—including provider associations and patient advocacy groups—on the development of real-world evidence to support regulatory, quality, effectiveness and safety requirements. Cameron holds a master of public health degree from The University of North Carolina at Chapel Hill and a bachelor of science degree in international economics from Georgetown University's Walsh School of Foreign Service in Washington, D.C. Cameron is a frequent writer and speaker and has guest lectured at New York University's Stern School of Business and the Tuck School of Business at Dartmouth College.

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