Worldwide Clinical Trials

Key Study Design & Outcomes Projects from the FDA's Oncology Center of Excellence

Shortly after President Barack Obama signed the 21st Century Cures Act into law, the FDA established its Oncology Center of Excellence (OCE). The OCE facilitates the development and clinical review of oncology products by uniting scientific experts across the FDA to conduct expedited reviews of drugs, biologics, and devices. The OCE also leads research and educational outreach projects and programs to advance the development and regulation of medical products for patients with cancer.

Since its founding in 2017, the OCE has initiated over 300 programs and projects, ranging from diversity and inclusion to dose optimization and research. OCE offerings can be a helpful resource for clinical trial sponsors, and Worldwide is happy to provide guidance on how to use these programs to support your clinical development goals.

Here's what you need to know about the key OCE projects focused on study design and outcomes and how they might assist your drug development efforts.

Project Optimus: Dose Optimization

Introduction: For decades, oncology drugs were highly toxic and non-specific, with severe side effects that were seen as inevitable. Sponsors often expected linear dose-response curves in which higher doses correlated with better responses. Achieving the maximum tolerated dose, or MTD, became the goal.

This MTD paradigm led the FDA to approve many drugs that reduced tumor size but were also highly toxic. Fortunately, the rise of molecularly targeted therapies has rendered excess toxicity unacceptable to physicians, patients, and regulators.

While the MTD goal remains appropriate for some classes of cytotoxic agents, targeted therapies are moving toward a newer dose objective, the optimal biologic dose. These targeted agents require a more rational, scientifically derived set of endpoints for dose selection. Examples of an optimal biologic dose include:

- Reaching a predefined pharmacologic parameter
- Escalating until target saturation
- Optimally altering a biologic pathway

Key Intent

The goal of Project Optimus is to systematically refine dose optimization and selection in early phase drug development.

How to Apply to Your Program: To ensure that sponsors address dose optimization, the FDA now requires clinical trial sponsors to justify their selection of the recommended Phase 2 dose (RP2D) prior to subjecting a large cohort of patients to it during a pivotal or registrational investigation. This requirement provides additional data that may support dose adjustments during therapy.

The clinical pharmacology dose optimization meeting, also known as an FDA Type D Meeting, is another important Project Optimus requirement. Sponsors must include their rationale for the selection of the RP2D and dosage modifications for adverse reactions. The required data includes:

- Safety
- Preliminary antitumor activity
- Pharmacokinetics and pharmacodynamics
- Integrated dose- and exposure-response analyses
- Modeling and simulation summaries
- Potential drug interactions
- Effects of intrinsic factors on safety and pharmacokinetics, including organ impairment, age, and race
- Effects of extrinsic factors on safety and pharmacokinetics, including food and concomitant medications
- Relevant nonclinical data

Sponsors should know that presenting a dose to the FDA without sufficient justification may put their program on clinical hold and jeopardize their development goals and timelines.

Learn more about Project Optimus →

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Project Confirm: Accelerated Approvals

Introduction: Accelerated approval, the FDA pathway allowing expedited drug and biologic approvals across therapeutic areas, was developed in 1992 in response to the HIV/AIDS crisis. In 2012, the program was included in the Food and Drug Safety and Innovation Act to codify earlier access to drugs and biologics that showed initial evidence of safety and efficacy with the understanding that sponsors must complete a post-market confirmatory study.

Accelerated approvals are granted on the basis that products have an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit but can be measured earlier than irreversible morbidity or mortality. However, during the first 25 years of this approval pathway, only 20% (19/93) of cancer drug accelerated approvals based on a surrogate endpoint led to verified survival benefits during the confirmatory trial.

Key Intent

Project Confirm provides a revised framework for accelerated approvals to enhance the balance of access and benefit verification for patients.

How to Apply to Your Study: This project came from the realization that the accelerated approval pathway needs increased oversight as many early surrogate endpoints don't adequately correlate with patient survival. For instance, the U.S. government spent an estimated $1.8 billion in Medicare funds in 2019 alone on drugs whose clinical benefits remained unconfirmed.

In 2023, the FDA provided new draft guidance for clinical trial considerations to support accelerated approval of oncology therapeutics. Additionally, recent legislation has made it easier for the FDA to withdraw approvals for agents unable to verify clinical benefit or excessively delay their confirmatory studies.

These developments do not mean that the accelerated approval pathway is not still a potentially lucrative development approach. However, Worldwide believes it does require early discussion with the FDA to gain acceptance of the trial design and primary endpoint(s) of interest. Notably, the confirmatory trial should be close to completing accrual when the application for accelerated approval is submitted.

Learn more about Project Confirm →

Project FrontRunner: Earlier Access

Introduction: It has long been the oncology clinical development paradigm to enroll clinical trial patients who have exhausted available therapeutic options. As targeted therapies and adverse event mitigation strategies have evolved and led to safer therapies, sponsors face new development opportunities with a larger pool of potential patients. One such opportunity is to move innovative drugs up in the treatment hierarchy and provide earlier access to treatments.

Drug development companies have encountered logistical issues when trying to enroll subjects and complete the post-market confirmatory study. For example, enrolling subjects for a trial when the investigational agent is already commercially available can be difficult. It can also be challenging to determine an appropriate comparator agent for patients who have already exhausted therapeutic options.

How to Apply to Your Program: No formal guidance for Project FrontRunner currently exists. However, the FDA has provided some hints as to their expectations for sponsors looking to use this pathway.

FrontRunner is currently directed toward late-stage therapies in the advanced or metastatic setting where treatment is not expected to be curative. The most likely scenario for Project FrontRunner's use will be to amend the current accelerated approval and confirmatory evidence requirements. Once an agent receives accelerated approval, the confirmatory study may be initiated in an earlier line of therapy than was used in the initial investigation.

A confirmatory study as an earlier line of therapy provides clinical development benefits through improved enrollment as a larger pool of patients will be available for treatment and improved commercialization opportunities. Sponsors should consider whether this program makes sense for their business goals.

Key Intent

Project FrontRunner is an opportunity to enroll patients in an earlier line of therapy and still provide the confirmatory evidence necessitated by the accelerated approval. This framework allows therapies under development for the treatment of advanced or metastatic disease to be used as earlier lines of therapy.

Learn more about Project FrontRunner →

Project Pragmatica: Pragmatic Trial Design

Introduction: In real-world clinical practice, patient populations are diverse, assessments are sporadic, and variables are innumerable. The reverse is true in clinical trials, where disease assessments, safety monitoring, and follow-up data collection can overburden trial participants, investigators, and sponsors.

Key Intent

Project Pragmatica modernizes clinical evidence generation through pragmatic clinical trial designs.

How to Apply to Your Study: Project Pragmatica combines the data collection focus of clinical trials with the patient-centric aspects of real-world care. Known as pragmatic clinical trials, these study designs aim to increase investigator flexibility, reduce burdens on trial participants, and allow faster enrollment while reducing patient attrition.

The pragmatic trial approach is most suitable for trials where the drug being studied has already received approval, allowing community-based investigators to make informed choices about their patients' eligibility. Pragmatic clinical trials also provide opportunities to expand drug labels, identify responder subgroups, and assess new drug combinations.

These trials can impose some potential challenges that sponsors should consider. For example, a broader patient population or variations in clinical care patterns can introduce more "noise" to a dataset, which may require increasing the study's sample size. Additionally, more validation must happen for pragmatic clinical trial design to become more accepted, including how to:

- Handle missing data
- Manage protocol deviations
- Create assessments relevant to real-world clinical practice

In early 2023, the National Cancer Institute launched the Pragmatic-Lung Study, one of the first large Phase 3 clinical trials to use the pragmatic approach. Its design encourages community-based physicians to enroll their patients, thereby creating a broader and more diverse trial population. This trial can provide a model to help sponsors develop their own pragmatic clinical trials.

Learn more about Project Pragmatica →

Worldwide: A Valuable Resource

In 2022, President Joe Biden reignited the United States Cancer Moonshot initiative. The Moonshot's centerpiece goal—reducing the cancer death rate by half within 25 years—requires that trial sponsors take advantage of all available resources to enhance oncology drug development.

Worldwide stands ready to assist sponsors with developing a strategic understanding of all available tools to support a successful clinical development program. The Clinical Research Methodology team, led by Worldwide's Chief Medical and Scientific Officer and founder, Michael Murphy MD, PhD, provides strategic scientific, medical, and operational support across all phases of clinical development.

This team offers expertise in program de-risking initiatives through multi-domain portfolio reviews, fit-for-purpose assessment creation, and bespoke commercialization initiatives. Additionally, team members can assist with the creation and review of necessary regulatory documents for formal FDA meetings and IND submissions. Whether you're in IND-enabling research or coordinating a multi-regional registrational study, the Clinical Research Methodology team offers a collaborative partnership for success.

Contact us for clinical research support →

Interested in the OCE's projects on inclusivity and accessibility? Check out our guide on these projects →