ARTICLE

The complexity paradox: Why better science is delaying oncology trials

A KEY QUESTION

How can oncology sponsors overcome the execution complexity created by precision science?

KEYWORDS Oncology, Clinical Trial Complexity, Precision Oncology, ctDNA, Radiopharmaceuticals, Liquid Biopsy, Regulatory Strategy

The perspectives presented reflect professional experience and interpretation of publicly available evidence.

The same advances making cancer drugs more precise are making the trials that test them harder to run. For sponsors, closing this gap is now a strategic imperative—not an operational footnote.

Cancer research has never moved faster. Treatments that were unimaginable a generation ago, including drugs that target a single mutation, therapies that train the immune system to attack tumors and radioactive compounds delivered directly to cancer cells, are now reaching patients. In 2024, 2,162 new oncology trials were initiated—12% more than in 2019[1]—reflecting continued expansion of cancer R&D.

Despite unprecedented scientific progress in oncology, development timelines have not shortened in a meaningful or consistent way. Analysis of anticancer drugs approved in Europe between 2010 and 2019 show that the average time from first-in-human testing to approval remains approximately 6.7 years, with biologics taking significantly longer than small-molecule therapies, and only selective acceleration achieved through expedited regulatory pathways.[1]

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At the same time, a machine-learning analysis of more than 16,000 clinical trials demonstrates that increasing scientific precision through biomarker-driven designs, narrower eligibility criteria and novel endpoints, has materially increased operational complexity, a trend that has intensified over the past decade.[2] The result is a structural execution challenge: scientific and regulatory advances are being offset by rising trial complexity, constraining speed, predictability and capital efficiency in oncology drug development.

This is the **Complexity Paradox:** the better the science, the slower the trial. For sponsors, the consequences are real, including delayed revenue, eroded competitive advantage and above all, patients waiting longer for treatments that may already work.[2]

Rapidly growing, innovation-led market

>$250B

Global cancer medicine spend in 2024*

Oncology remains the most active therapeutic area

2,000+

Oncology trial starts annually**

A leading cause of delayed site activation

>2 in 3

Sites face recurring budget/contract delays***

A top contributor to site burden and timelines

~3 in 4

Sites cite communication gaps as a delay driver****

*Global spending on cancer drugs to increase to $409 billion, *Managed Healthcare Executive*
**Trends and charts on registered studies, *ClinicalTrials.gov*
***Overcoming study start-up delays: Best practices for research sites, *ACRP*
****Advarra publishes 2024 site-sponsor-CRO collaboration survey results to improve clinical research, *Advarra*

Three Engines of Complexity

1. Biomarker dependency: From tissue to blood—and beyond

Eligibility criteria in contemporary cancer trials often include molecular testing. NGS panels, IHC quantification, FISH confirmation and increasingly, liquid biopsy,[2] now sit upstream of randomization.[4]

The use of circulating tumor DNA (ctDNA) has rapidly increased in early stage solid tumor development, with the U.S. FDA's November 2024 guidance formally recognizing its role in molecularly defined patient selection, biomarker-based stratification, minimal residual disease (MRD) detection and potential use as a surrogate endpoint.[5]

Consistent with these regulatory advances, postoperative ctDNA detection in the GALAXY study (CIRCULATE-Japan) was strongly prognostic of recurrence and survival in resectable colorectal cancer, underscoring the clinical relevance of ctDNA-guided risk stratification.[6]

The operational consequence is that assay validation standards are still evolving and assay selection made today will face scrutiny at submission. Screen-failure rates in heavily biomarker-selected indications remain high, and the infrastructure to deploy validated liquid biopsy platforms across diverse global site networks is uneven. The CRO's role is to turn biomarker strategy from a scientific decision into a logistics architecture.

> *"The FDA's November 2024 ctDNA guidance formalized liquid biopsy as a trial design tool—but the operational infrastructure to deploy it at scale remains a critical gap."*

2. Radiopharmaceuticals: The newest frontier of compound complexity

No modality illustrates the **Complexity Paradox** more acutely than radiopharmaceuticals. Radiopharmaceuticals represent one of the most operationally complex therapeutic modalities in development. Growth following the approvals of lutetium-177–based therapies has driven a rapid expansion of clinical activity, while reliance on short lived isotopes such as Lu-177 and Ac-225 necessitates just-in-time manufacturing and highly coordinated, site-specific logistics. Limited global production capacity and the need for additional nuclear medicine and radiation-safety approvals at each site further complicate trial activation, requiring feasibility assessments that extend well beyond conventional clinical infrastructure.[7-9]

3. Combination therapies and global regulatory divergence

Combination regimens amplify protocol complexity in a non-linear manner. Each additional agent introduces its own manufacturing and supply considerations, safety and toxicity monitoring requirements, pharmacokinetic interaction risks and in some cases, distinct regulatory review pathways. In multi-sponsor or multi-asset collaborations, these factors compound operationally, placing disproportionate pressure on budgeting, contracting and site activation processes relative to single-agent trials.

At the same time, the regulatory landscape continues to evolve. The EU Clinical Trials Regulation (CTR) became fully applicable in January 2025, ICH E6(R3) GCP is now in force across the EU and the U.S., and the UK's updated *Medicines for Human Use (Clinical Trials) (Amendment) Regulations 2025* take effect in April 2026. Despite this progress, meaningful divergences remain across major agencies, including the FDA, EMA, NMPA and PMDA, particularly for novel endpoints, ctDNA-enabled submissions and radiopharmaceutical dosimetry requirements. As a result, regulatory strategy must be integrated at the protocol synopsis stage to avoid downstream delays in global trial execution.

An execution framework: Five disciplines that scale with science

The solution is not to simplify trial designs—sponsors who do so produce data regulators, payers and clinicians cannot act on. The goal is structured execution: disciplines that allow scientifically ambitious studies to run at the pace their evidence deserves.

1. Protocol constructability review before lock

Every complex protocol should undergo a structured operational feasibility assessment before finalization, including addressing biomarker logistics, site capability distribution, IMP supply architecture and regulatory alignment simultaneously.

2. Biomarker logistics as a primary workstream

ctDNA and companion diagnostic strategy should be managed as a dedicated sub-program with its own project lead, screen-failure modeling and real-time tracking by site tier. Given the FDA's November 2024 ctDNA guidance and evolving ESMO standards for liquid biopsy, assay validation documentation must be planned from day one, not assembled retrospectively for submission.[5]

3. Radiopharmaceutical-specific site and supply governance

For radiopharmaceutical trials, a standard supply chain model is insufficient. Requirements include just-in-time isotope logistics planning, site qualification against imaging and dosimetry standards, proactive nuclear medicine and radioisotope review committee engagement in each country and pre-agreed shortage protocols that protect patient safety without stalling enrolment. SNMMI's Radiopharmaceutical Therapy Centers of Excellence program provides a benchmark framework for site readiness standards.[11]

4. Multi-agency regulatory alignment from synopsis stage

With EU CTR/CTIS now fully operational and ICH E6(R3) in force, the regulatory baseline has shifted. But NMPA, PMDA and agency-specific expectations for ctDNA endpoints, RDC dosimetry and ADC combination safety data remain divergent. Global programs need parallel, not sequential, agency engagement, with divergences mapped and resolved at the design stage.[7-9]

5. Data-driven site portfolio management

In biomarker-selected populations, sites that perform in broad-eligibility studies may structurally underperform because patient flow through the required molecular subtypes is insufficient. Site selection must be driven by molecular epidemiology data and historical screen-failure rates, with pre-agreed contingency activation frameworks that remove political friction from performance management decisions.[10-11]

CRO Perspective

For sponsors navigating liquid biopsy logistics, radiopharmaceutical supply chains or multi-agency submissions for combination programs, the conversation about execution complexity belongs at the protocol synopsis stage. CROs with deep therapeutic, regulatory and operational integration, such as Fortrea, are positioned to challenge design assumptions early, helping to prevent downstream delays that cannot be mitigated after site activation.

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