Chapter 8

Reducing ‘white space’: Pursuing achievable efficiencies in clinical trials

Executive Summary:

Implementing targeted initiatives that optimize efficiency is a critical objective for any clinical trial. Overall trial efficiency impacts timelines and expenditures, both of which can help or hinder ROI for the drug sponsor. Meanwhile, the ability to streamline trial operations and reduce redundancy of effort and lag time, can improve overall quality and increase satisfaction among enrolled patients, trial investigators and related healthcare professionals.

Clinical trials often experience “white space,”[1] the delays and bottlenecks that can occur both within an individual trial phase and between subsequent phases. Such delays may have a negative impact on drug sponsors as delays can compound together to add costs and timelines to the successful delivery of new treatments for the healthcare community. However, with a thoughtful framework, conscientious effort and the implementation of targeted initiatives to improve the efficiency of specific activities and workflows, white space can be significantly reduced throughout any trial. Such activities include the use of best practices, increased automation, streamlined technology integration, a robust working relationship with the chosen contract research organization and more.

In this paper, we explore some of the best practices and considerations that can help minimize such delays.

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Complexity abounds in drug discovery

Today's trial landscape is shaped, in part, by the fast pace of ongoing scientific advances, with growing focus on developing biologics, cell-and-gene therapies, novel treatments for orphan drugs and other complex modalities. These promising advances often result in complex trial designs and burdensome trial protocols, daunting data volumes, challenging patient enrollment criteria and issues with patient adherence. All these factors can impact trial budgets and timelines.

At the same time, the pursuit of novel investigational pathways brings additional risk, in terms of high failure rates. The statistics are sobering:

- 67% increase in trial procedures and 27% rise in endpoints between 2009 and 2020[2]
- 183% more data collected per trial from 2006 to 2021[3]
- 57% of trials undergo major protocol amendments, creating delays of three months or more[4]
- 33% increase in the mean number of investigative sites in Phase II and III protocols from 2009 to 2020[5]
- 85% of trials miss enrollment targets; 80% of delays are tied to patient-recruitment challenges[6]
- 60% of sites use 20 or more technology systems on a daily basis[7]

As a result, drug development costs continue to soar. In a recent publication, McKinsey & Company estimates the attrition-adjusted development cost per novel drug at roughly $2.8 billion.[8] Clinical trials have also become longer, with Phase II durations increasing from 37 to 41 months and Phase III trials growing from 41 to 44 months between 2011 and 2021.[8] This further underscores the need for drug sponsors to wring every bit of efficiency out of their trial design and execution, and to reduce costly white space within individual trial phases and idle time between subsequent trial phases.

Working with a strong contract research organization (CRO) should bring a wide range of experience and specialized knowledge to help developers wade through the challenges. Working closely with such an organization can help the sponsor to develop a thoughtful framework to explore a wide array of initiatives that are explicitly designed to increase trial efficiency and reduce white space. An experienced CRO also provides access to ongoing innovation and best practices that are available to remove bottlenecks and close efficiency gaps.

The cost of white space in drug development

When trial inefficiency and idle time between phases slow down the drug's timeline for regulatory submission, it delays market entry and the onset of revenue. It may result in the sponsor forfeiting first-to-market advantages or create additional risk and loss of opportunity over time by allowing additional competitors to enter the market and develop competitive advantages. The longer it takes to reach commercialization, the shorter the patent window for the product. All of this can hinder the sponsor's ROI objectives and, importantly, delayed commercialization also slows patients (and physicians) access to the medication.

Improving trial efficiency reduces white space

Any program that aims to reduce white space should be built on the following four pillars.

Figure 1. Campaign themes

Proactive planning

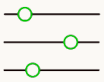
Making decisions in advance based on modelled trial outcomes

- How can we embed white space elimination into our culture of operational excellence?
- What tools or frameworks can help us anticipate and plan for potential delays?
- How can we use scenario planning to proactively manage risks that lead to white space?
- How early should we begin planning to minimize gaps between clinical phases?

Parallel processing

Conducting regulatory interactions, data analysis and trial preparations simultaneously

- Which activities in our current development model could be run in parallel rather than sequentially?
- What planning tools or frameworks can help us map out parallel workstreams effectively?
- How early in the development process should we begin identifying opportunities for parallel execution?



Advanced analytics

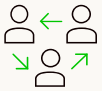
Using predictive modeling to anticipate trial results and plan next steps

- How can we use historical data to inform smarter planning and forecasting?
- How can we embed analytics into our standard planning workflows to drive consistency?
- What future capabilities (e.g., AI, machine learning) could further enhance our planning precision?

Cross-functional alignment

Ensuring regulatory, clinical and operational teams are synchronized

- How early should cross-functional teams be engaged to ensure seamless planning?
- What best practices can we adopt to improve handoffs between functions and phases (e.g., from clinical pharmacology to clinical development, or clinical to regulatory)?
- How can we better synchronize timelines and deliverables across clinical, regulatory, medical and operations?



Throughout this eight-part series,* Fortrea subject matter specialists have provided detailed recommendations for how drug sponsors can increase productivity throughout the clinical trial process. This chapter discusses specific opportunities related to these four pillars that will help drug sponsors to shrink white space within and between trial phases and reap the rewards of doing so.

Working closely with an experienced CRO, sponsors have access to a broad toolkit of proven options, experienced personnel and best practices to improve trial efficiency and close white space. When a drug sponsor enlists a trusted CRO in the early stages of the clinical development phases and then continues to collaborate through subsequent phases as the trial evolves (rather than switching to a different CRO), additional synergies can be exploited.

For example, by maintaining CRO continuity, the need to establish new contracting arrangements can be avoided. This might seem to be a small, inconsequential detail, but such a decision reduces ongoing onboarding and training requirements and minimizes technology and workflow integration that cost time and money. Ongoing collaboration from phase to phase also allows for planning for the next phase to begin much earlier in the process, and promotes seamless knowledge transfer and data quality and integrity.

Collectively, these advantages can further benefit the overall drug development effort, streamline compliance and transparency and optimize resource efficiency. The resulting efficiency gains help to reduce delays within each trial phase and can enable the next phase to begin more quickly and seamlessly.

* This paper is part of a multi-part thought leadership series on how to improve productivity throughout all stages of the clinical trial. All chapters can be found at **www.fortrea.com/insights**

Actionable recommendations for removing bottlenecks and shrinking delays

Bottlenecks and delays have the potential to arise at every stage of any clinical trial, from upstream trial design and protocol development through site selection, patient recruitment and startup, to downstream trial execution, data analysis and regulatory submission. As detailed in the earlier chapters in this series, sponsors and their CROs should critically evaluate all operations and then implement initiatives to streamline processes and workflows.

Deploying state-of-the art automation, AI, machine learning (ML) and related advances, can help to create opportunities for improved efficiency through both automation and enhanced decision support. Opportunities for such advances arise in every major stage of the trial, as discussed below.

Thoughtful protocol design

The protocol is the defining document that governs any clinical trial, and how well it is envisioned and written has a profound effect on how efficiently and effectively the trial is operated. Efforts to create a thoughtful, streamlined trial protocol, with the explicit goal of recognizing and eliminating potential sources of complexity and redundancy, offers a powerful way to reduce white space. A well-designed protocol helps to both increase efficiency within each trial phase and support smoother transitions between subsequent phases. Importantly, such improvement helps to reduce protocol amendments, which are not only costly in terms of both time and money but create further delays during the trial.

Working in close concert with a CRO collaborator, drug sponsors should dig deep to anticipate as many issues as possible during protocol development, challenging themselves with queries such as these:

- How will proposed inclusion/exclusion requirements and other requirements impact patient recruitment and retention (since maintaining the required cohort size is critical)?
- Do our chosen clinical endpoints and actual trial demands (blood draws, imaging procedures, visits to the clinic, reporting requirements, etc.) consider the real-life experiences and limitations of patients and care providers in terms of potential pain or discomfort, excessive burden and cost implications?
- Does our protocol confirm that site requirements are streamlined in ways that maximize efficiency while reducing frustration and burnout among the trial investigators and staff?
- Have we consulted with patient-advocacy groups in the space to gather relevant insights on the concerns, challenges and capabilities of real patients to inform and improve protocol development?

CROs typically maintain strong relationships with a network of potential trial sites. This community can bring significant experience and can be an invaluable resource to drug sponsors. Leveraging the practical experience of sites in conducting a trial provides the opportunity to create the most effective trial ecosystem for any given trial. This includes anything from protocol review to “dry run” visits before the protocol design has been finalized. Such dry runs seek to identify and address bottlenecks and other overlooked challenges before a real patient enters the clinic, using the gathered insights to confirm the right kits and equipment are in the right places, equipment is calibrated and ready to use, freezer space is available and staff training and paperwork is all in order, thereby aiming to create the most patient-friendly and streamlined trial operations possible.

Activities such as these help to anticipate and identify problems in advance so that white space can be avoided. Simply ensuring that what is being asked of a patient is achievable in the time allotted could be the difference between a patient dropping out or a data endpoint being missed.

Note: For a more-detailed discussion of many best practices related to protocol design, see Chapter 3 *"Improving clinical trials: Unlock the power of productivity through protocol design"* in the Fortrea multi-part series on improving trial efficiency.
Chapter 3

Regulatory target product profile and clinical development plan

Gaining regulatory approval at numerous points throughout the stages of drug development is critical. As noted earlier in this series, the most efficient and effective drug development journeys begin with the end goals in mind, whatever that milestone may be. To support this, two critical planning documents should be developed early in the process:

- A target product profile (TPP)
- A comprehensive or clinical development plan (CDP)

Both provide detailed frameworks to help sponsors anticipate and eliminate avoidable delays throughout the trial.

The TPP outlines the anticipated characteristics of the new drug, in terms of such critical attributes as:

- Potential indication(s) and usage
- Dosage and administration
- Safety
- Efficacy
- Contraindications
- Adverse reactions and drug interactions
- Additional proposed label language and more

The CDP provides additional findings (based on specifics developed in the TPP) to inform clinical development and market-access strategies. For example, the CDP establishes the specific requirements that will be necessary to achieve regulatory approval, so the trial design and protocol can be created to yield the required insights. Specifically, the CDP includes information related to budget estimates, personnel assignments and timelines. Such details are crucial for coordinating clinical activities, such as the sequence of specific studies, endpoints and more. Importantly, the CDP establishes critical "Go/No-Go" criteria the drug sponsor will use to advance or suspend clinical development of the therapy.

By developing these two informative blueprints as early as possible in the process, sponsors and CROs can design and carry out clinical trials in ways that reduce wasted time and effort, and prepare the investigational therapy for the most successful regulatory submission package. When drug sponsors don't have the internal proficiency or bandwidth to develop these critical planning documents, working with an experienced CRO can help to close that gap.

Note: For a more-detailed discussion of how to develop the TPP and CDP documents, see Chapter 6 *"A clear regulatory strategy: Maximizing development productivity by keeping the end in mind"* in the Fortrea multi-part series on improving trial productivity.
Chapter 6

Site engagement and patient recruitment
Clinical trials typically involve a complex ecosystem of diverse trial sites.* When site engagement and productivity lags at any given trial site, it can depress overall productivity and create budget and timeline escalation, which creates white space within and between trial phases. First patient in (FPI) is a milestone in any clinical trial, but last patient in (LPI) at the last site is arguably what really matters for timelines.

A range of factors may impact the readiness of any given space. These include the level of prior trial experience, the level of clinical experience in the given therapeutic space (as well as overall administrative experience), facility size, geographic location, access to target patient populations, available equipment, technology infrastructure and more.

Efforts to work closely with each candidate trial site can help to identify and rectify issues quickly. The goal is to set up a systematic process that can be used to:

- Evaluate the specific strengths and weaknesses of potential trial sites
- Assess the overall competence and readiness of individual sites
- Identify and rectify site-specific issues, challenges and pain points promptly

Carrying out such an exercise enables sponsors and their CRO to set up the trial for success and address any site deficits before they have a chance to negatively impact trial execution and create delays, (i.e., white space).

A strategic mix of sites
When evaluating overall site selection for a given trial, sponsors can benefit from embracing a diverse set of sites. Trial robustness benefits from a mix of locations, a mix of experienced trial sites and researchers and sites that are new or emerging (sometimes unhelpfully referred to as "research-naïve" sites). Such a strategic mix supports site availability challenges and site engagement levels, as well as fostering the next generation of trial investigators, sites and key opinion leaders (KOLs).

Engaging sites across a range of geographic locations, and across both academic settings and smaller community care settings, also enables a more robust patient-recruitment strategy. This is especially important for rare diseases and trials with very narrow inclusion/exclusion criteria. Creating a stronger recruitment pipeline reduces delays in trial startup and execution.

* **Note:** For a deeper discussion and actionable recommendations on how to assess site readiness and improve site engagement and patient recruitment, see Chapter 5 of Fortrea's multi-part series on improving trial productivity *"Increasing trial productivity: Addressing site-specific challenges to improve site engagement"*. **Chapter 5**

Model-informed drug development and the use of data and AI
Model-informed drug development (MIDD) is a data-driven approach that integrates biological, pharmacological and statistical models to inform drug development decisions. By leveraging simulations and predictive analytics, MIDD enables sponsors to optimize trial design, refine dosing strategies and anticipate outcomes. This often reduces the need for extensive empirical testing.

The MIDD methodology holds particular value in complex therapeutic areas such as oncology and rare diseases, where patient populations are small and trial designs are often complex. MIDD can streamline early-phase trials by simulating dose-response relationships and predicting efficacy, thereby reducing the number of required participants and trial duration, contributing directly to reducing white space.

Recent analyses suggest that the use of MIDD can cut development timelines by up to ten months and save approximately five million dollars per program.[9] Regulatory bodies such as the U.S. Food and Drug Administration (FDA) have embraced MIDD through initiatives such as the MIDD Paired Meeting Program, recognizing its potential to enhance efficiency and regulatory success.[10,11]

Allied to this are ongoing advances in artificial intelligence and machine learning (AI/ML). Such capabilities are helping drug developers and CROs to improve efficiency throughout each step in the clinical trial.

The individual steps and workflows required for any clinical trial represent an integrated ecosystem. With the ability to analyze large data sets and generate actionable, data-driven insights, today's arsenal of AI/ML tools combines automation and enhanced decision support at every step, helping to drive efficiency and close white space.

Specifically, such a powerful technology-enabled paradigm allows sponsors to:

- Leverage data-driven insights to optimize trial design and protocol development, enhance patient recruitment and site selection, strengthen data analytics and decision support, improve risk detection and compliance, identify patterns and trends, streamline regulatory submission preparation and more
- Automate repetitive tasks and text analysis and streamline workflows in ways that reduce labor and training requirements, while also reducing the chances of human induced errors

Note: This strategic use of AI/ML initiatives is discussed in greater detail in Chapter 2 *"Clinical trials: Using AI to drive productivity in clinical development"* of Fortrea's multi-part series on improving clinical trial efficiency.
Chapter 2

Streamlining dose-escalation decisions
Streamlining dose-escalation decisions between cohorts in first-in-human studies also presents an opportunity to remove whitespace. By anticipating the data flows that need to come together for presentation to inform escalation decisions (adverse events, safety laboratory results, pharmacokinetic outputs, etc.), the most efficient approach to collate and present this data can be pre-designed. Anticipating how and when each dataset will be available, aligning stakeholders early and creating clear, rapid-turnaround presentation formats help to make sure that decision-making is both timely and high-quality, ultimately saving valuable study time and maintaining momentum across cohorts.

Budgeting and contracting delays
Focusing on efforts to streamline contracting and budgeting provides a prime opportunity to reduce white space. As noted above, the strategic decision to work consistently with a single CRO through all phases of a given trial brings many benefits. One of them is the ability to streamline contracting arrangements, eliminating the need to start over again with each trial phase. This can provide both budget and timeline savings, while also potentially enhancing efficiency and transparency, which aims to minimize redundancy and delays in the process, contributing to a reduction in overall white space throughout the trial.

Focus on streamlining phase-to-phase transitions

Within any clinical trial, the handoffs between successive phases create many opportunities for costly and unproductive white space to arise. Drug sponsors should consider these additional techniques and tactics to reduce idle time between phases.

Preparing for first-in-human trial
Transitioning from preclinical research to first-in-human (FIH) trials is one of the most critical and risk-prone steps in drug development. Many promising programs stumble here due to avoidable mistakes. Below are the most frequent pitfalls and some practical ways to prevent them:

- **Incomplete preclinical data for intended regulatory environment:** One of the most frequent obstacles is insufficient or poor-quality preclinical evidence. Regulators expect comprehensive toxicology, pharmacokinetics (PK) and pharmacodynamics (PD) data to justify human dosing conducted in line with their regulatory guidelines. Gaps in Good Laboratory Practice (GLP) compliance or missing studies can lead to costly delays or even clinical holds. Ensuring a full battery of GLP toxicology studies along with Absorption, Distribution, Metabolism and Excretion (ADME) profiling and genetic toxicity screens is essential to build confidence in safety and efficacy
- **Poor dose selection and escalation strategy:** Incorrect starting doses or overly aggressive escalation plans can expose participants to unnecessary risk. Incorporating staggered dosing and sentinel subjects for high-risk compounds adds an extra layer of protection. Moreover, adverse events caused by avoidable subject-level risk not only jeopardizes participant safety but also draws increased regulatory attention, raising the chance of a clinical hold that can significantly delay the program
- **Chemistry, manufacturing and controls (CMC) gaps:** Even when the science is sound, trials can stall if clinical material is not GMP-compliant or formulations lack stability. Manufacturing readiness often lags behind clinical timelines, creating bottlenecks. Early alignment between formulation development and clinical strategy, validated processes and completed stability studies are critical to help achieve uninterrupted supply and regulatory compliance
- **Misaligned timelines:** Drug supply delays frequently occur when manufacturing and clinical planning operate in silos. If timelines aren't coordinated, delays in product availability can slow down site activation and ethics approvals. Building supply chain planning into trial milestones from the outset helps prevent these avoidable disruptions
- **Regulatory missteps:** Late or incomplete Investigational New Drug (IND) or Clinical Trial Application (CTA) submissions and failure to meet evolving European Medicines Agency (EMA) or FDA requirements can derail progress. Engaging regulators early through pre-IND meetings, staying current with global guidelines and preparing contingency plans for potential holds are key strategies to keep development on track

- **Translational gaps:** Animal models rarely predict human outcomes perfectly and assuming direct translation can lead to unexpected failures. Incorporating Phase 0 microdosing studies or physiologically based pharmacokinetic (PBPK) modeling helps validate human PK predictions before committing to full-dose trials, thereby helping to reduce uncertainty and improve decision-making. In addition, evaluating pre-clinical data through both NOAEL (No Observed Adverse Effect Level) and MABEL (Minimum Anticipated Biological Effect Level) frameworks provides a more balanced and risk-informed foundation for selecting safe, scientifically justified first-in-human starting doses
- **Weak risk management:** Finally, inadequate safety monitoring or the absence of clear stopping rules can turn manageable issues into catastrophic setbacks. Robust adverse event monitoring, dose-limiting toxicity criteria and adaptive trial designs provide the flexibility and safeguards designed to protect participants and preserve trial integrity

Moving into a FIH trial is not just about avoiding pitfalls—it's about actively creating conditions for speed, cost control and operational excellence. Here are five high-impact actions that sponsors and CROs can take to set the trial up for success:

1. Align early on strategy and roles

Clear, early alignment between sponsor and CRO on objectives, responsibilities and decision-making processes prevents duplication and confusion later. A joint kick-off that covers timelines, escalation pathways and risk management frameworks helps confirm everyone is working toward the same milestones.

2. Lock down CMC and supply chain readiness

Drug supply delays are one of the most common sources of white space in early-phase trials. Sponsors should confirm GMP manufacturing slots, stability data and packaging well ahead of regulatory submissions. CROs can help by integrating supply chain checkpoints into the clinical timeline and monitoring readiness continuously.

3. Optimize regulatory engagement

Regulatory delays can derail even the best-planned trial. Sponsors should schedule pre-IND or scientific advice meetings early and share draft protocols for feedback. CROs can streamline this process by preparing submission-ready documentation which aims to factor in global requirements from the start.

4. Use data-driven dose planning

Efficient dose selection and escalation strategies aim to reduce risk and avoid unnecessary amendments. Sponsors should leverage modeling and simulation tools to predict human PK/PD, while CROs can implement adaptive designs and sentinel dosing to help to maintain safety without slowing progress.

5. Build an integrated risk and communication plan

Unexpected issues are inevitable, but delays do not have to be. Sponsors and CROs should co-create a risk register with predefined mitigation actions and clear communication channels. Rapid decision-making frameworks (such as agreed-upon stopping rules and escalation triggers) help keep the trial moving even when challenges arise.

Why efficiency frameworks matter—and how early investment pays off

When a trial moves from the lab to human participants, complexity multiplies. Every delay (whether in drug supply, regulatory clearance or site activation) creates white space that inflates costs and erodes momentum. Imposing a clear framework of protocols and processes at this stage is not bureaucracy; it is a strategic safeguard against inefficiency. A well-defined structure helps confirm that decisions are made quickly, responsibilities are clear and critical path activities stay aligned.

Investing time and effort up front to design this framework can pay dividends throughout the trial. Early integration of timelines, risk management plans and communication pathways reduces the likelihood of last-minute surprises and reactive fixes. By anticipating bottlenecks and embedding efficiency into the operating model, sponsors and CROs can compress timelines, cut unnecessary costs and maintain the pace needed to move from first dose to meaningful data without avoidable gaps.

Phase Ib as a strategic short cut?

Phase Ib trials sit between the traditional first-in-human Phase Ia studies and the more expansive Phase II trials. Unlike Phase Ia, which typically involves healthy participants and focuses on safety and pharmacokinetics, Phase Ib introduces the investigational drug to patients with the target condition. The goal is to refine dosing, confirm safety in a real-world disease context and explore early signals of efficacy.

An important consideration often overlooked in Phase Ib planning is the motivational gap for patients. Because these studies frequently involve short treatment periods and sub-therapeutic dose levels, participants may have little realistic prospect of meaningful clinical benefit. This can impact both recruitment and retention, and underscores the importance of clear communication and ethically sound study design.

The growing interest in Phase Ib stems in large part from the pressure to accelerate development timelines and generate patient-relevant data earlier.[12] Sponsors and investors increasingly view these studies as a way to de-risk Phase II by validating assumptions sooner, particularly for complex biologics or targeted therapies where healthy participant data may not translate well to patient populations.

The appeal of Phase Ib lies in its ability to provide actionable insights at a critical juncture. By enrolling patients rather than healthy participants, these studies can uncover pharmacodynamic trends, biomarker responses and preliminary efficacy signals that inform dose selection and trial design for later phases. They also enable early stratification of patient subgroups, which is particularly valuable in oncology and immunology where heterogeneity can obscure outcomes. For sponsors, Phase Ib can serve as a strategic shortcut—compressing timelines by combining safety and exploratory efficacy assessments and sometimes paving the way for adaptive Phase Ib/II designs that regulators increasingly support.

However, these studies are typically more resource-intensive, require specialized sites, protocols or greater complexity and rigorous ethical oversight. Recruitment challenges also need to be considered, especially when dealing with small, biomarker-defined cohorts, and the data generated—often from limited sample sizes and sub-therapeutic doses—may not provide the statistical power needed to guide pivotal decisions. There is also a risk of introducing delays if Phase Ib becomes an additional step rather than a well-integrated part of the development plan. Sponsors should weigh the true value of the data against the cost and complexity, asking whether it adds meaningful insight beyond what a robust Phase II study could deliver.

Phase Ib can be a powerful tool when deployed thoughtfully, but it demands clarity of purpose. The decision to run such a study should hinge on whether early patient data will materially influence development strategy, such as validating a mechanism of action, refining dosing or identifying responsive subgroups. Without that rationale, Phase Ib risks becoming an expensive detour rather than an accelerator. In short, success depends on aligning scientific objectives with operational realities and engaging experienced alliances who can navigate the regulatory, logistical and ethical complexities inherent in early patient trials.

Preparing for marketing authorization application

As outlined above, preparation is key when engaging regulators, and failure at any stage with regulators equates to white space. None more so that when it comes to preparing for marketing authorization applications. Thoughtful, deliberate effort up front can proactively identify what is required and help drive efficiency in the overall timeline. Here are some tips for keeping the focus and the effort tight:

1. Engage early with regulatory authorities

Such efforts include scheduling pre-New Drug Application (NDA) or Biologics License Application (BLA) meetings (or equivalent) to confirm expectations. At each meeting, sponsors should discuss data requirements, labeling strategy and post-marketing commitments. Early discussions throughout the process will help to minimize surprises and delays later in the process.

The goal is to align with regulators on CMC readiness, especially for complex products such as biologics or gene therapies.

2. Confirm robust data package and quality

Rigorous effort expended to confirm that clinical trial data integrity and statistical analyses meet International Council for Harmonization (ICH) and regional standards will help to avoid disruptions later that can extend the trial duration and delay market entry for the therapy.

Sponsors should also work to validate CMC documentation (in terms of, for instance, manufacturing consistency and stability data). They should also prepare comprehensive safety and efficacy summaries, including risk-benefit analysis, as early as possible in the process to keep the trial moving and reduce white space.

3. Plan for global harmonization and lifecycle management

A best practice for reducing white space during this phase of the drug development process is to map regional regulatory requirements (related to various agencies, including the FDA, EMA, PMDA and others) to enable simultaneous submissions.

To do this, sponsors should develop a core dossier that can be adapted for multiple markets. The goal is to anticipate post-approval commitments (related to such requirements as pharmacovigilance, risk management plans and more). This should be done as early as possible in the trial to help reduce delays so that the regulatory submission process can be as streamlined as possible.

Market access

Even the best product development journey is only successful if the resulting product is adopted by health agencies and administered to patients. A market access strategy for any new therapy relies on robust clinical evidence and related health economic data. Such evidence supports the messaging that will be used to maximize reimbursement and uptake following product launch and throughout its lifecycle.

Efforts to clearly define the long-term clinical and commercial potential of the investigational therapy should begin as early as possible in the process (ideally during Phase I and Phase II) so that early signals and critical insights can also inform trial design and execution. When sponsors wait to begin their earnest focus on a market access strategy, they may miss the opportunity to generate the type of evidence that will be needed to position the product appropriately, and to develop the type of evidence that will inform key decision makers and help to differentiate the therapy in existing treatment pathways.

Identifying white space risk here is best seen through the lens of missed opportunity and/or the need to repeat studies to gather missing evidence. The goal is, therefore, to formulate a strategy in Phase I or Phase II and add incremental market access activities through all subsequent trial phases. Doing this can help steer the development of evidence to avoid white space in the development timeline.

The further you go toward your main data collection package (Phase III), the more important it is that the data you're collecting will be relevant in supporting not only the marketing application, but also help the market access team to provide the necessary evidence to articulate why this new drug should be preferred over existing treatments (in terms of enhanced efficacy, side effect profile, safety, etc.). Specifically, to strengthen both the market access strategy and the trial design, sponsors must articulate unmet needs and market gaps in the therapeutic space, identify specific attributes that could make the therapy valuable and then generate the evidence that is needed to support the messaging and positioning to key stakeholders (not only payers, physicians and patients, but key opinion leaders, angel investors, venture capitalists, potential licensing collaborators and more).

A robust market access strategy aims to:

- Understand the market landscape
- Build awareness of comparative value and positioning options
- Understand the evidence needs of various stakeholders
- Develop a persuasive, flexible value proposition that can be updated throughout the product lifecycle
- Develop iterative evidence to support pre- and post-launch activities
- Coordinate and integrate cross-functional efforts to drive efficiency and maximize opportunities

There is a natural synergy among evidence-generation activities, stakeholder engagement and value proposition development. They can benefit from and inform each other, and when sponsors focus on building the market access strategy at the onset of clinical development (rather than waiting for Phase III of the trial), these crucial activities can be integrated better and generate actionable insights that can further refine the trial design and execution.

Several factors are often to blame for waiting too long to begin a robust market access strategy, including lack of funding, organizational structure and experience, conflicting goals and more.

Considering the inherent complexity of developing a market access strategy early in the process, sponsors should consider working closely with an experienced CRO that brings a broad and deep bench of experience to the table.

Drug-diagnostic and drug-device co-development

When an investigational drug will require (or benefit from) a companion diagnostic test or a companion medical device to improve its overall clinical value, demonstrable time and cost efficiencies can be gained by exploring all requirements of both components as early as possible in the development and trial process.

- **A companion diagnostic test** is one that is used to identify which patients are most likely to benefit from the drug, or to monitor response to the drug
- **A drug-device combination product** involves developing a drug and a medical device together, whereby the device is necessary to deliver the drug, to monitor its use or to check its effectiveness. The product may be integral (as a single device) or individual products (which are then sold as separate or kitted products that are clearly cross labeled for use together). One example includes radio labeled drugs that are used with a CT scanner. Another is the continuous glucose monitoring (CGM) device, which functions as a diagnostic that communicates directly with an insulin pump to improve drug delivery
- **A device-drug combination** is a device-led combination where the device is the primary product providing the mechanism of action, but a drug is added to provide secondary/ancillary action. The product can be integral (one device) or separate (as a cross-labeled combination product that is labeled to be used together but can be kitted together or sold separately). Examples include a steroid used on a cardiovascular lead or a drug-eluting cardiovascular stent

When a given investigational therapy has a relatively narrow target patient population, the ability to envision and pursue a companion diagnostic test or device early in the process provides direct advantage, in terms of helping to efficiently identify which patients will be eligible for treatment with the study drug. The development of a companion diagnostic is often pursued during the development of gene therapy treatments or for patients with very specific biomarkers or genetic mutations.

When trials can then be designed to align the diagnostic component with targeted patient selection, the effort helps to both reduce the overall development timeline as compared to conducting a study on the diagnostic as a standalone and subsequently studying the drug treatment, and aid market adoption.

Similarly, if a companion diagnostic is validated in an early trial phase, derived insights can help to improve recruitment and reduce white space both during and between subsequent trial phases. Sponsors should explore opportunities to hold joint meetings with regulatory agency divisions that are responsible for reviewing each of the separate components, to help minimize delays and streamline the development and approval process.

Likewise, the ability to create a drug-device combination or a device-drug combination early in the process can help to create distinct advantages for the sponsor, by helping to make the regulatory submission package more compelling and potentially creating a competitive advantage in the therapeutic space once the product is launched.

Parallel processing during the pursuit of such combination products can bring efficiencies when it comes to white space reduction. However, sponsors should also consider potential risk scenarios as well. For example, if the companion diagnostic that is being evaluated in a parallel study does not meet the expected requirements, this can delay the development process for the associated therapy.

If a companion diagnostic can be validated during an early trial phase, it can be included in the Phase III study with the drug treatment. To explore such opportunities, sponsors should consider whether it is possible to hold joint meetings with regulatory agency divisions responsible for reviewing the two components.

In all cases, early planning will help to streamline trial timelines. Here are some things to consider when pursuing drug-diagnostic of drug-device combinations:

- Be cautious of terminology. Combination products are not called 'drugs/biologics' or 'devices' but "combination products". Regional differences can vary depending upon how the final product will be marketed (for instance, as a separate product, kitted or packaged separately but cross-labeled for use together)
- Create an early, thorough development plan for any combination products; failure to do this may result in sponsors having to repeat certain aspects of the testing later
- Working with an experienced CRO collaborator and developing all associated agreements to guide the development and marketing of your combination product can help reduce white space
- When there is more than one component, a combination product or a companion diagnostic, consider developing both the device and drug/biologic together to take advantage of important synergies; such early integration enables the creation of the technical information needed by regulatory authorities to support clinical studies and marketing applications
- For clinical studies to advance, applications to authorities (such asEC/IRBs) will require both the device and the drug information. In some cases, separate clinical trial applications may need to be made to study the combination of product or the companion diagnostic. Trial protocols will need to include both drug/biologic and device information

Consider devoting dedicated internal or experienced CRO resources to help confirm that all requirements are appropriately anticipated during the development of combination products.

Closing thoughts

The overall efficiency of any clinical trial has direct impact on timelines and expenditures. Delays and bottlenecks throughout the process create costly and frustrating white space, both within and between individual trial phases. Investing the time and effort to identify the sources of inefficiency, develop a detailed plan to address them and then deploy targeted initiatives gives drug sponsors a powerful opportunity to help their life-changing and lifesaving new therapies reach patients and physicians more quickly. In addition to reducing overall development costs, conscientious efforts to reduce white space throughout any clinical trial can also shorten the timeline for regulatory submission. This is particularly important when the sponsor is hoping to gain competitive advantage or gain first-to-market status with its new therapy. Earlier regulatory review helps to initiate the flow of revenue sooner and satisfy the sponsor's ROI objectives for the therapy.

This paper—along with the earlier chapters in Fortrea's multi-part series on driving productivity in clinical trials—reviews some of the common causes of white space and discusses a range of options for sponsors and their CRO collaborators to consider when trying to reduce costly delays and bottlenecks. Many options are available, ranging from best practices and developing a strong working relationship with a skilled CRO to increasing the use of automation and streamlining technology integration and more.

Especially important for sponsors is to make certain that the overall regulatory strategy is developed as early in the process as possible, so that the trial design and execution can be carried out in ways that aim to reduce white space throughout clinical development. When sponsors work with an experienced CRO, they can be better positioned to anticipate complex global regulatory requirements, streamline decision making and enable earlier engagement with health authorities. By integrating regulatory insights into clinical planning from the outset, teams can reduce or eliminate avoidable delays, optimize study designs and accelerate overall development timelines—ultimately supporting efforts to bring innovative therapies to patients faster.

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Ken Park, MD, has spent the last 20 years in healthcare, focused on building and delivering innovative businesses and solutions to the life sciences industry. He advises clients on their R&D strategy and leads Fortrea's productivity initiatives.

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