DECREASING TIMELINES IN INFECTIOUS DISEASES DRUG DEVELOPMENT

A discussion with Medpace's Medical and Operational Experts: Brian Murphy, MD, MPH Vice President, Medical Department, Infectious Diseases and Vaccines and Lorie Nugent, Sr. Director, Clinical Trial Management

CHALLENGES AND BEST PRACTICES FOR OVERCOMING POTENTIAL DELAYS

Regulators, Institutional Review Boards, and Ethics Committees: The clinical development of biologics, phages, microbiome-related products, as well as other newer technologies can encounter numerous questions from country regulators and local ethics committees needing to become familiar with the technology.

Best Practice: Anticipate and Act Early. Many of these questions can be anticipated a priori to submission and are for the most part addressable. Otherwise, additional review times with back-and-forth questions can significantly impact timelines, especially among groups or indications that have mainly been accustomed to small molecule drug development.

For those of us living in the world of clinical research—with the mission to advance the approval of safe and effective medical therapeutics—we are acutely aware of the pressure to accelerate development. As a global CRO with specialized infectious diseases experience, we have identified a number of areas that may present specific challenges to timelines and prioritize a few here.

Asia-Pac: The regulatory environments in India and China have become more favorable and are attracting an increasing number of sponsors developing anti-infectives—especially those looking at the region for indications with a high incidence of specific Multi-drug Resistant Organisms (MDROs) (eg, MDR-Acinetobacter or metallo-ß-lactamase (MBL)-producing Enterobacteriaceae) and viral indications (eg, HBV, HCV, or vector-borne viral diseases). Clearly, the volume of potential patients in those regions can help with enrollment and potentially bring studies in sooner if the initial start-up timelines can be navigated quickly.

Best Practice: Work with a CRO with Established In-Country Labs or Relationships. In India and China in particular, there are certain restrictions on getting samples (including microbiology samples) out of the country. In-country labs that follow similar techniques and SOPs as the global CRO can integrate lab data within the overall dataset from the rest of the world. Therefore, it is essential to have established in-country laboratories, the ability to get samples out of a country, or pre-existing relationships with regional microbiology laboratories. Without one of these capabilities, studies in these regions will face certain roadblocks.

Site Relationships and Logistics: Especially for inpatient studies (regardless of geography), start-up timelines can be delayed if the site-specific logistical issues and the number of internal hospital committees are not fully appreciated. Some of the challenges include the following:

- More and more, academic centers and institutions require review by several different committees, especially if the technology is novel.
  This has to be fully elucidated during the feasibility process.
- If institutions receive funding from the NIH for research, submission to an Institutional Biosafety Committee (IBC) will be required for studies that involve recombinant DNA or synthetic nucleic acid molecules. This can increase timelines to account for review and approval of the study at these institutions.
- Multi-departmental collaborations may require multiple contracts (lab, pharmacy, hospital, PIs, and sub-investigators). If the sponsor is not prepared for the start-up costs that will be coming through or do not delegate this out to the CRO with a dedicated start-up team, then a bottleneck can occur and start-up will be delayed.
- Sites will generally rely on the sponsor to provide ancillary supplies and equipment (i.e., refrigerators, IV pumps, centrifuges, etc). Many times, the site will not identify needs until the site initiation visit, so it is extremely important to understand the equipment and logistics required and identify these needs early during the qualification of sites.
- Understanding patient flow, communication pathways between site departments, and early alert systems to ensure a wide catchment so that patients can be enrolled quickly is critical. Over-relying on past experience can lead to false security because of site staff turnover or the changing epidemiology of the disease. Here again, past performance may not be predictive of future performance.

Best Practice: Understand and Be Fully Prepared for the Challenges of Site Start-Up.

Treatment Requirements and SOC: While the agencies have been more flexible in the number of patients acceptable in the safety database for approval, there is clearly still the need to demonstrate that a new product is well-tolerated and endpoints are meaningful—for regulators and payers. If there is agreement with the agencies on a more streamlined or accelerated development pathway, the study may be able to enroll a smaller sample size or evaluate the drug in a limited population. Still, sponsors may find it necessary to increase the number of days a patient is on treatment or in observation to provide sufficient data for an analysis of risk of exposure or to develop sufficient PK/PD models.

In the context of antibiotic drug development, this clearly becomes problematic for IV drugs with no oral step down—especially in the US where payers want patients out of the hospital quickly. Home health agencies are an option for outpatient IV administration, but with q8 infusions that may be prolonged (to two hours or more in some cases), this can quickly become cost prohibitive. It is also important to understand the standard of care (SOC) not only at an institution level, but also on a country specific level. Having local experts that can do the research to understand the SOC requirements and provide guidance and recommendations to the study team will be imperative to avoid start-up challenges and negatively impact timelines.

Best Practice: Spend Time Upfront on Focused Feasibility. Prepare to appropriately place the studies in institutions or regions where a longer inpatient management of the disease is acceptable and the local SOC is understood.

PATHOGEN-SPECIFIC TRIALS

Pathogen-specific trials (especially CREs, ESBLs, Acinetobacter, Pseudomonas, and *S. aureus*) face a number of additional challenges.

Rapid Diagnostics: In order to identify and enroll patients in pathogen-specific trials quickly, rapid diagnostic tests (RDTs) are often utilized. However, site access to appropriate RDTs to allow for this timely enrollment of patients can be a challenge. This can be particularly difficult in pathogen-specific trials in light of restrictions around the duration of prior or empiric antibiotic administration. Some sponsors have co-developed companion RDTs, but that presents its own set of challenges. Partnering with companies that are developing RDTs is not always as straight forward due to the complexities of negotiating contracts and business agreements between the companies themselves. Further, even with regulatory-cleared RDTs, agencies still rely on the traditional culture techniques to define the primary analysis population. If the RDT proves to have a lower-than expected sensitivity/specificity, then the microbiologically-evaluable population can be jeopardized and the study may be underpowered.

Best Practice: Have Your Plan for Rapid Diagnostics Fully Operationalized as Early as Possible. Securing agreements and contracts with companies with RDTs or developing the RDT needs to be done as quickly as possible so sites know what they will have access to and can hit the ground running. Allowing treatment failures (microbiologically and clinically) can mitigate this to some degree.

THE MEDPACE WAY: MICROBIOLOGY SURVEILLANCE TEAM

Medpace has developed a microbiological surveillance team that works closely with sites and local microbiology labs during the feasibility process to truly understand their local antibiograms so as to enrich the population as much as possible (i.e., ensuring that the study does not waste time enrolling patients that may not contribute to the primary analysis). This, combined with data from global surveillance programs from partner microbiology laboratories, helps us to position the studies optimally. Just relying on publications or historical records is a recipe for failure.

In many infectious disease indications, once a MDRO or unique virus has been reported, infection control practices are altered in efforts to address the outbreak or other epidemiological factors change so significantly that the local incidence has decreased and the risk is now elsewhere. In many cases, the result is that the organism is now at such a low endemic level that it may not enrich the population sufficiently. In other cases, (eg, MDR-Acinetobacter in Asia-Pac), endemic levels stay sufficiently high and it still makes the site attractive.

Additionally, this microbiology surveillance team stays active during the course of the study to monitor data coming in from sites in real-time. Remediation (eg, education) and restrictions on enrollment (i.e., only allowing sites to enroll culture-proven cases or only cases that are high suspicion of the MDRO after discussing on a case-by-case basis with the medical monitor) can be put in place. Sites that are not contributing to the primary analysis, despite these efforts, are closed quickly so that resources can be focused on more productive sites. The end goal is to get the study to enroll evaluable patients as quickly as possible.

Comparator Studies: Comparators (single or best available therapy) need to be carefully considered as alterations to the recommended dose or frequency (perhaps in an effort to maintain a blind) from the packing insert or SmPc can confuse local IRBs and Ethics Committees and cause delay during the back-and-forth explanations. A thorough understanding of resourcing the comparator at a local level (in global trials) will be imperative to ensure there are no unanticipated delays with study enrollment.

Best Practice: Identification of the Appropriate Comparator(s) Needs to be Made in Light of Posology, Acceptability to Regulators and Local Investigators, and Appropriateness to the Expected Spectrum of Activity of the Investigational Drug.

CONCLUSION

Nothing derails a clinical study timeline more than poor planning and not anticipating and preparing for the potential roadblocks. While you may not be able to anticipate everything, many of the risks and challenges outlined above can in fact be averted if you understand the landscape and prepare accordingly.

FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.