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STRATEGIC INNOVATIONS IN STROKE TRIALS: OPTIMIZING TRIAL DESIGN, PROTOCOL DEVELOPMENT, AND IMAGING

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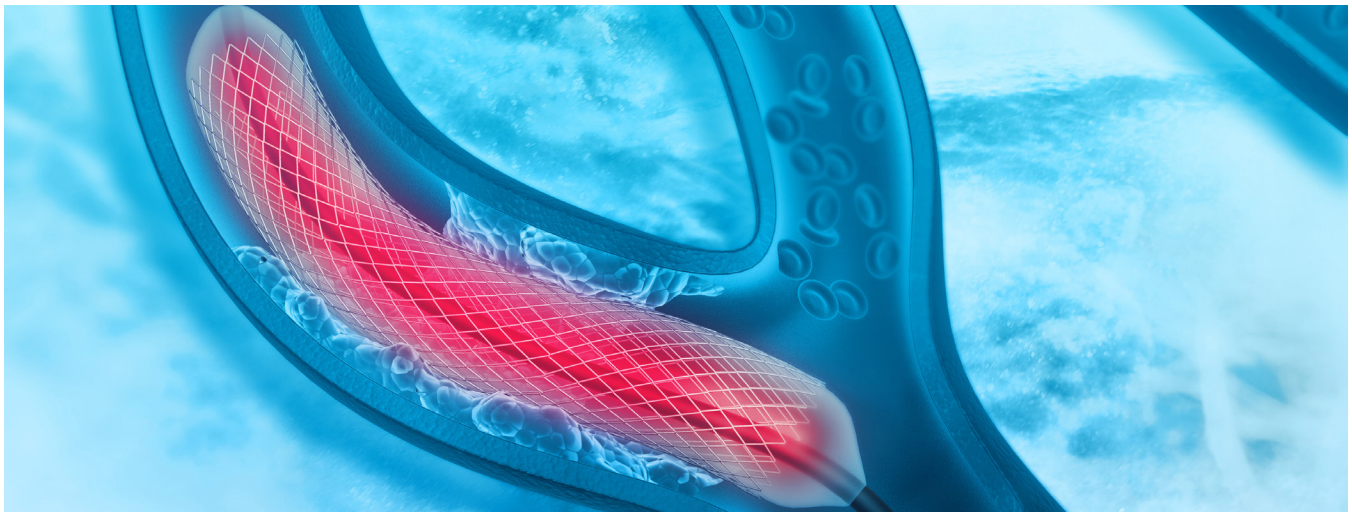

STROKE DRUG DEVELOPMENT: EVOLVING LANDSCAPE

The stroke treatment landscape continues to evolve at a remarkable pace, with each year bringing new evidence that fundamentally alters clinical trial design considerations. The watershed moment came in 2015 when MR CLEAN and ESCAPE definitively demonstrated endovascular thrombectomy's efficacy for large vessel occlusions in the 6–9-hour window, finally providing the robust evidence the field had long sought. In the decade since, we have systematically explored the boundaries of acute stroke intervention: extending treatment windows, evaluating medium vessel occlusions, integrating advanced imaging for patient selection, and reconsidering the role of thrombolysis as both bridge and adjunct therapy. Today's drug developer faces a fundamentally different standard-of-care environment than in 2015, requiring careful consideration of patient selection criteria, treatment timing, and background therapies. Whether developing neuroprotective agents, novel thrombolytics, intracranial devices, or restorative medicines, successful trial design now demands a nuanced understanding of current treatment paradigms and their evolving patient populations.

Medium vessel occlusions (MeVOs) are strokes caused by clots in mid-sized brain arteries: smaller than the large vessels where clot removal is proven to work, but bigger than the tiny vessels where only drugs can reach. Three major trials testing blood clot removal in these medium vessels: ESCAPE-MeVO, DISTAL, and DISCOUNT—all reported no significant benefit when adding EVT to best medical care for patients with MeVO strokes. In speaking with trial sites, we know these results have caused a rethink, not a wholesale change in practice. There are several possible explanations for these negative results. Selective enrollment may have excluded patients with the highest likelihood of benefit, i.e., those who are younger, have good collaterals, or dominant hemisphere symptoms. MeVOs often supply terminal territories with limited collateral flow, leading to rapid infarct completion that may limit the benefit of delayed reperfusion. Additionally, a substantial proportion of patients in the control arms achieved favorable outcomes without EVT, and symptomatic ICH in the EVT arms may have offset gains in this population with relatively mild strokes.

The "one and done" era of EVT is ending as stroke teams increasingly use advanced imaging on the angiography table to guide further treatment decisions. CT perfusion immediately post-EVT can reveal whether reperfusion was successful at the tissue level, not just the vessel level, and identify patients who might benefit from additional interventions. This real-time assessment can detect residual clot burden in distal vessels or incomplete tissue reperfusion despite successful large vessel recanalization, driving interest in adjunctive treatments like intra-arterial thrombolysis. The positive results from PEARL and ANGEL-TNK trials for intra-arterial tenecteplase, despite the dose-dependent hemorrhage risk seen in the DATE trial, suggest this approach may become standard practice for patients with TICI 2b or better recanalization but evidence of residual perfusion deficits. For drug developers, this represents both an opportunity and a challenge. Treatments that can be delivered directly to the target tissue may show enhanced efficacy, but trial designs must account for this evolving standard of care where post-EVT imaging increasingly drives treatment decisions.

The role of thrombolysis in acute stroke continues to evolve along multiple dimensions that significantly impact trial design considerations. The potential extension of the alteplase treatment window to 24 hours, beyond the traditional 4.5-hour limit, could dramatically expand the eligible patient population for any stroke intervention trial, thus limiting patients eligible for replacement therapies. Simultaneously, the field is reexamining whether IV thrombolysis serves primarily as a bridge to EVT or maintains independent therapeutic value. Recent data on intra-arterial tenecteplase post-EVT suggests thrombolysis may have a future role as an adjunctive therapy delivered directly to target tissues, while questions remain about the optimal timing and dosing to balance efficacy against hemorrhage risk. For drug developers, these shifting paradigms mean that background thrombolytic therapy can no longer be treated as a simple binary variable. Trial designs must account for timing of administration, route of delivery, and whether the investigational agent will be tested alongside, instead of, or in sequence with evolving thrombolytic protocols.

Advanced imaging has fundamentally changed our understanding of large core strokes, overturning long-held assumptions about treatment futility. Patients with low ASPECTS scores (3-5) were historically excluded from EVT trials due to feared poor outcomes and high hemorrhage risk, but systematic evaluation through recent trials has clearly demonstrated this was not justified. The ASA large-core advisory now supports EVT for ASPECTS 3-5 patients, backed by meta-analysis of seven randomized trials showing improved functional independence and reduced mortality. However, we're learning that ASPECTS may not actually measure "core" infarct but rather early ischemic changes, leading to more nuanced approaches to patient selection. The relationship between imaging findings, infarct volume, and treatment benefit is proving more complex than initially understood, with perfusion imaging revealing that mismatch ratios and penumbral volumes provide different insights than traditional structural imaging alone.

STROKE DRUG DEVELOPMENT: TRIAL DESIGN CONSIDERATIONS

The fundamental principle remains "time is brain," but successful drug development now requires a nuanced understanding of which patients are receiving which standard-of-care interventions, when those interventions occur, and how investigational therapies can be integrated into this increasingly complex treatment landscape. These evolving paradigms demand a fundamental rethinking of stroke trial design, starting with patient population stratification. The classic, fast-presenting large vessel occlusion patients remain the core population where speed and standard-of-care integration are critical. Consent and screening must occur rapidly, often with randomization timing shifted to post-successful EVT completion rather than at presentation. Medium vessel occlusions now represent two distinct populations: those receiving EVT and those managed medically. These have potentially different baseline characteristics and outcomes that must be accounted for in trial design. Background thrombolytic strategies can no longer be treated uniformly, requiring protocols that accommodate extended time windows, varying routes of administration, and evolving dosing paradigms.

Conducting stroke trials presents unique operational challenges that distinguish this therapeutic area from other emergency medicine settings. The emergency nature of stroke care, where standard-of-care is driven by speed and "door-to-needle" times measured in minutes, creates a complex environment for trial execution. Enrollment and stratification increasingly rely on advanced imaging, not just for patient selection but as critical endpoints, from quantified stroke severity scale scoring to early imaging biomarkers that can demonstrate changes in stroke size or progression. These early imaging endpoints are particularly valuable in drug development, providing proof-of-concept data before larger outcome trials. The global nature of most stroke trials adds additional complexity, requiring coordination across different healthcare systems, imaging protocols, and regulatory environments. Site identification becomes challenging given high competition for qualified stroke centers, while patient recruitment demands careful attention to each trial's unique population requirements and qualification criteria.

To overcome these complexities, successful stroke drug development requires an experienced CRO partner with deep therapeutic area expertise. The partner must thoroughly understand current standard-of-care protocols and evolving patient populations, possess strong scientific and medical knowledge of stroke pathophysiology and treatment paradigms, and have active experience conducting stroke trials in the current landscape. Protocol development and amendments require specialized knowledge of stroke-specific requirements, from imaging vendor coordination to rapid consent processes that fit within emergency care workflows. Site staffing and retention present ongoing challenges given the specialized nature of stroke care and competition among trials. Only CRO partners currently engaged in stroke trials can navigate these operational realities while ensuring high-quality data collection in this fast-moving, complex therapeutic environment.

DEEP DIVE INTO A STROKE CLINICAL TRIAL: EXPLORING KEY STRATEGIES FOR SUCCESS

Several challenges can arise in stroke clinical trials when early-stage planning does not align with multi-center implementation. Sponsors often rely on KOLs with stroke trial participation experience when the Sponsor lacks expertise in multi-central protocol and overall compound development.

KOL advice often includes study design modeled after the standard of care at a single site, which limits flexibility when needing to expand to additional sites and regions required to complete enrollment. The lack of adaptability in the protocol causes problems downstream when the study shifts to a multi-center, multi-region trial.

In the case of a narrow-designed protocol, feasibility and site selection efforts can be challenging. Many sites decline to participate in the study due to the expectation and requirements of the study deviating from standard facility procedures—including labs and imaging if tailored to a single or few KOLs' recommendations. In some cases, participation could require sites to change their standard of care for every stroke patient in their hospital, which is not feasible.

Imaging can present one of the most significant challenges during the implementation of a stroke clinical trial. The protocol being tailored to a single site or specific region's standard of care can make it challenging in terms of what imaging scans can be performed—such as CT or MRI. This is particularly difficult in a stroke clinical trial, where there are differences in software and machinery across institutions. If a study imaging protocol is developed with an academic insight only, there is a tendency to include additional data collection, much of which is not essential for the primary endpoint. This often causes increased site burden and monitoring requirements.

Strategic Processes Implemented to Overcome Challenges

Stroke studies face complex challenges inherent to conducting research in an uncharted space. To address these, Medpace has implemented several strategies designed to align protocol design, imaging processes, and site operations while tapping into the expertise of the Medpace neuroscience experts.

1. ***Protocol Development & Site Feasibility Assessment***

   Medapce will assess the protocol for barriers to enrollment stemming from the inclusion/exclusion criteria based on misalignment with industry standards. Medpace medical experts provide real-time insights into evolving trends, including discussions at major conferences such as the International Stroke Conference (ISC). Medpace expertise and ongoing updates help provide feedback and protocol clarification to Sponsors, so amendments can be made to modify the inclusion/exclusion criteria. This emphasizes the importance of involving an experienced CRO and experts early in protocol development to avoid barriers and ensure broader trial applicability.

2. ***Central Reads Associated with Stroke***

   Central review allows for consistency and accuracy in trials, yet the urgency of acute care makes traditional central review to support eligibility not a viable option. To balance accuracy and urgency, the Medpace Core Lab team may recommend a confirmatory central review. In this approach, the local team is responsible for assessing eligibility for the trial in real time, and then subsequently submits the images for central review to confirm the local assessment adhered to the protocol. If disagreements are noted between the local and central review results, feedback is provided to the site to mitigate future disagreements.

   This method ensures consistency across all sites in including the same group of patients, eliminating differences in assessment criteria. To support this approach, the Medpace team provides training to sites to ensure they are aware of the eligibility criteria, understand how to properly assess locally imaging-based eligibility criteria, and know the tools available to support local review.

3. ***Academic Team & Sponsor Training to Ensure Endpoints Are Captured***

   It is essential to align all stakeholders, including the Sponsor and academic KOLs, through training of the most efficient and effective approach. There should be a focus on what data is critical for analysis at the beginning. By clearly defining endpoints from the onset, the team can outline the minimum requirements for data acquisition while allowing for flexibility across various standard practices. This allows multiple sites to participate while ensuring that critical imaging data is acquired to support the endpoints to demonstrate that the drug is safe and efficacious.

LESSONS LEARNED IN STROKE STUDIES

Medpace's experience managing stroke clinical trials over the years highlights key takeaways for the design and execution of complex stroke studies in this evolving era. Key lessons include the importance of flexible protocols, early planning, clear and collaborative communication, and imaging strategies. Read on to explore these insights.

Consistency with Standard of Care Procedures

Operationalizing the protocol effectively begins with a solid understanding and consistent application of the standard of care, whenever possible. This consistency is critical to ensure patient eligibility and timely enrollment. However, it is important to recognize that the standard of care is subject to change as new research emerges and the clinical development landscape for stroke evolves. Protocols need to be flexible to be able to accommodate any changes while maintaining regulatory compliance.

The Importance of a Collaborative Team

It is essential to have open communication and strong collaboration across all key stakeholders, including CROs, Sponsors, sites, KOLs, and vendors. Communication gaps can lead to misalignment and errors in execution. Early alignment on roles and expectations—coupled with routine meetings to discuss progress and expectations—helps to hold the whole team to the same standard and avoid communication issues, ultimately minimizing operational risks.

Engaging with the imaging team early on is critical, particularly in stroke studies where imaging is critical in understanding drug efficacy and safety. Given the large role of imaging in endpoints, input early on from imaging experts with strong backgrounds in clinical trial implementation ensures a seamless clinical trial. Medpace has the experience to guide Sponsors through the complexities of stroke studies, including imaging components.

Early and Strategic Planning

Site selection and engagement must be considered early on. It is critical to evaluate site feasibility based on current capabilities and patient access, not just reputation or historical performance. Data-driven site selection using enrollment history and patient demographics yields more accurate projections and better site performance.

Education and Training

Challenges can arise when vendors and academic KOLs share in the protocol development. Some of these individuals are still developing their understanding of clinical trial best practices and are working toward implementing standard processes. It is essential to share experiences for both the sites and central imaging analysis groups on the best processes for a sponsored trial. Additionally, the CRO must support the Sponsors based on recent experiences on how to execute a trial efficiently to meet both regulatory and scientific goals.

Flexibility

In acute care studies, time is of the essence. Protocol language must allow for flexibility at the site level, particularly around patient identification, consent, and IP preparation. These steps often need to be executed within minutes before the patient arrives for this type of trial to be successful. Things must go so smoothly and quickly for patient safety, in addition to trial conduct.

Global Considerations and Informed Consent

Differences in regulatory requirements and clinical practices around the world can complicate global trial execution. For example, there are regional differences in informed consent that must be considered. Investigators must have knowledge of the relevant laws and regulations regarding informed consent, but there is limited knowledge due to the lack of sponsored trials of new drugs in this space. Medpace understands the nuances of setting up trials across different geographies and can guide Sponsors in navigating global clinical trials.

CONCLUSION

"Ongoing trials continue to explore adjunctive therapies, including antiplatelets, anticoagulants, and novel thrombolytics. As these therapies undergo further validation, they may soon reshape clinical guidelines and standard practice in stroke care globally."

– James Vornov, MD/PhD, Vice-President, Medical Department, Neuroscience

The stroke clinical development landscape is continuously evolving, driven by advancements in scientific understanding and technology. Despite significant progress in treatment options over the years, stroke remains one of the leading causes of death and disability worldwide and there is a large unmet need for new and effective treatment options. Looking ahead, the field of stroke holds immense promise for reshaping the clinical development landscape and improving the lives of patients globally through transformative changes in patient care.

LEADING CRO PARTNER FOR STROKE CLINICAL DEVELOPMENT

As an experienced, therapeutically-focused CRO, Medpace has the medical, regulatory, and operational leadership and disciplined operating approach to overcome the complexities of stroke clinical development and position your trial for long-term success. With extensive stroke experience and proven strategies, our unique collaborative model delivers a truly seamless clinical trial process for Sponsors of all sizes.

Our global reach and experience across all phases of development allows us to navigate languages, cultures, and clinical and regulatory environments around the world. Our comprehensive CRO services are supported by our wholly-owned Central Laboratories, Bioanalytical Lab, Imaging Core Lab, ECG Core Lab, and Phase I Unit, as well as a Clinical Trial Management System that ties all study data together in a single platform. This full-service, single-vendor outsourcing strategy helps to streamline even the most complex stroke clinical trial with higher levels of efficiency and productivity.

Do you have an upcoming stroke clinical trial that needs seamless execution? Contact us today to discuss how Medpace can help accelerate your clinical development.