Perspectives on Modern Lower Extremity Revascularization Trials

Insights from the FDA Center for Devices and Radiological Health on CLTI clinical trial design and conduct, including endpoint evolution and application of surrogate endpoints, advantages and disadvantages of adaptive trial designs, and more.

With Misti Malone, PhD, and Donna Buckley, MD

What common challenges have you recently observed in the successful design and conduct of clinical trials in the peripheral artery disease (PAD) population? Specifically in the chronic limb-threatening ischemia (CLTI) population?

The Center for Devices and Radiological Health (CDRH)'s Office of Cardiovascular Devices has readily engaged with stakeholders to develop PAD and CLTI clinical trial designs while maintaining flexibility and adaptability based on the lessons learned from earlier trials. We recognize that the patient population and treatment strategies for CLTI are heterogeneous, with clinicians often making decisions based on specific patient and lesions characteristics. Hence, development of clear, data-driven approaches to treating these patients is an important goal.

Common challenges in clinical trials arise from the complexity, heterogeneity, and frailty of this patient population, including missing data at later timepoints due to patient loss and high rates of protocol deviations due to comorbidities in CLTI patients. In turn, these issues lead to challenges in interpreting the resulting clinical data, particularly if there is high missingness or the procedure involves multiple devices (eg, atherectomy with or without a secondary treatment, bailout). Therefore, it's helpful to plan prospectively to mitigate potential issues and biases, such as actively monitoring the trial to reduce deviations and missingness, prespecifying statistical analyses to account for missingness, clearly defining how secondary devices will be used (eg, bailout), and using standard definitions via core labs and independent adjudication committees to objectively and consistently evaluate imaging and events.

How have you seen endpoints in below-the-knee trials evolve in recent years?

Endpoints are evolving based on lessons learned from early clinical trials. For example, clinical trials evaluating stents and balloons treating CLTI originally used a 6-month primary effectiveness timepoint based on the anticipated complexity and morbidity associated with CLTI patients; however, as the trials have enrolled less sick patients to reduce confounders, we have seen more companies switch to 12 months as the primary endpoint to better ascertain treatment differences and evaluate the durability of benefit.[1] There is also greater use of composite primary endpoints (eg, target lesion revascularization [TLR]–free survival, amputation-free survival [AFS]), with greater emphasis on secondary endpoints (eg, wound healing metrics, quality-of-life [QOL] assessments). Endpoints and timepoints are specific for the device, intended use, and patient population, and with increased learning, it may be useful to consider incorporating a variety of outcome assessments and endpoints in the trial to evaluate clinically meaningful benefit.

How do you view the use of composite endpoints in PAD/CLTI trials?

CLTI trials often use composite endpoints (eg, primary patency plus a variety of related endpoints such as

AFS or TLR-free survival), and there is growing interest in hierarchical endpoints, which should include clinically meaningful endpoints in a reasonable hierarchy. However, this approach comes with a potential risk that the treatment effect may be diluted if the less relevant component(s) dominate or the endpoints go in opposite directions, which in turn can add uncertainty to the regulatory process since primary endpoint composite components and key secondary endpoints may require clinical interpretation separate from formal statistical hypothesis testing. Therefore, it might be beneficial to consider developing a prespecified hierarchy and analytical plan, including consideration if higher-level endpoint(s) do not meet expectations.

What potential applications might there be for applying surrogate endpoints in CLTI trials? What is your perspective on wound healing as a surrogate or primary endpoint?

Wound healing is important to both the patient and clinician, and it has traditionally been treated as a key secondary endpoint with a favorable trend essential to supporting primary endpoints. Due to the complex patient population and large heterogeneity in wound etiology and treatment, data collection has been poor or variable,[2] which is commonly complicated by (1) high loss to follow-up; (2) inconsistent measurement methods, variable definitions of healing, and confounding factors (eg, infection); and (3) biases in which the patient experiences improvements due to trial enrollment rather than device treatment. Additionally, as many CLTI studies enroll patients with and without wounds, there is typically inadequate power to perform robust hypothesis testing on wound healing. To mitigate these issues, consider including consistent wound treatment strategies into the protocol, prespecifying objective measurements and timepoints, and including a concurrent control arm, if possible.

How does one assess the reliability and reproducibility of functional and QOL endpoints?

Like wound healing, QOL is an important secondary endpoint for both patients and clinicians. It's important to use or develop well-defined and validated instruments (eg, Walking Impairment Questionnaire, Vascular Quality of Life Questionnaire) with standardized data collection protocols and blinding to minimizing bias in patient-reported outcomes.

How has FDA advised sponsors post–paclitaxel signal regarding long-term follow-up?

CDRH closed the signal for paclitaxel-coated devices to treat arterial disease based on the totality of data from clinical studies and real-world evidence.[3] Based on the lessons learned from this signal, we continue to encourage ≥ 5-year follow-up for mortality and safety, transparency in paclitaxel dose and exposure, and proactive monitoring to minimize missingness in pivotal clinical trials.

What potential advantages and disadvantages might there be to incorporating adaptive trial designs in PAD studies? Are there any design/statistical pitfalls observed in recent PAD submissions?

Sometimes an adaptive design approach may reduce the resources and time required if the device performs better than expected, while reducing potential risk for companies and patients if the device does not perform as expected. However, these designs are more complex and require statistical planning to control the type 1 error rate and increase risk of potential bias due to operational bias and unblinding. FDA guidance on this topic may be helpful.[4]

Common pitfalls for PAD and CLTI trials include underpowered trials and key endpoints, lack of prespecified subgroup analysis or hierarchy, and higher than expected amounts of missing data, particularly at later endpoints.[5] While missingness should be minimized through monitoring and careful follow-up, it could be mitigated by capturing primary endpoint data at later follow-up timepoints (eg, duplex ultrasound) or using a method to minimize bias. The impact of missing data may be assessed and overcome through prespecified sensitivity analyses (eg, tipping point, multiple imputations). Prospectively planned adaptive trials may be helpful to minimize some of these issues, allowing for enrollment of additional patients based on prespecified criteria and ensuring a sufficiently powered study to ascertain differences between the subject device and the control or performance goal.

How can industry and investigators optimally collaborate with FDA to streamline PAD/CLTI trial designs and approval timelines?

We continue to recommend that companies and investigators engage with CDRH as part of the presubmission process to develop testing strategies, clinical protocols, and statistical analysis plans.[6] This engagement can be beneficial even while the clinical trial is ongoing to adapt to unexpected issues (eg, pandemic, higher than expected missingness). ■

1. Yokoi H, Ho M, Iwamoto S, et al. Design strategies for global clinical trials of endovascular devices for critical limb ischemia (CLI) - A joint USA-Japanese perspective. Circ J. 2018;82:2233-2239. doi: 10.1253/circj.CJ-18-0014
2. Weinberg I, Weinberg MD. Why is it hard to study chronic limb-threatening ischemia? 2025;24:55-60.

https://evtoday.com/articles/2025-may/why-is-it-hard-to-study-chronic-limb-threatening-ischemia
3. US Food and Drug Administration. Update: paclitaxel-coated devices to treat peripheral arterial disease unlikely to increase risk of mortality–letter to health care providers. July 11, 2023. Accessed August 20, 2025. https://www.fda.gov/medical-devices/letters-health-care-providers/update-paclitaxel-coated-devices-treat-peripheral-arterial-disease-unlikely-increase-risk-mortality
4. US Food and Drug Administration. Adaptive designs for medical device clinical studies: guidance for industry and Food and Drug Administration staff. July 2016. Accessed August 20, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/adaptive-designs-medical-device-clinical-studies
5. Lottes AE, Whatley EM, Royce SM, et al. Important considerations for trials for peripheral arterial disease: Lessons learned from the paclitaxel mortality signal: A report on behalf of the registry assessment for peripheral interventional Devices (RAPID) Paclitaxel Pathways Program. Am Heart J. 2021;232:71-83. doi: 10.1016/j.ahj.2020.10.070
6. US Food and Drug Administration. Requests for feedback and meetings for medical device submissions: the Q-Submission program: final guidance for industry and Food and Drug Administration staff. May 28, 2025. Accessed August 20, 2025. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/requests-feedback-and-meetings-medical-device-submissions-q-submission-program

Misti Malone, PhD
Assistant Director
Office of Cardiovascular Devices
Center for Devices and Radiological Health, US Food and Drug Administration
Silver Spring, Maryland
misti.malone@fda.hhs.gov
Disclosures: None.

Donna Buckley, MD
Medical Officer
Office of Cardiovascular Devices
Center for Devices and Radiological Health, US Food and Drug Administration
Silver Spring, Maryland
Disclosures: None.