Harmonization by Doing Proposal for Global Clinical Trial Designs for Endovascular Devices for Treatment of Critical Limb Ischemia: The United States Food and Drug Administration Perspective

To the Editor:
The following commentary discusses how the article by Yokoi et al. aligns with the mandate of the U.S. Food and Drug Administration (FDA) to promote public health through the regulation of clinical studies and marketing approval of new cardiovascular devices.

FDA medical device approval is based on valid scientific evidence demonstrating a reasonable assurance of safety and effectiveness for the proposed use in the intended patient population, through a determination that the expected benefits of such use outweigh the anticipated risks. Although there can be multiple ways to collect persuasive safety and effectiveness data for a given product, the utility and interpretation of clinical data can be optimized through the use of standardized study elements.

Multi-stakeholder collaborative activities can serve an important role in reaching consensus on key clinical study elements in a given area and promoting their adoption in the medical community, and these efforts have been previously successful for clinical evaluations of treatments for various manifestations of peripheral vascular disease. Such efforts are especially important for treatments for CLI, which have proven to be more challenging to evaluate than for other forms of peripheral arterial disease, such as iliac or femoral artery claudication.

In seeking to ameliorate these challenges, HBD continued its long history of productive engagement between industry, academic, and regulatory leaders to foster an environment conducive to timely approval of safe and effective products in the U.S. and Japan. Such goals are consistent with the FDA’s global public health mission and the increasingly international nature of cardiovascular device evaluation. In addition, the FDA has found HBD’s “proof of concept” approach, where potential improvements are tested in specific project areas, to be beneficial in piloting novel US-Japanese pre-market and post-market clinical and regulatory projects.

The resulting CLI guidelines serve as an important reference for the design of any future CLI trial, particularly studies with a global scope. These recommendations are especially robust because of international, multi-stakeholder participation and the perspectives provided by physicians from multiple medical specialties traditionally involved with CLI treatment. Furthermore, the HBD effort is exceptionally well timed, as CLI affects a growing patient population that is underserved by currently approved treatment options and these clinical studies are in their relatively early stages in the U.S. and Japan. The use of harmonized study definitions at this crucial stage can therefore increase the overall quality of the clinical evidence collected. Finally, by identifying the key comorbidities of CLI patients in both countries, and ensuring that representative populations are included in these studies, the proposed paradigm is well equipped to capture data that approximate clinical outcomes in the “real-world” CLI population.

We believe that use of the HBD proposals will be beneficial in planning clinical investigations of CLI treatments and will stimulate future clinical evidence development in this area. Because CLI is a complex disease and the devices used to treat it vary greatly in their design and intended use, the design of a given clinical study should be tailored to the specific device and clinical indication being studied. For example, studies of combination products incorporating both drug and device components may involve different types of clinical follow-up than studies of better-understood medical devices, because of the potential time course and mechanism of drug action. Similarly, longer-term safety data are likely to be more important for implant-based CLI treatments, because of the greater potential for device-related adverse events at later time points. Conversely, a randomized study involving comparison of a new treatment to an active control may not always be necessary. For example, if the technology is very well established and if sufficiently informative historical data involving comparable treatments, lesion types, and patient demographics are available, a patient-level data set or a clinically relevant performance goal comparator could potentially be developed.

As with all clinical studies, the validity of the resulting data will depend heavily on the inclusion of robust study elements such as appropriate blinding, mitigation of potential bias and confounding factors, and maximization of follow-up compliance. The FDA encourages interested study sponsors to work with us early in the development cycle to design the most suitable clinical study for their individual devices and regulatory plans. We also hope that the groundwork laid by HBD stimulates further collaborations to standardize and validate methods for assessing and analyzing other clinical measures of potential value for the CLI population, such as wound healing and tissue perfusion pressure. In addition, as more safety and effectiveness data from CLI studies become available, the clinical utility of shorter-term outcomes and their suitability as key study endpoints can potentially be established, thus reducing the time required for clinical evaluation.

The FDA commends the HBD Working Group for developing consensus-based design parameters and definitions for clinical studies involving endovascular devices intended to treat CLI. Although the particular design of any clinical study depends greatly on the proposed technology and patient population, this proposal provides a sound basis for designing international studies intended to
evaluate the safety and effectiveness of CLI devices and support US marketing approval. We strongly support the promotion of CLI studies and the continued refinement of optimal study design characteristics as new clinical evidence becomes available, and we welcome early discussion of CLI clinical study designs with interested device manufacturers and physicians.

**References**


Kenneth J. Cavanaugh Jr, PhD
Donna C. Buckley, MD
Misti L. Malone, PhD
Division of Cardiovascular Devices,
Office of Device Evaluation,
US Food and Drug Administration,
Silver Spring, MD, USA