WHITE PAPER

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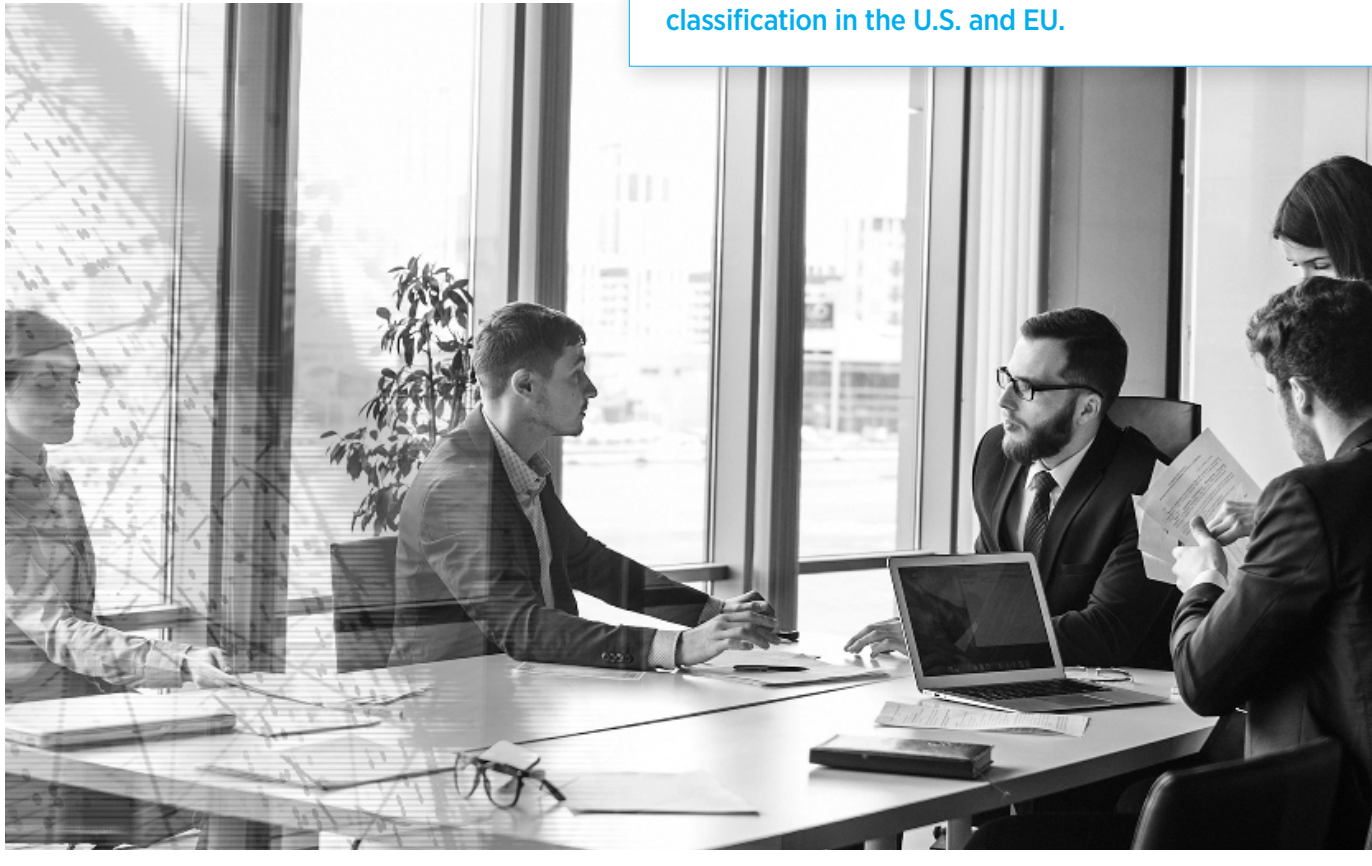
# MEDICAL DEVICE AND DIAGNOSTICS

## Best Practices for Interventional Cardiovascular Medical Device Trials in Asia-Pacific


**ABSTRACT**

The emerging markets of the APAC region offer tremendous potential for clinical research. Best practices for cardiovascular medical device development in Asian countries can offer insights on navigating the regulatory and clinical landscape of this region.

**Medical device development is distinct from pharmaceutical development and requires different clinical development strategies and regulatory pathways depending upon device classification in the U.S. and EU.**



## Introduction

Widely recognized as one of the most important growth frontiers for medical devices, the Asia Pacific (APAC) region comprises a complex mix of people, regulations, and payment models. According to one forecast, the APAC surgical and medical device market is expected to grow at a compound annual growth rate (CAGR) of 6.5 percent from 2017 to 2026, reaching $167 billion by the end of the forecast period.[1] For device manufacturers who hope to tap into the potential of this burgeoning market, it is critical to understand the regulatory and clinical nuances of this diverse region.

Medical device development is distinct from pharmaceutical development and requires different clinical development strategies and regulatory pathways depending upon device classification in the U.S. and EU. In contrast, APAC markets have evolving and developing regulatory environments. To succeed in APAC markets, device manufacturers have used various approaches to approval, from integrating regulatory activities with global clinical trials to establishing local infrastructures through mergers and acquisitions of local players.

In this white paper, we explore best practices for cardiovascular medical device development in Asian countries and offer insight on navigating the regulatory and clinical landscape of this region.

## APAC cardiovascular disease overview

As the worldwide population ages, cardiovascular disease (CVD) has become a leading global health issue. By 2050, one in four people in the APAC region will be over age 60, representing 1.3 billion people.[2] Given that the majority of the world's population resides in the APAC region, it is expected that at least half of the world's cardiovascular (CV) burden will be concentrated in that region.[3] In China alone, an estimated 4.2 million people are living with heart failure.[4] It is not surprising, then, that CV clinical trial activity in the APAC region is robust, accounting for 14 percent of all studies in India and 55 percent of all studies in Japan.[5]

Despite notable declines in the prevalence of certain CV risk factors – including uncontrolled hypertension, elevated low density lipoprotein cholesterol, and tobacco use – and improvements in quality of care and CVD treatments, other influencers of CVD rates such as diabetes are on the rise. According to the American Heart Association, nearly 85 percent of people age 65 or older with diabetes die from heart disease or stroke.[6] The 2018 edition of the EvaluateMedTech® World Preview predicted that the global cardiology device industry would grow at a CAGR of 6.4 percent per year between 2017 and 2024, achieving global sales of $72.6 billion in 2024.[7]

## Trends in cardiovascular research

A recent examination of cardiovascular publication output from 2004 to 2013 revealed significant shifts in cardiovascular research topics over that ten-year period. Notably, research focused on evidence-based treatment guidelines, outcomes, and risk factors has become more prevalent, reflecting an increased emphasis on evidence-based and preventative medicine. This analysis also showed a larger focus on atrial fibrillation, novel treatments, transcatheter aortic valve interventions, and imaging, likely driven by advances in technological innovation.[8]

## Conducting clinical trials in the APAC region

A key benefit of conducting clinical trials in the APAC region is the availability of a large pool of genetically diverse – and often treatment-naïve – patients. Data quality is also an emerging differentiator for the region. In 2015, one-quarter of citable journal articles came from the APAC region, as compared with 19 percent in 2005, demonstrating significant improvements in data quality.[9] In fact, data quality from the APAC region is recognized by both the U.S. and Europe, Middle East, and Africa (EMEA).

At present, device trials are still 30 to 60 percent less expensive to conduct in the APAC region than in the U.S. In addition, cardiac procedures in Asian countries are priced relatively low, potentiating the cost savings (see Figure 1). Coupled with an increased government focus on healthcare ecosystem improvements and a positive perception of clinical trials, the APAC region is an attractive geography for the conduct of clinical trials.

## APAC regulatory environment

The medical device regulatory environment in the APAC region is relatively new compared with the U.S. and EU. While device regulations were instituted in the U.S. in 1976, the first device-specific regulation in APAC was introduced in Japan in 2005. Regulations for medical devices across the APAC region vary, ranging from comprehensive to none, and pre-market requirements vary for different regulatory bodies.

A conformity assessment procedure, which is often dependent on device risk classification, will be required for all devices. Low-risk products may require only a supplier's declaration of conformity (SDOC), a self-declaration statement indicating that the product complies with the relevant requirement(s). Higher-risk products will require a conformity assessment of the manufacturer's documentation performed by the regulatory authority. Most APAC countries classify permanent, implantable CV devices in their highest risk category, but requirements for approval differ among regulatory agencies.

### China

In China, the National Medical Products Administration (NMPA), formerly the China Food and Drug Administration, is responsible for medical device regulation. Their regulations, published in 2014, introduced a new device classification system based on level of risk to the human body. Low-risk (Class I) devices only require filing, but moderate-risk (Class II) and high-risk (Class III) devices require clinical trial data unless the manufacturer receives an exemption. In the years since 2014, the NMPA has published a number of reforming policies, including extensions to clinical trial exemptions and revisions on expectations regarding local clinical trials.

**Figure 1. Cost comparison for certain cardiovascular procedures, 2016 (USD)**[10]

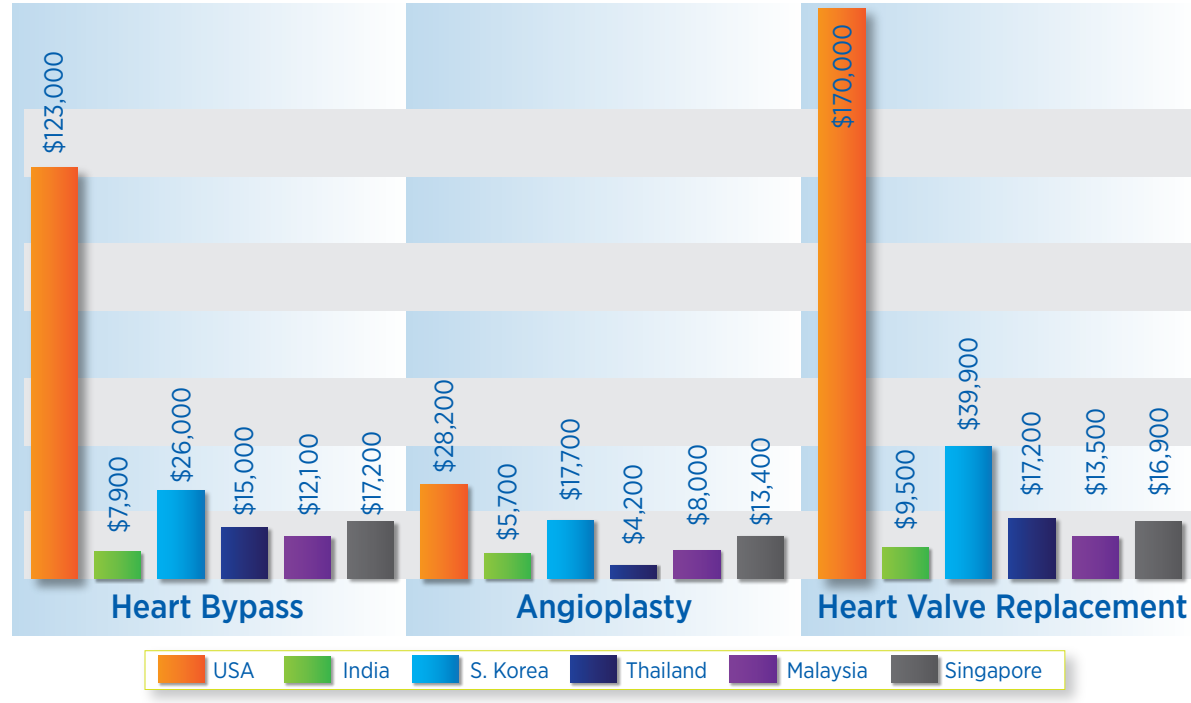


**Figure 2. Comparison of device risk classifications in the APAC region**

| Country | Device Risk Classification | Device Examples |
|---|---|---|
| China | Class I: low risk | Hemostatic forceps, microscope forceps, cranial drill |
| | Class II: moderate risk | Vacuum freezing drying oven, pneumatometer |
| | Class III: high risk | Intravascular stent, pacemaker |
| Korea | Class I: medical devices with few potential harm | Stethoscope (mechanical), centrifuge (tabletop) |
| | Class II: medical devices with low potential harm | Stethoscope (electronic), thermometer (electronic) |
| | Class III: medical devices with moderate potential harm | Bone absorptiometric ultrasound system |
| | Class IV: medical devices with high potential harm | Prosthesis vascular (central) |
| Thailand | Class I: license medical devices | Hypodermic syringe, insulin syringe, HIV test kit |
| | Class II: notification medical devices | Physical therapy products, alcohol detector |
| | Class III: general medical devices | Medical devices excluded from groups I and II |
| Singapore | Class A: low risk | Surgical retractors, tongue depressors |
| | Class B: low-moderate risk | Hypodermic needles, suction equipment |
| | Class C: moderate-high risk | Lung ventilator, bone fixation plate |
| | Class D: high risk | Heart valves, implantable defibrillator |
| Malaysia & India | Class A: low risk | Tongue depressor, liquid-in-glass |
| | Class B: low-moderate risk | Hypodermic needles |
| | Class C: high-moderate risk | Lung ventilator |
| | Class D: high risk | Active implantable devices |
| Japan | Class I: general medical devices | X-ray film, steel surgical instruments |
| | Class II: controlled medical devices | MRI units, electronic endoscopes |
| | Class III: specially controlled medical devices | Hemodialysis equipment, artificial bones and joints |
| | Class IV: specially controlled medical devices | Pacemakers, artificial cardiac valves |

### Japan

In Japan, medical devices are regulated by the Pharmaceuticals and Medical Devices Act and classified by risk-based concept: general medical devices (Class I), controlled medical devices (Class II), and specially controlled medical devices (Class III and IV).[11] For Class I devices, manufacturers need only submit notification/self-declaration for regulatory affairs. Designated controlled medical devices are to be certificated by the third-party certification bodies based on certification standards which are pre-authorized by the Ministry of Health, Labor, and Welfare (MHLW). Other controlled medical devices are reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA). Specially controlled medical devices are to be reviewed by the PMDA and approved by the Minister of MHLW. They are reviewed based on separately specified approval standards or guidance documents which are authorized by the MHLW.

## Preparing regulatory assessments

Detailed regulatory assessments for each relevant APAC agency should be among the first documents written for the Design Control process. These assessments must be specific to the device type and its intended use and should include, at minimum:

- Rationale for product classification
- Rationale for risk significance
- Summary of pathway to clearance
- Applicable guidance documents
- Comparison to predicate devices (if any)
- Design verification (i.e., bench) testing requirements
- Animal study requirements
- Clinical study requirements
- Post-market requirements
- Submission type, content, and format requirements and ancillary document list

Given the regulatory variability across the APAC regions, it is recommended that sponsors familiarize themselves with the regulations and requirements of each regulatory jurisdiction in which they plan to commercialize a device.

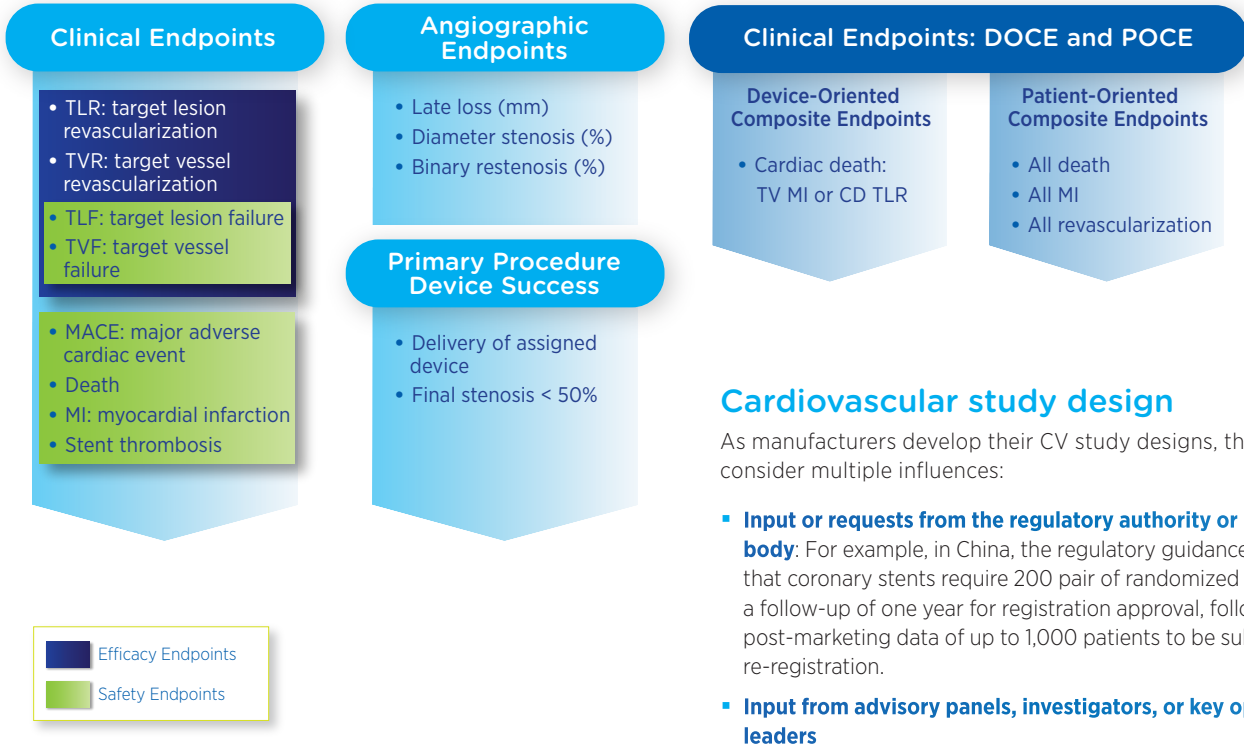
## Cardiovascular device clinical evaluation plans

CV device clinical evaluation plan requirements in Asian countries are typically in line with requirements in other parts of the world (see Figure 3).

**Figure 3. Components of a device clinical evaluation plan**

| |
|---|
| **General safety and performance requirements** (GSPRs), with support from relevant clinical data |
| **Intended purpose of the device** |
| **Intended target group(s)**, with both indications and contraindications |
| **Intended clinical benefits**, with relevant and specified clinical outcome parameters |
| **Methods to be used for examination** of qualitative and quantitative aspects of clinical safety, with reference to determination of residual risks and side effects |
| **Listing and specification of parameters to be used** to determine, based on state of the art in medicine, acceptability of the benefit-risk ratio for various indications and for the intended purpose of the device |
| **Description of how benefit-risk issues** relating to specific components, such as use of pharmaceuticals and non-viable animal or human tissues, are to be addressed |
| **A clinical development plan** delineating progression from exploratory investigations (e.g., first-in-man, feasibility, and pilot studies) to confirmatory investigations (e.g., pivotal clinical trials) and post-market clinical follow-up (PMCF), with an indication of milestones and a description of potential acceptance criteria |

**Figure 4. Common clinical trial endpoints in interventional cardiology**




## Cardiovascular study design

As manufacturers develop their CV study designs, they must consider multiple influences:

- **Input or requests from the regulatory authority or notified body**: For example, in China, the regulatory guidance dictates that coronary stents require 200 pair of randomized data with a follow-up of one year for registration approval, followed by post-marketing data of up to 1,000 patients to be submitted at re-registration.
- **Input from advisory panels, investigators, or key opinion leaders**
- **Input from management**
- **Marketing claims**
- **Reimbursement questions**

The use of adaptive designs allowing ongoing clinical trial evaluation of CV devices is relatively new within the APAC region. As such, manufacturers considering adaptive designs should consult proactively with regulators to explore and negotiate the acceptability of such designs.

## Cardiovascular endpoints

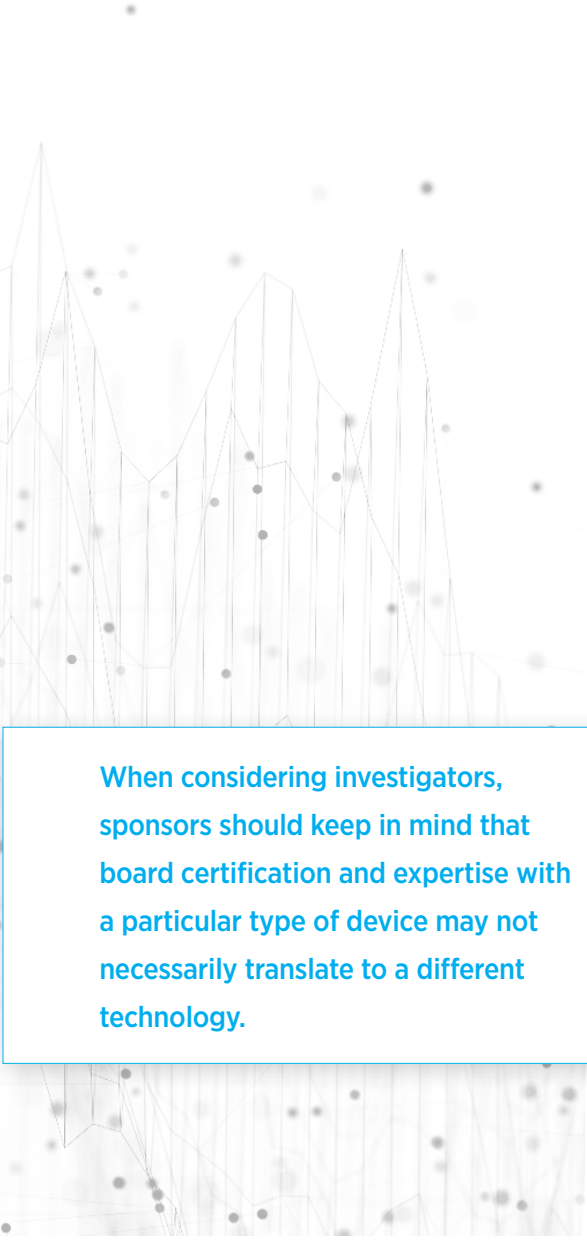
When considering primary endpoints for CV device studies in Asian countries, manufacturers should ensure that they have selected endpoints that can provide sufficient data to fully categorize the clinical effect of the device to support a regulatory claim for the treatment. In other words, the treatment effect must have clinical relevance and must be measured accurately, reliably, and objectively. Composite endpoints may be used to capture the effect of the treatment on disease burden, but have the potential to dilute the effect. To that end, co-primary endpoints may be a useful alternative.[12]

Commonly used clinical endpoints for interventional cardiology are consistent with international guidance focusing on efficacy (e.g., target lesion failure, target vessel failure) and safety [e.g., major adverse cardiovascular events (MACE), death, myocardial infarction, stent thrombosis]. Depending on the device and imaging modalities, angiographic, optical coherence tomography (OCT), or intravascular ultrasound (IVUS) endpoints may also be appropriate. Manufacturers should also consider endpoints that reflect patient-centric benefits.

**Figure 5. Common clinical endpoints for valve repair devices**

| Safety Endpoints |
| --- |
| **Mortality** |
| • All-cause mortality, cardiovascular mortality, non-cardiovascular mortality, procedural mortality – 30 days from procedure or discharge from the hospital, whichever is longer |
| **Neurological Events** |
| • Stroke: stroke disability, non-disabling stroke, disabling stroke, stroke classification |
| • Ischaemic, haemorrhagic |
| **MI** |
| • The occurrence, nature, and frequency of treatment-emergent adverse events, in particular severe device-related serious adverse events |
| • Additional safety endpoints should be considered based upon the patient population, the investigational design, and the device |

| Performance & Effectiveness |
| --- |
| • Acute endpoints |
| • Device success: survival with successful placement of device(s) in the intended anatomical location and acceptable function of the device |
| • Procedural success: device success plus lack of major adverse events |
| • Mean aortic valve pressure gradient at pre-discharge – from independent Echo CoreLab |
| • Functional status (e.g. New York Heart Association class) |
| • Heart failure hospitalizations – or their equivalent – and interventions |
| • Change in heart failure status – improvement or worsening |
| • Six-minute walk test, Peak VO2 |
| • Patient-reported outcomes – Minnesota Living With Heart Failure, Kansas City Cardiomyopathy Questionnaire, EuroQOL, Medical Outcomes Study Short Form – 36, Short Form - 12 |



When considering investigators, sponsors should keep in mind that board certification and expertise with a particular type of device may not necessarily translate to a different technology.

## APAC study considerations

Careful consideration and selection of principal investigators, sites, and patients as well as treatment protocols, data, and endpoints are vital to the success of CV device trials.

### Principal investigators and sites

The emerging markets of the APAC region offer tremendous potential for clinical research, but regional differences in patient populations, infrastructure, and availability of qualified interventional cardiologists make completing studies on time and within internationally recognized quality standards a complex undertaking.

It is imperative for manufacturers to incorporate a data-driven approach to uncovering the right investigators and sites. Country-specific site mapping is one technique for ensuring appropriate selection. Many countries in the APAC region have regulatory agency-approved sites for conducting device clinical trials. For example, in China, departments within a hospital are accredited by the CFDA to conduct clinical trials and accreditations are re-evaluated every three years.

It is estimated that 36 percent of trial-experienced investigators reside in the APAC region. When considering investigators, sponsors should keep in mind that board certification and expertise with a particular type of device may not necessarily translate to a different technology. As such, operator performance with the device under investigation should be factored into investigator selection.

### Treatment protocols

For investigational devices, most Asian countries require sponsors to pay for standard of care, which must be factored into the clinical trial budget.

Another aspect of trial design that should be considered carefully is the stratification of patients into treatment groups and the goal of treatment. A CV device is seldom an isolated treatment, hence data collection must account for all study-related interventions, whether investigational or not. In many pivotal device trials, the design calls for randomization of device-treated patients in comparison to patients treated with standard of care to define the device's long-term safety and efficacy.

### Data and endpoints

Although many medical device clinical trials measure virtually identical safety and efficacy endpoints, differences in definitions and timing of assessment have created confusion in interpretation across studies. Recommendations from global gatekeepers such as the Academic Research Consortium set the foundation for country-specific study design requirements, but data and endpoint requirements may differ across countries in the APAC region. For example, coronary stents require six months of data in India, but nine months to a year of data in China, and endpoints vary from late loss to stent thrombosis.

## Vendor selection

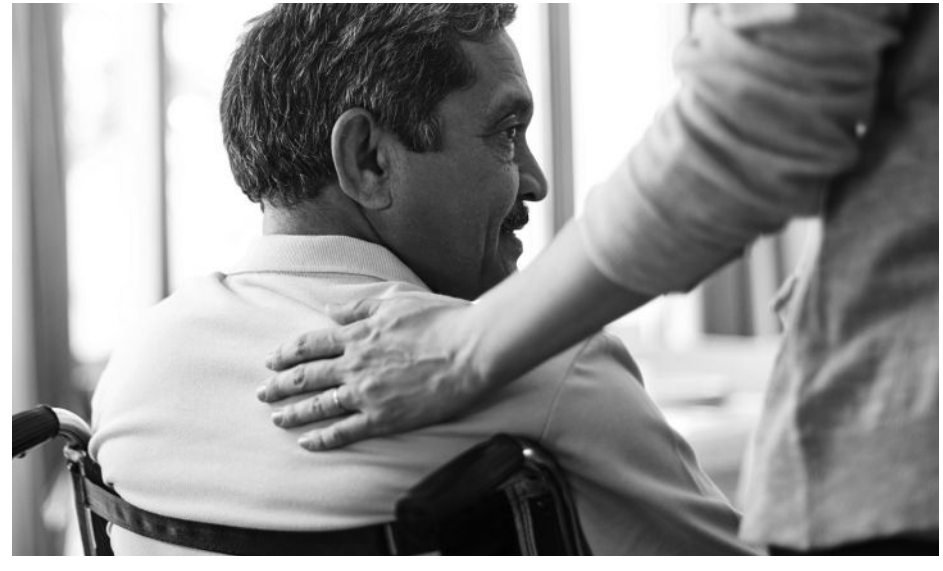
To optimize the likelihood of CV device trial success, manufacturers may benefit from working with strategic partners who are versed in the therapeutic area and the regulatory and reimbursement landscape. A contract research organization (CRO) with first-hand regulatory and trial knowledge can help sponsors select experienced, certified vendors for study conduct, data analysis, and regulatory submissions. For instance, sponsors should expect their CROs to make recommendations not just for investigators and sites, but also for core laboratories, data and safety monitoring boards (DSMBs), and clinical event committees (CECs).

When selecting a CRO, manufacturers should ask whether the CRO team has the requisite skills in the appropriate therapeutic settings, such as cardiac catheterization laboratories. Such practice-based knowledge helps clinical research associates (CRAs) understand the nuances of the investigative device and procedure. It can also help CRAs address protocol deviations and non-compliance at the time of the intervention.

## Conclusion

The global outlook for medical devices is stronger than ever. While the U.S. continues to be the world leader based on the number of patent awards, clinical trials and product launches, the landscape is changing. Affluent APAC countries such as Japan, Singapore, and Taiwan are demanding innovative therapies, and powerhouses like China and South Korea are focused heavily on new technology and device development.

For manufacturers considering the APAC region for clinical trials, it is critical to remember that Asia comprises a diverse group of nations, each with unique patient, sociocultural, and standard medical practice nuances that may impact trial design and conduct. Collaborating with a knowledgeable partner with both global reach and local knowhow can contribute to development of the robust regulatory and clinical strategy needed for commercial success.



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## Ashish Jain | Vice President, Asia-Pacific

Ashish Jain has more than two decades of clinical research experience in India, Singapore, and the U.S. Ashish is responsible for Premier Research's business in Asia-Pacific region and ensuring company's continuous expansion, smooth project delivery and customer satisfaction. Mr. Jain is also responsible for commercial opportunities in the Asian market and established a Premier Research corporate support services center in Asia.

Mr. Jain has vast experience in creating and implementing business strategies, effectively managing human resources, developing effective customer relationships, and managing financial plans. He has set up new clinical research units and built businesses across Asia Pacific, acquired companies, and integrated businesses across continents.

## About Premier Research

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## Vicki Gashwiler | Contributor | Executive Director, Medical Device

Vicki Gashwiler joined Premier Research in 2019 as the executive director of strategic development in the Medical Device group. She brings over 20 years of health care experience and 15 years of experience in the medical device industry, both on the sponsor and CRO sides. Prior to her industry experience, Vicki began her career as a registered nurse in 2000, working on cardiac, critical care and out-patient orthopedic surgical units. She started her industry career as a clinical research associate at Abbott Vascular and had the opportunity to advance in the operations group as a clinical trial manager and then as a project manager. During her time at Abbott Vascular, Vicki supported global clinical trials spanning across Europe, Canada, Latin America, Australia, the US and the Asia-Pacific. Her time at Abbott provided her an extensive understanding of complex trial execution on a global scale, diverse team management and global regulatory processes and timelines.

In 2014, Vicki joined Novella Clinical in a project manager role, gaining experience on the vendor side of clinical trial delivery. She filled roles of increasing responsibility while at Novella, including senior project manager, program director, associate director, and director of Strategic Development & Market Access. During her time at Novella, Vicki gained experience in oncology and dermatologic devices, endocrinology, weight management, orthopedics, as well as additional cardiac and vascular device trials. Vicki brings a high level understanding of market development and trends as well as a deep therapeutic knowledge of many disease processes and the clinical trials to intervene upon them.