Future Roadmap for Mitral Valve Therapies

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship	Company
• Equity	• Micardia, Guided Delivery Systems

Clinical Trial Design for Transcatheter Mitral Valve Therapy: Major issues

- How should the disease be classified?
- How should “severe” MR be defined and measured, and what constitutes a meaningful reduction in MR?
- What is the appropriate control arm therapy?
- How should high risk be defined?
- Is a sham control necessary?
- What are appropriate inclusion and exclusion criteria?
- What are appropriate primary and secondary endpoints – imaging/anatomic, functional, QOL, clinical – and how should they be defined?
- What are the roles of the heart team, eligibility committee, and central core laboratories?
- What is optimal analysis group and statistical methodology?

Mitral Valve ARC (MVARC): Mission

- Goal: To provide clarity, uniformity and direction to facilitate meaningful development of the emerging subspecialty of mitral transcatheter valve therapies
- Specific objectives:
  1. Recommend detailed methodology for pivotal clinical trials, including patient eligibility criteria, control arm selection, study processes, and endpoints

     and

  2. Establish consensus regarding definitions and nomenclature

MVARC: ~50 Participants

- Cardiologists
  - Valve specialists
  - Heart failure specialists
  - Interventional cardiologists
  - Imaging specialists
  - Electrophysiologists
- Mitral valve surgeons
- Epidemiologists
- Statisticians

ARC Foundation

CRF, Cardialysis, DCRI, HCRI

FDA advisors

Clinical Trial Design Principles and Endpoint Definitions for Transcatheter Mitral Valve Repair and Replacement. A Consensus Document from the Mitral Valve Academic Research Consortium. Part 1: Clinical Trial Design Principles

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MVARC Highlights: Investigative and Regulatory Perspectives (i)

CE mark: Requires demonstration that the device is safe, and functions both medically and technically as the manufacturer intends. Either randomized trials or well-performed registries may support CE mark approval. Effectiveness is usually investigated after CE mark approval, and postmarketing surveillance is an integral part of ongoing clinical evaluation.

PMA approval: High-risk Class III devices must demonstrate "reasonable assurance" of both safety and effectiveness in a well-defined population for its intended use. Pivotal evaluations of breakthrough technologies such as transcatheter mitral repair systems or percutaneous implantable valves will, in most cases, necessitate RCTs wherein the new device is compared to the currently established standard of care. Depending on the comparator group, either a superiority or noninferiority design for the primary endpoint may be appropriate.

MVARC Highlights: Investigative and Regulatory Perspectives (ii)

Primary effectiveness should be evaluated with a clinically relevant endpoint, either a single event type (e.g. hospitalization for heart failure) or a composite measure (e.g. death or hospitalization for heart failure).

Additional support for effectiveness can be obtained through use of validated instruments demonstrating improved QoL, improvement in symptom status (e.g. NYHA functional classification), and improved exercise performance (although at the present time these measures are not usually sufficient for principal FDA regulatory device approval).

Evidence of meaningful MR reduction which is sustained over time is important to demonstrate, and improvement in ventricular volumes and function during follow-up are additional supportive secondary effectiveness endpoints that should be assessed.

MVARC Highlights: Investigative and Regulatory Perspectives (iii)

Safety assessments may include both short- and long-term procedural and device-related complications, and a primary safety endpoint (separate from the primary effectiveness endpoint) should be pre-specified.

The duration of follow-up must be sufficient to assure adequate device durability, relevant to the population being studied and comparable to alternative therapies, if available.

Late device failures may occur after the primary endpoint of pre-market studies, necessitating robust post-market surveillance to monitor long-term device performance after regulatory approval.

Primary vs. secondary MR: Since the pathophysiology, prognosis, control groups, and response to therapies for primary vs. secondary MR vary greatly, these 2 conditions should in general be studied in separate investigations.

MVARC Highlights: Investigative and Regulatory Perspectives (iv)

Inclusion and exclusion criteria must be carefully selected to define the population of use.

Determining operative risk is central to defining the population for intended use of a new device as well as selecting the appropriate comparator arm. Current scoring systems such as the STS and EuroSCORE II indices may not by themselves be sufficient to define risk or operability in all patients. Assessment of patient operability (which may define clinical trial eligibility) should be determined by a local multidisciplinary Heart Team.

Use of sham controls (if possible) are desirable and in most cases are ethically justifiable. When a sham control is not feasible, additional efforts should be considered to blind the patient and participants involved in data collection to the extent possible.

MVARC Highlights: Conclusions

- **In contrast to calcific aortic stenosis,** a relatively simple disease with limited etiologies and a straight-forward pathophysiology, MR is a more complicated entity, owing to the greater complexity of the MV structure and the numerous lesions and mechanisms that may lead to its failure.
- **Continuing the analogy,** developing effective therapies (and surgical approaches) for MR, and demonstrating their safety and effectiveness in clinical trials is much more challenging than for aortic stenosis, and requires the intimate collaboration between physician-scientists across numerous disciplines, clinical trialists, statisticians, industry and regulatory authorities.
- **Although each device trial will entail its own nuanced considerations,** adopting MVARC principles as a template for clinical investigation should allow sponsors and investigators to avoid the most common errors that can render interpretation of their findings problematic.