Challenges in Development of Innovative Device

Robert Thatcher

HBD East 2017 Think Tank Meeting
At National Institute of Global Health and Medicine
Tokyo, Japan: December 7, 2017

Disclosure Statement of Financial Interest

I, Robert Thatcher, DO have a financial interest/arrangement or affiliation with 4C Medical Technologies, Inc. that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation

What is EFS?

Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

---

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

The draft of this document was issued on November 10, 2011.

For questions regarding this document, contact CDRH's Andrew Farb, 301-796-6343, Andrew.Farb@fda.hhs.gov or Dorothy Abel, 301-796-6366, Dorothy.Abel@fda.hhs.gov, or CBER's Office of Communication, Outreach and Development at 1-800-835-4709 or 301-827- 1800.

Why EFS?

Allows for early clinical evaluation of device

Proof of principle and initial clinical safety data

Clinical experience is necessary because nonclinical testing methods are not available or adequate to provide the information needed to advance the developmental process

Sooner introduction of the needed treatment to patients

Risk to patients associated with the lack of treatment available may be higher than risk associated with participation in EFS

EFS Can Obtain Initial Insights Into:

In Preparation Of Pivotal Study Design

Assess device-specific aspects of the procedure	• Whether the device can be successfully delivered, implanted or used • the clinical safety of the device (e.g., evaluation of device-related serious adverse events)
Define procedural details/flow/steps	• Operator technique challenges with device use
Define patient selection	• Patient characteristics that may impact device performance (e.g., anatomical limitations)

EFS: Driver of Medical Device Innovation

- FDA recognizes the value of encouraging medical device innovation to address clinical needs and improve patient care, particularly when alternative treatments or assessments are unavailable, ineffective, or associated with substantial risks to patient safety.

- FDA developed guidance to facilitate the early clinical evaluation of medical devices in the United States under the IDE regulations, using risk mitigation strategies that appropriately protect human subjects in EFS.

The First Potential HBD EFS

The treatment of moderate to severe MR in patients who are considered high risk for mortality and morbidity during open-heart surgery.

Estimated Prevalence of Mitral Regurgitation (MR) in Japan (2017)

- Older age is an independent determinant of all forms of valve disease that arise with considerable frequency in elderly people.[1]
- The estimated prevalence of **Moderate/Severe MR** drastically increases with age:
  - **from 0.5% (aged 18 to 44 years) to 9.3% (aged ≥75 years)**[1-2]

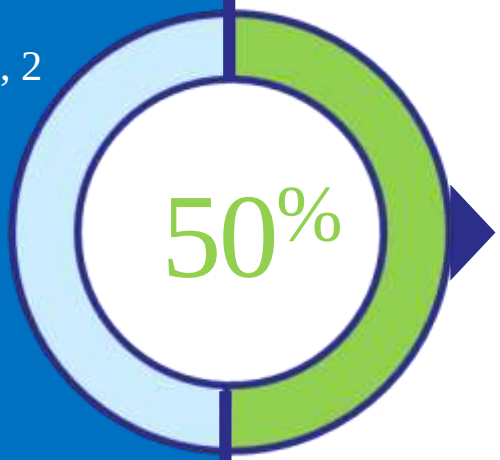
With the projected shift to an older population, the burden of valvular diseases will probably increase substantially in the future.[1]

1. Nkomo et al. *Lancet* 2006; 368: 1005–11.
2. Benjamin et al. *Circulation.* 2017;135:e146–e603
3. *Japan Statistics* Bureau. 2017 http://www.stat.go.jp/english/data/jinsui/tsuki/index.htm

New Treatment Options Needed for MR Patients

>2 MILLION Japanese people suffer from MR[1, 2]

MR affects nearly 1 in 10 Japanese aged 65+[1]

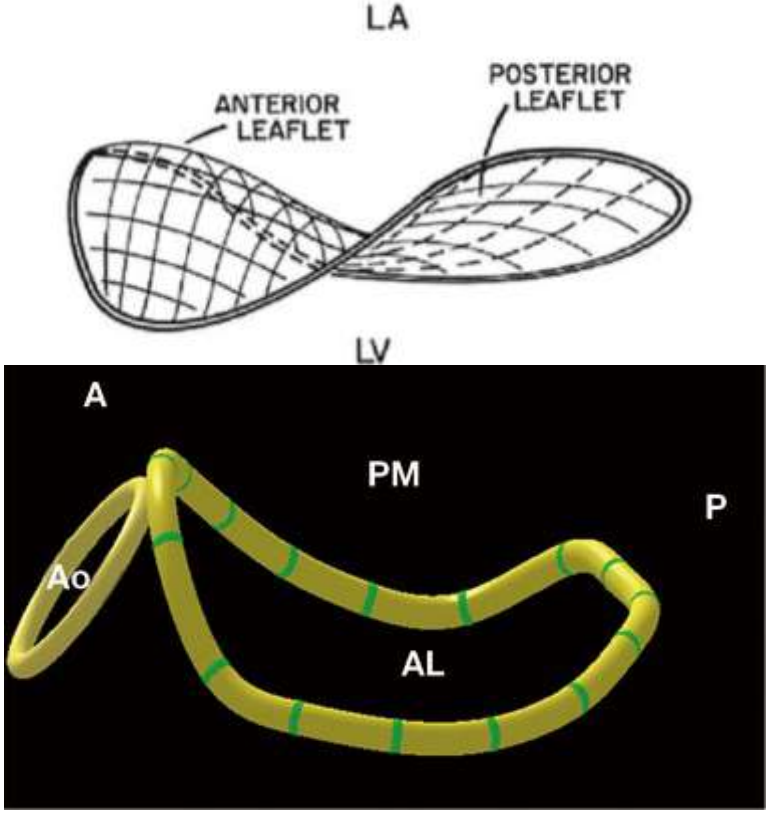


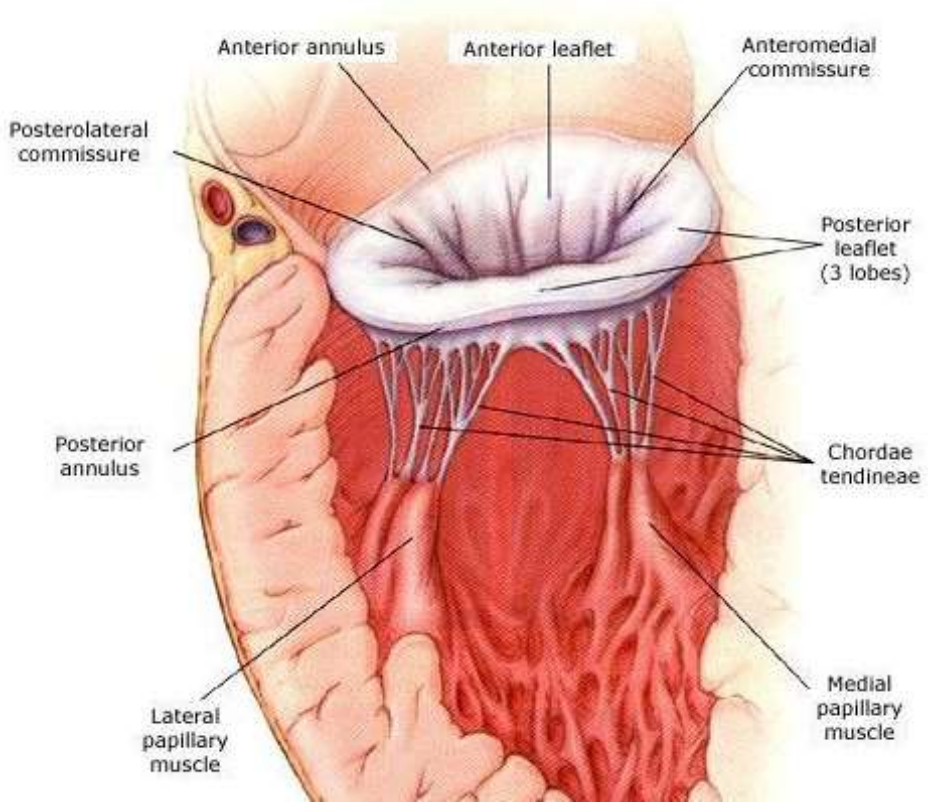
50% of all symptomatic MR patients are **NOT ELIGIBLE** for open-heart surgery due to the procedure risk.[3]

1. Nkomo et al. *Lancet* 2006; 368: 1005–11.
2. Benjamin et al. *Circulation.* 2017;135:e146–e603
3. Mirabel M, et al. *Eur Heart J. 2007;28:1358–1365.*

Dynamic, Irregular and Variable Anatomy of Mitral Valve

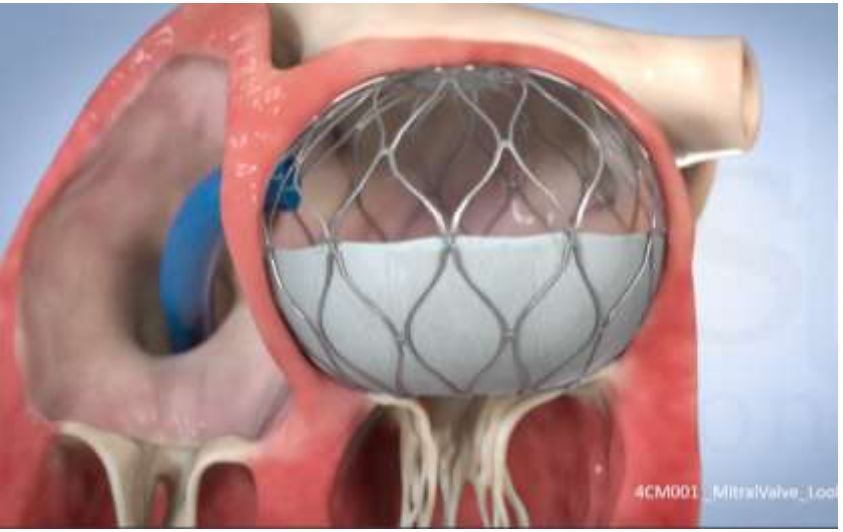
Difficult sizing and anchoring device due to various shapes and sizes of mitral valve annulus



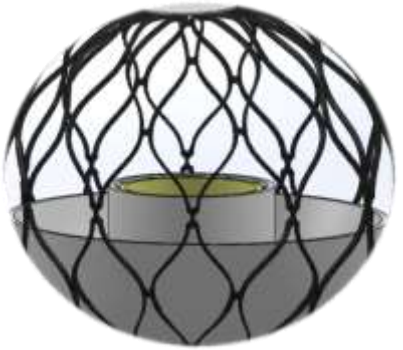


LEFT IMAGE: Levine, et al. Circulation 1989.
RIGHT IMAGE: http://www.heart-valve-surgery.com/heart-surgery-blog/2008/09/02/mitral-valve-annulus-definition-diagrams-prolapse-calcification-treatment/. Accessed 3/13/17.

4C Valve Potential Benefits

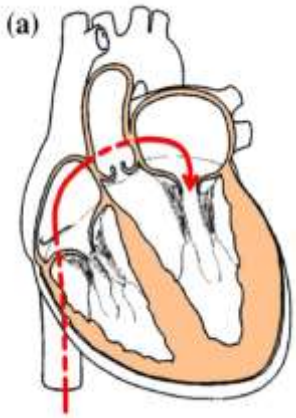


- Supra-annular placement preserves native mitral valve and left ventricle (LV)
  - No risk of LVOT obstruction
  - No sub-valvular mitral valve apparatus interaction
- Expands treatable patient population
  - MR mechanism agnostic
  - Suitable for any anatomy
- Provides transseptal or transapical delivery options
  - Ease of use



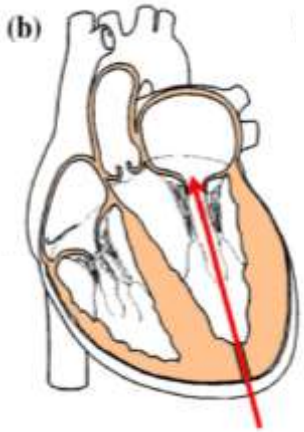
4C Delivery System Flexibility

Supra-annular design does not require fitting in the native annulus & allows transseptal delivery, minimally invasive approach



TRANSSEPTAL

Crossing the septum to gain access to the left atrium

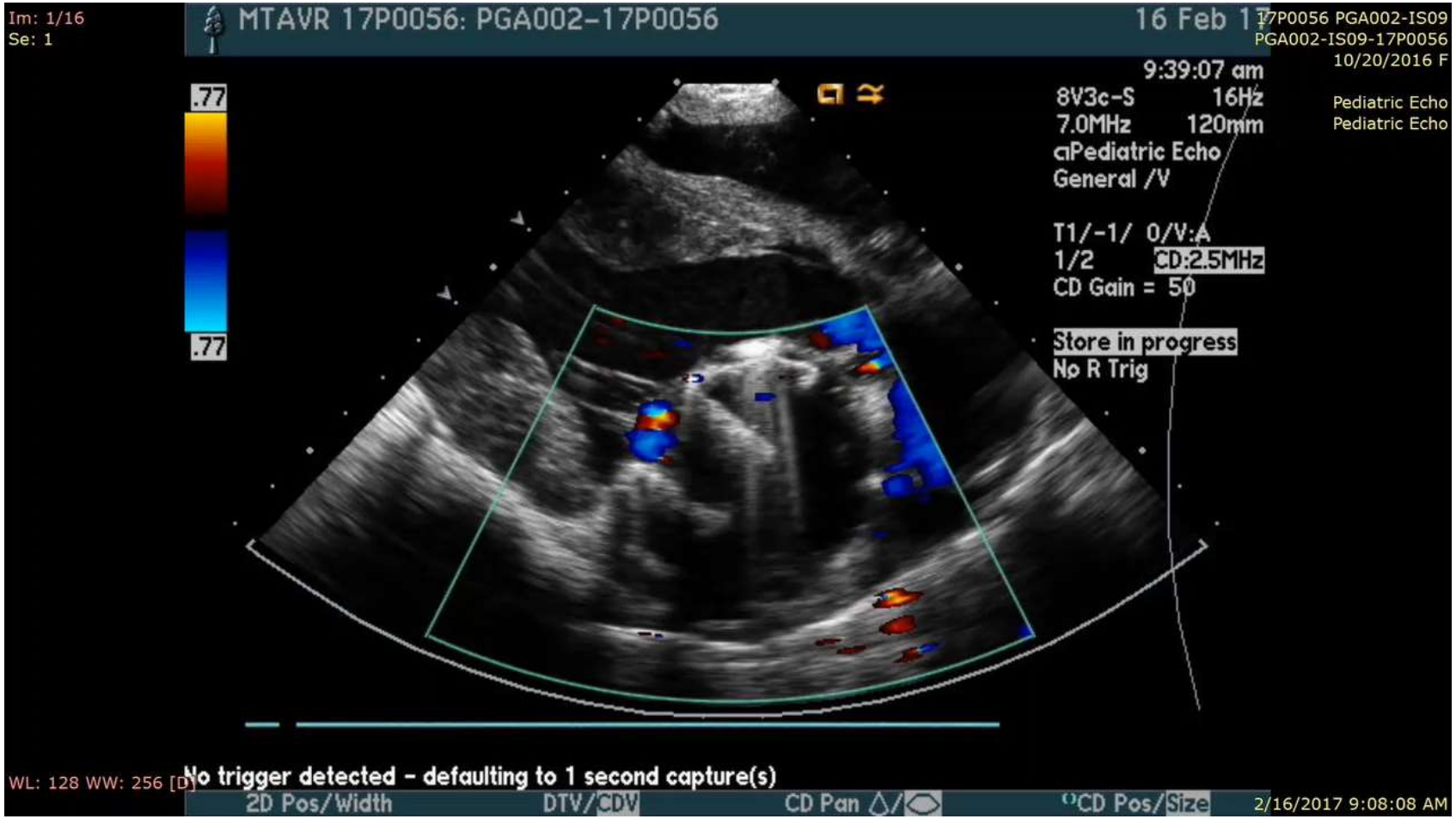


TRANSAPICAL

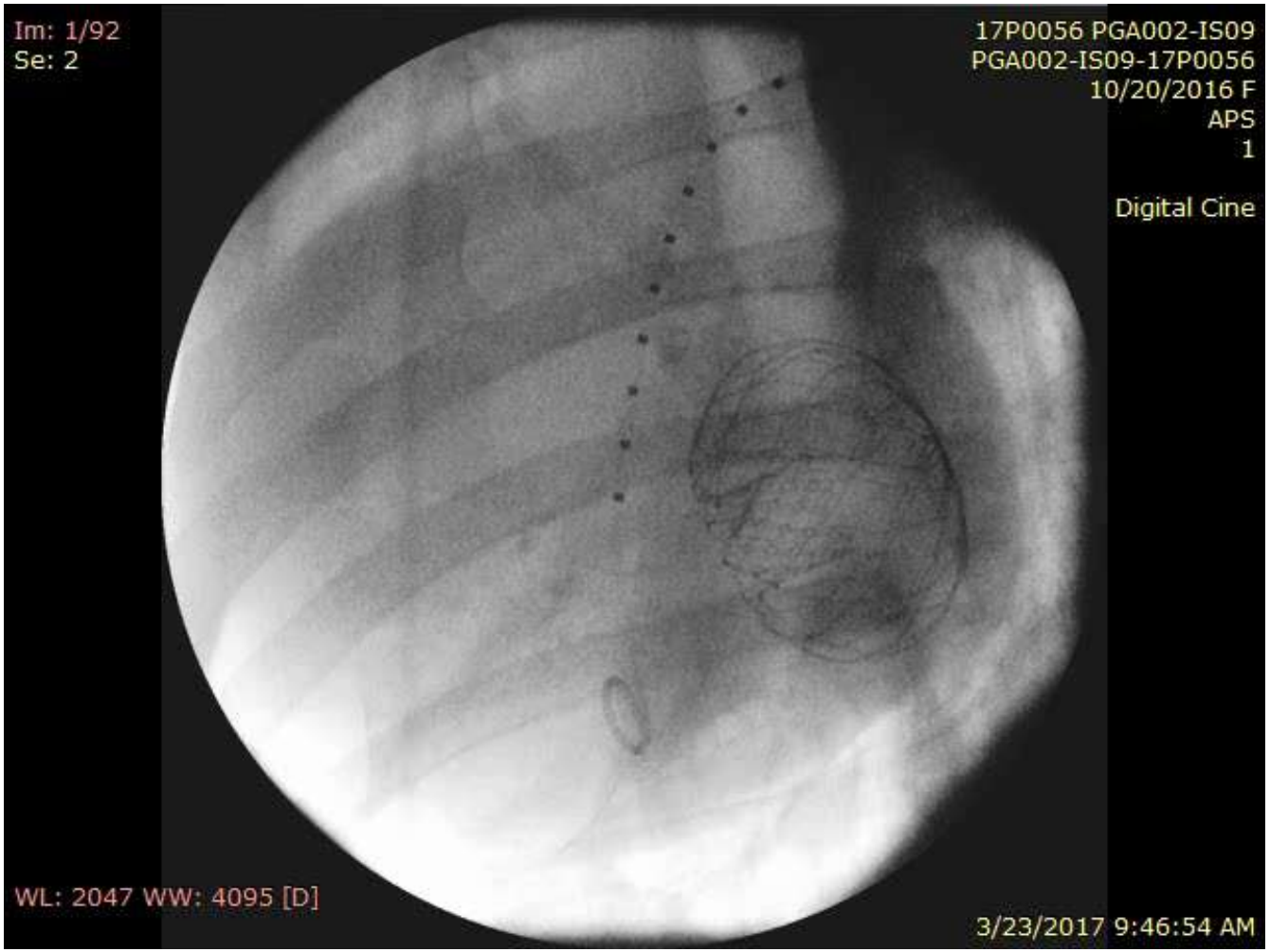
Surgical entry through the chest, left ventricle, and into the left atrium

SOURCE: Preston-Maher, et al. A Technical Review of Minimally Invasive Mitral Valve Replacements. Cardiovascular Engineering and Technology. November 2015.

4C Valve Hemodynamic Assessments: Doppler Assessment



4C Valve Hemodynamic Assessments: LV Gram Assessment



4C Medical EFS Design

- Purpose: to assess safety and performance of the 4C valve for the treatment of moderate to severe MR in patients who are considered high risk for mortality and morbidity during open-heart surgery.

- **Endpoints will include:**
  - Technical success
  - Device success
  - Procedural success
  - Change in MR grade
  - Change in NYHA class

With the help of HBD, the goal is to conduct an EFS study in both Japan & USA

- **Global Enrollment:** 20-30 patients at up to 10 sites
  - Japan and United States
  - Harmonization by Doing (HBD)

Thank You!