EFS BEST PRACTICES WORKSHOP PRESENTATIONS

OMNI HOTEL AT BOSTON SEAPORT
BOSTON, MA
FEBRUARY 1, 2023
MDIC would like to acknowledge the efforts of everyone who participated in the 2023 Rejuvenating the U.S. Electrophysiology Clinical Trial Ecosystem: EP Early Feasibility Studies Best Practices Workshop. Your expertise and substantial contribution are critical to the mission and goals of the EFS program and we thank you for your work!

To all of those that attended, MDIC thanks you for joining us for a collaborative half-day of discussions with stakeholders from across the medical device ecosystem. Your participation and feedback are invaluable to driving our initiative forward.

We look forward to our continued work and collaboration with you all!

Please see the enclosed agenda and slides from the workshop.

Sincerely,
The Medical Device Innovation Consortium
Early Feasibility Studies Best Practices Workshop

1 FEBRUARY, 2023  |  1:00–5:00 PM
BOSTON, MA  |  THE OMNI HOTEL
# Rejuvenating the U.S. Electrophysiology Clinical Trial Ecosystem: EP Early Feasibility Studies Best Practices Workshop

## Program Overview
This workshop is intended to bring together the FDA, CMS, Industry, and clinical site partners to discuss how to implement EFS trials. It will provide a half day of presentations delivered by recognized thought leaders in the medical device ecosystem. The agenda will consist of lectures and engage in high level panel discussions focused on EFS in Electrophysiology.

## Co-Chairs
- Justin Klein, MD, JD  
  Vensana Capital
- Pete Weiss, MD, MSC  
  Banner University of Arizona

## MDIC Board Champion
- Chip Hance

## FDA Early Feasibility Study Program Co-Leader
- Andrew Farb, MD

## MDIC Staff
- Keondae Ervin
- Eileen Mihas

### External Faculty
- **Amin Al-Ahmad, MD**  
  Texas Cardiac Arrhythmia Institute at St. David’s Medical Center
- **Samuel Asivatham, MD**  
  Professor of Medicine, Professor of Pediatrics  
  Mayo Clinic College of Medicine and Science
- **Ken Coffey**  
  CEO, Atria Medical
- **Kate Dalton, MS, RD, CCRC**  
  Director, Cardiology Research, New York-Presbyterian/Columbia University Medical Center
- **David Hazlewood, PhD**  
  Biomedical Engineer, Office of Cardiovascular Devices, FDA
- **Avi Fischer, MD**  
  Senior Vice President, Medical Affairs & Innovation, Orchestra BioMed, Inc.
- **Holger Friedrich, MD**  
  CEO, Aquaheat
- **Lynne Goodreau, RN, MS**  
  Administrative Director, Bluhm Cardiovascular Institute Clinical Trials Unit, Northwestern University
- **Anthony Hong**  
  VP, Preclinical & Clinical Research and Medical Affairs, Biosense Webster
- **Brad Horst**  
  Global Vice President, Clinical Management, Rhythm Management Division at Boston Scientific

### Additional Faculty
- **Jerome Kalifa, MD, PhD**  
  Co-Founder, Volta Medical
- **Aaron Kaplan, MD**  
  Founder & Chief Medical Officer, Conformal Medical  
  & Director, Clinical Research, Heart & Vascular Center Dartmouth-Hitchcock Medical Center
- **Moussa Mansour, MD**  
  Director of the Cardiac Electrophysiology Laboratory and Director of the Atrial Fibrillation Program at Massachusetts General
- **Devi Nair, MD**  
  St. Barnard’s Medical Center
- **Andrea Natale, MD**  
  Executive Medical Director, Texas Cardiac Arrhythmia Institute at St. David’s Medical Center
- **Vivek Reddy, MD**  
  Director of Cardiac Arrhythmia Services, Mount Sinai
- **Kit Schneider**  
  Sr. Director of Clinical and Preclinical, Engineering, FARAPULSE, Inc, Boston Scientific
- **Ken Stein, MD**  
  Senior VP and CMO, Rhythm Management and Global Health Policy, Boston Scientific
- **George Van Hare, MD**  
  Medical Officer, Implantable Electrophysiology Devices Team, Division of Cardiac Electrophysiology, Diagnostics, and Monitoring Devices
- **Jaime Walkowiak, JD**  
  Bram Zuckerman, MD  
  Director, Office of Cardiovascular Devices Center for Devices & Radiological Health (CDRH) at FDA
EFS

Can Banner University of Arizona Medicine Walk the Walk?

SHOW ME, DON'T TELL ME
We are Trying Right Now!

Challenge:

• 3 party agreements: Sponsor, UofA, Banner
• History of 9-12 month start up times
  • Wilber Su – Cryoballoon trial
    • Almost a year
    • Last day before being dropped
    • Ended up #1 Enrollment
Infrastructure

Strong track record of conducting numerous clinical trials of different sizes and complexity, but never EFS

Specialized Cardiac Research Unit (SCRU)

- Cardiology research has a dedicated office space and expanded research team.
- Weekly multidisciplinary meetings discussing a wide scope of research on advanced heart failure, cardiac imaging, cardiology, and cardiac electrophysiology enhance the collaborative efforts of the research team with the clinical investigators.
Progress

Week 1 of study intake (12/20-1/5)
12/23 (Day 4): Completed feasibility approval; 1/3 (Day 5): NLID 78879 with UAHS workflow
1/5 (Day 7): Draft CTA from UAHS and submitted it to Banner legal for assignment, Budget pending update;

Week 2 of study intake (1/6-1/12)
1/6 (Day 8): Budgeting team working on CA; 1/8 (Day 9): UA Contract sent CTA back to sponsor, 1/9 sponsor sent back

Week 3 of study intake (1/13-1/19)
1/13 (Day 13) CA conditional approved; 1/17 (Day 15): CARM approved, not ready to route a UAR for this project,
Not clear how the funding and CMS approval is moving forward for this project.

Week 4 of study intake (1/20-1/26)
1/23 (Day 19) Sponsor on SCRU meeting to discuss, pending feedback

Week 5 of study intake (1/26-2/2)
1/27 (Day 23) followed up with sponsor and pending feedback, Agreed to move forward
### Rejuvenating the U.S. Electrophysiology Clinical Trial Ecosystem: EP Early Feasibility Studies Best Practices Workshop

<table>
<thead>
<tr>
<th>Time</th>
<th>Session/Activity</th>
</tr>
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<tbody>
<tr>
<td>1:00 PM</td>
<td>Welcome  Pete Weiss, MD and Justin Klein, MD, JD</td>
</tr>
<tr>
<td>1:10 PM</td>
<td>History of the Early Feasibility Pathway for Novel Medical Devices  Andrew Farb, MD (FDA)</td>
</tr>
<tr>
<td>1:15 PM</td>
<td>MDIC led Transformation of the Structural Heart Regulatory Pathway: The Return of Early Feasibility Studies to the U.S.  Chip Hancke</td>
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<tr>
<td>1:20 PM</td>
<td>Session I: The Evolving Regulatory Pathways for Novel EP Devices  Ken Stein, MD and Vivek Reddy, MD</td>
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<tr>
<td>1:55 PM</td>
<td>Open Discussion / Q&amp;A  Jaime Walkowiak, JD</td>
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<tr>
<td>2:00 PM</td>
<td>Break  Jaime Walkowiak, JD – “Yes We Can Negotiate Contracts in 60 Days!”  Kate Dalton (Columbia) – “Institutional Alignment in a Teaching Hospital for Early Feasibility Studies”  Lynne Goodreau (NMH) – “10 Successful EFS Studies and Counting at a Leading Clinical Site – It can be Done”  Brad Horst (Boston Scientific) – “Tips and Tricks of Contract Negotiation from a Sponsor’s Point of View”  David Hazlewood, FDA – “FDA Categorization of IDE Applications to Assist CMS Coverage Decisions”</td>
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<tr>
<td>2:45 PM</td>
<td>Session II: EFS and the Bridge to Pivotal – Clinical Site Experience  Anthony Hong and Devi Nair, MD</td>
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<tr>
<td>3:20 PM</td>
<td>Open Discussion / Q&amp;A</td>
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<tr>
<td>3:50 PM</td>
<td>Break  Eileen Mihas</td>
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<tr>
<td>4:05 PM</td>
<td>Session 3: Shortening Time to First Patient In: Timely and Effective Contracting  Jaime Walkowiak, JD</td>
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<tr>
<td>4:35 PM</td>
<td>Open Discussion / Q&amp;A  Eileen Mihas</td>
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<tr>
<td>5:05 PM</td>
<td>Wrap Up and Closing Remarks  Pete Weiss, MD and Justin Klein, MD, JD</td>
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<tr>
<td>5:30 PM</td>
<td>Cocktail Networking Reception  Bram Zuckerman, MD</td>
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<tr>
<td>6:30 PM</td>
<td>Special Dinner Event  Keynote Speaker Bram Zuckerman, MD</td>
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History of the Early Feasibility Study Pathway for Novel Medical Devices

Andrew Farb, MD
Co-Leader of FDA’s Early Feasibility Studies Program
Chief Medical Officer, Office of Cardiovascular Devices
Food and Drug Administration
andrew.farb@fda.hhs.gov
Purposes of Early Feasibility Studies

Early clinical experience
- Provides the basis for iteration & product improvement
- Integral to the device development process
Acknowledging Problems With Medical Device Innovation and Development in the US

• Migration of initial clinical testing of novel devices overseas
• Time lag in the access to beneficial medical devices for US patients
• Delay in physician experience with new products

Many clinical trial ecosystem factors contributed to these trends including FDA’s requirements for non-clinical testing prior to initiating clinical studies of new devices.
Elements that define an EFS:

– Small number of subjects
– Device that may be early in development, typically before the device design has been finalized
– Provides initial insights into device proof of principle and safety
– Does not necessarily involve the first clinical use of a device

Needed when information to advance device development cannot be obtained with additional nonclinical testing or nonclinical tests unavailable
Early Feasibility Studies (EFS) Program Objectives

- Increase early **patient access** to potentially beneficial medical devices in the US
- Expand US site participation in the early clinical evaluation of innovative medical devices
- Enhance collaboration among developers, industry, regulators, and investigators
- Utilize the IDE regulations to protect study participants during the EFS
Key Guidance Principles

• Less nonclinical data may be needed for IDE approval vs. a larger study of a finalized device design
• Use *Just-In-Time Testing* (JITT): Doing the right nonclinical tests at the right time
  – May defer some nonclinical testing until device design finalized for a pivotal study
  – Comprehensive testing in early phases of device development may add cost but provide limited value
• Incorporate *Just-in-Case* measures
  – Greater use of risk mitigation strategies and patient protection measures compared to larger studies

**Increased opportunities for leveraging information and data for EFS**
Learn-as-you-go: Continue EFS with a modified device and/or procedure

Continue EFS with additional patient enrollment
- Bring new sites and investigators onboard
- Gain further clinical experience
- Refine safety and effectiveness event rate estimates for pivotal trial planning

Transition to a pivotal study
CMS

• Medicare coverage can be a critical step for EFS initiation and continuation
• CMS generally will not cover true a first-in-human EFS IDEs
  o Clinical data with positive health outcomes in a small number of initial patients to support proof-of-principle and basic safety needed for a coverage consideration
• Complications in Medicare beneficiaries are covered regardless of whether or not the EFS IDE itself is covered
• Sponsors encouraged to discuss EFS investigational plans with CMS
FDA EFS Review Metrics FY 2021

- Approximately 60 EFS/year since FY17
- >350 EFS IDEs approved, including >3000 study participants

58 EFS IDEs submitted in FY 2021
- 47 (81%) approved
  - 39 of 47 (83%) approved in 1 review cycle
EFS Distribution Across CDRH

- EFS in wide distribution across the CDRH
- In FY21, highest utilization in cardiovascular, neurological, and GI/renal/GU device areas
- US is the go-to location for select EFS device areas:
  - Ophthalmics, ENT, Respiratory & Anesthesia
  - Cardiovascular
  - Gastro, Renal, Urological, Devices
  - Surgical
  - Neurological and Physical Medicine
  - In Vitro Diagnostics and Radiological Health

Office of CV Devices EFS IDEs

- Structural heart: Transcatheter valve repair and replacement
- Aortic endografts
- Heart failure devices

EP Technologies EFS
Building a successful EP EFS ecosystem requires teamwork!
MDIC Led Transformation of the Structural Heart Regulatory Pathway: Return of Early Feasibility Studies to the U.S.

Chip Hance – Industry Veteran and MDIC-EFS Initiative Board Champion
Eileen Mihas – MDIC EFS Program Director

February 2023

MDIC is a 501(c)3 and the first public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit

More than 75 members including FDA and CMS
MDIC is a 501(c)(3) public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit through multiple pre-competitive projects.

MDIC: Who We Are

- 75 participating member organizations
- 800 subject matter experts involved in working groups
- 70+ resources available to download in our digital resource library
- 61 active working groups and committees
Our Core Initiatives and Program Areas

MDIC’s activities advance the medical device regulatory process for patient benefit.

**NEST COORDINATING CENTER (NESTcc)**
- Real-World Evidence for Research Questions
- Fee for Service
- Network Collaborators
- Active Surveillance
- *QUALITY EVIDENCE BY DESIGN*

**CLINICAL DIAGNOSTICS**
- Artificial Intelligence and Machine learning for IVD
- Systemic Harmonization and Interoperability Enhancement
- Cancer Genomic Somatic Reference Sample Initiative
- Open Hand – previously COVID RWE Project

**DIGITAL HEALTH & TECHNOLOGY**
- Digital Health
  - Predetermined Change Control Plan, Excellence Appraisal,
- Cybersecurity
  - Benchmarking, Threat Modeling, Penetration Testing
- Medical Extended Reality (MXR)
  - Terminology, Image Quality, Human Factors, Education
- 5G Enabled Health Technologies

**CLINICAL SCIENCE**
- Early Feasibility Studies
  - Site Pilot Network, EFS Electrophysiology & Neurovascular Initiatives
- Science of Patient Input
  - Patient Preference Early Phase, Post Market, Accessibility
Need for Collective Stakeholder Efforts for Improvement

2016

Overcoming the Challenges of Conducting Early Feasibility Studies of Medical Devices in the United States

David R. Holman, Jr, MD; Robert Califf, MD; Andrew Farb, MD; Dorothy Abel, BSMBB; Michael Mack, MD; Tamara Syrek Jensen, JD; Brian Zuckermandl, MD; Martin Leon, MD; Jeff Shuren, MPP

Abstract

Initial clinical studies of new medical technologies involve a complex balance of research participant benefits versus risks and costs of uncertainty when novel concepts are tested. The Food and Drug Administration Center for Devices and Radiological Health has recently introduced the Early Feasibility Study (EFS) Program for facilitating the conduct of these studies under the Investigational Device Exemption regulations. However, a systematic approach is needed to successfully implement this program while affording appropriate preservation of the rights and interests of patients. For this to succeed, a holistic reform of the clinical studies ecosystem for performing early-stage clinical research in the United States is necessary. The authors review the current landscape of the U.S. EFS and make recommendations for developing an efficient EFS process to meet the goal of improving access to early-stage, potentially beneficial medical devices in the United States. (J Am Coll Cardiol 2016;68:1908-15) © 2016 by the American College of Cardiology Foundation. All rights reserved.

Executive Committee

Aaron Kaplan/Chip Hance (Co-Chairs)
David Holmes (Chair Emeritus)

FDA
- Andrew Farb
- Bram Zuckerman
- Jeff Shuren

CMS
- Tamara Syrek-Jensen

MDIC
- Chip Hance
- Eileen Mihas

CLINICAL SITES

Karen Alexander
Dan Burkoff
Aaron V. Kaplan
Martin Leon
Michael Mack
Jaime Walkowiak

We Work Together Under the MDIC Construct
While FDA Processes Were Timely, Other Issues Arose

MDIC Baseline Sponsor Metrics (FY14-17)

Target for a U.S. Study:
120 Days to Begin Enrollment
• After IDE Approval
• IRB/Contracting running in parallel

“60/60/60” Site/Sponsor Goal
• 60 Days for IRB Approval
• 60 Days for Contract Execution
• 60 Days for First Patient Enrollment

Baseline metrics collected by MDIC from EFS trials conducted FY14 – FY17, compiled from 13 EFS trials and 48 sites
While FDA Processes Are Now Timely, Other Issues Have Arisen

MDIC Baseline Sponsor Metrics (FY14-17)

**2017 Average Time From Site Packet Received to 1st Patient Enrolled = 320 Days!**

‡Baseline metrics collected by MDIC from EFS trials conducted FY14 – FY17, compiled from 13 EFS trials and 48 sites
A Look Toward Tentative EFS Program Workshop & Events in 2023:
- Session at Heart Rhythm Society (HRS) 2023 Meeting
- Session at 20th Annual SNIS Meeting 2023
- 3D Dartmouth Device Development Symposium
- MDIC Hosted EFS Best Practices Workshop

Previous Workshops & Sessions:
- 2022: SNIS 19th Annual Meeting: Breakout Session
- 2022: HRS Roundtable & Stanford Biodesign Meeting
- 2020: EFS Budgeting Workshop
- 2019: EFS Best Practices Workshop, TVT, TCT
- 2019 & 2017: EFS Metrics Reports

Publications:

Host an EFS Best Practices Workshop in Conjunction with the 28th Annual Atrial Fibrillation Symposium

Revision of the MCTA & ICF Templates by the Neurovascular Working Groups

Convening of the Electrophysiology and Neurovascular Therapeutic Areas as EFS Steering Committees

Creation of the EFS Master Clinical Trial Agreement (MCTA) Template

Hosted Sponsor and Site Best Practices Workshop

Creation of EFS Informed Consent Form (ICF) Template

Patient Introduction to Consent for EFS

EFS Background Information: IRBs and Site Study Staff

Creation of the Contract Language Library Negotiation Tool

MDIC 2016 Blueprint for Early Feasibility Study Success

https://mdic.org/program/early-feasibility-studies-efs/
EFS Studies Have Been Challenging to Execute But Ecosystem Has Improved

![Diagram showing mean time (days) for IDE Approval, IRB Approval, Contract Approval, and 1st Subject Enrollment with comparison for FY14-FY17 and FY18-FY19.]

Source: MDIC Annual Public Forum presentation by Liliana Rincon-Gonzalez, September 2019. FY18-19 data from an additional 19 EFS trials across 60 Sites
Fast Forward…
Many Innovative Cardiovascular Therapies Now Begin Clinical Experience with U.S. EFS

- Earlier access to new medical devices for US patients and investigators
- Geographic proximity of manufacturers to clinical trial sites facilitates interaction
- No language issues
- Familiarizes US regulators with the device earlier
- Familiarizes clinical sites with device/procedure before pivotal trials
Emerging Global Clinical Strategies

Traditional Approach

First-in-Man (FIM)
(Eastern Europe/Aust-NZ/South America)

Feasibility Study
(in Europe; Optional)

CE Mark Study
(Europe)

Pivotal Study
(U.S.)
Emerging Global Clinical Strategies

Emerging Approach

First-in-Man (FIM)
(Eastern Europe/Aust-NZ/South America)

Feasibility Study
(EFS in U.S.)

Pivotal Study
(U.S./Europe)

File CE Mark with Global Pivotal Data
Changing Global Environment for Conducting Early Stage MedTech Clinical Research

- MDR and new EU regulations have made studies in Europe more challenging to conduct.
- Conversely, FDA has created a dedicated pathway for early clinical research (EFS).
- Aspects of conducting U.S. EFS have become streamlined (e.g. IRB reviews, contracting, etc.).
- For some therapies, site procedural volumes can be higher in U.S. centers than other parts of the world.
- Largest MedTech market in the world remains the U.S.
Interested in working with us?

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Session I: The Evolving Regulatory Pathways for Novel EP Devices

Session Leader:
Vivek Reddy, MD
MDIC: Early Feasibility Studies: Best Practices Workshop

Trends in Electrophysiology Studies and the Need for an Effective Clinical Trial Ecosystem

Vivek Y. Reddy, MD
Helmsley Trust Professor of Medicine
Director, Cardiac Arrhythmia Service
The Mount Sinai Hospital

vivek.reddy@mountsinai.org
Disclosures

- **Consultant and/or Grant Support:**

  * I have an equity stake / stock options in these companies

- **I will be discussing investigational devices without FDA or CE-Mark approval.**
Clinical Advances in AF Management
Increasing Role for Rhythm Control

1. Rhythm Control of AF
   - **Past**: To control symptoms (& Tachycardiomyopathy)
   - **Now**: To improve clinical outcomes

2. New/emerging data:
   - **EAST-AFNET4**:
     - Asymptomatic AF should be treated to achieve rhythm control
   - Rhythm control in AF+HF<sub>R</sub>EF
   - AF Disease Progression
   - Stroke and Dementia
   - First-line ablation trials
1. Clinical Data with PFA is quite robust / favorable
   ➢ (Pentaspline PFA cases in Europe >10,000 cases)
   ➢ Speed / Workflow
   ➢ Safety:
     ✓ AE Fistula, PV Stenosis & Steam Pops
     ✓ Phrenic Nerve injury, Stroke/TIA
     ✓ (“Novel” issues: Coronary spasm, )
   ➢ Efficacy

2. Little doubt that PFA will improve outcomes
Pulsed Field Ablation

Regulatory Needs are Increasing

1. PFA is the most obscure of all black boxes
   - Most waveforms are proprietary
   - And even if not...
   - Raises the importance of empiric data

2. Expect a Lot of Innovation
   - Currently 1st generation PFA devices
   - Important to optimize approval pathways

3. Pentaspline PFA catheter approval
   - CE Mark approval in early 2021
   - US approval in early 2024

- 250,000 AF cases/year in US
- AE Fistula: 0.1%
- Severe PV Stenosis: 0.5%
Pulsed Field Ablation

What can be done?

1. Goal: Should be to get trials going
2. Consider parallel paths during clinical trial pathway
   ➢ Leverage OUS data
   ➢ Allow preclinical data to be acquired in parallel
3. But there are “Watch Outs”
   ➢ Lesion durability (no crutches like with thermal ablation)
   ➢ Remap studies vs clinical remap data
   ➢ Unusual complications (eg, coronary spasm)...but keep perspective
   ➢ Solution: Post-market registries (appropriate goals)
Beyond AF Ablation

There is a Lot Happening!

1. VT Ablation
   - 2022 saw 3 new clinical trials
   - Desperate need to VT ablation tools
   - Make VT Trials easy to perform!!
   - (PFA may play an outsized role in VT ablation)

2. LAA Closure Device Optimizations
   - Less peri-device leak
   - Enhancing device endothelialization
MDIC Early Feasibility Workshop

FARAPULSE Clinical and Regulatory Journey
Lots of Problems to Solve

Efficacy → Ground Up Therapy Development

IT ALL HAS TO WORK!

Safety → Esophagus, etc.

Regulatory Compliance → IEC, etc.

Ease of Use → Fast, Familiar

System Robustness
The Virtuous Development Cycle

Bench and Computational

Clinical

Preclinical

Meanwhile You Are Spending a Lot of Money!
The FARAPULSE Journey

- Epicardial FIH (2016)
- Endocardial FIH (2017)
- Epicardial EU Feasibility (2018)
- Endocardial Feasibility (2019)
- Endocardial Focal FIH (2020)
- ADVENT Pivotal IDE (2021)
- EU Pilot
- CE Mark
- Farapoint FIH
PFA History: Durable Lesions

Detailed remapping studies conducted to optimize the waveform for proven durable PVI.

All Achieved 100% Acute PVI

- **Light:** per PV
- **Dark:** per Pt

---

- **Monophasic**
  - (11 pts)
  - 45% durable remapped

- **Early / Other Biphasic**
  - (55 pts)
  - 84% durable remapped

- **PFA\textsubscript{OW}**
  - (44 pts)
  - 96% durable remapped

---

- **110 pts** remapped
- **44 pts** treated with optimized dose
- **96% durable** PVI at 3 months
- **AVG 89±29 days**


CAUTION: Devices shown in this presentation have CE Mark for sale in European and other applicable geographies only. All Products limited by Federal (or United States) Law to investigational use in the United States.
Clinical - Regulatory Considerations

High-Quality Operators and Data

EFS or OUS???

High-Volume Centers to Support Rapid Iteration

Predictable Regulatory Timelines and Expectations

AN ELECTROPHYSIOLOGY START-UP’S PERSPECTIVE ON THE CLINICAL PATHWAY

Ken Coffey, CEO

www.atrianmedical.com
ATRIAN MEDICAL SUMMARY

Novel Afib Treatment

**CLINICAL STAGE COMPANY**

- Company based in Ireland
- 36 Patients treated (Open Chest)
- 24 safety, feasibility
- 12 efficacy
- Moving towards minimally Invasive

**UNIQUE SOLUTION**

- Pulsed Field Ablation
- Targeting autonomic nervous system
- Treating outside of the heart
- Mayo Clinic-origin

**FINANCE**

- Funding 2019
- $6M Funding
Why is it New?

**TARGETS AUTONOMICS**
- Targets autonomic nerves outside the heart
- Non-injury of healthy tissues

**PULSED FIELD ABLATION (PFA)**
- First PFA on the exterior of the heart
- Selectively disables originating nerves permanently
- Spares healthy heart muscle

**EXISTING SOLUTIONS**
- Intentionally injures (burn/freeze) healthy tissue-creating scar tissue
- Attempt to block pathways
- Signals remain and may eventually cause recurrence of arrhythmia

**MINIMALLY INVASIVE**
- Small needle access in the chest
- Can also treat patients with AF undergoing surgery
- Allows direct access to autonomic origin of AF
ATRIAN

PFA System

SYSTEM

- PFA Generator
- ECG Synch
- Catheters
- Infusion Pump

APPROACHES

- PFA-Open Chest
- PFA-Sub-Xiphoid
Clinical FIH Trials

- EU + oEU
- oEU
- Early Feasibility US

- FIH 24 Patients S&F
- FIH +12 Patients Efficacy
- Sub-Xiphoid Approach

Completed
Desirable
Critical Factors- AtriAN

1. Burn Rate “Runway”
2. Ethics / Regulatory Timelines
3. Contract agreement timeline
4. Enrollment of Patients
5. CRO
6. Expertise / Cohesiveness of team
Site Experience Critical

- Logistics of EP system equipment in cardiac surgery lab
- Use of a CRO that is familiar with the site and technology- especially non English speaking countries.
- Investigators that have expertise within the field-a good technical ability and intuition on how the device operates.
- Site understands that the technology may iterate over time and is not the final form.
- Scheduling Patients
EFS for AtriAN

+ Provide FDA Opportunity to understand early
  - Ease transition to future studies beyond EFS
  - FDA World’s Gold Standard
+ Direct engagement with US Physicians
  - Specialized Centers

- Travel Costs for a EU company
- Review time and potential delays with new technology
- Contract agreement timeline
- Need to understand potential unforeseen costs for extended stay of patients
FDA Perspectives on Clinical Electrophysiology Studies

George Van Hare, MD
Medical Officer
Office of Cardiovascular Devices
Center for Devices and Radiological Health, FDA

Early Feasibility Studies Best Practices Workshop
1 February, 2023 | 1:00–5:00 PM
Boston, MA | The Omni Hotel
How a new device moves through FDA’s EFS Regulatory Pathway

• Q-submission program
• Breakthrough Device Designation
• Investigational Device Exemption (IDE) for EFS
• Medical Device Development Tools
• Transition to pivotal trial
Q-submission program

• Voluntary method for getting feedback from FDA prior to formal submission
• Informational meeting:
  – Allows FDA staff to get a head start on understanding the device
• Presubmission: prior to submitting marketing application
• Request for Breakthrough Device Designation (optional)
• Sponsor provides specific questions
• FDA responds in writing
  – 510(k) vs De novo vs PMA
  – Plans for non-clinical and clinical testing
• Option for face-to-face discussion (Zoom)
Breakthrough Device Program

• **Breakthrough Device Designation** may be granted for devices that provide more effective treatment or diagnosis of life-threatening or irreversibly debilitating human disease or conditions, as compared with currently available alternatives
  – e.g. AF, HF, VT

• Sprint discussions with FDA:
  – timely resolution of potentially novel issues (~45 days)
  – Single topic, specific goals
  – Highly interactive

• Start-up companies seem to see value in the designation

• Many EFS devices can qualify

https://www.fda.gov/medical-devices/how-study-and-market-your-device/breakthrough-devices-program
• Sponsor presents evidence that provides both a reasonable expectation that the device could function as intended (technical success) and that a functioning device could more effectively treat or diagnose the identified disease or condition (clinical success)
• Evidence can come from multiple sources
• Allows for expanded use of intermediate or surrogate endpoints to support device approval when appropriate & evidenced-based
• Doesn’t change the requirements for final approval
Investigational Device Exemption (IDE) for EFS

• IDE required for a clinical study of a significant risk investigational device or a clinical study of a new use of an approved significant risk device
  – e.g. a change to a commercially available pacemaker

• EFS devices will require an IDE
  – Anticipation that early clinical experience may lead to device or procedure changes
  – additional nonclinical testing would not provide the information needed to advance the developmental process
  – IDE approval may be based on less nonclinical data than would be expected for a traditional feasibility or a pivotal study
Investigational Device Exemption for EFS

• IDE review provides scrutiny and advice from engineers, clinicians, statisticians, human factors reviewers
  – thorough risk analysis
  – sufficient risk mitigation strategies
  – adequate human subject protection measures
  – appropriate clinical study protocol
  – consent procedures and forms

• Goals:
  – Patient safety
  – Proof of principle
  – Data gathered will support transition to pivotal trial
Medical Device Development Tools (MDDT)

• FDA-qualified tools that medical device sponsors can use in the development and evaluation of medical devices
• Can improve predictability and efficiency in device development and regulatory review.
• Examples applicable to EP:
  – Minnesota Living with Heart Failure Questionnaire (MLHFAQ)
  – Kansas City Cardiomyopathy Questionnaire (KCCQ)
  – MRI safety evaluations
Transition from EFS to feasibility or pivotal trial

• Device is near-final or final
• Results support initial safety and proof of principle
• Request transition via IDE supplement under the same IDE number as the EFS
  – Revisions to clinical investigation plan
• Criteria:
  – Availability of nonclinical and clinical data to justify larger study
  – Based on sound nonclinical assessments and appropriate risk-based rationales
EFS Best Practices Workshop

Early feasibility clinical evidence: using the US-EU regulatory paradigms to advance innovative technologies: The Volta Medical experience

Wednesday February 1st 2023
Jerome Kalifa, MD; PhD
Introducing Volta Medical

Transforming EP Data Into AI Solutions

70+ employees- France-USA
The Volta Medical Data Collection & Enrichment Process

A framework for bringing AI solutions to electrophysiology

1. It all Starts with a Data Inspired Hypothesis
   to Improve Complex Arrhythmia Outcomes.

2. We Collect Physician Directed Real Time EP Data.
   Data Capture from Real-Time Events
   Patient Epidemiological Data
   Acute and Long-Term Outcomes
   Peri-Procedural Data

3. We Curate the Vast Data Lake.
   Organize & Interpret Sufficient Data Quantity to Ensure Reliable Outcome.

4. We Train.
   Our Enriched Data Transforms into Machine Learning Algorithms.

VX1 by VOLTA
AI Decision Support System
Multipolar Intracardiac Signals during Persistent AF
**Multipolar Electrogram Dispersion**

**Dispersion** areas are defined as clusters of electrograms presenting with various features.

At each bipole in a dispersion area, **1 or more of the following fractionated or nonfractionated electrogram morphologies** were found:

- Continuous, low voltage fractionated electrograms ("continuously fractionated signal").
- Bursts of fractionated electrograms ("trains of fractionation").
- Fast nonfractionated electrograms (AFCL <120 ms ("rapid fires").
- Slow nonfractionated electrograms (AFCL >120 ms)
VX1: Volta’s Solution for AF Ablation

Digital AI companion that easily integrates into the standard workflow while providing a patient-tailored approach

Compatibility with most mapping catheters, EP recording, and 3D navigation systems

VX1 guides real-time decision-making with machine and deep learning algorithms designed to evaluate drivers responsible for the arrhythmia

Supports a tailored and intuitive workflow using the physician's preferred mapping system

Matches the expert analysis of physician techniques targeting dispersed EGMs
Simple User Interface for Real-Time Regions of Interest Identification
VX1 is an AI companion technology designed to simplify complex AF and AT procedures.

Fast learning curve with intuitive workflow using the physician’s preferred mapping system and catheter.

Evaluates the substrate during extra-PV atrial fibrillation mapping, indicating regions of interest.
## Continuing to Build Clinical Evidence for Volta VX1

<table>
<thead>
<tr>
<th>Study Type</th>
<th>IDE- OUS+US</th>
<th>Post-market OUS+US</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ONGOING</td>
<td>STARTING SOON</td>
</tr>
<tr>
<td><strong>The Tailored-AF Trial</strong></td>
<td>Multicentric RCT Model</td>
<td>Multicentric Prospective Study</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>377</td>
<td>92</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>Establish Volta as a Standard-of-Care</td>
<td>Establish the efficacy and clinical outcomes of the technology in real world situation across multiple centers</td>
</tr>
<tr>
<td></td>
<td>for persistent and long-standing persistent AF patients.</td>
<td>for AF patients undergoing multiple ablations</td>
</tr>
</tbody>
</table>

### IDE- OUS+US
- **RESTART Trial**
  - Multicentric Prospective Study
  - **Patients**: 92
  - **Objective**: Set the stage for VX1 to be used as a treatment-of-reference for AF patients undergoing multiple ablations

### Post-market OUS+US
- **Clinical Registry**
  - Multicentric Prospective Study
  - **Patients**: 500
  - **Objective**: Establish the efficacy and clinical outcomes of the technology in real world situation across multiple centers

### Total Patients
- **TOTAL**: 962+ Patients
Regulatory Pathway

OBJECTIVE

Ensure performance improvement while building clinical evidence

VX1, VX1+, VX2

VX1 510k-2020  VX1+ 510k-2023  VX2 510k-2024

Large Scale Clinical Validation  Clinical Validation  Clinical Validation

De Novo- 2024

EFS? Predetermined Change Protocol?
- Transforms EP Data Into AI Solutions
- Data Collection & Enrichment Process
- VX1 is a human experience-based algorithmic software solution
- Real-time mapping of regions of interest during persistent AF
- Outcome standardization of VX1-based ablation
- Multiple data-inspired products in the pipeline
How can the EFS program be adapted to companies developing iterative/continuous-learning software solutions, and facilitate the validation of updates?

Could the EFS be used to evaluate software/device modifications prior to submission of a 510k, De Novo, PMA?

Could the EFS be used to validate a Predetermined Change Control Plan (PCCP)/Algorithm Change Protocol?

Can automation be introduced to establish quality/efficacy of incremental steps in algorithm development?
Thank You
CAUTION: Federal (United States) law restricts this device to sale by or on the order of a physician. See User Manual/Instructions for Use for full prescribing information, including indications, contraindications, warnings, precautions and adverse events.

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**VX1 indication for use:**
The VX1 assists operators in the real-time manual annotation of 3D anatomical and electrical maps of human atria for the presence of multipolar intra-cardiac atrial electrograms exhibiting spatiotemporal dispersion during atrial fibrillation or atrial tachycardia. The clinical significance of utilizing the VX1 software to help identify areas with intra-cardiac atrial electrograms exhibiting spatiotemporal dispersion for catheter ablation of atrial arrhythmias, such as atrial fibrillation, has not been established by clinical investigations.
Session II: EFS and the Bridge to Pivotal – Clinical Site Experience

Session Leaders:
Anthony Hong and Devi G. Nair, MD, FACC, FHRS
Conducting Early EP Clinical Research in the U.S.: A Clinical Site Success Story – Site Learnings

Dr. Devi G Nair, MD, FACC, FHRS
Director of Cardiac Electrophysiology & Research
St. Bernards Medical Center
White River Medical Center
Arrhythmia Research Group
Jonesboro, AR

@drdevignair
DISCLOSURES

Abbott Medical: Consultant, Advisory Board, Research Grants

Boston Scientific Corporation: Consultant, Advisory Board, Research Grants

Medtronic Inc.: Consultant, Advisory Board, Research Grants

Biosense Webster: Consultant, Advisory Board, Research Grants

Adagio: Consultant, Research Grants
Arrhythmia Research Group

• Founded in 2018 as solution to create a Quality EP program in North-East Arkansas to maintain site specific and program specific Quality Metrics.

One EP Investigator and One Coordinator

Vision: To empower patients with choices, access to quality care, and control over their health by transforming cardiac care through science and research.

Mission: Our mission is to be the leading independent research organization to daily impact heart care by introducing quality clinical trials in our community, through a commitment to our core values and leading principles.
Arrhythmia Research Group

- Local Registry for AF ablation / CRT / CHF Readmissions
- Investigator initiated Clinical Trials
- Industry sponsored Clinical Registries
- Industry sponsored IDE Trials
Arrhythmia Research Group in 2020

- 35 Projects Completed
- 10 IDE Clinical Trials – Industry Sponsored
- Multiple Industry Audits
- FDA Audits for IDE Trials with no findings

Are we Ready for the next step?
Early Feasibility Studies - Structural Heart
Dramatic Shift from Europe to US

- 2010
  - Europe
  - USA
  - Australia

- 2020
  - USA
  - Europe
  - Australia
Arrhythmia Research Group

- Local Registry for AF ablation / CRT / CHF Readmissions
- Investigator initiated Clinical Trials
- Industry sponsored Clinical Registries
- Industry sponsored IDE Trials
- Early Feasibility Studies
Conformal CLAAS Device

Compliant endoskeleton conforms

ePTFE cover less thrombogenic

Flexible tether eliminates cable attachment site
Conformal EFS 10 Sites

- Choo / Christ Hospital
- Coylewright / Erlanger
- Doshi / Pac Heart
- Ellis / Vanderbilt
- Gray / Main Line Health
- Kim / Catholic Med Ctr
- Nair / St Bernards
- Reddy / Mt Sinai
- Sommer / Columbia
- Szerlip / Baylor

Great Diversity
Introduction to a partner looking at EFS Study

COVID Didn’t Help
ARG put initiation of all clinical trials on hold for Resource Re-utilization and caring for our patients who were already in clinical Trials

Budget – New Process but still in respectable time
Conformal EFS-1: Site Experience

<table>
<thead>
<tr>
<th></th>
<th>Fastest Site</th>
<th>Slowest Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Final Budget (Days)</td>
<td>26</td>
<td>301</td>
</tr>
<tr>
<td>Number of Rounds</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Observations</td>
<td>Responsive</td>
<td>Unresponsive</td>
</tr>
<tr>
<td>Contacts</td>
<td>Single Contact</td>
<td>Multiple</td>
</tr>
</tbody>
</table>
95 days to IRB Approval

4 IRB meetings
1. Presentation of trial
2. Why EFS Study
3. Feasibility / Concerns of doing EFS at our site
4. Final Q&A

What could we have done better?
What will we do better Next time?

Utilize resources from MDIC to educate local IRB to navigate the Qualms and Concerns regarding EFS
MDIC Early Feasibility Studies Content

2020: Sponsor and Site Budgeting Best Practices Workshop Findings
2019: EFS Master Clinical Trial Agreement (MCTA) Template
2019: Sponsor and Site Best Practices Workshop Findings
2018: EFS Informed Consent Form (ICF) Template
2018: Patient Introduction to Consent for EFS
2018: EFS Background Information: IRBs and Site Study Staff
2017: Contract Language Library & Negotiation Tool
2016: MDIC 2016 Blueprint for Early Feasibility Study Success

https://mdic.org/program/early-feasibility-studies-efs/
Despite Delta Variant and scheduling issues, despite

IRB Approval

29 days to SIV
149 days to first patient in

- Challenge with product Delivery
- Patient Consent Process
- Scheduling Coordination for first cases
130 days from first patient in - to study completion

10 Total patients enrolled

<table>
<thead>
<tr>
<th></th>
<th>Combined</th>
<th>EFS-1&lt;sup&gt;1&lt;/sup&gt;</th>
<th>EFS-2&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Prague&lt;sup&gt;2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enrolled</td>
<td>84</td>
<td>22</td>
<td>43</td>
<td>19</td>
</tr>
<tr>
<td>Implanted</td>
<td>79</td>
<td>18</td>
<td>42</td>
<td>19</td>
</tr>
</tbody>
</table>
CONFORM Pivotal Trial
IDE Approved: 1st Patient in Q2 2022

Design | Prospective, Randomized Controlled
--- | ---
Randomization | 1:1 (n=1,600)
Location | US and Canada
CHA2DS2-VASc score ≥ 3 or CHADS2 score ≥2
1° Efficacy | Stroke and Systemic Embolism (18 mos)
1° Safety | Procedural-Related complications, all cause death & major bleeding (12 mos)
Study PI’s | S Doshi, MD Pacific Heart
W Gray, MD Main Line Health
Study Oversight | A Lansky, MD Yale-HVC Research
L Sugeng, MD Yale/Northwell
Sponsor | Conformal Medical

Procedure - DAPT
45D TEE-DAPT
6M DAPT to ASA
12M TEE RX UC
18M F/U
Phone F/U
2, 3, 4, 5 years

Procedure - OAC/DAPT
45D TEE-DAPT
6M DAPT to ASA
12M TEE RX UC
18M F/U
Phone F/U
2, 3, 4, 5 years
Conformal EFS Experience: Elements for Success

• Principle Investigator:
  Engaged Leader of an Established Program

• Site Research Team:
  Well infra-structured
  Deep ‘C-Suite Support’ (Particularly important for EFS)

• Clinical Program:
  Well established moderate/high volume with unified leadership
Future for Arrhythmia Research Group and EFS

• Work in Collaboration with MDIC to help create workflows that will help sites participate and complete EFS studies successfully

• Share best practices between successful EFS sites and optimize workflows locally to optimize access to EFS to our patients
Thank You

Dr. Devi G Nair, MD, FACC, FHRS
@drdevignair
9177748369
drdevignair@gmail.com
Ambitions and Challenges in Conducting Early Research in the U.S

Moussa Mansour, MD
Director, Atrial Fibrillation Program
Jeremy Ruskin and Dan Starks Endowed Chair in Cardiology
Professor of Medicine, Harvard Medical School

February 2, 2023

Disclosures:
Consultant: Biosense-Webster, Abbott, Medtronic, Boston Scientific, Siemens, Philips.
Equity: NewPace Ltd
FIH Studies Outside US

- AFFERA SPHERE 9 and SPHERE PVI

- CryoCath
FIH Outside the US

- SMART TOUCH force sensing
- nMARQ
- Helios RF balloon
- QDOT focal ablation catheter
- VARIPULSE
• FARAPULSE: EU

• Polar X: EU

• WATCHMAN 2.5
– TACTICATH

– Amulet
FIH Rarely in the US

- PULSE SELECT

- WATCHMAN FLX
• More FIH device studies for AF treatment in the US
Mass General Hospital Process for FIH Studies

• IRB
  • FIH allowed
  • Follows the same protocol as non FIH
  • Follows FDA regulations
  • No significant additional scrutiny
    – Possibly a few more questions from the IRB panel

– FIH cancer medications are routinely investigated at MGH
– Contract, legal:
  • Follows the same protocol as non FIH
MGH AF Program Research Team

- Project Manager
- Research nurse
- 3 research coordinators
- Statistical analysis expert readily available via Harvard Catalyst
- Easy access to IRB and Clinical Trials Office (contacting, legal)
Challenges to conducting Early Feasibility studies in the US (TCA Model)

Amin Al-Ahmad,. MD, FACC, FHRS, CCDS
Texas Cardiac Arrhythmia Institute
Austin, Texas
Texas Cardiac Arrhythmia

• 25 Electrophysiologists

• Practice locations:
  • Texas
    • Austin (5 locations)
    • Houston
    • Dallas
    • El Paso
    • Amarillo
    • Bryan/College Station
  • California
  • North Carolina
St. David’s Medical Center (Main center)

- Primary service area population: 1.9 million
- 5 St David's Hospitals
- Population growth: 2.9% 5-year (US:0.8%)
- Fastest growing city in the fastest growing state in the nation
  - 1,000 people move to Texas every day
  - 150 people move to Austin every day
  - Fastest population growth to the north and south of Austin
- Rapid growth in 65+ population: 5-yr CAGR = 9.5% (US: 3.6%)
- Unemployment rate = 2.6% (TX: 4.2%, US: 5.4%)
St. David’s Medical Center

- Six EP Labs
  - State of the art (built 2019)
  - Fully connected - ability to transmit cases
- Anesthesia available for all cases
- 3000 Atrial fibrillation cases per year
- 480 VT cases per year
- 300 LAAO devices per year
St. David’s Medical Center

• Dedicated space for early or non-approved technology with limited access
Texas Cardiac Arrhythmia Institute

- Internal research arm of TCA
- Prospective data collected on all AF and VT ablations for database
- Prospective data collected on all LAAO cases
- New database of all lead extraction procedures
- Research director and statistician
- Funding for 4 Research fellows
- Multicenter collaborations (national and international)
Texas Cardiac Arrhythmia Research Foundation (TCARF)

• Industry sponsored research
• Total staff of 13
• Handle contracts and IRB
• 9 Study coordinators
  • assigned to each clinic
  • All patients screened for various studies
  • Includes studies with different operators
• 35 active industry studies
IRB and Contracts

• Central IRB
  • One month approval on average

• Hospital contracts
  • Can take the most amount of time
  • Template contracts
  • Obstacles:
    • Hospital legal counsel (research wording is different)
    • Billing, device cost (if any), liability
    • Can generally be overcome with face-to-face communications
Can TCA initiate an early feasibility study in 90 days?

YES!
Thank you
A Sponsor’s Perspective:

Utilizing the EFS Pathway for a Novel Electrophysiology Device

Aaron V. Kaplan, MD FACC
Co-Founder and Chief Medical Officer, Conformal Medical
Professor of Medicine, Geisel School of Medicine at Dartmouth

February 1, 2023
Disclosure

Aaron V. Kaplan, MD FACC
Founder, Chief Scientific Officer
Conformal Medical, Inc

Interventional Cardiologist
Designed to Conform

Compliant endoskeleton
conforms

ePTFE cover
less thrombogenic

Flexible tether
eliminates cable attachment site
Conformable Foam Matrix

Only 2 sizes

Regular (27 mm)  Large (35 mm)

Shallow 10mm landing zone
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Enrolled Patients</strong></td>
<td>84</td>
</tr>
<tr>
<td><strong>Implanted Patients</strong></td>
<td>79</td>
</tr>
<tr>
<td><strong>Device Procedural Complications</strong></td>
<td>1</td>
</tr>
<tr>
<td>Regular CLAAS Size Used (%)</td>
<td>62 (78%)</td>
</tr>
<tr>
<td>Leaks ≥ 5mm (45 Days)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Device Related Thrombus</td>
<td>3 @ 45 days, 1 @ 6 months</td>
</tr>
<tr>
<td>Device Embolization</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Death (CV, Unexplained)</td>
<td>4 (6.8%), not attributed to device</td>
</tr>
</tbody>
</table>
Approved **CONFORM** Pivotal Trial

**PROSPECTIVE, MULTICENTER, OPEN LABEL, RCT**

<table>
<thead>
<tr>
<th>Randomization</th>
<th>1:1, non-inferiority</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>1,600</td>
</tr>
<tr>
<td>Locations</td>
<td>US, Japan</td>
</tr>
<tr>
<td>Selection criteria</td>
<td>Consistent with NCD</td>
</tr>
</tbody>
</table>

1° Powered Endpoint

- Safety: Procedural-related complications, all-cause death & major bleeding through 12M
- Effectiveness: Ischemic stroke and systemic embolism through 18M

**Anti-Thrombotic Therapy**

<table>
<thead>
<tr>
<th>&lt; 45D</th>
<th>DAPT</th>
<th>OAC + ASA / DAPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>45D – 6M*</td>
<td>DAPT</td>
<td>DAPT</td>
</tr>
<tr>
<td>6M+</td>
<td>ASA</td>
<td>ASA</td>
</tr>
</tbody>
</table>

**Anti-Thrombotic Therapy**

| CLAAS         | Watchman / Amulet |

| 45D TEE-DAPT  |
| 6M DAPT to ASA |
| 12M TEE RX UC |
| **18M F/U**   |

**Procedure-DAPT**

- 45D TEE-DAPT
- 6M DAPT to ASA
- 12M TEE RX UC
- **18M F/U**
  
**Phone F/U**

- 2, 3, 4, 5 years

**Procedure-OAC / DAPT**

- 45D TEE-DAPT
- 6M DAPT to ASA
- 12M TEE RX UC
- **18M F/U**

**Phone F/U**

- 2, 3, 4, 5 years

1° Endpoint

*45+ antithrombotic therapy based on TEE results*
<table>
<thead>
<tr>
<th>Year</th>
<th>1990’s</th>
<th>2010’s</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company Location</td>
<td>Santa Clara, CA</td>
<td>Raleigh, NC</td>
<td>Nashua, NH</td>
</tr>
<tr>
<td>Preclinical Studies</td>
<td>Stanford</td>
<td>Dartmouth</td>
<td>Minneapolis</td>
</tr>
<tr>
<td>First Clinical Use</td>
<td>Germany</td>
<td>Germany</td>
<td>New York</td>
</tr>
<tr>
<td>Initial 50 cases</td>
<td>Europe</td>
<td>Ger, Neth, France</td>
<td>US and Czech Rep</td>
</tr>
</tbody>
</table>

Europe or US
MDD to MDR
LAA Market Considerations
Answer is Yes (Both)
Key Learnings

• Sponsor
  • Operator-Engineer Interaction
  • Sponsor-FDA Interactions
  • MDIC Tool Kit

• Site Success
  • PI: Engaged and skilled in the procedure
  • Clinical Research Team: Established and Supported
  • Population: Access to appropriate Patients
Considerations as a Study Sponsor
Bringing an EFS to the US

Avi Fischer, MD FACC FHRS
SVP, Medical Affairs & Innovation
Orchestra BioMed
Disclosure

I am a full-time employee of Orchestra BioMed
The pendulum has swung...

*Increased momentum to bring early studies to the US*

Historically faster patient recruitment, operational costs, and early exposure for novel technologies were some of the benefits of performing early clinical studies OUS

The EFS pathway is a valuable method to facilitate investigation of novel, innovative, and clinically valuable technologies in the US by engaging key stakeholders early in the process
Potential challenges for OUS companies?

**Education & Collaboration**

- **Is there a knowledge gap?**
  - There may be more familiar with and integration into the CE Mark/MDR system
  - Uncertainty about mechanisms in-place to leverage early clinical activities in the US
  - Underappreciation of the true collaborative approach of the EFS submission/review process
  - Differing cultural, scientific, patient, and logistical issues
  - Financial considerations

- **Is there an appreciation for the value of the EFS pathway for**
  - Development timelines
  - Clinical Maps/Pivotal Study plans
  - Contracting
  - Reimbursement

- **Are there implications for funding/investment opportunities?**
  - European Innovation Council, In-Country Grants, Local investors, etc...
Considerations - Think Global

Ensure the correct infrastructure is in place & logistics are well planned

- Ensure that there is familiarity with the EFS program
- Establish a clear clinical study plan & regulatory strategy
- Identify a CRO with Global experience
- Engage key physicians and consultants for additional guidance
- Leverage shared documents and processes (templates, IRBs, etc...)
Use available shared resources

Efficiency saves time and money

Startup Finalizes EFS Contract with Brigham & Women's in Less Than 3 Months

Sponsor:
Company Size: Startup
Device Type: Transcatheter Mitral Valve Replacement (TMVR)

Finalizing an EFS contract takes an average of 164 days, according to metrics collected and presented by MDIC. But, by using the MDIC EFS Master Clinical Trial Agreement (MCTA) template, a medical device startup finalized their clinical trial agreement with Brigham and Women's Hospital in less than three months (90 days).

“We only needed to make a few minor modifications to the template. Most of the legal language was fine with us because MDIC put so much effort into working with multiple stakeholders and legal departments to make sure that every stakeholder had an opportunity to comment.

The company also used the MDIC EFS Informed Consent Form (ICF) template with Brigham and Women’s Institutional Review Board (IRB). The IRB approval process was simple and took less than one month, because MDIC made sure the template fulfilled all the regulations and requirements.
Get Informed and Engage key stakeholders early

Develop a sound Clinical & Regulatory Strategy

Leverage existing resources for efficiency
„Quality Enrollment is Essential, But Time is Money“
Boston, Feb. 1st 2022

Holger Friedrich, MD, PhD, CEO of AquaHeart inc.
• AQUAHeart® has developed a groundbreaking, disruptive cardiac ablation catheter system, powered by steam.

• The goal is to be able to completely insulate each PV in < 10 s.

• Real time PV signal feed back allows for individualized therapy.

• Company is going into a chronic animal study shortly and anticipates FIH procedures starting in early 2024.

• Founded in 2018, privately financed.
The idealistic typical life-span of a start up in the EP space

1. Idea, foundation
2. R&D, early feasibility
3. Animal work, testing, preparation of the chronic animal study
4. Chronic animal study, design freeze, GLP
5. First in Human study
6. Regulatory approval studies US/Europe
7. Exit?

The “Window of opportunity”

Only if 5 to 7 meet the window of opportunity, an exit Start up will be feasible and successful. More flexibility will increase the chances of success dramatically!
Seen through the “Start up Eyes” -
What objectives should a research institution meet to be ideal for early feasibility study (FIH)?

- Local and personal accessibility
- Interactive protocol discussions
- Fast, seamless and proactive enrollment of patients
- High quality procedural skills
- Good contact to the patients to ensure a complete follow up
- Incorporation of the highest clinical and regulatory standards throughout the entire process
- Solid scientific reputation and credibility for data presentation
- Trustful relationship with the sponsor
The early feasibility study: Time factors are cost factors

<table>
<thead>
<tr>
<th>Time Factors controlled by company</th>
<th>Time Factors out of control</th>
<th>Cost Factors controlled by company</th>
<th>Cost Factors flexible</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design, R&amp;D, development</td>
<td>IRB approval</td>
<td>R&amp;D expenses</td>
<td>Travel</td>
</tr>
<tr>
<td>DV work and Biocomp testing</td>
<td>Site selection and contracting</td>
<td>Design verification testing</td>
<td>Burn rate x lost time</td>
</tr>
<tr>
<td>Follow up and data collection</td>
<td>Governmental approvals</td>
<td>Biocomp Testing</td>
<td></td>
</tr>
<tr>
<td>Data analysis and presentation</td>
<td>Patient selection and enrollment</td>
<td>Approval cost</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hospital fees</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical engineering</td>
<td></td>
</tr>
</tbody>
</table>
Time and money saved through effective study management

Slow process: one task after the other

- R&D, DV, Biocomp
- Product file
- HEC approval
- Governmental approval/admin
- Contracting
- Study in various sites, slow enrollment

Parallel Processing: Efficient development

- Product file development during DV
- HEC approval, admin approvals and Contracting in parallel
- Study in a few high volume sites with effective clinical department
Conclusion: what are we looking for in an ideal world for EFS??

- Excellent clinical skills and open mind towards research with start up companies
- Transparent and predictable regulatory approval process
- Transparent and predictable contracting process with sites
- "One stop shopping" (for IRB, selection, contracting) – Contracting groups? Clinical study cooperations?
  - Reasonable pricing
  - Respect from both sides
Session III: Shortening Time to First Patient
In: Timely and Effective Contracting

Session Leader:
Jaime Walkowiak, JD
Yes, We Can Negotiate Contracts in 60 Days!

Jaime Walkowiak
MDIC approached four attorneys representing sites and sponsors to discuss some frequent key choke points in EFS contract negotiations:

- Indemnification
- Subject Injury
- Intellectual Property
- Third Party Payer
Conception of Legal Roundtable

Develop an EFS-specific Master Clinical Trial Agreement (MCTA) to facilitate efficiencies in the EFS contracting process which provides:

- balance between site and sponsor concerns, serving as a starting point for contract negotiations with a priori agreement of 90% or greater, and
- allowing both parties to focus remaining legal resources on the remaining 10% (or less) of the EFS MCTA requiring negotiation
- BSWRI took the lead on drafting a MCTA template using the provisions from the Language Library developed by MDIC Working Group
- Draft MCTA circulated for review to the Legal Roundtable participants prior to the meeting
Legal Roundtable Representatives

Sites

• Baylor Scott & White Health
• Cedars Sinai
• Dartmouth Hitchcock
• Emory
• Columbia
• Intermountain Healthcare
• Lankenau/ Main Line
• Mayo Clinic
• Houston Methodist
• Northwestern
• Piedmont

Sponsors

• Abbott
• Boston Scientific
• Edwards Lifesciences
• Medtronic
• Mitralign
• Abiomed

FDA

MDIC
**Legal Roundtable**

**Day 1**

- Participating attorneys from the MDIC Working Group facilitated contract language discussions on the four choke points
- Edits made in real time in alignment with feedback received from the participants
- Revision to select sections was rather challenging due to differing viewpoints on these key items

**Day 2**

- Review of the MCTA language
- Addressing additional sections not identified as key choke points
- Revised template sent to the group at the conclusion of the meeting to perform a secondary review
Reconciliation and Development of MCTA and Industry- and Sponsor- specific supplements

• Second review of the MCTA draft resulted in better understanding of organization's variances from the template and led roundtable participants to the conclusion that MCTA alone would not resolve all concerns and that supplemental information would be necessary.

• Written summaries of variances along with narrative explanation serve as a supplement to the MCTA that equips people to efficiently make decisions on which institutions and sponsors to approach – reduces timeline to establish - eliminates meaningless negotiations.
Institutional Alignment in a Teaching Hospital for Early Feasibility Studies

Kate Dalton MS, RD, CCRC
Director of Cardiology Research
NewYork-Presbyterian Hospital
Columbia University Medical Center
Why participate in EFS

CLINICAL & ACADEMIC IMPACT

Patient access to new technology

Differentiates our medical center

Academic reputation

Leadership role in future clinical trials

* Lead in EFS then lead in pivotal (access to pivotal)
Why participate in EFS
FINANCIAL IMPACT

- Staying ahead of the curve allows for more impactful strategic planning
- Better forecasting to increase hospital/university’s competitive advantage
- Change is inevitable—be proactive not remedial
- Research budget may be economically attractive
FIND THE BALANCE

TO CREATE INSTITUTIONAL ALIGNMENT
FOCUS ON THE MISSION

**Words Matter**

---

**Columbia University Medical Center**

- As a premier institution in health care, research, and education, our mission is to provide continuing medical education to Columbia faculty, professional trainees, and to the larger community of physicians and other healthcare professionals in the New York area and beyond.

**New York Presbytial Hospital Mission**

- In collaboration with two renowned medical schools, Weill Cornell Medicine and Columbia University College of Physicians and Surgeons, NYP is dedicated to:
  - Educating the next generation of health care professionals,
  - Developing groundbreaking research,
  - Advancing innovative, patient-centered clinical care,
  - Serving the needs of our local, national and global community.
Maneuvering Barriers

- Time is critical. Education is key
- Overcoming traditional paradigms (TR)
- Enrolling in studies with commercially available alternatives (MR after COAPT)
- Institutional risk tolerance
- Finding comfort in being uncomfortable
Highlight Teaching Aspect

• Teaching hospitals follow a three-way mission of clinical care, education and research.*

• Clinical care is the primary focus of teaching hospitals and is bolstered by education and research.

EFS provides uncommon clinical care training opportunities

LEADING CHANGE
IMPORTANCE OF COMMUNICATION

MANAGING COMPLEX CHANGE

VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = CHANGE
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = CONFUSION
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = ANXIETY
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = RESISTANCE
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = FRUSTRATION
VISION + SKILLS + INCENTIVES + RESOURCES + ACTION PLAN = FALSE STARTS
• EFS have clinical, academic and financial institutional benefits
• Barriers are to be expected but can be overcome
• Communication (and speed) are critical
Northwestern Medicine
Bluhm Cardiovascular Institute

10 Successful EFS and Counting
It can be Done

Clinical Trials Unit
Lynne Goodreau RN, MS Administrative Director BCVI CTU
Clinical Trial Agreements

Metrics – 60/60/60 goal
• 60 Days for IRB Approval
• **60 Days for Contract Execution**
• 60 day to first enrollment

Steps to success:
• Establish institutional buy-in
  o Prioritize EFS
• Create the partnership with the industry sponsor
• Rely on existing contracts:
  Industry - master agreements
  MDIC template

Areas requiring flexibly:
 o Study budgets
 o Scheduling off site training
Additional Considerations

Metrics – 60/60/60 goal
  • 60 Days for Contract Execution

Value Analysis Committees
  o Ancillary equipment purchase approvals

Proctors/credentialling
  o Organizational requirements

Case recording
  o Confidentiality language/consent

Compassionate use
  o Separate contracting
## Early Feasibility Studies (EFS) Start-up Timelines

<table>
<thead>
<tr>
<th>Study Type*</th>
<th>Days to IRB</th>
<th>Day to Contract</th>
<th>Days to Enrollment</th>
<th>Comments</th>
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<tbody>
<tr>
<td>Heart failure</td>
<td>89</td>
<td>68</td>
<td>12</td>
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<tr>
<td>Heart failure</td>
<td>130</td>
<td>134</td>
<td>136</td>
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<tr>
<td>Heart failure</td>
<td>70</td>
<td>43</td>
<td>118</td>
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<tr>
<td>Transcatheter valve - mitral</td>
<td>56</td>
<td>56</td>
<td>180</td>
<td>first consent at 74 days</td>
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<tr>
<td>Transcatheter valve - mitral</td>
<td>41</td>
<td>61</td>
<td>&gt;1 year</td>
<td>first consent at 77 days- 15 screen fails, technology change delays</td>
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<td>Transcatheter valve - mitral</td>
<td>74</td>
<td>95</td>
<td>206</td>
<td></td>
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<tr>
<td>Transcatheter valve - tricuspid</td>
<td>63</td>
<td>53</td>
<td>55</td>
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<tr>
<td>Transcatheter valve - tricuspid</td>
<td>58</td>
<td>83</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Transcatheter valve - tricuspid</td>
<td>36</td>
<td>69</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Transcatheter valve - tricuspid</td>
<td>54</td>
<td>57</td>
<td>97</td>
<td>Covid implementation delay</td>
</tr>
</tbody>
</table>

**Mean time**  
67  
72  
98**

**Median time**  
60.5  
64.5  
97**

*reflects 2015-2022  
**excludes > 1 year
60/60/60 It can be done!

• Essential elements for success:
  - Institutional buy-in
  - Industry partnership
  - Flexibility
  - Collaboration
  - Ongoing process refinement
Thank you!
60/60/60 – It can be done!!
Tips and Tricks on Contract Negotiation from a Sponsor Point of View

Brad Horst
Group Vice President, Rhythm Management Clinicals
• Build a strong high-performance culture where all individual team members know the priorities

• Dedicated teams focused on SSU

• Metrics focused on cycle times and driving accountability in the teams

• Master Agreements help significantly
  – Extra time to implement
Tips and tricks

• ‘At risk’ or wait for FDA letter?
  – Know where you are willing to take business risk and where you are not

• Develop a good budget that meets the needs of the company and the sites

• ‘Relationships Matter’
  – Invest time to get to know your sites
  – Share SSU data with sites to gain alignment on improvement
  – If all else fails, live meetings between lawyers
FDA Categorization of IDE Applications to Assist CMS Coverage Decisions

David Hazlewood, PhD
FDA
Office of Cardiovascular Devices
Cardiac Ablation, Mapping, and Imaging Team
OHT2 EFS Representative / Lead Reviewer
Disclosures

I have no relevant conflicts of interest.
Limitations

• FDA makes recommendations to CMS, **not** coverage decisions.

• Presentation should not be viewed as an FDA guidance document.

• Do not rely on the content of this presentation without independent review of relevant statutes, regulations, guidance, consensus standards, and related materials.

• Presentation does not contain any confidential commercial information or protected health information.
Summary of CMS Requirements for IDEs

1. Study tests whether device improves health outcomes in appropriate population
2. Scientific rationale for the study
3. Study is not duplicative
4. Appropriate methodology and number of enrolled subjects
5. Sponsor is capable of success
6. Complies with federal regulations for protection of human subjects
7. Does not test toxicity or disease pathophysiology in health subjects
8. Registered at ClinicalTrials.gov
9. Protocol specifies release of results (even if negative)
10. Protocol describes how Medicare beneficiaries may be affected

https://www.cms.gov/medicare/coverage/ide or search “CMS IDE coverage”
Determination is based upon “absolute risk” or initial questions of safety and effectiveness

- Is there initial clinical use for this device? (~10 patients)
- Is this device similar to other devices with clinical use?

FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions

https://www.fda.gov/media/98578/download
Example Health Co.
% John Doe
Regulatory Consultant
Example Consulting
123 Main Street
City, MD 12345

Re: G220000
  Trade/Device Name: Example Device
  Dated: January 1, 2023
  Received: January 1, 2023
  CMS Category: B
  Annual Report Due: One Year from the Date of This Letter

Dear John Doe:

The Food and Drug Administration (FDA) has reviewed your Investigational Device Exemption (IDE) application regarding your feasibility study (Example Study) for a significant risk device. FDA has determined you have provided sufficient data to support initiation of a human clinical study; this means that...
Re-classification

- Submit re-classification request to FDA
  - IDE supplement (reviewed in 30 days)
- Submit FDA decision letter to CMS

- CMS disagrees with FDA decision
- Initial clinical data is available
- Additional information on similar devices is provided
Q-Submission Program
Come talk to us!

Informational Meeting Request

Good if you’re still in the development phase. Gives an opportunity to build FDA staff’s familiarity with your device. Generally, an open discussion with high-level questions (but no specific feedback).

Pre-Submission Meeting or Written Feedback Request

Best when you’re closer to submitting an application to FDA. Get responses to tailored questions w/ or w/o a teleconference.

Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program

www.fda.gov
Contact Me
OHT2_EFS@fda.hhs.gov or David.Hazlewood@fda.hhs.gov

CMS IDE website
https://www.cms.gov/medicare/coverage/ide

CMS reimbursement request “Crosswalk”

FDA classification guidance document
https://www.fda.gov/media/98578/download

FDA EFS resources
https://www.fda.gov/medical-devices/investigational-device-exemption-ide/early-feasibility-studies-efs-program
Thank you for your attendance and participation in the EFS Best Practices Workshop hosted by the Medical Device Innovation Consortium (MDIC)