EFS Symposium:
Implementation Strategies for Early Feasibility Studies
Sponsored by MDIC in collaboration with CRF

Event Materials

June 12, 2019
Chicago Ballroom X
Sheraton Grand
301 E North Water St., Chicago, IL 60611
AGENDA

7:00 – 7:10 p.m.: David Holmes – Welcome and Introductions

7:10 – 7:20 p.m.: Pamela Goldberg and Chip Hance – Introduction to MDIC and Update of the Initiative

7:20 – 7:50 p.m.: Topic # 1: Identification of relevant patient population/Patient screening
  • Scott Chadderdon – OHSU (10 min)
  • Blessie Concepcion – Boston Scientific (5 min)
  • Panel discussion (15 min)

7:50 – 8:20 p.m.: Topic # 2: Patient consent issues
  • Charlie Davidson – Northwestern (10 min)
  • Jill Trekell – Edwards (5 min)
  • Panel discussion (15 min)

8:20 – 8:50 p.m.: Topic # 3: Procedural and clinical follow-up issues
  • Tamim Nazif – Columbia (10 min)
  • Chris Cain – Conformal Medical (5 min)
  • Panel discussion (15 min)

8:50 – 9:20 pm: Aaron Kaplan - Round table discussion focused on audience participation

9:20 – 9:30 p.m.: David Holmes and Michael Mack - Wrap up and Next Steps

Panelists:

• Howard Herrmann – Penn Medicine
• Vinod Thourani – Medstar Heart and Vascular Institute
• Michael Mack – Baylor Scott & White
• Scott Lim – University of Virginia
• Bernard Vasseur – FDA
# EFS Symposium: Implementation Strategies for Early Feasibility Studies

Sponsored by MDIC in collaboration with CRF

## Attendees

<table>
<thead>
<tr>
<th>1. Helen Scotch</th>
<th>VP Clinical &amp; Regulatory</th>
<th>Abbott</th>
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<tbody>
<tr>
<td>2. Neil Moat</td>
<td>Chief Medical Officer, Structural Heart</td>
<td>Abbott</td>
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<tr>
<td>3. Josh Schumacher</td>
<td>Sr. Clinical Project Manager</td>
<td>Abbott</td>
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<tr>
<td>4. Stefano Osta</td>
<td>Researcher</td>
<td>Aortic Lab</td>
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<tr>
<td>5. David Heimansohn</td>
<td>Cardiac Surgeon</td>
<td>Ascension Indianapolis</td>
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<tr>
<td>6. Melanie Glover</td>
<td>Executive Director, CV Research</td>
<td>Ascension Indianapolis</td>
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<tr>
<td>7. Jaime Walkowiak</td>
<td>COO, SVP</td>
<td>Baylor Scott &amp; White</td>
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<tr>
<td>8. Michael Mack</td>
<td>Cardiac Surgeon</td>
<td>Baylor Scott &amp; White</td>
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<tr>
<td>9. Necole Kell</td>
<td>Clinical Research Supervisor</td>
<td>Baylor Scott &amp; White</td>
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<tr>
<td>10. Laoti Bussone</td>
<td>Senior Clinical Trial Manager</td>
<td>Boston Scientific</td>
</tr>
<tr>
<td>11. Blessie Concepcion</td>
<td>Director Global Clinical Trials</td>
<td>Boston Scientific</td>
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<tr>
<td>12. Yoshi Kaneko</td>
<td>Assistant Professor of Surgery, Cardiac Surgeon</td>
<td>Partners Healthcare (B&amp;W Health)</td>
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<tr>
<td>13. Ilia Hariton</td>
<td>VP of R&amp;D</td>
<td>CardioValve</td>
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<td>14. Nitza Shoham</td>
<td>VP CA &amp; RA</td>
<td>CardioValve</td>
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<tr>
<td>15. Tamim Nazif</td>
<td>Assistant Professor of Medicine</td>
<td>Columbia UMC</td>
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<tr>
<td>16. Martin Leon</td>
<td>Mallah Family Professor of Cardiology</td>
<td>Columbia UMC</td>
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<tr>
<td>17. Chris Cain</td>
<td>VP, Clinical &amp; Regulatory Affairs</td>
<td>Conformal Medical, Inc.</td>
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<tr>
<td>18. Ori Ben-Yehuda</td>
<td>Executive Director, CRF Clinical Trials Center</td>
<td>Cardiac Implants</td>
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<td>19. Martin Quinn</td>
<td>Cardiologist</td>
<td>CroiValve</td>
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<tr>
<td>20. Aaron Kaplan</td>
<td>Director, Device Development, Cardiovascular Medicine</td>
<td>Dartmouth-Hitchcock Heart and Vascular Center</td>
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<tr>
<td>22. Bernard Vasseur</td>
<td>Medical Officer, Structural Heart Device Branch</td>
<td>FDA</td>
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<tr>
<td>23. Ryan Wright</td>
<td>President</td>
<td>Flow-FX</td>
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<tr>
<td>24. Patrick Sweeney</td>
<td>CEO / Medical Director</td>
<td>Flow-FX</td>
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<tr>
<td>25. Patrick Brady</td>
<td>VP of Sales</td>
<td>Hawthorne Effect, Inc.</td>
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<tr>
<td></td>
<td>Name</td>
<td>Title/Position</td>
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<tr>
<td>26.</td>
<td>Neil Kleinman</td>
<td>Preventative &amp; Interventional Cardiology</td>
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<td>27.</td>
<td>William Gray</td>
<td>Systems Chief</td>
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<td>28.</td>
<td>David Holmes</td>
<td>Interventional Cardiologist</td>
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<td>29.</td>
<td>Lisa Beck</td>
<td>Director Clinical Affairs</td>
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<td>30.</td>
<td>Liliana Rincon-Gonzalez</td>
<td>Program Director Clinical Science</td>
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<td>31.</td>
<td>Pamela Goldberg</td>
<td>President &amp; CEO</td>
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<td>32.</td>
<td>Chip Hance</td>
<td>Board of Directors</td>
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<tr>
<td>33.</td>
<td>Charles Davidson</td>
<td>Vice Chair for Clinical Affairs, Department of Medicine</td>
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<td>34.</td>
<td>Scott Chadderdon</td>
<td>Assistant Professor of Medicine</td>
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<td>35.</td>
<td>Yael Kislev</td>
<td>Senior Clinical Manager</td>
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<td>36.</td>
<td>Raghu Basude</td>
<td>VP of R&amp;D</td>
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<td>37.</td>
<td>Mano Thubrikar</td>
<td>President</td>
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<td>38.</td>
<td>Steven Bolling</td>
<td>Professor of Medicine</td>
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<td>39.</td>
<td>Marissa Donatelle</td>
<td>Program Coordinator</td>
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<td>40.</td>
<td>Scott Lim</td>
<td>Professor</td>
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<td>41.</td>
<td>Howard Hermann</td>
<td>Cardiology</td>
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Welcome and Introductions

David Holmes
EFS Symposium:
Implementation Strategies for Early Feasibility Studies

David R. Holmes, Jr., MD

TVT
Chicago IL
June 12-15, 2019

The following relationships exist related to this presentation:

None
EFS Initiative
Where did it come from?

- FDA
- Industry
- Patients
- Congress – 21st Century Cures
- ACT
- Hospitals/Health Care institutions
- Physicians
Early Feasibility Studies (EFS)

• EFS is a path to early access of innovative device therapies for U.S. patients

• Small, highly monitored studies of the first use of novel, potentially life saving technology

• Device modifications may occur as outcomes dictate

• Typically conducted at sites with highly skilled physician and research staff
• The EFS Pilot is the first phase of establishing a National EFS Site Network
• A voluntary, open research network of sites committed to high quality, efficient EFS
• Vision to advance US first-in-world patient access to novel therapies and technologies
Optimal EFS Site Qualities

- A culture of clinical study quality, and a commitment to and enthusiasm for EFS
- A well-developed infrastructure to support clinical studies
- A track record of human subject monitoring and protection and excellence in maintaining study data integrity
- Technically qualified site investigators
- Commitment from the site IRB to expeditiously review EFS submissions or a willingness to defer to a central IRB
- Parallel and timely contracting and IRB processes
- Access to sufficient patient populations with the disease being treated (the intended treatment population); sites with electronic health records may have readily available information in this regard
- A commitment to constrain both direct and indirect costs

CV EFS Pilot: Site Demographics*

Indicates Possible Sites – Selections TBD

Non-profit, Academic
Non-profit, Community
Private
Identified Challenges

• Contracting
• Indemnification
• IRB performance
• Patient Informed Consent
• Development of clinical site Centers of Excellence for carrying out EFS
• CMS Reimbursement
EFS Pilot: Tools and Methods

- Contract:
  - Master Clinical Trial Agreement
  - Contract Language Libraries
- Patient Advocacy: Informed Consent Form Template
- Education: Information for IRBs, research staff, and potential subjects

http://mdic.org/cts/efs/
Questions to be addressed

• What are tangible benefits
  • Sponsors
  • Institutions
  • Regulatory agencies
  • Patients

• How to monitor site performance
  • Target goals

• Will certification be required
  • By whom?

• Can CMS funding issues be resolved?
18 Lawyers Met February 14, 2018
Draft Master Agreement and
Standardized Contract for EFS
EFS Initiative
What have been the deliverables - Educational

- Patient Advocacy: Informed consent template
- Information for IRB’s on specifics of:
  - EFS
  - Device studies
  - Role of Central IRB’s
  - Patient protection
Purpose
The Medical Device Innovation Consortium (MDIC) is a public-private partnership that brings together representatives of the FDA, NIH, CMS, industry, non-profits, and patient organizations to improve the processes for development, assessment, and review of new medical technologies.

MDIC has been formed to add value at the intersecting needs of the medical device industry, regulators, and the related organizations that are together responsible for a vibrant medical device industry that serves the public health needs of the United States.

Our Work
MDIC, through its public-private partnership, aims to advance the regulatory process in the medical device industry. MDIC coordinates the development of methods, tools, and resources used in managing the total product life cycle of a medical device in an effort to improve patient access to cutting-edge medical technology.

MDIC’s initiatives focus on four areas:

- **Clinical Science** – Address the biggest barriers to collecting adequate clinical evidence in the support of new medical technology by creating blueprints for innovative clinical trials techniques, developing standards and metrics for effective clinical trial designs and encouraging the collection of adequate and appropriate clinical and patient preference data.

- **Data Science & Technology** – Fulfill the promise of advances in data analysis by creating tools and methods to use advanced data analysis techniques and new technology to accelerate the collection of clinical data, remove barriers to patient access and monitor product safety, quality and effectiveness.

- **Health Economics & Patient Access** – Create predictability and transparency of evidentiary requirements for coverage and improve pathways for coverage, coding and payment to speed patient access and amplify the patient voice in selection of treatment options.

- **National Evaluation System for Health Technology Coordinating Center (NESTcc)** – Work with stakeholders across the medical device ecosystem to catalyze the timely, reliable, and cost-effective development of Real-World Evidence to enhance regulatory and clinical decision-making.

MDIC’s informative series of online teleconference workshops, the MDICx series, features emerging trends in medical technology regulatory science, MDIC projects, and subject matter experts sharing perspectives, progress and opportunities. Visit mdic.org/mdicx-series to view upcoming webinars or submit a proposal.

ANNUAL PUBLIC FORUM
Every year, MDIC’s Annual Public Forum (APF) brings together MDIC members and the broader medical device and diagnostics community to share insights on current trends in the regulatory process and the progress MDIC has made in advancing the field.

Past panel topics have included:
- Why Patient Input Matters
- Efficiency in Evidence Generation
- Real-World Evidence

Past guest speakers have included:
- Alex Moazed, Applico
- FDA Commissioner
- Tamara Syrek Jensen, CMS

LEARN MORE
Learn more about MDIC by visiting www.mdic.org, sending a message to info@mdic.org, or calling (202) 828-1600

www.mdic.org.
Initiatives
Several MDIC Initiatives have one or more programs designed to meet a specific need:

Clinical Science
- Clinical Diagnostics
- Early Feasibility
- Science of Patient Input

Data Science & Technology
- Case for Quality
- Computational Modeling and Simulation
- Cybersecurity
- External Evidence Methods

Health Economics & Patient Access
- Coverage
- Reimbursement

National Evaluation System for Health Technology Coordinating Center (NESTcc)
- Governance
- Data-Network
- Test-Cases
- Data Quality and Methods

Membership
MDIC members are leaders in the medical technology industry. MDIC focuses on providing patients access to innovative medical technologies, so many of our members are companies that can help us serve this mission.

Member organizations are substantially involved in medical and/or medical device research, development, treatment, or education; the promotion of public health; or expertise in regulatory science.

LEARN MORE ABOUT MDIC
Learn more about MDIC by visiting www.mdic.org, sending a message to info@mdic.org, or calling (202) 828-1600

www.mdic.org
MDIC WORKS TO HELP PATIENTS GAIN ACCESS TO INNOVATIVE MEDICAL TECHNOLOGIES

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.
MDIC METHODOLOGY

<table>
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<th>Create a forum for collaboration</th>
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<tbody>
<tr>
<td>Flexible</td>
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<td>Multi-stakeholder</td>
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<td>Focus on patients</td>
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<tr>
<th>Identify strategic investments in regulatory science</th>
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<td>Improve efficiency</td>
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<td>Unmet needs</td>
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<td>Innovation timeline</td>
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<tr>
<th>Provide tools and methods to drive innovation</th>
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<tbody>
<tr>
<td>Evidence generation</td>
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<td>Patient engagement</td>
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<td>Quality/Safety</td>
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Coordinate the development of tools and methods used in managing the total product life cycle to improve patient access to novel medical technology.
OUR CORE INITIATIVES DRIVE OUR WORK TO IMPROVE HEALTH OUTCOMES

MDIC facilitates a number of programs and activities to advance the medical device regulatory process for patient benefit. These programs are housed within four core initiatives of MDIC.
Early Feasibility Studies (EFS) may provide patients early access to innovative devices and therapies.
## EFS STAKEHOLDER BENEFITS

### PATIENTS

- Access to novel, potentially life saving technology
- Mitigation of risks inherent to clinical trials

### FDA

- Early exposure to novel technology
- Better definition of requirements for demonstrating safety & efficacy; reduces development risks.

### SITES

- High quality U.S. healthcare data & networks
- Innovative treatment options
- Expert Key Opinion Leaders stay involved in innovation

### SPONSORS

- Earlier access to high-quality EFS data and outcomes
- Improved innovation and feedback opportunities
EFS PROGRAM GROWTH – FIRST 5 YEARS

EFS IDE Submittal and Approval Trends: CDRH Office of Device Evaluation

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Number of IDEs Submitted</th>
<th>Number of IDEs Approved</th>
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<tbody>
<tr>
<td>FY14</td>
<td>26</td>
<td>24</td>
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<tr>
<td>FY15</td>
<td>47</td>
<td>43</td>
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<tr>
<td>FY16</td>
<td>48</td>
<td>40</td>
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<tr>
<td>FY17</td>
<td>57</td>
<td>45</td>
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<tr>
<td>FY18</td>
<td>73</td>
<td>53</td>
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Legend:  
- Blue: Submitted  
- Gray: Approved
In 2013 FDA published the EFS/FIH Guidance document:
• This EFS Guidance successfully improved average EFS IDE approval times.

2013 - FDA Published EFS Guidance

2015 – Blueprint for Early Feasibility Study (EFS) Success
• Commissioned the EFS/FIH Industry Perspectives survey
• Published the Blueprint for EFS Success, supplementing the 2013 FDA Guidance

2017 – Baseline EFS Performance Metrics
• MDIC, Sponsors, and FDA: 1st ever collaboration to share de-identified EFS Administrative and Clinical metrics.
• Baseline represents approximately 25% of EFS trials started FY14 – FY17

2018 – Tools & Processes
On MDIC’s website:
• Master Clinical Trial Agreement
• Patient Informed Consent template
• Education Tools: IRB, Research teams and Patients

2019 – EFS Network
• 18 sponsors – 31 sites
• Best Site Practices Workshop
• EFS workstream development
EFS Site Network Pilot

Chip Hance
MDIC-EFS Initiative Board Champion
EFS Site Network Pilot - Purpose

Develop a national EFS learning system

• Track and report EFS metrics
• Test the utility and effectiveness of EFS-specific tools and methods
• Serve as a launching point for a future network of high-performing EFS sites
  • Nation-wide coverage
  • Multiple therapeutic areas
EFS Site Network Pilot: 60:60:60 GOAL

EFS Metrics: Administrative Baseline

<table>
<thead>
<tr>
<th>EFS Metric Category</th>
<th>IDE Approval</th>
<th>IRB Approval</th>
<th>Contract Approval</th>
<th>1st Subject Enrollment*</th>
</tr>
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<tbody>
<tr>
<td>Mean Time from EFS IDE Approval (Days)</td>
<td>68</td>
<td>72</td>
<td>133</td>
<td>187</td>
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<tr>
<td>Next 60 Days</td>
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MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM
EFS Site Best Practices Workshop

March 6-7, 2019, Arlington, VA.

• Over 65 attendees were present, including representatives from 20 sites, 14 sponsors, FDA, CMS and service providers

• Topics covered:
  • Managing Risk, SAEs & IRB Reporting
  • Timely & Effective Contracting
  • Budgeting between EFS Sites and Sponsors
  • EFS Staffing and Resources
  • Patient Identification, Enrollment & Retention
  • Coverage Determinations & Site Budgets
EFS Site Network Pilot

Completed Tools and Methods

• Development of a Master Clinical Trial Agreement
• Patient Informed Consent Form Template
• Tools for educating IRB, research staff and potential patients on EFS

http://mdic.org/cts/efs/
EFS Site Network Pilot: Plans for 2019

I. Communications
   • Continue with EFS Express Communications
   • Webinars on Best Practices

II. Workshops
   • TVT Symposium/Workshop on Site Best Practices for Patient Screening/Enrollment
   • Contracting Webinar
   • IRB/Informed Consent Workshop

III. Working Groups
   • Budgeting Working Group

IV. Metrics
   • Data on 2017/18 EFS Study Metrics
   • Site Survey
Questions?

Contact:
Liliana Rincon Gonzalez, PhD
Program Director
Clinical Trial Sciences (CTS)
Office: 202-559-2973
lrincon-gonzalez@mdic.org

MDIC Website:  http://mdic.org
EFS Email:  EFSPilot@mdic.org
Identification of Relevant Patient Population/Patient Screening

Scott Chadderdon *OHSU*

Blessie Concepcion *Boston Scientific*
Early Feasibility Studies:
Identification of Relevant Patient Populations and Patient Selection

Scott M. Chadderdon, MD.
Assistant Professor of Medicine
Outline

• Introduction to Early Feasibility Studies
• Knight Cardiovascular Institute Structure
• Identification of Appropriate Patients and Patient Selection
Early Feasibility Studies

• Guidance for Early Feasibility Studies
  - FDA website: Early Feasibility Studies Program-
    https://www.fda.gov/medical-devices/device-advice-
    investigational-device-exemption-ide/early-feasibility-studies-
    efs-program

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
EFS - Construct and Goals

• Early Feasibility Study
  - Proof of principle and early clinical safety
  - Limited investigation early in development to obtain clinical experience
  - Evaluate device safety & function
  - Modification of device or delivery
  - Obtain clinical safety experience
  - Iterative process on the path to a Pivotal Trial
Initiation of an EFS

• Goal is for learning
  - Device, device refinement, and safety
  - Patient selection for progression to pivotal trial
• Flexible process that relies on appropriate risk-based rationales
• Decisions should be justified by an appropriate risk-benefit analysis to ensure adequate subject protection
EFS in Oregon

• Challenges
  - Rural communities
  - Travel & time commitment for patients
  - Access to studies - may have to seek care outside of state

• Opportunities
  - Research opportunities for patients are built into fabric of the institution
  - Academic Structure and well structured IRB help facilitate EFS
KCVI Clinical Trials Structure:
Disease Based Centers of Excellence

- **Valvular & Interventional**
  - 4 Physician Leads
  - 2 Advanced Practice Prov
  - 3 Research Coordinators
  - EFS Pivotal Standard

- **HCM & Amyloid**
  - 3 Physician Leads
  - 3 Research Coordinators
  - EFS Pivotal Standard

- **EP**
  - 3 Physician Leads
  - 3 Advanced Practice Prov
  - 2 Research Coordinators
  - EFS Pivotal Standard
Success in Patient Selection

• Clinical Structure
  - Invested Lead Physicians in each group
  - Weekly Clinical Review – scheduled time
  - Weekly PI Review – scheduled time

• Integrated Research Coordinators
  - Pre-clinic visit screening for enrollment
  - Pre-Identification and consent on first visit
  - Additional time with patients for questions

• Empowering Advanced Practitioners

• Interdisciplinary Teams
Success in Patient Selection

• Database Screening
  - Useful for early enrollment
  - Low yield for ongoing patient selection

• Personal Patient Connection
  - Long term patient-provider relationship
  - Establish trust and confidence

• Personal Physician Connection
  - Communication with referral sources

• EFS Referrals - Internal Providers

• Pivotal Trial Referrals - Internal and External Providers
EFS Patient Selection

- Finding the Right Patient
  - Inclusion and Exclusion Criteria
  - Finding Symptomatic Patients
  - Matching Symptoms to Risk

- Patient Compliance & Engagement
  - Identify Potential Barriers to Follow-up

- Screen Failure is not a Failure
EFS Patient Selection

• Clinically Driven Care
  - Know your toolbox from EFS to commercial therapies to advance patient care
  - Full scope integration of interdisciplinary physician leaders, APP’s, nursing care & coordination, and research coordinators
  - Communication – Patients
  - Communication – Referring Providers
  - Communication – Internal Research Team
  - Communication – Industry and Trial Participant Partners
Success in EFS patient selection is in the integration of all aspects of clinical trials selection into clinical care.
MDIC-CRF EFS Symposium

Identification of Relevant Patient Population/
Patient Screening

June 12, 2019

Blessie Concepcion
Director, Global Clinical Trials
Boston Scientific
Clinical Development Process for Medical Devices

**Novel device/technology developed to address unmet clinical need**

**Phase I**
- **Type**: FIM or EFS
- **Purpose**: Assess safety
- **Patient Population**: Identify relevant patient population: restrictive inc/exclusion criteria, may need to be expanded
- **Sample Size**: Small (10-40)

**Phase II**
- **Type**: Feasibility (Expand EFS)
- **Purpose**: Assess safety and performance/effectiveness
- **Patient Population**: Confirm relevant patient population: refined inc/exclusion criteria
- **Sample Size**: Medium (~100)

**Phase III**
- **Type**: Pivotal Study: RCT or OPC
- **Purpose**: Demonstrate safety and effectiveness in a large patient population compared to current standard or control or placebo
- **Patient Population**: Defined patient population
- **Sample Size**: Large (≥ 300)

**Phase IV**
- **Type**: Post-Market Surveillance
- **Purpose**: Monitor safety and effectiveness in real world clinical setting
- **Patient Population**: Real world patients
- **Sample Size**: Very large (≥1000 based on commercial use)
Collaborate with a team of experts early in identifying relevant patient population based on:

- Clinical criteria
- Functional criteria
- Anatomic criteria based on imaging assessments (consider use of specialized imaging software, measurements, core labs as needed)

- Overall Heart Team assessment: clear benefit to patients when decisions utilize a collaborative multidisciplinary approach
Collaborate with sites early

- Understand patient referral pathways at each site and create customized plan to recruit patients: provide materials for internal and external referral awareness, patient education materials
- Train sites on novel device/therapy and inc/exclusion criteria
- Train on complex assessments required: imaging software/measurements, create tools (e.g. youtube video of specific images required)

*Source: Writing Committee et al. JACC 2017;j.jacc.2017.09.019*
Ongoing collaboration with sites:
- Understand challenges in identifying patients and screen failures
  - Referrals, Heart Team, Screening Committee
  - Inc/exclusion too restrictive
- Allow for screening consent to enable sites to screen early and facilitate process for patients
- Allow for clinically reasonable windows for assessments
- Expedite core lab analysis turnaround time and central screening committee reviews

Ongoing collaboration with FDA

*Source: Writing Committee et al. JACC 2017; j.jacc.2017.09.019
• Continue to leverage lessons learned from foundations built to optimize management and treatment of patients with aortic stenosis or mitral regurgitation
  – Collaborative multidisciplinary approach in managing patients to optimize outcomes: clinical, functional, anatomic, and Heart Team assessments

• Ongoing collaboration with sites
  – Create customized recruitment plan: provide materials for internal and external referral awareness, patient education materials
  – Continuously review recruitment challenges and screen failures, update patient process and inc/exclusion if appropriate
  – Mitigate complexities: create tools and provide support to facilitate complex assessments required, allow for screening consent, expedite core lab analysis and central screening committee turnaround reviews

• Ongoing collaboration with FDA
Patient Consent Issues

Charlie Davidson Northwestern
Jill Trekell Edwards
Patient Consent Issues
Best practices and “lessons learned”

Charles J. Davidson, MD, FACC, FAHA, FSCAI
Professor of Medicine
Vice Chairman for Clinical Affairs, Dept. of Medicine
Clinical Chief, Division of Cardiology
Medical Director, Bluhm Cardiovascular Institute
Northwestern University Feinberg School of Medicine
• It may be a transcatheter valve trial...
  – But EFS do not mirror Partner 3 CAP nor do they resemble Partner 1

• Patients are not necessarily extreme or high risk
  – Therefore, they have approved choices

• Predicate large datasets with outcomes are nonexistent
• Survival benefit of transcatheter therapy for TV disease is unknown
• Patients need to be screened, recruited and informed differently than your usual valve clinic initial encounter
While patients may get personal treatment benefit from participating in a clinical trial, they must understand that they:

– may not benefit from the clinical trial,
– may be exposed to unknown risks,
– are entering into a study that may be very different from the standard medical practices that they currently know.
It is difficult to be precise about safety or efficacy regarding:

– magnitude and/or likelihood of potential risks associated with the treatment

– time after procedure for recovery and QOL improvement.

– extent that the therapy is clinically competitive with existing alternatives.
What are Patient and Family questions in an EFS

• What is your experience with this device and with similar technologies?
• How many patients have been treated in US and OUS?
  – Is it approved OUS?
• What QOL Improvement expectation?
• What and how many adverse events have occurred?
  – What are the alternatives?
  – What are the additional options if the procedure or technology fails?
• What is the number and Frequency of pre-procedure and follow-up visits?
EFS Trials: The Conversation

• When we don’t know, we use terms such as “likely” or “unlikely” vs. “great” or low”.
  – These terms can be interpreted by patients in many ways.

• Instead of using general terms, focus on issues such as:
  – What outcomes have been studied in humans in previous trials?
  – What were the results in those studies?
  – Is there something that we wish that we knew, but they don’t yet?
EFS Trials: The Conversation

• **Step 1.** What are the patient and family goals?

• **Step 2.** What aspects of therapy does the patient consider important for decision-making?
  – What is the access route and anesthesia used?
  – What is the reversibility of therapy?

• **Step 3.** How proven is the treatment in this trial?

• **Step 4.** What are the alternatives for this patient?
EFS Trials
Additional Considerations

• Consent for testing
  – Timing of approaching patient for study
  – Who approaches the patient first?
    • MD should be first contact
    • How to initially approach patient by investigator, research team and clinical team

• Consent for Core lab Evaluation of prior testing
  – How to approach out of window screening studies
• Timing of additional testing, screening and review process
• Timing of scheduling the actual procedure
EFS Recruitment
Recipe for Success

• Screening of EHR and echo databases
• Assessment of medical conditions and I/E before contacting patient
• Communication with referring MD for contacting patients
• Show a video of the technology
• Explanation of other studies and various requirements to qualify
  – How to approach consent for multiple trials as anatomic qualification is not known on first visit
Patient Consent
Issues in Early Feasibility Studies

Jill Trekell
Edwards Lifesciences
June 12, 2019
21 CFR 50 Informed Consent Requirements

- Informed consent involves providing a potential participant with:
  - adequate information to allow for an informed decision about participation in the clinical investigation.
  - facilitating the potential participant's understanding of the information.
  - an appropriate amount of time to ask questions and to discuss with family and friends the research protocol and whether they should participate.
  - obtaining the potential participant's voluntary agreement to participate.
  - continuing to provide information as the clinical investigation progresses or as the subject or situation requires.

https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials
Informed Consent Challenges

While research subjects may get personal treatment benefit from participating in a clinical trial, they must understand that they:
- may not benefit from the clinical trial,
- may be exposed to unknown risks,
- are entering into a study that may be very different from the standard medical practices that they currently know.

To make an informed decision about whether to participate or not in a clinical trial, people need to be informed about:
- what will be done to them,
- how the protocol (plan of research) works,
- what risks or discomforts they may experience,
- participation being a voluntary decision on their part.

https://www.fda.gov/patients/clinical-trials-what-patients-need-know/informed-consent-clinical-trials
Challenges Unique to Early Feasibility Studies

- EFS programs have frequent learnings, translating into informed consent updates → IRB updates → reconsenting of previously enrolled patients
- Unknown/unanticipated risks and occurrence rates due to limited experience.
- Language can be intimidating to patients, ex: “An Early Feasibility Study like the one you are being asked to join means you will be among the first patients in the world to receive this experimental device. Prior to this study, the device has been used in an extremely limited number of patients (<15) …”
- Use of short form and screening informed consents to streamline process
Challenges Unique to Early Feasibility Studies

- Non-native English speaking patients
  - challenges for consent process
  - leads to higher translation costs due to the frequency of amendments.

- Managing patient expectations – the ‘experimental’ procedure may not contribute to the improvement of their condition as they may have hoped.

- Even with extensive informed consent process patients and their families may not fully understand risk of early feasibility studies and early device development process

- Sites with little EFS trial experience may not fully appreciate the nature of EFS, impact of learning and how it impacts risk/liability to the hospital
Procedural and Clinical Follow-Up Issues

Tamim Nazif Columbia
Chris Cain Conformal Medical
Implementation Strategies for Early Feasibility Studies
Topic 3: Procedural and clinical follow-up issues

Tamim Nazif, MD
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Clinical Perspective on EFS

• EFS: New procedures intended for diseases not previously treated or at least not treated in this way

• Devices often still in evolution

• Procedure not well established and may require flexibility/creativity

• Require organizational focus and additional resources

Rube Goldberg: Professor Butts and the Self-Operating Napkin
Communication with patient and family

- Honest communication focusing on unknowns is critical to establishing trust and appropriate expectations.

- Beyond simple device safety and efficacy, important unknowns may include:
  - Duration of procedure and hospitalization
  - Impact of unanticipated complications
  - Need for additional tests and/or procedures

- Clear commitment to follow-up requirements
Procedure Scheduling and Coordination

• Not just the patient and operator!

• Additional necessary personnel
  • Cardiac imagers, anesthesiologists
  • Industry personnel, proctors
  • Case example: Only 1 Proctor worldwide, requires month notice

• Device availability
  • Case example: “In short, it is held up in customs in Memphis and we will not have the device in time”
Additional Procedure Scheduling Concerns

• Training requirements
  • Bench and animal models
  • Refresher training if cases infrequent
  • Case examples:
    • Animal training on 3 separate occasions
    • Team to Israel for training

• Final Device and Case Review
  • Same week, night before, morning of?
When the day of the Case finally arrives!

• Patient may require admission prior
  • Case Example: ICU admission and Swan

• Very unpredictable, may take longer than expected

• Issues related to device availability, uncommon equipment requirement, ergonomics, etc

• Number of observers
  • Case Example: Sponsor requested ~ 10 people

• Unusual Requests
  • Case Example: Videotaping initial cases?
Clinical Follow-up Issues (In-Hospital)

- Duration of hospitalization, ICU stay may not be predictable
- Significant post-procedure burden on coordinators
  - More intensive follow-up, imaging studies, labs, etc.
- Financial implications
  - Case Example: Tricuspid case >30 day ICU stay, not reimbursed
- Sponsor expectations
  - Case Example: Request for daily progress updates for all patients
Clinical Follow-up Issues (long-term)

- EFS tend to be small studies and therefore more sensitive to loss of follow-up
  - Case examples:
    - Israel patient withdrawn from study
    - Texas patient successfully followed in NY

- May require more frequent or more intensive follow-up
  - Frequent visits
  - Additional imaging procedures

- Role for home visits, telehealth, etc?
Conclusions

• EFS are complex: new procedures for new diseases using devices that may still be in evolution

• Multiple challenges related to procedure scheduling, personnel availability, training requirements, costs

• Intra-procedural issues often require flexibility and creativity.
  • Minimize observers to those absolutely necessary

• Complete follow-up is critical and requires appropriate resources and strong commitment from both investigators and patients
Implementation Strategies for Early Feasibility Studies

Topic 3: Procedural and clinical follow-up issues

Chris Cain
VP, Clinical & Regulatory Affairs
Conformal Medical, Inc.
“An Early Feasibility Study (EFS) is a small clinical study designed to gain early insights into an innovative medical technology **during the development** process.”

MDIC Website
Prep for First Patient In…(the World/Hospital)

• Training
  • First in Human - unknowns
  • Animal Lab – model is not optimal
    • Scheduling
    • Create a training video
    • Additional device testing
  • Site Initiation Visit – Device/Procedure Training

• Scheduling Cases
  • Schedule 2-3 first day
  • Coordinating with many different stakeholders
When the day of the Case finally arrives!

- Hands-on refresher training
  - Operator
  - Imaging
  - Staff
- Not all is predictable
  - Anatomy may differ from pre-clinical
  - Device may not be final
- Making sure everything is the room
Clinical Follow-up

• EFS tend to be small studies and therefore more sensitive to missed visits and loss to follow-up
  • Patient Selection
  • Consent Process
  • Experienced Research Coordinators

• May require more frequent and more intensive follow-up
  • Additional visits, long-term follow-up (5-10 yrs)
  • Additional imaging, procedures

• Adverse Events
  • We don’t know what we don’t know
  • Monitors need to review case histories and other source documents with a clinical quality assurance mindset
Conclusions

Critical Team Attributes

• Experienced
• Skilled
• Flexible
• Collaborative
Wrap Up & Next Steps

David Holmes
Michael Mack
Conclusions

- Success in patient selection for EFS trials relies on integrating all aspects of the clinical trial into clinical care
- Identifying relevant patient population involves a lot of collaboration from Sponsors with:
  - Experts that can identify a relevant patient population based on trial specifics
  - Sites to understand their specific challenges in identifying and screening patients
  - FDA
Conclusions

• When communication with patients and getting consent
  • Patients must be screened differently than regular clinical trials
  • Use general terms with patients when communicating the technology that cannot be misinterpreted
  • MD should always be the first contact for patients
  • Need to clearly manage patient expectations
Conclusions

• Procedural and Clinical Follow-Up Issues
  • EFS is complex and involves devices that are still developing, need room for flexibility
  • Complete follow-ups are very important and require involvement from both investigators and patients
  • As a smaller study, may require more frequent and intensive follow-up to ensure every patient’s experience is accounted for