Society of Neurointerventional Surgery (SNIS)
EFS Breakout Session and Presentations

Westin Harbour Castle Hotel
Toronto, Ontario, Canada

July 25-29, 2022
MDIC would like to acknowledge the efforts of everyone who participated in the 2022 Society of Neurosurgeons Meeting July of 2022 in Toronto, Ontario, Canada. Your expertise and substantial contribution are critical to the mission and goals of the EFS program and we thank you for your work. Please see enclosed agenda and slides from the SNIS 2022 Annual Meeting. We look forward to our continued work and collaboration with you all.

**SNIS 19th Annual Meeting**

**Breakout Session on Early Feasibility Studies in the US**

**TUESDAY, JULY 26, 2022**

3:00 pm – 5:00 pm  Welcome

**DIDACTIC SESSION** A New Study Paradigm for Novel Medical Devices in the US-Early Feasibility Studies & NeuroVascular Device Development

“Trends in Neurovascular Clinical Studies and the Needs for an Effective Clinical Trial Ecosystem”

Moderated by:
Adnan Siddiqui, M.D., Ph.D., Vice-Chairman and Professor of Neurosurgery
State University of New York at Buffalo
&
Ansaar Rai, M.D., MBA, Chairman of Neuroradiology & Professor of Neuroradiology, Neurosurgery, & Neurology
West Virginia University

**Setting the Stage**

3:00 pm – 3:10 pm  EFS Origin Story – “EFS: A Useful Tool in the Development of Novel Medical Devices”
Andrew Farb, M.D., Co-Leader of the CDRH Early Feasibility Study Program
U.S. FDA

3:10 pm – 3:20 pm  MDIC Mission & Achievements to Date – “Process Improvement in the EFS Clinical Trial Ecosystem: A Collaborative Effort”
Chip Hance
MDIC Board Champion

3:20 pm – 3:30 pm  The Academic Side – “Leveraging the University of California System to Improve Stroke Care”
Steve Hetts, M.D., Professor and Chief of Interventional Neuroradiology  
*UCSF*

**Real World Case Studies**

3:30 pm – 3:40 pm  
“*A Sponsor’s View: Utilizing the EFS Pathway for a Novel Neurointerventional Device*”  
Bruce Van Deman, MBA, Sr. Director, Global Clinical Operations, Neurovascular | CSF  
*Medtronic*

3:40 pm – 3:50 pm  
Start Up Perspectives –  
Adel Malek, M.D., Ph.D., Co-Founder  
*Cerevasc*

3:50 pm – 4:00 pm  
EFS vs Pivotal Lessons Learned: A Sponsors Perspective  
Dave Haan, Sr. Director Global Clinical Affairs  
*Stryker*

4:00 pm – 4:10 pm  
FDA Review Perspectives – “Perspectives on Neurovascular Clinical Studies”  
Xiaolin Zheng, Ph.D., Division Director, Office of Neurological and Physical Medicine Devices  
*U.S. FDA*

**Neurovascular Initiative Working Group Updates**

4:10 pm – 4:20 pm  
MCTA Working Group  
Chip Hance  
*MDIC Board Champion*

4:20 pm – 4:30 pm  
ICF Working Group  
Nora Hadding, J.D., Sr. Vice President, Regulatory Affairs, Clinical Affairs, Quality Assurance  
*Imperative Care*

**Open Discussion**

4:30 pm – 5:00 pm  
How should all the stakeholders come together to ensure a robust ecosystem for the conduct of neurovascular clinical studies in the U.S.?  
*Discussion among all presenters and attendees*
Early Feasibility Studies
A Useful Tool in Developing Novel Medical Devices

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

- Provides the basis for iteration & product improvement
- Integral to the device development process
Early Feasibility Studies (EFS)

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 if nonclinical tests are 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 EFS Guidance Principles

• Less nonclinical data may be needed for IDE approval vs. a larger clinical study of a finalized device design.

• Just-In-Time Testing (JITT): Doing the right nonclinical tests at the right time
  – May defer some nonclinical testing until the device design has been finalized for use in a pivotal study
  – Comprehensive testing in early stages of device development may add cost without return

Increased opportunities for leveraging information and data for EFS
The EFS Journey

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
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 neurological, cardiovascular, and GI/renal/GU device areas
- US is the go-to location for select EFS device areas
Building a Successful US EFS Ecosystem

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

David R. Holmes, Jr, MD,a Robert Califf, MD,b Andrew Farb, MD,b Dorothy Abel, BSBME,b Michael Mack, MD,c Tamara Syrek Jensen, JD,d Bram Zuckerman, MD,b Martin Leon, MD,e Jeff Shuren, MDb

- Gov’t: FDA and CMS
- Industry Sponsors
- Inventors/Innovators
- Investigators
- Clinical Sites
- Private Funders and Payers
- Patients
- IDE approval
- IRB approval
- Insurance coverage
- Contracting, budgeting, and indemnification
- Site start-up
- Patient enrolment
MDIC CV EFS Site Consortium

- MDIC Tools
  - Master clinical trial agreement
  - Informed consent document template
  - Educational materials for IRBs, research staff, and study subjects

- Commitment to efficient completion of key EFS administrative steps
  - (60/60/60 days)
    - FDA IDE and IRB approval
    - Contract and budgeting execution
    - 1st Subject Enrolled

Vision: A voluntary, open research network of clinical sites committed to high quality, efficiently executed EFS
EFS Site Consortia Best Practices

• Managing risk, adverse events, and IRB reporting
• Developing strategies to speed up site start-up processes
• EFS staffing and resources
• Timely and effective contracting and budgeting

• Patient identification, enrollment, and retention
• Consent challenges and solutions
• Optimizing in-hospital procedures and out-patient clinical follow-up
• Coverage determinations
CMS

• CMS coverage can be a critical step for EFS initiation and continuation
• CMS generally will not cover true a first-in-human EFS
  o Some 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

<table>
<thead>
<tr>
<th>No EFS IDE CMS EFS Coverage</th>
<th>EFS IDE CMS Coverage Category A Experimental</th>
<th>EFS IDE CMS Coverage Category B Nonexperimental/Investigational</th>
</tr>
</thead>
</table>
| Reasonable and necessary care & services costs and device cost not covered | • Reasonable and necessary care & services costs covered  
• Device cost not covered | Reasonable and necessary care & services costs and device cost covered |

Complications in Medicare beneficiaries are covered regardless of whether or not the EFS IDE itself is covered

• Can transition from Category A to Category B with supportive clinical data and knowledge base
• Sponsors encouraged to discuss investigational plans with CMS
Starting EFS Conversations With CDRH

• Begin interactions early to discuss device development and test plans
  – Utilize Q-Submission program
  – Informational meetings useful for complex novel devices or target populations

• Reach consensus on data needed for EFS IDE approval
  – Device evaluation strategy to support basic safety and proof of principle
  – Use of leveraged data
    • Testing on prototypes
    • Clinical data (if available)
    • Information in the public domain
  – Animal studies
  – Clinical study risk mitigations for enhanced patient protections
  – Clinical study protocol

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

Guidance for Industry and Food and Drug Administration Staff

https://www.fda.gov/media/114034/download
Andrew Farb, MD
andrew.farb@fda.hhs.gov
MDIC Initiative for EFS in the US: Cardiovascular Experience Applied to Neurovascular Studies

Co-Chairs
Adnan Siddiqui, MD – Director of Neurological Research, University of Buffalo
Chip Hance – Industry Veteran and MDIC-EFS Initiative Board Champion
Eileen Mihas – MDIC EFS Program Director

July 2022

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 60 members including FDA and CMS
MDIC: Who We Are

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

60+ participating member organizations

300+ subject matter experts involved in working groups

70+ resources available to download in our digital resource library

35+ active working groups and committees

Example Members
Defining Regulatory Science

The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products.
Our Core Initiatives and Program Areas

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

**CLINICAL SCIENCE**
- Clinical Diagnostics • Early Feasibility Studies • Science of Patient Input

**DATA SCIENCE AND TECHNOLOGY**
- Case for Quality • Cybersecurity • Computational Modeling & Simulation • External Evidence Methods • SHIELD • 5G-Enabled Health Technologies • Pathology Innovation Collaborative Community

**HEALTH ECONOMICS AND PATIENT VALUE**
- Real-World Evidence • Patient Preference Research

**NEST COORDINATING CENTER (NESTcc)**
- Real-World Evidence • Research Methods • Data Quality • Research Implementation • Data Network • Active Surveillance • Unique Device Identifier Adoption • Collaborative Community
Background on EFS in the United States

The Early Feasibility IDE pathway in the U.S. was established by the FDA in 2013. FDA has streamlined the approval process of EFS studies to less than 60 days on average. Industry Sponsors, especially for structural heart innovations, have been very active with EFS.

After early take-up of EFS, bottlenecks appeared between the Sites and Sponsors, especially Contracting and Budget negotiations.

- The median time for 1st Subject Enrollment was almost one year (2014-17); not competitive with international standards.
- The best sites were achieving less than 4 months; fully competitive with expectations.

MDIC championed an effort with leading sites to lift the overall EFS clinical trial ecosystem to Best-in-Class performance.

- Have set a target of “60/60/60” to shave months of study prep time.

Perceptions (and Reality) are changing – the U.S. is increasingly a preferred destination for early study of these novel patient therapies.

Improvement in the clinical trial ecosystem contributes to FDA’s Vision:

“Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.”
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)

Early Feasibility Study (EFS) Metrics Baseline

<table>
<thead>
<tr>
<th>EFS Metric Category</th>
<th>2017 Average Time From Site Packet Received to 1st Patient Enrolled</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDE Approval</td>
<td>60 days</td>
</tr>
<tr>
<td>IRB Approval</td>
<td>60 days</td>
</tr>
<tr>
<td>Contract Approval</td>
<td>60 days</td>
</tr>
<tr>
<td>1st Subject Enrollment*</td>
<td>60 days</td>
</tr>
</tbody>
</table>

‡Baseline metrics collected by MDIC from EFS trials conducted FY14 – FY17, compiled from 13 EFS trials and 48 sites
Need for Collective Stakeholder Efforts for Improvement

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

David R. Holmes, Jr., MD,1 Robert Califf, MD,1 Andrew Farb, MD,1 Dorothy Abel, BS,MBE,1 Michael Mack, MD,2 Tamara Syrek Jensen, JD,4 Bram Zuckerman, MD,4 Martin Leon, MD,4 Jeff Shuren, MD4

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

We Work Together Under the MDIC Construct
Commit to pursue efficient administrative steps:
- IRB Approval
- Contract Execution
- 1st Subject Enrolled
- “60/60/60” (Days)

Track and report EFS Metrics

Test the utility of EFS specific tools and methods

Serve as a launching point for a future network of high-performing sites
- Nationwide coverage
- Multiple therapeutic areas
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/
EFS Studies Have Been Challenging to Execute But Ecosystem Has Improved

Source: MDIC Annual Public Forum presentation by Liliana Rincon-Gonzalez, September 2019. FY18-19 data from an additional 9 EFS trials across 60 Sites
Experienced Sites Achieve Excellent Results

What is Possible?

Northwestern Medicine Bluhm Cardiovascular Institute in Chicago, IL timelines for 10 Early Feasibly Studies (EFS) including:
- 3 Heart failure studies
- 7 Transcatheter valve studies

<table>
<thead>
<tr>
<th>Start-up timelines</th>
<th>Days to IRB</th>
<th>Days to CTA</th>
<th>Days to Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>67.0</td>
<td>72.0</td>
<td>98*</td>
</tr>
<tr>
<td>Median</td>
<td>60.5</td>
<td>64.5</td>
<td>97*</td>
</tr>
</tbody>
</table>

Definitions:
- Days to IRB: days elapsed from receipt of regulatory/budget packet to IRB approval
- Days to Clinical Trial Agreement (CTA): days elapsed from receipt of regulatory/budget packet to fully negotiated CTA
- Days to Enrollment: days elapsed from the later IRB or CTA to first enrollment

Personal Communication: Lynne Goodreau, RN, MSN
Administrative Director, Bluhm Cardiovascular Institute- Clinical Trials Unit, Northwestern Medicine
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
Vision for a Neurovascular EFS Working Group

In recent years, neurovascular companies with innovative transformative products conducted their feasibility clinical research outside the U.S. for timeliness and efficiency among other reasons.

Lack of participation by U.S. clinicians and regulators (FDA) in early-stage clinical research limits the opportunity for U.S. input into product design and clinical application of novel device technology.

We envision a collaboration between Industry Sponsors, leading neurovascular clinical sites and FDA under the umbrella of the Medical Device Innovation Consortium (MDIC).

Following the model established for cardiovascular EFS research, we are striving to streamline Neuro EFS clinical research in the U.S. through:

• Identifying collaboratively the common ecosystem challenges for EFS clinical research
• Developing (or adapting existing) tools to facilitate the conduct of more EFS clinical research in the U.S.

MDIC helps coordinate the collaboration of willing and interested Sponsors and Sites in the volunteer effort.

Improvement in the clinical trial ecosystem will contribute to FDA’s Vision:

“Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.”
Clinical Sites

- West Virginia University
- Mount Sinai
- Emory Healthcare
- Prisma Health
- Cooper University Hospital
- Advocate Aurora Health
- Atrium Health
- Baptist Health South Florida
- Brigham and Women’s Hospital
- Cedars Sinai
- Cleveland Clinic
- Columbia University Irving Medical Center
- Dartmouth-Hitchcock
- Greer Memorial Hospital
- Grady
- Houston Methodist
- NYU Langone Health

MDIC
Medical Device Innovation Consortium
Industry
At This Session, Two Working Groups Reporting Their Work

- Master Clinical Trial Agreement Working Group
- Informed Consent Working Group
To Conclude
Lessons Learned from Cardiovascular to Achieve Meaningful Clinical Trial Ecosystem Improvement:

• Sustained multi-stakeholder leadership and engagement (5+ years)
• Measure system performance and establish metric expectations
• Collaboratively develop tools to streamline processes
• Frequent communication throughout the ecosystem
Interested in working with us?

Contacts:

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chiphance@regattamedical.com

MDIC Website: [http://mdic.org](http://mdic.org)
EFS Email: [EFSPilot@mdic.org](mailto:EFSPilot@mdic.org)
Leveraging the University of California System to Improve Stroke Care: The UC Stroke Consortium

Steven W. Hetts, MD
Professor of Radiology
Neurointerventional Radiology
University of California, San Francisco
steven.hetts@ucsf.edu
Disclosures

- Founder equity: Filtro Medical
- Scientific advisory, Stock Ownership: ThrombX
- Data Safety and Monitoring Committee: Route 92, Imperative
- Core Imaging Lab: MAPS, SURMOUNT, ATLAS, SCENT, FRED
- Grant support: NCI, NIBIB, NINDS, Siemens
Take Home Point

• Working together benefits operations, research, and patient care
What does this sign mean?
In the ICU, slipping hazard
At the beach, watch for cliff
At the mall, no breakdancing
During the apocalypse, no zombies
High technology imaging


High imaging technology and health care expenditures

A. R. Margulis, J. Kucharczyk, S. W. Hetts, A. M. Werne

Special Report

AJNR: 16, January 1995

‘... and Do No Harm.’

Steven Hetts, Alison Werne, and Grant B. Hieshima

Alexander Margulis, MD

Grant Hieshima, MD
UCSF IR Research Laboratory
Hospitalizations for Ischemic Stroke

https://nccd.cdc.gov/DHDSPAtlas/?state=County

Data Sources

Medicare Provider Analysis and Review (MEDPAR)
Centers for Medicare & Medicaid Services, Part A
Website
Strokes in California
Mechanical Thrombectomies in Urban Cores despite Strokes Everywhere
Leveraging the University of California System to Improve Stroke Care

- Unique opportunity for statewide stroke care system: CSCs at multiple UC med centers, each with regional hub-and-spoke network
- Can we leverage this to make California the safest place to have a stroke?

**Improved coverage:** rural and distant areas, underserved areas and communities, telestroke

**Improved patient flow:** EMS

**Improved care:** quality

**Improved efficiency:** reducing variability and cost

**Improved research:** NINDS StrokeNet, multisite clinical trials
UC Stroke Consortium: Research Collaborations, Clinical Trials, Common IRB, & Data Group

Goals
• To create standardization in data collection and implementation across the system
• To understand what’s already being collected and could be easily standardized between sites
• To be intentional about what we collect; we don’t want to mine data without purpose
• To leverage Common IRB

Objective
• Determine minimum amount of data to be collected on each stroke patient beyond GWTG
• Create inventory of current data being collected, and gap analysis of what to standardize
• Implement a standardization plan for data collected across campuses
• Determine feasibility of Reliance Registry for Common IRB

Metrics / measures of success
• Implement the Reliance Registry for Common IRB use across campuses
• Creation of standardized data dictionary for use at the state level
• Standardized data collection
In 2018, UC Collectively Received More than 50% Greater NCI-Funding Than Any National Peer

Total 2018 NCI Funding by Institution

<table>
<thead>
<tr>
<th>Institution</th>
<th>Percent</th>
<th>Total Funding</th>
</tr>
</thead>
<tbody>
<tr>
<td>UC Davis</td>
<td>13%</td>
<td>$30,126,744</td>
</tr>
<tr>
<td>UC Irvine</td>
<td>5%</td>
<td>$10,724,671</td>
</tr>
<tr>
<td>UC Los Angeles</td>
<td>28%</td>
<td>$63,843,988</td>
</tr>
<tr>
<td>UC San Diego</td>
<td>16%</td>
<td>$35,703,665</td>
</tr>
<tr>
<td>UC San Francisco</td>
<td>38%</td>
<td>$85,203,576</td>
</tr>
<tr>
<td>UC Total</td>
<td>100%</td>
<td>$225,602,644</td>
</tr>
</tbody>
</table>

Source: NIH Database - 2018 NCI Award Funding

Having received 50% more NCI funding than the closest competitor, UC faces a unique opportunity to leverage its resources to lead high impact research and clinical excellence.
NINDS Funding: UC System

NINDS Project Grant Funding FY18-20

- UC Davis
- UC Irvine
- UCLA
- UCR
- UCSD
- UCSF

[Bar chart showing funding distribution for UC campuses.]
NINDS Funding: Individual Institutions

NINDS Funding FY 2018 ($M)
UC Data Warehouse Review
Total UC Patient Cohort
7/2018-6/2020
Aneurysmal Subarachnoid Hemorrhage Across the UC System

From UC Data Warehouse on October 23, 2020
All Patients with Ruptured Brain Aneurysms or SAH
7/2018-6/2020
Embolizations for Ruptured Aneurysm/SAH Treatment 7/2018-6/2020
Craniotomies for Ruptured Aneurysm/SAH Clipping 7/2018-6/2020
Build a Cohort
(Two years of data last refreshed June 2020)

Click on one of the Tabs above to start building your cohort by adding specific Diagnoses, Labs, Medications, & Procedures.
Patient counts reflect criteria displayed in the frames to the right of the graphs below. Criteria are selected from within their respective Tabs (above).

CNS Infusion for Intracranial Vasospasm
7/2018-6/2020
CNS Infusion “with” Verapamil for Intracranial Vasospasm 7/2018-6/2020
Build a Cohort (Two years of data last refreshed June 2020)

Click on one of the Tabs above to start building your cohort by adding specific Diagnoses, Labs, Medications, & Procedures. Patient counts reflect criteria displayed in the frames to the right of the graphs below. Criteria are selected from within their respective Tabs (above).

PTA for Intracranial Vasospasm 7/2018-6/2020
Acute Ischemic Stroke Across the UC System

From UC Data Warehouse on October 23, 2020
Patients with acute ischemic stroke undergoing catheter angiography
Patients with acute ischemic stroke undergoing intracranial mechanical thrombectomy
Patients undergoing intracranial mechanical thrombectomy
Rare and Wonderful Diagnoses and Procedures Across the UC System

From UC Data Warehouse on October 23, 2020
Patients who have had an encounter with a squirrel

Mystery diagnosis - any guesses?

Patients who have had an encounter with a squirrel
Cerebral angiograms in children
Patients with hereditary hemorrhagic telangiectasia (HHT)
**NIH Enrollment Table**  (Two years of data last refreshed June 2020)

Patient counts reflect criteria displayed in the right frame which are selected in their respective tabs.

<table>
<thead>
<tr>
<th>Racial Category</th>
<th>Hispanic or Latino</th>
<th>Not Hispanic or Latino</th>
<th>Unknown</th>
<th>Grand Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Indian or Alaska Native</td>
<td>1</td>
<td>21</td>
<td>1</td>
<td>33</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td>178.0</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1</td>
<td>8</td>
<td>9</td>
<td>18</td>
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<tr>
<td>MultiRace</td>
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<td>6</td>
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<tr>
<td>Native Hawaiian or Other Pacific Islander</td>
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<td>Other Race</td>
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<tr>
<td>Unknown</td>
<td>41</td>
<td>15</td>
<td>34</td>
<td>149</td>
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<tr>
<td>White</td>
<td>34</td>
<td>235</td>
<td>7</td>
<td>455</td>
</tr>
<tr>
<td>Grand Total</td>
<td>90</td>
<td>289</td>
<td>47</td>
<td>700</td>
</tr>
</tbody>
</table>
UC Stroke Consortium: CSC/GWTG Best Practices

Rationale
• Each UC site has established workflows intended to optimize patient care and meet stroke center standards.

Scope
• This workgroup will serve as a forum to explore variations in approaches, disseminate successes, and solve stroke center problems.

Goals
• Our initial focus will be on optimizing EVT systems by comparing the workflows of each site.
UC Stroke Consortium

University of California Health

Steering Committee
Steve Hetts, Chair
Alex Khalessi, VC

Executive Sponsor
Don Larsen

Research, Trials & Data
Comprehensive Stroke Center Best Practices & Education
Pediatrics
Robotics
Strategic Sourcing
Rehab & Recovery
Telehealth/Telestroke

Systemwide Workgroups
Objective
• 1. To advance robotic assisted Neurointerventional procedures
• 2. To enable/advance remote robotic procedures
• 3. To develop integration throughout the UC system to achieve these aims

Goals
• 1. Share experience with Robot via the Group to accelerate improvements
• 2. Create prospective database of cases
• 3. Plan and implement Study to test remote work
• 4. Achieve cross credentialing to enable 3 above

Metrics / measures of success
• 1. approved UC Reliance study for prospective database
• 2. successful implementation of remote work
  • A. first using models (no IRB required)
  • B. application for IRB in clinical study
When will we have remote controlled image-guided endovascular robots performing thrombectomies for strokes in distant hospitals?
Objective
• To create a forum for leaders to collaborate across UC Health for purpose of improving clinical, financial and operational metrics

Goals
• Learn, create and share best practice to improve quality and outcome
• Collaborate on strategic sourcing initiatives and new product introductions
• Identify and/or implement utilization strategies (i.e. procedural, products, process, resource)

Metrics / measures of success
• Improved Price Competitive Index
• Inventory reduction
• Improved resource utilization and Supply Intensity Metrics
• Improved Clinical Quality and Outcomes
• Improved Action Operational Intelligence (OI) Scores
## Strategic Sourcing Impact

<table>
<thead>
<tr>
<th>Site</th>
<th>Supplier 1</th>
<th>Supplier 2</th>
<th>Supplier 3</th>
<th>Supplier 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCD Health</td>
<td></td>
<td>$ 60,245.88</td>
<td>$ 2,941,853.60</td>
<td></td>
<td>$ 3,002,099.48</td>
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<tr>
<td>UCI Health</td>
<td>$ 117,292.00</td>
<td>$ 112,892.48</td>
<td>$ 1,636,954.50</td>
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<td>$ 1,867,138.98</td>
</tr>
<tr>
<td>UCLA Health</td>
<td>$ 364,408.00</td>
<td>$ 438,138.72</td>
<td>$ 166,645.00</td>
<td></td>
<td>$ 6,119,775.94</td>
</tr>
<tr>
<td>UCSD Health</td>
<td>$ 1,041,300.00</td>
<td>$ 128,581.77</td>
<td>$ 2,614,685.38</td>
<td></td>
<td>$ 3,784,567.15</td>
</tr>
<tr>
<td>UCSF Children’s Hospital Oakland</td>
<td>$ 5,210.70</td>
<td></td>
<td></td>
<td></td>
<td>$ 5,210.70</td>
</tr>
<tr>
<td>UCSF Health</td>
<td>$ 131,084.00</td>
<td>$ 161,014.30</td>
<td>$ 12,455,168.80</td>
<td></td>
<td>$ 12,747,267.10</td>
</tr>
<tr>
<td><strong>Total Sum by supplier</strong></td>
<td>$ 1,654,084.00</td>
<td>$ 906,083.85</td>
<td>$ 166,645.00</td>
<td>$ 24,799,246.50</td>
<td></td>
</tr>
</tbody>
</table>

Achieved $2.2M by introducing a more competitive environment.
UC Stroke Consortium: Recovery and Rehabilitation Group

Objective
- To facilitate **swift, equal access** to stroke recovery and rehabilitation **clinical care** and **research participation opportunities** for all UC patients
- To identify and **champion emerging recovery and rehabilitation science** that will improve lives after stroke
- To **set the standards for scientifically informed treatments** at UC and beyond

Goals
1. To develop searchable UC Stroke Recovery & Rehabilitation website for patients, caregivers, potential research collaborators.
2. To create a detailed living library of site-specific resources for enhanced internal and external collaboration.
3. To execute a multi-site telerehabilitation project and, as byproducts:
   a) develop an integrated clinical/research database, and
   b) evidence-based domain-specific assessments to include clinical, neuroimaging, biospecimen, and other elements.

Metrics / measures of success (Relative to Goals above):
1. Published website
2. At least 1 new instance of cross-site research collaboration, research participant referral, mentorship, or care delivery
3. IRB approval and successful participation across at least 3 UC sites, with:
   a) data infrastructure with multimodal capacity (e.g., imaging, neurophysiology, biospecimens), and
   b) harmonized assessments across sites toward a “UC Stroke RnR Battery”
Objective

1. To advance Telestroke care, throughout the spectrum of stroke care, for stroke patients throughout the region.
2. To develop integration throughout the UC system to achieve this aim.

Goals

1. To share best practices throughout the UC system for advancement of telestroke care
2. To develop optimal patient care
3. To develop financially sustainable initiatives to support that care.

Metrics / measures of success

1. Successful implementation of collaborations.
2. Increased numbers of patients seen using collaborative/standardized processes
UC Multi-Campus Research Initiative

- SA1. Establish a data science training program & perform data science projects on systemwide stroke data
- SA2. Centralize & streamline IRB
- SA3. Facilitate contracting & legal review
- SA4. Coordinated community outreach
- SA5. Enhanced educational content
- SA6. Best clinical practices database
- SA7. Competitive internal pilot grants
  - Robotics project for 2023
Take Home Point

• Working together benefits operations, research, and patient care
Thank You

steven.hetts@ucsf.edu
A Sponsor’s View:
Utilizing the EFS Pathway for
Novel Neurointerventional Devices

Bruce Van Deman
Sr. Director, Global Clinical Research | Medical Sciences
Medtronic Neurovascular

July 2022
Background for Early Feasibility Study (EFS)

The 21st Century Cures Act and Early Feasibility Studies

Enacted by Congress in 2016, the 21st Century Cures Act was designed to help accelerate medical product development and bring new innovations and advances to patients who need them faster and more efficiently.¹

The U.S. Food and Drug Administration (FDA) early feasibility study (EFS) guidance document is an important component of these efforts.²


Early Feasibility Study Objectives

An early feasibility study (EFS) is a limited clinical investigation of a device early in development, typically before the device design has been finalized, for a specific indication.

Holmes et al., Early Feasibility Studies for Cardiovascular Devices in the United States. JACC State-of-the-Art Review. JACC Vol 76, No 23, 2020

Innovative device/novel therapy for a new or established intended use, marketed device for a novel clinical application.
Clinical | Regulatory Strategy: Purpose of Early Feasibility Studies

*Insights into proof of concept*

These early proof of concept studies may form the basis for further device iteration and improvement.

Create an early opportunity for collaboration between sponsors, investigators, and regulators.

**Design robust pivotal trial**
Clinical | Regulatory Strategy: Iterative Device Development Process

Early clinical experience obtained from an EFS increases the efficiency of the device development process

- Experience and knowledge gained from initial study subjects can guide device or protocol changes
- The EFS Guidance includes new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study
- Enables sponsors and regulators to think in new ways about:
  - Fostering innovation and device development
  - The appropriate evidence needed to move from bench to initial clinical experience- ‘Just in time’ testing approach*
  - The implementation of timely device and clinical protocol modifications

Ref: Early Feasibility Studies Overview. EFS Site Best Practices Workshop
*Andrew Farb, Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies
Clinical | Regulatory Strategy: Transition EFS to Pivotal

Streamlined transition to pivotal → reduced total time to Approval

- **EFS**
  - First generation

- **Pivotal**
  - Finalized Device design

- **Regulatory submission to FDA**
  - Complete Characterization

- **Market Clearance**

*Pre-Submission facilitates communication for the 30-day review period*
1. Early FDA involvement in device development lifecycle
   - Opportunity for less bench testing to support initial clinical experience

2. Incorporation of iterative changes
   - Proposed test plan are discussed with FDA in conjunction with contingent proposed test plan and 5-day reporting

3. Interactive review
   - Enhanced communication between FDA and the Sponsor for Supplements and Amendments
EFS Program Growth

Ref: Early feasibility studies overview. EFS Site Best practices workshop, 2019
EFS Submission and Approval Trends in the Neurovascular Space

EFS IDEs reviewed and approved by the FDA Office of Neurological and Physical Medicine Devices, 2015-2019.

Five-year summary of the types of EFSs that were submitted to and approved by the FDA Office of Neurological and Physical Medicine Devices.

Insights from a Medtronic Case Study

Investigational Device
- Novel neurological thrombectomy device
  - ClinicalTrials.gov Identifier: NCT05074186

Background
- Collaborative research partnership with the Jacobs Institute
- Submitted EFS application with preliminary bench and animal data
- Approval for 15 patients experience

Current Status
- Initial experience with 4 patients treated
- Insights into procedural characteristics and therapeutic parameters are assessed through the iterative process
Conclusions

1. The EFS framework provides a pathway to facilitate timely device and protocol modifications based on insights from human clinical use

2. The EFS pathway is applicable to products that are novel and first-in-class therapies

3. The EFS process creates review efficiencies that includes interaction with regulators

4. EFS human subject protection measures follow the same rigor and processes as for any IDE
Thank you!
EFS vs Pivotal Lessons Learned

A Sponsors Perspective

David Haan, MS, MBA, PMP
Sr Director, Global Clinical Affairs
Stryker Neurovascular

Trenza™ Embolization Device
**Trenza™ Embolization Device**

**Overview**

- Intrasaccular neck bridge for wide-neck (sidewall or bifurcation) aneurysms; allows placement of subsequent coils

- 6-12mm sizes (7 SKUs); DFT (Nitinol/Platinum) Braid
- Ease of use (delivery / sizing)
- Conformability for odd shaped aneurysms
- May reduce need for adjunctive devices such as stents / DAPT
Trenza™ Embolization Device

Familiar procedure

Frame
1-2 Trenza braids

Fill and finish
Coils per standard of care

Source: Images courtesy of Stryker R&D, not indicative of clinical performance
# Trenza™ Embolization Device
## First-in-Human → IDE US Study

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study Design</strong></td>
<td>Prospective, multi-center, single-arm, non-randomized clinical study</td>
</tr>
</tbody>
</table>
| **Intended Population**       | Unruptured + ruptured, saccular, **wide-neck between 6-12mm** Bifurcation or sidewall with D:N ratio <2 or neck ≥3  
  • Basilar apex (BA), middle cerebral artery (MCA) bifurcation, internal carotid artery terminus (ICA-T), or anterior communicating artery complex (ACOMM) |
| **Sites and Subjects**        | Up to 7 → 20 Sites / 30 → 150 Subjects                                                                                                        |
| **Primary Safety Endpoint:***  | Stroke-related neurological death  
  OR  
  Major ipsilateral or disabling stroke within 12 months                                                                                   |
| **Primary Effectiveness Endpoint:*** | Raymond I at 12 months  
  OR  
  Stable Raymond II                                                                                                                            |

---

TRENZA Embolization Device is the brand name for Citadel; Device referenced as Citadel Embolization Device in regulatory and clinical filings
Images courtesy of Stryker Corporation
CAUTION: Investigational Device – Limited by Federal (or United States) law to investigational use.
The Paradox of Early Feasibility

Breakthrough Technology
“EFS may be conducted on new devices without prior clinical experience and in some cases, may also be conducted on devices with limited prior clinical experience.”

Successful Trial
• Sponsor companies want successful trials to ensure success of new technology
• May lead to careful patient selection
• May lead to moderate physician training requirements

1 https://www.fda.gov/medical-devices/investigational-device-exemption-ide/early-feasibility-studies-efs-program#devices
# Stryker Feasibility → IDE Learnings

<table>
<thead>
<tr>
<th>Patient Eligibility</th>
<th>Original</th>
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</thead>
<tbody>
<tr>
<td>• All patients have specific model (15d image upload → procedure date)</td>
<td></td>
</tr>
<tr>
<td>• Unruptured patient population only</td>
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<th>Physician Training</th>
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</tr>
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<tbody>
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<td>• Single aneurysm model</td>
<td></td>
</tr>
<tr>
<td>• Single PI / site</td>
<td></td>
</tr>
<tr>
<td>• Enrollment capped at 6 pt / site</td>
<td></td>
</tr>
</tbody>
</table>

[https://www.reifyhealth.com/](https://www.reifyhealth.com/)
# Stryker Feasibility → IDE Learnings

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<th><strong>Patient Eligibility</strong></th>
<th>Original</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>• All patients have specific model (15d image upload → procedure date)</td>
<td></td>
<td>• Shorter pre-case activity timeframe</td>
</tr>
<tr>
<td>• Unruptured patient population only</td>
<td></td>
<td>• Added ruptured patient population</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Implementation of Reify StudyTeam's patient screening tool</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Physician Training</strong></th>
<th>Original</th>
<th>Current</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Single aneurysm model</td>
<td></td>
<td>• Multiple models, common anatomy</td>
</tr>
<tr>
<td>• Single PI / site</td>
<td></td>
<td>• Patient-specific model for complex only</td>
</tr>
<tr>
<td>• Enrollment capped at 6 pt / site</td>
<td></td>
<td>• Two sub-PI’s per site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Enrollment capped at 20% of total</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Quarterly investigator meetings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Quarterly newsletters</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Enrollment blasts for each new site or subject enrolled</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• I/E pocket cards</td>
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https://www.reifyhealth.com/
# Stryker Feasibility → IDE Learnings

<table>
<thead>
<tr>
<th></th>
<th>Original</th>
<th>Current</th>
<th>Future</th>
</tr>
</thead>
</table>
| **Patient Eligibility** | • All patients have specific model (15d image upload → procedure date)  
  • Unruptured patient population only | • Shorter pre-case activity timeframe  
  • Added ruptured patient population  
  • Implementation of Reify StudyTeam\(^1\) patient screening tool | • MRA or DSA imaging at 6-month timepoint  
  • + Eligibility committee members  
  • JPEG image upload |

| **Physician Training**   | • Single aneurysm model  
  • Single PI / site  
  • Enrollment capped at 6 pt / site | • Multiple models, common anatomy  
  • Patient-specific model for complex only  
  • Two sub-PI’s per site  
  • Enrollment capped at 20% of total  
  • Quarterly investigator meetings  
  • Quarterly newsletters  
  • Enrollment blasts for each new site or subject enrolled  
  • I/E pocket cards | • On-site visits at 6wk intervals to review screening logs / eligibility criteria  
  • + Steerco for physician-physician interaction and enrollment discussions  
  • Monthly study coordinator calls to share lessons learned and enrollment strategies |

https://www.reifyhealth.com/

August 8, 2022
Conclusions

• Trenza Embolization Device utilized the Early Feasibility Pathway
• EFS provided a more streamlined path to clinical trial
• New technology led Stryker to implement:
  • careful patient selection
  • physician training requirements
• These requirements have inhibited rapid enrollment
• Forums for sharing EFS best practices are encouraged
FDA Perspectives on Neurovascular Clinical Studies

Xiaolin (Lin) Zheng, PhD, MS
Director, Division of Neurosurgical, Neurointerventional and Neurodiagnostic Devices
Office of Neurological and Physical Medicine Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health
U.S. Food and Drug Administration
IDE Application

• Needed for clinical investigations conducted in the US for significant risk device studies
• 30 calendar day review time for all IDEs
• For timely approval of IDE studies, ensure that the application is complete and all device-related risks have been appropriately mitigated through the risk analysis
Significant Risk Device Study

Most new neurointerventional device studies will require an IDE to be conducted in the US if clinical performance data is needed to support a future marketing application because they are considered significant risk (SR) device studies (21 CFR 812.3(m)):

– Intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;
– Is purported or represented to be for use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
– Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or
– Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
Study Risk Determination

• **Other device study risk decisions**
  – Non-significant risk (NSR)
    • IDE is not needed and study can initiate after IRB approval
  – Exempt
    • If the device is being used per its FDA approved label and the study protocol and consent form comply with the labeled indication
  – Basic physiological research (BPR)
    • Only investigating a physiological principle; not evaluating the safety or effectiveness of any regulated device.
    • No IDE is needed, but IRB approval and informed consent are required.
  – Not a device study
Study Risk Determination Q-Submission

• For studies that are not exempt (SR, NSR, BPR), sponsors are responsible for making an initial study risk determination and presenting it to the IRB.

• FDA is available to help the sponsor, clinical investigator, or IRB in making study risk determinations in a Study Risk Determination Q-Submission.

• FDA is the final arbiter as to study risk.
IDE Study Types

• Pivotal Study
  – Designed to collect definitive evidence on safety and effectiveness for a specified intended use, typically in a statistically justified number of subjects

• Sponsor-Investigator Studies
  – Not intended to support a marketing application
  – Typically only for research purposes

• Traditional Feasibility Study
  – Capture preliminary safety and effectiveness data typically in a small number of subjects (typically to inform pivotal study)
  – Typically 20-30 subjects
IDE Study Types (Cont...)

• Early Feasibility Study (EFS)
  – Small number of subjects (generally < 10 subjects)
  – Device may be early in development, before final device design
  – Approval may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study on a more final device design
    • If additional nonclinical testing would not provide the information needed to advance the device design validation, verification, and development process.
  – EFS IDEs are often submitted for novel device designs or new patient populations where no or limited prior device treatments or experience exist to gather early human study data
    • It is difficult to assess device safety and performance that is clinically relevant in animal studies because there are not good surrogate animal models to represent neurovascular diseases (e.g., stroke, intracerebral hemorrhage, intracranial aneurysms)

– Guidance “Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies”
EFS IDE Application

• Risk Analysis
  – What are the potential risks to the patient?
  – Does the study mitigate the risks where possible?
    • Non-clinical performance testing
    • Clinical study design
  – Are the risks outweighed by the potential for benefit and/or value of the study?

• Informed Consent
  – Important part of risk mitigation to appropriately inform potential subjects of their risks, potential benefits, and alternative treatments by participating in the proposed clinical study
  – Must meet the requirements of 21 CFR 50.20 and must include the basic information required by 21 CFR 50.25(a).
EFS IDE Application

• Investigational Plan and Clinical Protocol (21 CFR 812.25)
  – Selection criteria
  – Study objectives and outcomes (formal statistical analysis plan not needed)
  – Patient safety monitoring procedures (e.g., data monitoring committee (DMC) and charter, stopping rules)
    • DMC may not always be required for a single site EFS, but is a useful study risk mitigation
  – Collect all adverse events, including transient events such as TIAs.
  – Follow-up plan
  – Sample size (< 10-15 subjects) and number of investigational centers, with justification
  – Usually a single-arm study
    • Uncertainty should be minimized as much as possible to ensure the outcomes can be used to inform subsequent clinical investigations
  – Cannot be used to support a marketing application to inform the safety and effectiveness of a medical device

• See FDA “IDE Application” website as a helpful resource (https://www.fda.gov/medical-devices/investigational-device-exemption-ide/ide-application)

www.fda.gov
FDA Decisions on IDEs
Three Outcomes

• **Approval**
  – Approves the trial for specified number of sites and subjects
  – Enrollment can begin once IRB approval is obtained

• **Approval with conditions**
  – Approves the trial for specified number of sites and subjects provided conditions (deficiencies) are addressed within 45 days
  – Deficiencies are usually minor safety concerns that can be addressed in a straight-forward manner
  – Enrollment can begin once IRB approval is obtained

• **Disapproval**
  – Study may not begin; sponsor must address deficiencies and obtain FDA approval to start study
Revision to FD&C Act, July 2012

• FDA shall not disapprove an IDE because:
  – The investigation may not support a substantial equivalence or de novo classification determination or approval of a device
  – The investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or an additional or different investigation may be necessary to support clearance or approval of the device

• This means that an IDE cannot be disapproved on the basis of FDA’s belief that the study design is inadequate to support a future PMA, 510(k), humanitarian device exemption (HDE), or de novo classification.
  – Disapproval is based on concerns related to subject safety and protections
FDA Additional Comments on IDEs

• **Study Design Considerations**
  – Recommendations (but not requirements) regarding study design to help study achieve its goals

• **Future Considerations**
  – Issues relevant for future submissions (e.g., future larger clinical studies (feasibility or pivotal) and marketing applications)

• **Sponsors are **not required** to respond to these elements although most do respond to ensure they have an adequate study design.**
Engage with FDA Early

• Pre-Submission Program
  – FDA guidance, “Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program”
  – Voluntary
  – Obtain FDA written feedback prior to an intended regulatory submission
  – Opportunity for a teleconference meeting after written feedback is received
References – FDA Guidances

- Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors: Significant Risk and Nonsignificant Risk Medical Device Studies
- Factors to Consider when Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions
- Requests for Feedback and Meetings for Medical Device Submissions: The Q-Submission Program
- FDA Categorization of Investigational Device Exemption (IDE) Devices to Assist the Centers for Medicare and Medicaid Services (CMS) with Coverage Decisions
Master Clinical Trial Agreement (MCTA) Neurovascular Working Group

MDIC Early Feasibility Studies Program
Chip Hance
MDIC Board Champion on Behalf of the Working Group

July 26, 2022
2

**Background:**

**Neurovascular MCTA Working Group**

- In recognition that Sponsor-Site contracting is the most time-consuming element of setting up a clinical trial, and each Sponsor and Site “reinvents the wheel” in establishing contracting parameters for each study...

- MDIC set out in 2018 to develop a Master Clinical Trial Agreement pre-negotiated between leading Sponsors and Clinical Sites

- Published in 2018, revised in 2019 and utilized by several Cardiovascular Sponsors for Structural Heart EFS studies, the MCTA has streamlined contracting in several instances.

- A neurovascular working group was convened in 2022 of interested Sponsors and Clinical Sites to review the MCTA and determine changes required for neurovascular studies.

18 Lawyers met Feb 2018 to draft EFS Master Agreement and Standardize Key Contract Language

Thanks to Our Working Group

Jaime Walkowiak, JD
Sarah Long, MS, Advocate Aurora
Ron Austin, JD, MBA, Imperative Care
Ryan Runella, JD, MBA, Johnson & Johnson
Robert Herrmann, PhD, MCRA
Lindsey Skerrett, JD, Medtronic
Nagesh Uppuluri, MBA, PhD, MicroVention

Ronen Eckhouse, MBA, Rapid Medical
Conor Flynn, JD, Sloan Kettering
Jessica Hoogs, JD, Stryker
Ted Chun, Stryker
Steve Hetts, MD, UCSF
Eileen Han, JD, UCSF
Tiffany Lutskus, JD, West Virginia University

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
The goal of the MCTA is to facilitate efficiencies in the EFS contracting process by providing:

- (1) a starting point for contract negotiations with a priori agreement of 90% or greater, and
- (2) allow both parties to focus on remaining legal resources on the remaining 10% (or less) of the EFS MCTA requiring negotiation in mind

The MCTA is truly a master agreement and is applicable for EFS and Pivotal Trial

- Between trials, the only elements that should change are the Statement of Work (SOW), Budget, and Informed Consent

---

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
The agreement contains several comprehensive components (including but not limited to):

- Several subheadings of contract-specific language applicable to the sponsor, clinical trial site, facilities (or CRO), and principal investigators and/or sub-investigators
- Subject Enrollment & Informed Consent - although a patient informed consent standalone template also exists
- Compensation and Financial Reporting
- Records, reporting, regulatory activities, IRB requirements
- Material ownership, Intellectual Property, and Work Product
- Confidentiality
- Privacy and HIPAA
- Publication and Trial Results
- Indemnification, Insurance, and Limitation of Liability

MDIC Master Clinical Trial Agreement (MCTA)
EFS MCTA (Sections 2-4)

2 Scope of Work.

2.1 Conduct of the Trial. The Institution, through the applicable Principal Investigator and Sub-investigators, shall use reasonable efforts to conduct each Trial, and shall do so in accordance with this Agreement, the applicable SOW, the applicable Protocol, and the applicable

3 The Principal Investigator and Sub-investigators. The Principal Investigator and Sub-investigators are employees of Institution (or its affiliate physician and/or hospital organization), are otherwise affiliated with Institution, are under contract with the Institution, or are members of the Institution’s medical staff. The Principal Investigator will be identified in

4 Representations and Covenants. The Institution and, to the extent that such representations and covenants relate to the Principal Investigator, the applicable Principal Investigator each make certain representations, certifications and covenants to SPONSOR, as follows:

4.1 the Principal Investigator is, and at all times during the course of the Trial shall be, qualified by training and experience with appropriate expertise to conduct the Trial;

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
5 **Facilities.** The Institution and the applicable Principal Investigator shall conduct each Trial at the Institution, or such other facilities as SPONSOR and the Institution may agree in writing (each, a “Facility”). Such agreement by SPONSOR may be conditioned on SPONSOR requirements communicated at the time a Facility is proposed, which requirements may without limitation include or be based on (i) site visit, (ii) review of site selection questionnaire, (iii) ... 

6 **Subject Enrollment and Informed Consent.**

6.1 **Subject Enrollment.** The Principal Investigator shall only enroll subjects into the Trial in accordance with the applicable SOW and the applicable Protocol (each a “Subject”). The Principal Investigator shall use reasonable efforts to complete enrollment prior to any Subject Enrollment Closing Date set forth in writing to the Principal Investigator by SPONSOR. The ... 

7 **Compensation; Fair Market Value.**

[Link to EFS MCTA (Sections 5-7) on MDIC website]
# EFS MCTA (Sections 8-11)

8 **Financial Disclosure and Reporting.**

8.1 **Financial Disclosures by Principal Investigator.** At SPONSOR’s written request, the Principal Investigator shall promptly provide to SPONSOR financial disclosure statements in compliance with 21 C.F.R. Part 54, in the form consistent with regulatory requirements as required by SPONSOR and applicable to the Principal Investigator under Sub-investigators under the

9 **Trial Device.** The Trial Device shall only be used as described in the applicable Protocol and in compliance with Applicable Laws, including those pertaining to Investigational Device Exemptions. The parties acknowledge that the Trial Device has not been cleared or approve

10 **Disclaimer.** WITHOUT LIMITING SPONSOR’S OBLIGATIONS UNDER THIS AGREEMENT, SPONSOR DOES HEREBY DISCLAIM ANY AND ALL ADDITIONA

11 **Records; Reports; and Regulatory Assistance.**

11.1 **Trial Documentation.** For each Trial, the Institution and the Principal Investigator ensure that the preparation, maintenance and retention of complete, current, accurate, organized and legible Trial Documentation (as defined below) is performed in a man

12 **Audit, Monitor and Review.** For each Trial, SPONSOR or its authorized representatives shall have the right, upon advance written notice, and at mutually agreeable times during regular business hours, to: (a) audit Institution and all Facilities used in performance of the Trial, up

13 **Changes to the Protocol.** No change in a Protocol shall be made by the Institution or the Principal Investigator without prior approval of SPONSOR and the IRB. Notwithstanding the foregoing, subject to any Applicable Laws relating to the safety of Subjects that may require a deviation from the Protocol, the Institution shall promptly notify SPONSOR and the IRB of the

14 **Regulatory Inspections.** If any governmental or regulatory authority (a) contacts the Institution or the Principal Investigator with respect to a Trial, (b) conducts, or gives notice of its intent to conduct, an inspection at any Institution or Facility in connection with a Trial, or (c) takes, or gives notice of its intent to take, any other regulatory action that is known to

15 **Ownership of Materials, Intellectual Property and Work Product.**

15.1 **Materials.** SPONSOR shall own all right, title and interest (collectively, “Rights”) in and to any equipment, materials, methods, documents, data, software and information supplied by or on behalf of, or purchased at the expense of, SPONSOR (collectively, “Materials”) in

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
EFS MCTA (Sections 16-25)

16 Confidential Information.

16.1 Definition. SPONSOR shall not disclose Confidential Information to Institution unless it is necessary to the Trial. For purposes of this Agreement, “Confidential Information” means any information of SPONSOR, institution, or trial that does not have the status of the Patent

17 Privacy and HIPAA.

17.1 Covered Entities. For each Trial, the Institution and the applicable Principal Investigator each represent, certify and covenant that they may be or have affiliates that are “Covered Entities”

18 Publication and Use of Trial Results.

18.1 Trial Data. For each Trial, the Institution and the applicable Principal Investigator acknowledge and agree that the data collected during the Trial as required by the applicable Protocol ("Trial Data"), except as otherwise provided in Section 15.8, is owned by SPONSOR

19 Use of Name; Advertising.

19.1 Use of Name. Subject to Applicable Laws, none of the Institution, the Principal Investigator or SPONSOR shall mention (in writing) or otherwise use the name, trademark, trade name or

20 Indemnification, Insurance and Limitation of Liability.

20.1 Indemnification by SPONSOR. SPONSOR will indemnify, defend and hold harmless the Institution, the Facility, where Institution conducts the Trial, the IRR, solely with respect to its

21 Term. Except as otherwise provided in this Section 21, this Agreement shall be effective as of

22 Termination.

22.1 Right to Terminate or Suspend Trial. SPONSOR or the Institution may terminate or suspend any Trial at the Institution’s facilities immediately upon written notice to the other for safety.

23 Independent Contractor. In undertaking to perform the respective services hereunder, the Institution and the Principal Investigator are doing so as independent contractors, and not as

24 Assignment. No party shall assign this Agreement or any rights or obligations hereunder without the prior written consent of the other parties, except that SPONSOR, without the

25 Severability. If any provision of this Agreement is held to be invalid, illegal or unenforceable, in any respect, then, to the fullest extent permitted by Applicable Law and if the rights or

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
EFS MCTA (Sections 26-37)

26 **Governing Law.** Intentionally omitted.

27 **Notices.** Any notice, request or other communication permitted or required under this Agreement shall be in writing, shall refer specifically to this Agreement and shall be deemed given only if hand delivered or sent by an internationally recognized overnight delivery service.

28 **Survival.** The respective rights and obligations of the parties set forth in Sections 6, 7 (other than the first sentence), 8-12, 14-20, 22, 27 and this Section 28 shall indefinitely survive the termination of this Agreement.

29 **Entire Agreement.** This Agreement, the applicable SOW, and all exhibits and schedules thereto, constitutes the entire agreement among the parties hereto with respect to the subject hereof.

30 **Amendment.** Any amendment or modification to this Agreement or any SOW must be in writing and signed by authorized representatives of each party.

31 **Waiver.** A party’s failure to enforce, at any time or for any period of time, any provision of this Agreement, or to exercise any right or remedy shall not constitute a waiver of that provision.

32 **Inconsistency.** In the event of any inconsistency between this Agreement or a SOW and a Protocol, the terms of the Protocol shall prevail with respect to matters of medicine, science,

33 **Construction.** Except where the context requires otherwise, whenever used the singular includes the plural, the plural includes the singular, the use of any gender is applicable to all genders, the word "includes" has the inclusive meaning represented by the phrase "including" and the

34 **Counterparts and Electronic Signature.** This Agreement may be executed in two or more counterpart copies, each of which shall be deemed an original and all of which taken together shall be deemed to constitute one and the same instrument. Electronic signatures by facsimile

35 **Force Majeure.** Neither party shall be liable for any failure to perform as required by an SOW to this Agreement to the extent such failure to perform is due to circumstances reasonably beyond such Party’s control, including without limitation, labor disturbances or labor dismutes

36 **Compliance with Laws.** In addition to Applicable Laws, the parties and their respective affiliates, as applicable, will to adhere to the provisions of (i) the United States federal anti-kickback statute 42 U.S.C. 1320a-7(b) and the related safe harbor regulations; (ii) the

37 **Rights of Third Parties.** Nothing in this Agreement is intended to confer on any party that is not a party (or Principal Investigator) to this Agreement any right to enforce any term of this Agreement.
EFS MCTA (Exhibits)

- In addition to the contract-specific language, the agreement also includes exhibits which can include:
  - The Statement of Work
  - Protocol
  - Trial Budget (and subsequent payment schedule)

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
Accelerating Timelines by Utilizing MDIC Tools

**EFS Success Stories Highlights**

**Start-up Conformal Medical**, was able to launch EFS in **26 days** using MDIC’s MCTA Template and mentioned MDIC’s tools as “a guiding light in the EFS space”

**Start-up preCARDIA**, has launched sites much faster using the EFS Background Information: IRBs and Site Study Staff document to help members understand EFS better. They also use MDIC’s MCTA Template and MDIC’s ICF Template and have been able to accelerate their time to Fist Subject Enrollment by **50%**!

**Start Up 4C Medical and Brigham and Women’s Hospital** completed clinical trial agreement using MDIC’s MCTA Template in **under 90 days**; completed IRB Approval using MDIC’s ICF Template in **under 1 month**!

EFS Clinical trial agreement negotiations used to take Northwestern Bluhm Cardiovascular Institute up to **6 months**. After adopting MDIC’s MCTA Template with start up companies, it only takes **4-6 weeks**!

**Columbia University Irving Medical Center**: Using the MCTA, research staff have been able to cut time needed to finalize an EFS **contract from about 45 days to about 30 days**. “That’s been a huge help to us...”

https://mdic.org/resource/efs-master-clinical-trial-agreement-mcta/
Interested in working with us?

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MDIC Website:  http://mdic.org  
EFS Email:  EFSPilot@mdic.org
Patient Informed Consent Form Template
Working Group Update

MDIC Early Feasibility Studies Program

Nora Hadding, JD, SVP, Regulatory Affairs, Clinical Affairs, Quality Assurance, Imperative Care
On Behalf of the Working Group

July 26, 2022
Thanks to Our Working Group

Jaime Walkowiak, JD
Katie Wozniak, Advocate Aurora
Suzanne LaScalza, Cerenovus/Johnson & Johnson
Nora Hadding, JD, Imperative Care
Mohamad Bydon, MD, Mayo
Devjani Saha, PhD, MCRA
Nathan Lampi, JD, Medtronic

Sheila Warner, MicroVention
Michaella Corso, Penumbra, Inc.
Holly Keller, BSN, RN, Stryker
Elizabeth Boyd, PhD UC
Steve Hetts, MD, UCSF
Maxim Mokin, MD, University of South Florida
An MDIC Structural Heart Working Group developed a template for Patient Informed Consent to help streamline Early Feasibility Studies in 2018; revised again in 2020.

As the Neurovascular Initiative kicked off in 2021, there were questions whether the Template was suitable for neurovascular studies:

- Emergent
- Planned

Our Group reviewed the template and considered the unique aspects of neurovascular and made some modest revisions

Specifically, we considered the differences for emergent and planned studies and determined a single template would still be suitable.

This revised template can streamline Sponsor development of an EFS Patient Informed Consent benefiting from the experience of many Sponsors and Clinical Sites
Patient Informed Consent Form Template

• The ICF Template targets adult patients considering participation in a study being conducted under an IDE (Investigational Device Exemption) for EFS Medical Device Clinical studies which include certain FIH (First in Human) studies

INFORMED CONSENT TO PARTICIPATE IN AN EARLY FEASIBILITY STUDY
Title of Study: EARLY FEASIBILITY STUDY OF THE [INSERT DEVICE NAME]

Principal Investigator: [INSERT INVESTIGATOR NAME]
Sponsor: [INSERT SPONSOR NAME]
Emergency Telephone: [INSERT INVESTIGATOR PHONE]
Elements of the EFS Informed Consent Form

INTRODUCTION
You have been invited to join an Early Feasibility Study to evaluate the [INSERT GOAL OF STUDY] of [INSERT NAME OF THE DEVICE]. The device is investigational and not approved by the FDA for your medical condition. A description of this study will be available at

PURPOSE AND BACKGROUND
The reason we are doing this research study is to look at the [INSERT STUDY DEVICE] to see if it can help treat [INSERT MEDICAL CONDITION]. This type of research study is called a “early feasibility study”. Early feasibility studies typically evaluate innovative devices or innovative uses

Elements of the EFS Informed Consent Form

PRIOR INFORMATION AVAILABLE ON THE DEVICE

[NOTE IF THIS IS A FIRST IN MAN STUDY OR INSERT PRIOR CLINICAL EXPERIENCE WITH THE DEVICE IN THE SAME OR DIFFERENT MEDICAL CONDITION]. *Examples: This early feasibility study is the first time the Study Device will be used to treat humans, or the device*

WHO CAN PARTICIPATE IN THE STUDY

To find out if you meet all the requirements for this early feasibility study, your Physician will ask you questions and check your medical records. Before you decide to be in the study, be sure you understand all the information given and ask your Physician any questions you may have about

Elements of the EFS Informed Consent Form

STUDY PROCEDURE

Once your Physician determines you are a good candidate for this study, your Physician will conduct study-related assessments to determine if you are eligible for the study. These assessments include:

GENERAL STUDY PROCEDURES

[DESCRIBE STUDY PROCEDURES AND INDICATE WHICH, IF ANY, ARE EXPERIMENTAL AND HOW THEY DIFFER FROM THE STANDARD OF CARE]

STUDY DURATION

Your participation in the study will end after [INSERT STUDY DURATION].

Your study doctor or [Sponsor] may stop the research study or may stop your participation at any

Elements of the EFS Informed Consent Form

PARTICIPANT RESPONSIBILITIES

If you decide to participate in this study, you must follow the instructions given by your study doctor and return to the hospital for all study follow-up visits. Completing all study visits and following the study doctor’s instructions is important to make sure that the study results are

RISKS AND DISCOMFORTS

There might be unexpected risks from being in this type of early feasibility research study. This is because there may be limited experience with the Study Device. New information from this research study may give the Sponsor useful information to improve the device and procedure to

RISK MITIGATION STRATEGIES:

[Bullets may be added or deleted as required.]

The Sponsor has done the following things to reduce the risks to subjects.

Elements of the EFS Informed Consent Form

POSSIBLE BENEFITS IF YOU JOIN THIS STUDY

There might be potential benefits to you, but there is limited information to predict how likely you will experience benefit. Potential benefits of the [INSERT DEVICE NAME] may include [INSERT POTENTIAL IMPROVEMENT OF PATIENT CONDITION OR DISEASE without overstating.

OTHER TREATMENTS AVAILABLE

Alternative therapies for your medical condition may include [INSERT POTENTIAL ALTERNATIVE THERAPIES AND THE BENEFITS, RISK AND LIMITS]. Your Physician will discuss your situation with you and will recommend the best treatment for you, including how the

YOUR PARTICIPATION IS VOLUNTARY

Your participation is entirely voluntary. If you wish to participate in this early feasibility study, you will be asked to sign this form. Please take time to read this information carefully and to discuss it with your family, friends, and Physician before you decide.

Elements of the EFS Informed Consent Form

CONFIDENTIALITY OF STUDY RECORDS AND MEDICAL RECORDS

Information collected for this study is confidential. Access to your personal medical information will be limited to the purposes of collection and processing information necessary for the completion of this study.

STUDY RELATED INJURY

If physical injury happens to you because of your involvement in this early feasibility study, medical treatment will be available, if appropriate, at the hospital. This may include [INSERT LIST OF TREATMENTS OR REFER TO SOURCE OF FURTHER INFORMATION]. Contact your

NEW STUDY FINDINGS

During the course of this study, you will be provided with any significant new findings that may affect your willingness to continue participating in this study.

Elements of the EFS Informed Consent Form

RIGHTS AND COMPENSATION

You will not be paid to participate in this study. Your hospitalization and procedures will be considered part of your routine medical care. By signing this form, you do not give up any of your legal rights and you do not release the study Physician or other participating institutions from their

WHO TO CONTACT IF YOU HAVE QUESTIONS?

If you have any questions about taking part in this study, or if you think you may have been injured because of your participation in the study, call [INSERT INVESTIGATOR NAME] at [INSERT INVESTIGATOR PHONE]. If you have any questions about your rights as a study patient, you

PATIENT'S STATEMENT

I have been given a chance to ask questions about this study. These questions have been answered to my satisfaction. If I have any more questions about taking part in this study, I may contact [INVESTIGATOR NAME] at [INVESTIGATOR PHONE].

One-Page Background Document on EFS

• In addition to the template, there also exists a separate one-page document entitled *Background Information on Early Feasibility Studies* that complements the ICF Template

• Both the one-page document and ICF Template are based on FDA Guidance “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”, issued on: October 1, 2013
  • The background document is intended for hospital administration, IRBs, Ethics Committees, Research Staff at clinical sites/institutions and others involved in the execution of an EFS

• The document addresses the following topics:
  • What is an “Early Feasibility Study”?  
  • What are the types of studies and options under EFS?  
  • What does participation in an EFS mean for the patient?  
  • What safeguards are in place for patient protection as an EFS participant?

MDIC Early Feasibility Studies Content

- **2022**: MCTA and ICF updates for Neurovascular Initiative
- **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**: EFS Background Information: IRBs and Site Study Staff & Patient Introduction to Informed Consent Form (ICF)
- **2017**: Contract Language Library & Negotiation Tool
- **2016**: MDIC 2016 Blueprint for Early Feasibility Study Success

https://mdic.org/program/early-feasibility-studies-efs/
Interested in working with us?

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