Early Feasibility Studies (EFS)
Administrative & Clinical Practices:
MDIC Working Group (WG) Kickoff

March 6th 2017
Welcome on behalf of our leadership:

• Co-Chairs
  – Dr. Andrew Farb (FDA)
  – Dr. Aaron Kaplan (Dartmouth-Hitchcock, Serial Entrepreneur)
  – Chip Hance (MDIC Board Champion)

• Program Management
  – Dan Schwartz (MDIC)
  – Owen Faris, Ph.D. (FDA Director, Clinical Trials Program)
  – Dr. Shawn Ahmad (Clinical Fellow-MBA Scholar, Dartmouth)
Agenda

- Welcome (Chip) 10 mins
  - Vision and Landscape
  - Goals and Objectives
  - Resources
  - Introductions

- FDA/CDRH Perspective (Andy/Owen) 10 mins

- Working Group Subgroups 30 mins
  - Performance Metrics
  - Contracting
  - Clinical & Site Practices

- Discussion and Next Steps 10 mins
Growing Interest in EFS Process Efficiency

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

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

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.
EFS Steering Committee Formation

Drs. David R. Holmes Jr (leader), Michael Mack, Marty Leon, Bram Zuckerman (FDA), Jeff Shuren (FDA), Joseph Chin (CMS), Tamara Syrek Jensen (CMS), Chip Hance (Industry/MDIC)

Co-Chairs:
Andy Farb
Aaron Kaplan
Chip Hance
Vision

Through the collaboration of its participants, the EFS Administrative and Clinical Practices Working Group will improve US Early Feasibility Study (EFS) efficiency through the development and dissemination of best practices and tools for both sponsors and sites, and continuous assessment via performance metrics.
# EFS Participation Landscape

## 2015/2016 EFS Participant Data

<table>
<thead>
<tr>
<th>Category</th>
<th>Company</th>
<th>Hospital/academic</th>
<th>Total per division</th>
<th>% of all EFS IDE submitted in 2015 &amp; 2016</th>
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<td>DCD (cardiovascular)</td>
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<td>DSD (surgical)</td>
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<td>9</td>
<td>10%</td>
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<tr>
<td>DNPMD (neuro)</td>
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<td>DRGUD (reproductive, gastro-renal, urological)</td>
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<td>DOD (orthopedic)</td>
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<td>DAGRID (anesthesiology, general hospital, infection control, dental)</td>
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<td>OIR (office of invitro diagnostics and radiologic health)</td>
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</table>

| Total                                 | 46      | 42                | 88                 | 100%                                   |
Goals and Objectives

1) Performance Metrics Subgroup:
   - Catalog EFS Performance Metrics (2015 & 2016)
   - Establish and publish IRB Best Practice Tools and Processes
   - Develop an annual EFS Database reporting process for publicly communicating performance metric updates (2017 and beyond)

2) Contracting Subgroup:
   - Develop EFS-specific Clauses and Templates
   - Establish and publish Contracting Best Practice tools and processes

3) Clinical and Site Practices Subgroup:
   - Identify differences between EFS and other studies
   - Establish and publish Clinical Best Practices tools and processes
Abstract: (From Slide #4)

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.
# Introductions

<table>
<thead>
<tr>
<th>Individual</th>
<th>Organization</th>
<th>WG Role</th>
<th>Organization Role</th>
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<tbody>
<tr>
<td>Chip Hance</td>
<td>MDIC Board of Directors</td>
<td>Co-Chair</td>
<td>Ecosystem</td>
</tr>
<tr>
<td>Andy Farb, MD</td>
<td>CDRH</td>
<td>Co-Chair</td>
<td>Ecosystem</td>
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<td>Aaron Kaplan, MD</td>
<td>Dartmouth</td>
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<td>Owen Faris</td>
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<td>Ecosystem</td>
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<td>Dan Schwartz</td>
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<td>Project Manager</td>
<td>Ecosystem</td>
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<td>Shawn Ahmad, MD</td>
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<td>Project Manager</td>
<td>Site</td>
</tr>
<tr>
<td>Jaime Walkowiak, JD</td>
<td>Baylor Research Institute</td>
<td>Sub-group Lead: Contracting</td>
<td>Site</td>
</tr>
<tr>
<td>Kenneth Wang, MD</td>
<td>Mayo: Gastroenterology (NinePoint Medical)</td>
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<td>Site (Sponsor)</td>
</tr>
<tr>
<td>Tamim Nazif, MD</td>
<td>Columbia</td>
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<td>Site</td>
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<td>Clay Cohorn</td>
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<td>Sponsor (Large)</td>
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<td>Julie Selstrom</td>
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<td>Cook (Med Institute)</td>
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<td>Todd Fonseca</td>
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<td>Mark Deem</td>
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<td>Sponsor (Small - Mid)</td>
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<td>NAMSA (CRO)</td>
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<td>Sara Vidmar</td>
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Acknowledging the US Early Feasibility Study (EFS) Problem

- Growing awareness of the time lag in the access to beneficial medical devices for US patients
- Initial clinical testing of novel devices moved to non-US sites
- Some devices developed exclusively for non-US markets
- Concern that device innovation may follow overseas

Many clinical trial ecosystem factors contributed to these trends including FDA’s requirements to initiate clinical studies of new devices in the US
Purposes of EFS

- Operator technique challenges
- Other human factors
- Patient characteristics that may impact device performance
- Safety
- Device failure modes
- Whether the device performs its intended purpose
- Therapeutic parameters

OBTAIN INSIGHTS

www.fda.gov
EFS Program Objectives

- Provide the *earliest* patient access to potentially beneficial medical devices in the US
- Maintain or regain US leadership in medical device innovation

- Encourage close collaboration between developers and users
- Provide clinical study continuity throughout:
  - Early clinical use
  - Pivotal studies
  - US approval
  - Post-approval
EFS Definition

Elements that define an EFS:
– Small number of initial subjects
– Device that may be early in development, typically before the device design has been finalized
– Does not necessarily involve a device’s first clinical use
– Needed when information to advance device development cannot be practically obtained with additional nonclinical assessments, or if nonclinical tests are unavailable

A US EFS may be done concurrently or in conjunction with non-US clinical studies
Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013
EFS Guidance

**Key Guidance Principle** - IDE approval of an EFS may be based on less nonclinical data than would be needed to support the initiation of a larger clinical study of a more finalized device design

**Guidance Provisions** - A toolkit that enables sponsors and regulators to think in new ways about device development

- Emphasizing
  - Clinical condition
  - Availability, benefits, and risks of alternative treatments
  - Incorporating risk mitigation strategies, enhanced monitoring, and tailored consent process to enhance patient safety
- Justifying the appropriate evidence needed to move from bench to clinical study
Just-In-Time Testing (JITT)

Doing the Right Testing at the Right Time

• It may be acceptable to defer some nonclinical testing until the device design has been finalized for use in a pivotal study

• Comprehensive testing in early phases of device development may add cost without return
  – Testing could have limited future applicability if the device is modified
  – Time-consuming, non-informative testing delays device access to patients who may have limited alternatives
Device Iteration During an EFS

- Experience and knowledge gained from initial study subjects can guide device or protocol changes
- Rounds of regulatory submissions and review can delay the implementation of changes and impede study progress

The EFS Guidance includes new approaches to facilitate timely device and clinical protocol modifications during an early feasibility study

- 5-day notices
- Contingent approval
- Interactive review
CDRH EFS Review Progress

Early Feasibility Study IDEs

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<th>Year</th>
<th>Received</th>
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<tr>
<td>FY 2016</td>
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# Performance Metrics Subgroup

## Deliverables
- Working Group participation letter
- Retrospective database of EFS performance metrics, 2015 though June 2017
- Prospective EFS Database updates, July 2017 forward
- EFS Performance Metrics Summary published by MDIC

## Process
- Develop EFS Performance Metric Intake Forms for sites and sponsors
- Establish protocols for data gathering and sharing with participants
- Conduct EFS Best Practice interviews with sites and sponsors
- Update database quarterly

## Action Items
- *Identify personnel for Metric and Best Practice telephone interview (Q2, 2017)*
- *Provide EFS Performance Metrics to MDIC (Intake Forms complete: Q2, 2017)*
- *Conduct EFS interviews (Q2, 2017)*

## Group Membership
- TBD
### SPONSOR EFS INTAKE FORM

#### SITE ENROLLMENT PERFORMANCE METRICS
(SINGLE OR MULTI-SITE EFS)

**MDIC WG Number**
(by EFS Project)

**Date Format:** Date entries should appear in the format DD-MMM-YYYY (e.g., 05-May-2009). The month abbreviations are as follows:
- January = Jan
- February = Feb
- March = Mar
- April = Apr
- May = May
- June = Jun
- July = Jul
- August = Aug
- September = Sep
- October = Oct
- November = Nov
- December = Dec

**Number Format:** Number entries should appear with a leading zero in the format where appropriate (e.g., 07 for the number seven).

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<th>Total Number of Subjects Enrolled</th>
<th>Did Site Reach Enrolment Goal?</th>
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**Version Date:** 17-FEB-2017
Performance Metrics Subgroup: Process & Confidentiality

Confidential EFS Metric Discussions* (CDA/NDA, if required)

- EFS Performance Metric Collection
  - EFS site or sponsor completes Performance Metric Intake form
  - Return Intake form to MDIC

- Performance Metric Anonymization
  - De-identify EFS performance metrics
  - Aggregate into Performance Metric Database
  - Bucket metrics by CDRH division

Public-Facing Outputs and Reporting‡

- Performance Metric Dissemination
  - Inform WG of Metric Database updates
  - WG review of performance trends
  - Identify & distribute EFS Performance Metric goals

EFS Learnings Discussions

- MDIC collects EFS narratives (phone)
- Review Clinical and Administrative successes
- Identify improvement opportunities

- EFS Learnings Anonymization
  - De-identify site or sponsor narratives
  - Generalize to highlight EFS wins and improvement opportunities

- EFS Learnings Dissemination
  - Ascertain clinical & administrative best practices
  - Develop EFS Regulatory Science tool & process

*2 – 6 hours per site or sponsor estimated
‡1 – 2 hours per monthly EFS WG Meeting
# Contracting Subgroup

## Deliverables

1. Sample a Library Documents
2. Streamlined Contracting Process
3. Harmonize Contract clause language with Informed Consent Form (ICF) language, where applicable

## Process

- Sharing of de-identified contracts and/or clauses (e.g. Indemnification)

## Action Items

- *Identify WG member/organization Subgroup contributors (Q1, 2017)*
- *Next Subgroup meeting (Q1, 2017)*
- *Blind/generalize contracts/clauses*

## Group Membership

- Jaime Walkowiak
- Dan Schwartz
Subject Injury

- **EFS Unique Considerations:** Unproven nature of device, Specific Circumstances of EFS (vs. other trials), etc.

- **Injury/Illness Reimbursement Scope from the Sponsor**
  - Injury/Illness coverage
  - Definitions: “Unanticipated” vs “Potential” Adverse Events (AE)s, “Reasonable and Necessary,” and “Study-related” expenses

- **Use of Private Insurance for study-related injuries**
  - Site, Sponsor, Private Payer, Public Payer (e.g. CMS)
  - Patient Out-of-Pocket: Co-payments, deductibles, etc.
Confidentiality Exceptions

• **EFS Similarity Considerations:** Emergent patient care, timely site-sponsor communications, focus on similarities to other pre-market trials.

• **Legally Required Disclosures**
  - Subpoena/Court Order/FDA vs. Protective Order timelines
  - Sponsor notification(s)

• **Medical Treatment Disclosures**
  - Confidentiality Obligation as a condition to treat
  - Medical judgement regarding treatment timing
Sponsor Termination

• **Immediate Agreement Termination vs. Site Remediation**
  – Remediation timeframe
  – Breach specificity:
    • Confidentiality Breach
    • Protocol Non-compliance (Gross non-compliance)
    • Compromises to patient safety
    • FDA or IRB action regarding study conduct
Informed Consent Harmonization

Opportunity: Clearly outline the uniqueness of EFS studies to potential subjects

- Evolving Device Design
- Potential Benefits Related to their specific disease state
- Unique risk mitigation strategies
- Financial Situation (who pays etc.) including a clear explanation of how third party payer (if any) billing will be handled
- Specifics concerning treatment that will be provided in the event of an injury, including an explanation of the obligations the sponsor has contractually accepted with respect to reimbursement for subject injury treatment cost
## Clinical & Site Practices Subgroup

<table>
<thead>
<tr>
<th>Deliverables</th>
<th>Process</th>
</tr>
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<tbody>
<tr>
<td>1) Roadmap for EFS initiation and execution</td>
<td>• Directed, confidential interviews with sponsors and sites</td>
</tr>
<tr>
<td>2) Target timelines for EFS</td>
<td>• Compiling, de-identifying, and curating study documents</td>
</tr>
<tr>
<td>3) Sample documents (redacted)</td>
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<td>4) Best Practices document</td>
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<table>
<thead>
<tr>
<th>Action Items</th>
<th>Group Membership</th>
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<tr>
<td>• Identify and provide access to appropriate internal personnel</td>
<td>• Chair: Kaplan &amp; TBD</td>
</tr>
<tr>
<td>• Review of metrics and learnings prior to MDIC analysis and aggregation</td>
<td>• Baylor Research Institute</td>
</tr>
<tr>
<td>• Identify Co-Chair</td>
<td>• Columbia University Medical Center</td>
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<td>• Dartmouth-Hitchcock Medical Center</td>
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<td>• Mayo Clinic</td>
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<tr>
<td></td>
<td>• Others TBD</td>
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Clinical and Site Practices Subgroup

How are EFS different from other studies?

- **IRB**
  - Documentation
  - Contracting

- **Consent Process**
  - Stimulation

- **Staffing**
  - Nurse Coordinator
  - Additional staff

- **Training**
  - Pre-procedural
  - Procedural
  - Post-procedural

- **Patient Advocacy**
  - Sponsor-Site (roles, budgeting)
  - Site-Public

- **Relations**
  - Sponsor-Site (roles, budgeting)
  - Site-Public
Discussion and Next Steps

• Identify and Confirm Working Group (WG) Members
  – Performance Metrics: Dan Schwartz & Shawn Ahmad
    • Identify sponsor point of contact
    • Complete intake forms
    • Schedule interviews
  – Contracting: Jamie Walkowiak, Sponsors (2-3) and Sites (2-3)
  – Clinical and Site Practices: Aaron Kaplan & Shawn Ahmad

• Collect EFS performance metrics

• Schedule subgroup meetings (for WG reporting)

• Determine Working Group Meeting Cadence: 6 weeks
  – Plenary meeting: Dartmouth Device Development Symposium, October 4, 2017