EFS Site
Best Practices Workshop
Event Materials

March 6-7, 2019
MDIC Offices
1501 Wilson Blvd.
Arlington, VA 22209
Thursday, March 7th, 2019

10:30 AM - 11:15 AM  
Panel Discussion: Topics  
Contracting Background: Creating the EFS Master CTA  
Case Examples: EFS Master CTA in Practice  
- Implementation at your Organization  
- Use of current Industry Master CTAs  
Getting to “Yes”: Tips to Mitigate Risk & Access Decision-makers  
EFS Start/Stop Communications: e.g. for device redesign, etc.

11:15 AM - 11:45 AM  
Open Discussion / Q&A
11:45 AM - 12:45 PM  Lunch & Site Presentations: Learnings from Sites Achieving “60/60/60” or Better

12:00 PM  Site Learnings: Oregon Health & Sciences University (OHSU)  Beth Wilson
12:15 PM  Site Learnings: Northwestern University  Lynne Goodreau
12:30 PM  Open Discussion / Q&A

12:45 PM - 2:15 PM  Session III: Budgeting between EFS Sites and Sponsors  Session Leaders:
Kathy Kioussopoulos (Franciscan)  
Gretchen Wild (Abbott)

12:45 PM - 1:30 PM  Panel Discussion: Topics  Panelists:
Differences from Pivotal trials:
  - Budgeting for Unknowns, AEs, etc.
  - Standard of Care Definitions

Alternative Payment Emphasis: Start-up vs. Per Patient Fees
Improvement Opportunities: Streamlining Site and Sponsor Budget Negotiations
Site & Sponsor Budgeting Differences: A Case Example

1:30 PM - 2:15 PM  Open Discussion / Q&A

2:15 PM  Break

2:30 PM - 4:00 PM  Session IV: EFS Staffing and Resources  Session Leaders:
Dr. Tanim Nazif (Columbia UMC)  
Lynne Goodreau (Northwestern)

2:30 PM - 3:10 PM  Panel Discussion: Topics  Panelists:
Institution Fit: How do we know if an EFS is right for us?
  - Physician Champions: Assessing protocols, patient populations and other considerations
  - PI Engagement/Oversight for EFS

Site Considerations: Special considerations for EFS trials
  - Data Collection: Rigor & Requirements
  - Staff Training & Experience

3:20 PM – 4:00 PM  Open Discussion / Q&A

4:00 PM  Wrap-Up  Chip Hance / Liliana Rincon-Gonzalez (MDIC)

6:00 PM – 8:00 PM  Evening Dinner & Session:  Evening Speaker:
Location: Hyatt Centric Hotel  Dr. Bram Zuckerman
1325 Wilson Boulevard, Arlington, VA, 22209  Director, Division of
6:15 PM –  Session: “EFS in the context of FDA Priorities and Initiatives”
6:45 PM
7:00 PM  Dinner
8:00 PM  Wrap-up  Liliana Rincon-Gonzalez (MDIC)
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<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Session Leaders</th>
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<tbody>
<tr>
<td>7:30 AM</td>
<td>Coffee, Tea, Rolls &amp; Fruit</td>
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<tr>
<td>8:00 AM – 9:45 AM</td>
<td><strong>Session V: Patient Identification, Enrollment &amp; Retention</strong></td>
<td>Sara Vidmar (preCARDIA)</td>
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<td>Necole Kell (BS&amp;W)</td>
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<td>8:05 AM –</td>
<td><strong>Patient Experience Presentation: EFS vs. Pivotal Studies</strong></td>
<td>Necole Kell (BS&amp;W)</td>
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<td>8:15 AM –</td>
<td><strong>Panel Discussion: Topics</strong></td>
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<td>8:15 AM –</td>
<td><strong>Site Tools: Outsourcing Recruitment, IRB Pre-Screening Waivers, etc.</strong></td>
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<td>9:00 AM</td>
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<td><strong>Patient Expectations &amp; Tools:</strong></td>
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<td>- Managing complexity, visit adherence, etc.</td>
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<td>- Beyond Inclusion/Exclusion: Identifying needs for childcare, travel, etc.</td>
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<td><strong>Site Engagement: Avoiding Competitive Enrollments</strong></td>
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<td>9:00 AM –</td>
<td><strong>Open Discussion / Q&amp;A</strong></td>
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<td><strong>Break</strong></td>
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<td>10:00 AM –</td>
<td><strong>Session VI: Coverage Determinations &amp; Site Budgets</strong></td>
<td>Dr. Rochelle Fink (CMS/FDA)</td>
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<td>Jill Trekell (Edwards)</td>
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<td>10:00 AM –</td>
<td><strong>Panel Discussion: Topics</strong></td>
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<td>10:45 AM</td>
<td><strong>Coverage Determination Roles: CMS, Sponsors &amp; Sites</strong></td>
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<td>- FDA: EFS designation (Category A/B)</td>
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<td>- CMS: Coverage of Standard of Care in EFS</td>
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<td><strong>“Standard of Care” Determinations:</strong></td>
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<td>- Site &amp; Sponsor Budget Discussions</td>
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<td>- Variations in “Standard of Care” across the U.S.</td>
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<td>- National vs. Local Coverage</td>
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<td><strong>Potential Waivers on CMS Approval to Expedite Start-up Coverage:</strong></td>
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<td><strong>A Case Study on Building your Budget</strong></td>
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<td>11:30 AM</td>
<td><strong>Wrap-up, Workstreams &amp; Next Steps</strong></td>
<td>Jaime Walkowiak (BS&amp;W)</td>
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<td>12:00 PM</td>
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<td>Dan Schwartz (MDIC)</td>
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# EFS Best Practices Workshop

**Attendees**

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<tr>
<th></th>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>1</td>
<td>Katherine Kumar</td>
<td>Executive Vice President</td>
<td>4C Medical</td>
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<tr>
<td>2</td>
<td>Melissa Broich</td>
<td>Director, Clinical Affairs</td>
<td>4C Medical</td>
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<tr>
<td>3</td>
<td>Gretchen Wild</td>
<td>Director, Clinical Research</td>
<td>Abbott</td>
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<td>4</td>
<td>Seth Bilazarian</td>
<td>Chief Medical Officer</td>
<td>Abiomed</td>
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<td>5</td>
<td>Carrie Cameron</td>
<td>Senior Clinical Program Manager</td>
<td>Abiomed</td>
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<td>6</td>
<td>Michael Zapien</td>
<td>VP Clinical Affairs</td>
<td>Ancora Heart</td>
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<td>7</td>
<td>Jaime Walkowiak</td>
<td>COO</td>
<td>Baylor Scott &amp; White</td>
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<td>8</td>
<td>Jennifer Thomas</td>
<td>Director of Clinical Research</td>
<td>Baylor Scott &amp; White</td>
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<td>9</td>
<td>Kristen Chionh</td>
<td>Director of Clinical Research, CV</td>
<td>Baylor Scott &amp; White</td>
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<td>10</td>
<td>Makshita Luthra</td>
<td>Project Analyst – Clinical Research</td>
<td>Baylor Scott &amp; White</td>
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<td>11</td>
<td>Necole Kell</td>
<td>Clinical Research Nurse</td>
<td>Baylor Scott &amp; White</td>
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<td>12</td>
<td>Lauren Baker</td>
<td>CEO</td>
<td>Boston Biomedical Associates</td>
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<tr>
<td>13</td>
<td>Michelle Nivala</td>
<td>Principal Regulatory Affairs Specialist</td>
<td>Boston Scientific</td>
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<td>14</td>
<td>Blessie Concepcion</td>
<td>Director Global Clinical Trials</td>
<td>Boston Scientific</td>
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<tr>
<td>15</td>
<td>Tricia Pearce</td>
<td>Associate Director, CTO</td>
<td>Cedars-Sinai</td>
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<tr>
<td>16</td>
<td>Nicole Leonard</td>
<td>VP &amp; Associate Dean, Research</td>
<td>Cedars-Sinai</td>
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<tr>
<td>17</td>
<td>Anna Teresa Valencia</td>
<td>Senior Director, Clinical Research Operations</td>
<td>College of Medicine, UoA</td>
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<tr>
<td>18</td>
<td>Martin Leon</td>
<td>Mallah Family Professor of Cardiology</td>
<td>Columbia UMC</td>
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<td>19</td>
<td>Tamim Nazif</td>
<td>Assistant Professor of Medicine</td>
<td>Columbia UMC</td>
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<td>20</td>
<td>Chris Cain</td>
<td>VP, Clinical &amp; Regulatory Affairs</td>
<td>Conformal Medical, Inc.</td>
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<td>21</td>
<td>Kate Stohlman</td>
<td>VP, Quality &amp; Regulatory Affairs</td>
<td>Corvia Medical</td>
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<tr>
<td>22</td>
<td>Allison J. Hawke</td>
<td>Research Operations Manager</td>
<td>Dartmouth-Hitchcock Heart and Vascular Center</td>
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<tr>
<td>23</td>
<td>Aarti Kenjale</td>
<td>Sr. Director, Clinical Affairs</td>
<td>Duke University Heart Center</td>
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<td>24</td>
<td>Jill Trekell</td>
<td>Director, Office of Product Evaluation and Quality Office of Neurological and Physical Medicine Devices</td>
<td>Edwards Lifesciences</td>
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<td>25</td>
<td>Mark Pierre</td>
<td>Director Clinical and Regulatory Affairs</td>
<td>Enspire DBS Therapy</td>
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<td>26</td>
<td>Kathy Kioussopoulos</td>
<td>Director Research Administration</td>
<td>Franciscan Alliance</td>
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<td>27</td>
<td>Jodi Akin</td>
<td>CEO</td>
<td>Hawthorne</td>
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<td>28</td>
<td>Susmitha Gadde</td>
<td>Research Administrative Director</td>
<td>Houston Methodist</td>
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<td>29.</td>
<td>Anne Marie Chikowski</td>
<td>Division Manager, Cardiovascular Research</td>
<td>Main Line Health</td>
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<td>30.</td>
<td>Dan Schwartz</td>
<td>Director, Clinical Trial Sciences (acting)</td>
<td>MDIC</td>
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<td>31.</td>
<td>Liliana Rincon-Gonzalez</td>
<td>Program Director Clinical Science</td>
<td>MDIC</td>
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<td>32.</td>
<td>Chip Hance</td>
<td>Board of Directors</td>
<td>MDIC</td>
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<td>33.</td>
<td>Megan Mueller</td>
<td>SVP, Regulatory Affairs</td>
<td>Metavention, Inc.</td>
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<td>34.</td>
<td>Megan Brandt</td>
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<td>Rick Geoffrion</td>
<td>CEO</td>
<td>Mitralign</td>
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<td>36.</td>
<td>Michael Parides</td>
<td>Chief, Division of Early Stage Technology and Exploration</td>
<td>Montefiore Medical Center</td>
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<td>37.</td>
<td>Lynne Goodreau</td>
<td>Administrative Director, Bluhm CV Institute CTU</td>
<td>Northwestern University</td>
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<td>38.</td>
<td>Trae Reichert</td>
<td>Contract Analyst</td>
<td>OHSU</td>
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<td>39.</td>
<td>Beth Wilson</td>
<td>KCVI Clinical Research Manager</td>
<td>OHSU</td>
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<td>40.</td>
<td>Susanne McGlothlin</td>
<td>Finance Administrator, Knight CV Institute</td>
<td>OHSU</td>
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<td>41.</td>
<td>Sarah Fishbein</td>
<td>Lead Device Research Coordinator</td>
<td>OHSU</td>
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<td>42.</td>
<td>Sara Vidmar</td>
<td>SVP, Clinical, Regulatory &amp; Strategic Affairs</td>
<td>preCARDIA</td>
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<td>43.</td>
<td>Gerri O’Riordan</td>
<td>Director of Clinical Research, CV</td>
<td>Stanford University Medical Center</td>
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<td>44.</td>
<td>Wini Wu</td>
<td>Principal Advisor</td>
<td>Strategic Regulatory Partners</td>
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<td>45.</td>
<td>Manal Al-Suqi</td>
<td>Clinical Research Operations Manager, Department of Cardiac Surgery</td>
<td>University of Maryland</td>
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<td>46.</td>
<td>Sarah Rubin</td>
<td>Clinical Research PM</td>
<td>University of Maryland</td>
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<td>47.</td>
<td>Jessica Oakley</td>
<td>Clinical Research PM</td>
<td>University of Maryland</td>
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<td>48.</td>
<td>Dan Menees</td>
<td>Assistant Professor</td>
<td>University of Maryland</td>
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<td>49.</td>
<td>Stanley Chetcuti</td>
<td>Professor</td>
<td>University of Maryland</td>
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<td>Steven Bolling</td>
<td>Professor of Medicine</td>
<td>University of Maryland</td>
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<td>51.</td>
<td>Kimberly Clinton</td>
<td>Regulatory Manager</td>
<td>University of Pennsylvania</td>
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<td>52.</td>
<td>Tiffany Sharkoski</td>
<td>Manager, Cardiovascular CRU</td>
<td>University of Pennsylvania</td>
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<td>53.</td>
<td>Karen Cooper</td>
<td>Associate Director</td>
<td>University of Pennsylvania</td>
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<td>54.</td>
<td>Regina Hollister</td>
<td>Valve Clinic Coordinator</td>
<td>UPMC Pinnacle</td>
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<td>55.</td>
<td>Anita Todd</td>
<td>Cardiovascular Institute</td>
<td>UPMC Pinnacle</td>
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<td>57.</td>
<td>Changfu Wu</td>
<td>Reviewer, Division of Cardiovascular Devices</td>
<td>US FDA</td>
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<td>58.</td>
<td>Andrew Farb</td>
<td>Medical Officer &amp; Senior Reviewer</td>
<td>US FDA</td>
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<td>59.</td>
<td>Bram Zuckerman</td>
<td>Director, Division of CV Devices</td>
<td>US FDA</td>
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<td>Rochelle Fink</td>
<td>Senior Health Science Specialist</td>
<td>US FDA/CMS</td>
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<td>61.</td>
<td>Mike Bowdish</td>
<td>Service Chief, Cardiac Surgery</td>
<td>USC Medical Center</td>
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<td>China Green</td>
<td>Clinical Research Coordinator</td>
<td>University of Virginia</td>
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<td>63.</td>
<td>Kristi DeHaai</td>
<td>Compliance Coordinator, Health Sciences Research IRB</td>
<td>University of Virginia</td>
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<td>64.</td>
<td>Andrew Garcia</td>
<td>Team Lead, Study Management</td>
<td>W.L. Gore &amp; Associates</td>
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Conclusions & Next Steps

Chip Hance | MDIC
Jaime Walkowiak | BS&W
Liliana Rincon-Gonzalez | MDIC
Dan Schwartz | MDIC
Session I: Managing Risks, SAE and IRB Reporting

IRB Timelines, Policies and Expectations

- Review of Consent Template by All Sites
- Parallel Review: IRB, Contracts & Budgets
- Upfront collaboration with IRB administrators/chairs
- Experienced EFS IRB: The use of central IRBs, local IRBs and/or identifying a Central IRB that can be utilized by all sites
Session I: Managing Risks, SAE and IRB Reporting

IRB Timelines, Policies and Expectations (contd.)

- Create Regulatory Playbook
- Identify EFS Champion at each site
- IRB Submission Template/Checklist
Session II: Timely & Effective Contracting

• Involving key decision makers
• Review the EFS MCTA template
• Pre-Study Startup agreements
• Share external legal resources
• Upfront communication with contracts team
• Create EFS summary document
• Communication/Education
Session III: Budgeting between EFS Sites and Sponsors

• Opportunities for risk-sharing
  • Pre-agreement/Start-up Contract: Front-load for administrative start-up work
  • Different fee for Screening vs. Screen Fails vs. Enrollment

• Standardized Budget Template
• Consider New Budget Model
• Reimbursement Guide/Coverage Analysis
Session IV: EFS Staffing and Resources

• PI Engagement

• Collaborating for success
  • Study Triage: PI, department MDs, Study Staff -> assess study viability and identify barriers

• Experienced Staff is Critical

• Create a team approach
  • Consider Staff Experience and Expertise
Session V: Patient Identification & Enrollment

• Sponsors help sites identify queries in EMR system
• Use of recruitment specialists: hourly nurses
• Sponsors creating registries with sites
  • Registry protocol
  • “Pilot clinical trial”
• Collaboration with other sites / Forums to discuss identification issues and retention resources
• Collaboration with sponsors on data
• New Common Rule: What should we include in the one-page document for EFS studies?
Session V: Patient Retention

• Patients understanding their responsibility
  • ICF Cover Page
• Patient Follow-up for Retention – consider satellite follow-up
• Collaboration with sites on what they are doing to retain patients
Session VI: Coverage Determinations & Site Budgets

- Category A: CMS will pay for SOC, routine procedures, and implant procedures but not the device
- Category B: CMS will pay for SOC, routine procedures, implant procedures, and the device
- No Reimbursement: the Sponsor will have to pay for everything
  - Sites and Sponsors need to find a middle ground within FMV for budgeting
- Developing Budgets
  - Differentiate which procedures are part of the Protocol and which are SOC
  - Establish Fair Market Value (FMV)
- Budget negotiations without CMS determination can take 2x to 3x longer
Proposed Next Steps

Following the meeting, we (Chip, Liliana, Dan and Jaime) held several calls to discuss how we might best build on the Best Practices Workshop with workstreams that we thought would have the greatest impact and fit within our available resources.

We focused on four areas: Communication, Workshops, Working Groups, Metrics

**Communications**

We think frequent, useful communications to our network is one of the best ways to get the word out about developments with EFS and Best Practices.

- **Continue with EFS Express communications.** We’ve issued two communications so far and believe the feedback has been positive. We have >150 people on the distribution and would like to add more. We have half a dozen topics planned (~1-2/month over remainder of the year)

- **Webinars on Best Practices.** We have several Site “Best Practices” presentations from the Workshop that could be given again in a Webinar to a larger audience. We also think a webinar for small company sponsors and a webinar for large company sponsors would be good. We imagine one Webinar every other month.

**Workshops**

There is strong interest in face-to-face communication on critical topics as was demonstrated by the interest in the Best Practices Workshop. We imagine three activities over next two quarters.

- **IRB/Informed Consent Workshop.** MDIC/Jaime Walkowiak would organize a meeting to standardize approaches for these critical activities. We plan a face-to-face workshop in Dallas (Baylor leading). Targeting May or September

- **Contracting Webinar to Reinvigorate Interest in the Master Clinical Trial Agreement.** MDIC/Jaime Walkowiak could reconvene over the web a working meeting to revisit the MTCA from last year’s meeting with more site and sponsor participation. Target audience would be site/sponsor attorneys. We would update the MTCA after the meeting.

- **TVT Symposium/Workshop on Site Best Practices for Patient Screening/Enrollment.** Would need clinician help to define a program, agenda and participation.
Proposed Next Steps (Cont.)

Working Groups

There is interest in establishing Site and Sponsor working groups to further advance best practices on any number of topics. We decided to focus on getting one off the ground that would have the greatest impact before embarking on other working groups that might stretch our resources.

• **Budgeting Working Group.** We plan to approach our Budget moderators from the Workshop to lead a working group on Budgeting. We would include participation from Sites and Sponsors and focus on developing templates/masters for budgeting that could expedite negotiations.

Metrics

The MDIC work on study metrics was instrumental in providing focus on critical areas. We want to add to the databases in 2019

• **Obtain Data on 2017/18 EFS Study Metrics.** Building on the MDIC work in 2016, we would like to collect studies in 2019 from a more recent time period to show how the administration of studies is changing. This work is done predominantly with Industry Sponsors to obtain study metrics.

• **Site Survey.** In 2019, we would like to survey and publish the results of our recruited site network on # of EFS studies performed, use of contract templates, Central IRB usage, etc.
THANK YOU!

Dan Schwartz  
Program Director (Acting)  
Clinical Trial Sciences (CTS)  
Medical Device Innovation Consortium  
Mobile: 612-501-8651  
dschwartz@mdic.org

Liliana Rincon Gonzalez, PhD  
Program Director  
Clinical Trial Sciences (CTS)  
Medical Device Innovation Consortium  
Phone: 202-559-2973  
lrincon-gonzalez@mdic.org
Workshop Overview

Chip Hance | MDIC Board Champion
EFS Site Best Practices Workshop

Chip Hance

March 6th, 2019
Welcome to First Ever EFS Best Practices Workshop

Meeting Objectives:

• To create a forum for exchange between sites and partners for improvement of the ecosystem

• To identify common challenges that could be tackled with follow-up collaborative efforts

• To be one more step on the road to FDA’s stated vision:

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

Session Leaders:
• Engage the audience; seek broad participation; keep the discussion moving; translate into possible actions and recommendations

Participants:
• Be active; establish new networks; benchmark others; share results when you return home; join future efforts
LEGAL REMINDER

Meetings of this kind are an example of lawful activity under federal antitrust law because the focus of the meeting is on government action or policy, including the industry’s responses or positions taken with respect thereto. However, antitrust monitoring is needed for companies’ own protection since they are direct competitors meeting together. These meetings need to stay within protected subject matters and be monitored to avoid inappropriate areas, such as:

- Pricing, price terms, marketing plans, or new products
- Company’s individual decisions regarding selection of suppliers or customers
- Other proprietary or competitively sensitive information

Today’s meeting will follow the written agenda and there will be no discussion of pricing or other prohibited topics. If the discussion veers into those topics, we will terminate the discussion. If you have questions or concerns about the propriety of a discussion, please raise it immediately, and we will determine how best to proceed.
THANK YOU FOR BEING HERE

• Slides to Liliana or Dan
• Coffee, tea, pastries, and fruit in the next room (Thank you, Brandon)
• Bathroom codes

MDIC EFS CONTACTS:
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Clinical Trial Sciences (CTS)
Medical Device Innovation Consortium
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dschwartz@mdic.org

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Program Director
Clinical Trial Sciences (CTS)
Medical Device Innovation Consortium
Phone: 202-559-2973
lrincon-gonzalez@mdic.org
Early Feasibility Studies Overview

Andrew Farb, MD
Chief Medical Officer, Division of Cardiovascular Devices
Co-Leader of the Early Feasibility Studies Program
Center for Devices and Radiological Health (CDRH)
Food and Drug Administration
andrew.farb@fda.hhs.gov
FDA’s Organizational Structure

- Center for Veterinary Medicine
- Center for Drug Evaluation And Research (CDER)
- National Center for Toxicological Research
- Office of Regulatory Affairs
- Center for Tobacco Products
- Center for Food Safety And Applied Nutrition
- Center for Biologics Evaluation and Research (CBER)
- Center for Devices and Radiological Health (CDRH)

Food and Drug Administration
Office of the Commissioner
What is an Investigational Device Exemption (IDE)?

• IDE approval is issued by the FDA to allow the use of significant risk investigational devices in humans.

• An approved IDE:
  – Provides protection to human subjects (e.g., informed consent);
  – Requires study monitoring; and
  – Allows shipping of devices

• Clinical study data collected under an IDE can be used to support a marketing application for a device.
Purposes of Early Feasibility Studies (EFS)

- Obtain insights
  - Early clinical experience
    - Provides the basis for iteration & product improvement
    - Integral to the device development process

- Safety
- Device failure modes
- Whether the device performs its intended purpose
- Therapeutic parameters
- Patient characteristics that may impact device performance
- Human factors
- Operator technique challenges
Acknowledging Problems With Medical Device Innovation and Development in the US

• Migration of initial clinical testing of novel devices overseas
• Growing 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.
EFS Program Objectives

• Re-establish and/or increase US participation in the early clinical evaluation of innovative medical devices under the current US regulations
• Provide the earliest patient access to potentially beneficial medical devices in the US
• Enhance collaboration among device developers, industry, regulators, and investigators
• Protect study participants
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
What’s an EFS?

Elements that define an EFS:
– Small number of subjects
– Device may be early in development and before the device design has been finalized
– Does not necessarily involve the first clinical use
– Needed when information to advance device development cannot be practically obtained with additional nonclinical assessments, or nonclinical tests are unavailable
How is an EFS Different From a Traditional Feasibility/Pilot Study?

• An EFS generally involves a device that is earlier in development compared one to those being evaluated in a traditional feasibility study, which typically involves a more finalized device design.

• For an EFS, clinical data may be needed to advance product development, with some nonclinical testing deferred until the device is more final or after the use is refined.

• An EFS may therefore be supported by less nonclinical data than would be expected for a traditional feasibility study.
Key EFS Program Provision

• Provides new ways for sponsors and regulators to support the transition from bench to bedside with an increased focus on:
  • Clinical condition
  • Availability, benefits, and risks of alternative treatments
  • Risk mitigation strategies, enhanced monitoring, and a tailored consent process to enhance patient safety
Device Iteration During an EFS

Experience and knowledge gained from initial study subjects can guide device or protocol changes.

The EFS Guidance includes new tools to facilitate timely device and clinical protocol modifications.
# Protecting Study Subjects

## IRBs, Consent, and Risk Mitigation Strategies

<table>
<thead>
<tr>
<th>EFS informed consent element examples:</th>
<th>Risk mitigation examples:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Define an EFS: A study of an innovative device or innovative use of a device in a small number of patients</td>
<td>• Study sites with sufficient expertise and resources to manage adverse events</td>
</tr>
<tr>
<td>• Explain that there may be unforeseeable risks associated with participation in an EFS due to limitations in available data and experience with the device</td>
<td>• Qualified investigators</td>
</tr>
<tr>
<td>• Indicate how the procedures and follow-up differ from the standard of care</td>
<td>• Enhanced monitoring and follow-up testing of study subjects</td>
</tr>
<tr>
<td>• Describe anticipated benefits but acknowledge that there may be limited information to support a likelihood of personal benefit</td>
<td>• Periodic patient outcome assessments prior to enrollment of additional patients</td>
</tr>
<tr>
<td></td>
<td>• Timely reporting of serious adverse events and device performance parameters to sponsors (and IRB and FDA, as needed)</td>
</tr>
</tbody>
</table>
EFS Program Growth

Finalized EFS Guidance document issued October 1, 2013

Number of EFS IDEs

<table>
<thead>
<tr>
<th>FY14</th>
<th>FY15</th>
<th>FY16</th>
<th>FY17</th>
<th>FY18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- Neurological & Physical Medicine Devices
- Cardiovascular Devices
- Ophthalmology, ENT, Respiratory & Anesthesia Devices
- Gastro, Renal, Urological Devices
- Surgical Devices and Infection Control
- Orthopedic Devices
- In Vitro Diagnostics & Radiological Health

Submitted
Approved or Approved with Conditions
Longitudinal EFS Benefits

- Familiarity with the technology and regulatory considerations throughout product development
- Consensus on data requirements to move forward from bench to clinical use
- Smoother transitions between types of clinical studies

First Generation
- EFS
- Traditional feasibility study (if needed)

Finalized Design
- Pivotal study

Complete Characterization
- Premarket approval (PMA) submission for marketing
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,a Bram Zuckerman, MD,b Martin Leon, MD,a Jeff Shuren, MDb

- Gov’t: FDA and CMS
- Industry Sponsors
- Inventors/Innovators
- Investigators
- Private Funders and Payers
- Study subjects
- Clinical Sites
Addressing the Clinical Trial Ecosystem to Improve the Climate for US EFS

Multi-stakeholder effort organized under the Medical Device Innovation Consortium (MDIC)

- Collaboratively develop and adopt best practices of study conduct
- Participants: Industry, FDA, CMS, clinical sites, investigators
- Targets for streamlining:
  - IRB approval
  - Contracting
  - Site start-up and enrollment
  - Reimbursement
- Vision: A voluntary, open research network of clinical sites that are committed to high quality, efficiently executed EFS

60/60 EFS goal: First 60 days for IRB and contract approval/Next 60 days to first patient enrolled
The EFS Program is integral to FDA’s mission and has fostered a paradigm shift in performing early phase device studies in the US.

FDA continues to facilitate interactions among stakeholders to address EFS start-up challenges.

A successful US EFS Program requires successful clinical sites.

Improving the EFS ecosystem requires the commitment of industry, investigators, regulators, and clinical sites.
EFS: Value to Innovation

Rick Geoffrion
President & CEO | Mitralign, Inc.
EFS: Value to Innovation

Rick Geoffrion
President & CEO, Mitralign, Inc.
March 6th, 2019
What was the Pathway for a Class III Device 7 Years Ago?

• FIM Outside the US, maybe outside EU
• Pre-CE Mark Study in the EU
• CE Mark Study in EU
• Use CE Mark data (partial or complete) to start a Feasibility Study in the US
• Commercialize in EU to financially support US pivotal
• US Pivotal Trial
What was the Impact of the Pathway that existed 7 years ago?

• In the US, access to new medical technologies lagged the EU by more than 4 years

• Cutting edge medical device research all but left the US in search of a faster pathway for clinical research and market approval.

• Investment money left the medical device space in search of technologies that could make it to market faster and more predictably.
EFS Arrived at the Most Opportune Time for MedTech

• Implant scandal in Europe has resulted in tighter regulations.

• Germany has transitioned from a decentralized system to a centralized one..... Effectively shut down to early stage studies.

• Without EFS, there would be no reputable outlet for early stage investigation.

• Many Class III technologies would have ceased to exist.
Benefits of the EFS Program: Value to Innovation

• Early access to reputable clinical sites
• Faster time to the single largest market in the world
• If company is based in the US, significant savings in travel cost and resource dilution
• Bring the FDA and CMS up to speed earlier, injecting more predictability into the future regulatory pathway
Benefits of the EFS Program: Value to Innovation

• Accelerate overall timeline to market by leveraging US cases into the CE Mark pathway
  • No need to forsake the EU in favor of the US
  • Once the design is stable, US cases may be credited towards the CE Mark to accelerate approval times
  • Concept can apply to certain other countries as well
Trialign Case Study: FDA EFS IDE Approval Timeline

A huge step forward on the front end, a lot of work to be completed on the back end
EFS: Value to US Innovation
The New Paradigm - When to Come to the US

• US Early Feasibility Study (EFS)
  ○ Could be your FIM (10—15 pts)

• US Extended Feasibility & CE Mark Combination

• US Pivotal Trial

Bottom Line: The US has once again become the place for early stage clinical research
EFS Site Best Practices Meeting

Presented by Martin B. Leon, MD on behalf of David R. Holmes, Jr, MD

EFS Site Best Practices Meeting
March 6 and 7, 2019
Washington DC
Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies, Including Certain First in Human (FIH) Studies

Guidance for Industry and Food and Drug Administration Staff

Document issued on: October 1, 2013

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

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

• Document addressed regulatory issues
• Local site issues were never the focus
• Outmigration of clinical studies OUS continued to fall to <50%
• New Zealand dominated the landscape for not only rugby but EFS
Federal Guidance Document

What didn’t it do

• Identification of the problem – site and implement issues
• Components of the problem – root cause analysis
• Approaches to the problem
• Consequences of problem
• Action items
Federal Guidance Document
Components to be considered

- Patients
- Investigators
- Sponsors
- FDA

- IRB’s
- Clinical study sites
- Payers
- Public and private funders
Fundamental next steps

• Address an ecosystem with multiple parts
What’s in it for me

• Goals: Improve patient care, solve unmet clinical needs
• Streamline and codify best practices at each institution
• Optimize resource utilization
• Maintain and enhance funding sources for research and development
• Enhance and maintain professional satisfaction
• Encourage IP development
• Enhance institutional profile
Potential Approaches to Address IRB Issues

<table>
<thead>
<tr>
<th>Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Submission of well-organized complete documents</td>
</tr>
<tr>
<td>Agreed upon goals of completion of review by IRB, sponsor, and investigator</td>
</tr>
<tr>
<td>Parallel processes of contract and legal review</td>
</tr>
<tr>
<td>Establish FDA liaison relationships to IRBs</td>
</tr>
<tr>
<td>Acceptance of central IRB and uniform consent forms</td>
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</tbody>
</table>
## Optimal EFS Site Qualities

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

| Knowledge of and interest in participating in EFS |
| Resources for protocol design and implementation |
| Commitment to patient-centric device development |
| Acceptance of the issues of site selection, protocol design, and legal contractual site issues |
| A close collaborative working relationship between the physician champions involved in the protocol design, and the FDA regulatory and design personnel |
| Ability to adapt to issues related to treating patients with new approaches |
| Resources for statistical design and methodology |
| Track record of working with AROs or CROs on data acquisition |
| Ability to provide expeditious device design and clinical protocol iteration in response to early protocol screening and case experiences |
Necessary Concessions By Ecosystem Participants

<table>
<thead>
<tr>
<th>Necessary Concessions</th>
<th>Patients</th>
<th>Investigators</th>
<th>Sponsors</th>
<th>FDA</th>
<th>IRB</th>
<th>Sites</th>
<th>Payers</th>
<th>Funders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accepting a greater degree of risk</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Submitting to additional oversight and reporting</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Expending additional time and resources</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Session II: Timely & Effective Contracting
EFS SITE BEST PRACTICES WORKSHOP

Jaime Walkowiak, JD
Chief Operating Officer, Baylor Scott & White Research Institute
SVP, Baylor Scott & White Health
Value of EFS to a Site

- **Patients:** Patients’ access to novel medical technologies

- **Research Program:** Earlier access to new medical device – supports research program growth

- **Pivotal Trials:** Familiarizes clinical sites with device/procedure before pivotal trials

- **Sponsor Relationship:** Strengthens relationship between the site and industry-sponsors
EFS – Contracting

Legal Roundtable

- MDIC Working Group
- Language Libraries
- Conception of Legal Roundtable
- Legal Roundtable
- Reconciliation and Development of MCTA and supplements
1. MDIC Working Group

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

- Indemnification
- Subject Injury
- Intellectual Property
- Third Party Payer
2. Language Libraries

• Each Library offers examples of clause language which has been acceptable to both sponsor and sites in the conduct of actual EFS trials, supplemented by respective Commentaries section.

• These commentaries describe important considerations and negotiation points, direct from some of the subject matter experts who engage in EFS contract negotiations.

• Intended to serve as a tool for sites and sponsors.
3. Conception of Legal Roundtable

- Develop an EFS-specific Master Clinical Trial Agreement (MCTA) to facilitate efficiencies in the EFS contracting process which provides:
  - balance between site and sponsor concerns, serving as a starting point for contract negotiations with a priori agreement of 90% or greater, and
  - allowing both parties to focus remaining legal resources on the remaining 10% (or less) of the EFS MCTA requiring negotiation

- Hosted by Baylor Scott & White Research Institute on February 8-9, 2018
3. Conception of Legal Roundtable

• BSWRI took the lead on drafting a MCTA template using the provisions from the Language Library developed by MDIC Working Group

• Draft MCTA circulated for review to the Legal Roundtable participants prior to the meeting
EFS – Legal Roundtable Representatives

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

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

FDA
MDIC
4. Legal Roundtable

Day 1

- Four attorneys from the MDIC Working Group facilitated contract language discussions on the four choke points
- Edits made in real time in alignment with feedback received from the participants
- Interactive and productive discussions
- Revision to select sections was rather challenging due to differing viewpoints on these key items:
  - Intellectual Property
  - Indemnity
4. Legal Roundtable

Day 2

• Review of the MCTA language

• Addressing additional sections not identified as key choke points

• Revised template sent to the group at the conclusion of the meeting to review the remaining terms of the agreement
5. Reconciliation and Development of MCTA and Industry- and Sponsor-specific supplements

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

• Written summaries of variances along with narrative explanation serve as a supplement to the MCTA that equips people to efficiently make decisions on which institutions and sponsors to approach – reduces timeline to establish - eliminates meaningless negotiations
Conclusion

• Overwhelming response from the participants implies shared enthusiasm to continue the Legal Roundtable to further improve the MCTA template

• Monitoring of contracting turn-around time by MDIC
Lunch & Site Presentations

Learnings from Sites Achieving “60/60/60” or Better
Who we are

- 21 Clinical Research Staff
  - 15 Coordinators, a research nurse, and a research APP
  - Operations Manager, Finance Manager, and Regulatory/Start-Up Specialist
- ~100 trials currently housed within the team
OHSU Approval Process - 2016

- REG PACKET RECEIPT: 15 days
- PI SUBMISSION
- STUDY REVIEWS
- IRB: 60 days
- CONTRACT
- BUDGET
- FINAL APPROVALS
- 75 days
- Enrollment
The 280 Day Study
The 280 Day Study

Risk Management

CMS

Purchasing

Hospital Feasibility

Storage Agreement

Coding and reimbursement analysis

50

130

Too Long
Lessons Learned

• Institution was not built to support device trials

• Development of new approval processes needed

• Stakeholders still needed to be verified

• OHSU needed a driver
Active Engagement

• Prospective reporting metrics
  – Internal deadlines for approvals and expectations of sponsor turnaround
  – Weekly PI meetings/Status Check-In
  – PI to sponsor relationships
Start-Up Timeline Reporting

Gowala, Harsh

Heitner, Steve

Party (group):
- contracts
- IRB
- PI
- Regulatory
- Sponsor

Days
Device Committee

- Identify institution stakeholders
- Eliminate artificial bottlenecks
- Develop efficient processes for necessary internal approvals
- Allocate Master Contract Support for all device sponsors
Round 2 in 2018
New Sponsor, New Opportunity
The 280 Day vs. New Study

Regulatory Timelines
- 280 Days
- 48 Days

Contract Timelines
- 130+ Days
- 55 Days
Key Considerations

• Identify all stakeholders involved in approval processes for your institution AND ENGAGE THEM.

• Approach relationship with sponsor as a partnership

• Master Contracts

• Active facilitation through approval process
Northwestern Medicine
Bluhm Cardiovascular Institute
Clinical Trials Unit
EFS Best Practice – Site Learning
March 6, 2019

Lynne Goodreau RN, MS Administrative Director BCVI CTU
EFS Experience: Northwestern Medicine
Agenda

• EFS Transcatheter Tricuspid Valve Experience

• Process Refinement – 60/60/60 Goal
  – IRB and Contracts
  – Subject enrollment
  – Data collection

• Special considerations
NU Experience Transcatheter Tricuspid Valve Repair

- Tricuspid valve disease impacts 1.6 million patients in the U.S. annually.
- Severe TR:
  - Two year mortality approaches 60%
  - Medical therapy is often ineffective
  - Isolated surgical repair has a 9%, 30-day mortality and an almost 50% major morbidity

- EFS participation
  - Trialign technology
  - Cardioband technology
  - Pascal tricuspid clip
Process Refinement – IRB and Contracts

Metrics – 60/60/60 goal
- 60 Days for IRB Approval
- 60 Days for Contract Execution

- IRB approval
  Special considerations for EFS
  Partner with IRB leadership

- Contract negotiation – Master agreements
  Industry
  MDIC

- Device Committee
Process Refinement – First Subject Enrollment

Metrics – 60/60/60 goal
  • 60 Days for First Subject Enrollment

• Site leadership support

• Research team training
  Scheduling outside training for investigators

• Screening initiatives
  Screening consent - remote provisions
  Submission of de-identified imaging prior to consent
  Scheduling coordination

• Clinical staff support
  Weekly meetings
  Imaging protocol oversight echo, CT, MRI

• Industry partnership

• Ongoing assessment/refinement of process
Process Refinement - Patient Experience

Pre-Procedure:
- Consent process
  - Screening consent
- Invasive screening procedures
  - Windows of acceptance
  - Numbers of procedures
  - Core lab turn around
- Scheduling uncertainties – early communication is critical
- Family/significant other involvement

Post-Procedure:
- Communication with referring clinicians
- Return to center follow-up
- Creating the relationship for the long run
Process Refinement - Data Collection

Timing – rapid turn-around

Imaging submission

Data submission – additional source documentation

AE/SAE interpretation:
- Coordinator support
- Industry involvement
- PI support/assessment required at a higher level
Special Considerations

• Proctors – credentialing
  Organization rules/regulations must be addressed
  Don’t let credentialing be a stress

• Compassionate use
  Identify your regulatory staff
  Educate the clinical staff
  Unrecognized workload for the research team
Lessons learned

• Essential elements for success:
  - Flexibility
  - Team communication
  - Institutional buy-in
  - Industry partnership
  - Patient experience assessment
  - Ongoing refinement of process

• Collaboration is needed to:
  - Align resources
  - Accelerate progress
  - Achieve results
Session III: Budgeting Between EFS Sites and Sponsors
Start-Up – Items for Consideration

FDA IDE Category Determination
CMS Approval
Device Cost
Other ancillary equipment costs (special imaging machine?)
Financial Analysis (collect patient volumes & comparative treatments)
Approved Vendor?
Create Charge Codes
Create Purchase Orders, if necessary
Procedure Coding – Discuss proper medical charting
Follow to completion
Study Startup Process

Interventional Device Clinical Trials

IRB
- Submission Created
  - IRB
  - Analyst Review
  - Board Review
  - Chair Approval
  - IRB approval

Regulatory
- Docs Rec’d
  - Prepares Items for IRB submission
  - Pushes IRQ to eCRIS
  - Submits for IRB review

Coordinator
- Creates Visit schedule
  - CRS
  - CRS created in eCRIS
  - Approvals received
  - CMS Approval
  - SIV entered

Finance
- Budget Received
  - Budget Developed
  - Budget and Payment Terms Negotiation
  - Finalized
  - Research Device Purchasing Form

Contracts
- Contract Received
  - Contract Negotiation
  - Sponsor provide device?
    - Y
      - Prepare CMS application
    - N
      - Purchasing Form
  - Contract execution

eCRIS
- Prepare basic study info
  - Coverage Analysis Approval
  - Approval by clinical services
  - Approval by PI, department, SoM

CRBO
- Receive CMS Submission
  - CMS Approval

Purchasing
- Research Device Purchasing Form
  - Receive approval from dept where device will be purchased
EFS in the context of FDA Priorities and Initiatives

Bram Zuckerman, MD | CDRH | FDA
Update on the Center for Devices and Radiological Health (CDRH) and Future Directions

Bram Zuckerman, MD
Director, FDA Division of Cardiovascular Devices
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Patients are at the Heart of What We Do

CDRH Vision
Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world
The ultimate measures of the FDA’s success should reflect its fundamental goals and go beyond such intermediate measures as the number of facilities inspected or drugs approved.”
### Estimated Cost of FDA Decisions on a 30 Employee Company

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Expense to Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>8 Week Delay in Scheduling a Meeting</td>
<td>$1.8 M</td>
</tr>
<tr>
<td>Additional 20 Animal Study (6 months)</td>
<td>$5.5 M</td>
</tr>
<tr>
<td>Extra Year in Negotiating an IDE</td>
<td>$10.8 M</td>
</tr>
<tr>
<td>Additional 100 patient study with 1 year Follow-up (24 months)</td>
<td>$24.1 M</td>
</tr>
</tbody>
</table>

**Versant Ventures**
Vision, Mission, and Shared Values
“Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world....”

Clinical Trials, Premarket/Postmarket Balance, & Customer Service
A different approach—holding ourselves accountable for achieving measurable outcomes in specific areas.

2012
Re-aligned our Strategic Priorities to support the achievement of our Vision MDIC, IMDRF, Entrepreneurs in Residence...

2013

2014-2015

2016-2017

NEST, Partner with Patients, & Culture of Quality
Building on success.
Risk-Based Paradigm for Device Evaluation
(Devices are not Drugs)

Medical Device Classes:

- **Class I**
  - General Controls
  - Most exempt from premarket submission

- **Class II**
  - Special Controls
  - Premarket Notification [510(k)]

- **Class III**
  - Premarket Approval
  - Require Premarket Application [PMA]

Additional Classification:

- **De Novo**
  - Device "types" that have never been marketed in the U.S., but whose safety profile and technology are now reasonably well understood

- **Humanitarian Device Exemption (HDE)**
  - Devices for orphan diseases intended to benefit patients in diagnosis and/or treatment of disease or condition affecting or manifested in fewer than 8,000 patients per year in the United States
Principles of Total Product Life Cycle Development, Regulation and Surveillance
FDA Device Approval: Critical Issues

1. Pre-clinical Testing
   Are bench and animal studies acceptable?

2. Pivotal Trial –
   Design: Minimize bias and confounding
   Design: Use sample size reestimation or Bayesian design to get sample size right
   Execution: Minimize amount of missing data
   Analysis: Rule out chance (i.e., several prospectively chosen, clinically relevant hypotheses with plan for alpha allocation)
   Have clinically meaningful results been clearly demonstrated?

3. Manufacturing
   Can device be built safely for commercial distribution?

4. Is the Device Label truthful and accurate?
<table>
<thead>
<tr>
<th>Premarket Performance Highlights</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>90% Reduction</strong></td>
</tr>
<tr>
<td>Since 2011</td>
</tr>
<tr>
<td><strong>36% Reduction</strong></td>
</tr>
<tr>
<td>Since 2009</td>
</tr>
<tr>
<td><strong>67% Reduction</strong></td>
</tr>
<tr>
<td>Since 2009</td>
</tr>
<tr>
<td><strong>95% Reduction</strong></td>
</tr>
<tr>
<td>Since 2010</td>
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</table>
Novel Device Approvals

~4-fold Increase in # of Novel Device Approvals

* Novel devices include original PMAs, panel track supplement PMAs, and de novos
Clinical Trials (IDEs)*

>90% Reduction in Time to IDE Approval

Median number of days to full IDE approval

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>2011</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>442</td>
<td>215</td>
<td>101</td>
<td>30</td>
<td>30</td>
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</tbody>
</table>

* IDE=Investigational Device Exemption
Importance of Early Feasibility Studies

- Earliest patient access
- Close collaboration between developers & users
- Clinical study continuity from early clinical use to post-approval
- U.S. leadership and contributor to medical device innovation

U.S. Sites Re-engaging in Early Clinical Research

FDA Early Feasibility Study Program
2015-2017

- >50 company participants
- >120 Early Feasibility IDEs
- ~50% Increase in Annual # of EFS IDEs
Breakthrough Device Pathway
(Formerly Expedited Access Pathway)

- 89 devices accepted into the program since April 2015
- 1st breakthrough device approved December 2017

- Interactive & Timely Communication
- Pre-Postmarket Balance
- Flexible Clinical Study Design
- Senior Management Engagement
- Priority Review
Acceptable Uncertainty

- Some degree of uncertainty exists around benefits and risks for most regulatory decisions.
- The regulatory standard is reasonable assurance – not absolute assurance.
- Flexible regulatory paradigm.

CDRH has Clarified Through Guidance Circumstances Where FDA is More Likely to Accept More Uncertainty

For example:
- IDE
- Breakthrough Device
- PMA with small patient population
- Established postmarket data collection mechanism
Use of Real World Data

FDA Guidance (August 31, 2017)
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices
Potential Benefits of Real World Evidence

Understand device performance in real-world environment to inform benefit-risk

Collect endpoints not feasible in traditional clinical trials (e.g. diverse patient populations, long-term outcomes)

Leverage existing data

Reduced time/cost to market
FDA-CMS Parallel Review

Exact Sciences
Cologuard – Colon cancer screening

Foundation Medicine
FoundationOne – genomic profiling companion diagnostic

FDA approval & CMS proposed NCD on Same Day
National Evaluation System for health Technology

NEST

Patient Groups
Industry
Clinician Groups
Health Systems

NESTcc

FDA CDRH
Payers

NEST SHARED RESOURCES
Data Partner Network
Clearinghouse of Expertise
Communications Platform

COORDINATING CENTER
NESTcc’s value proposition will be established through use cases that span the Total Product Life Cycle (TPLC) and include interventional and observational study designs.

### DEVELOP NESTcc’S ROLE

#### PRIORITY USE CASES

- **Pre-Market: PMA, 510(k), De Novo**
  - Using RWE to inform pre-market development or incremental improvement of medical devices

- **Label Expansion**
  - Using RWE in a regulatory submission to support an expanded indication for use of medical devices already on the market

- **Post-Market Approval Studies (PAS)**
  - Using generated RWE to track medical device’s safety and effectiveness as part of its condition of approval

- **Surveillance**
  - Using generated RWE to track and document medical device safety and effectiveness for products on the market

- **Coverage**
  - Using generated RWE to support coverage and reimbursement decisions by public and private payers

The NESTcc has established relationships with **11** data partners, **150** hospitals, and **thousands** of outpatient clinics. Taken together, they represent nearly **470 million** patient records.
Opportunities To Obtain Payer and Health Technology Assessment Input

Current Participants:
- BlueCross BlueShield Association
- CareFirst BlueCross BlueShield
- Duke Evidence Synthesis Group
- ECRI Institute
- Humana
- Kaiser Permanente
- National Institute for Health and Care Excellence
- United Health Group

* New additions!

- Voluntary Program
- Obtain input on clinical trial design or other plans for gathering clinical evidence

For more information: Google Search “CDRH Payer Program”
Digital Health Innovation Action Plan

Refine policies & provide guidance

- Issue guidance conforming to software provisions of the 21st Century Cures legislation
- Publish Clinical and Patient Decision Support Software Guidance

Explore new streamlined pathway for software

- Launch pilot Precertification (Pre-Cert) program to build a new approach to digital health technology, working with our customers and leveraging internationally harmonized principles for software regulation

Building bench strength and expertise

- Build Digital Health unit with right technical expertise
- Launch digital health Entrepreneurs-in-Residence program for building the new paradigm
Concept: A Reimagined Approach Using FDA Pre-Cert

Based on SaMD Risk + Pre-Cert level

Streamlined Premarket Review

e.g. lower-risk software, certain modifications

Commercial Distribution & Real-World Use

Real World Data Collection (NEST)

Assessment
effectiveness feedback

FDA Pre-Cert effectiveness feedback

DH FEEDBACK

Older Pre-Cert level

DH FDA Pre-Cert

FDA Pre-Cert level

Regulatory Science

Clinical Trials Outcomes research

Real-World Evidence

Patient preference
Medical Device Safety Plan

Outlines a vision for how CDRH can continue to enhance our programs and processes to assure:

- Safety of medical devices throughout the TPLC
- Timely identification and resolution of safety issues
- Advance innovative technologies that are safer, more effective and address unmet needs

Published on FDA website July 19, 2018
Healthcare Data Breaches Among U.S. Consumers

1 in 4
Consumers had their healthcare data stolen

1 in 2
Breaches resulted in identity theft

FROM THESE LOCATIONS:

- Hospitals
- Urgent Clinic
- Pharmacy

Highest percentage of breaches occurred

OUTCOME FOR VICTIMS:

$2.5K
in average out-of-pocket costs per incident

STOLEN DATA USED TO:

- 37% Purchase items
- 35% Fraudulently bill for care
- 26% Fraudulently receive care
- 26% Fraudulently fill prescriptions
- 12% Access/modify health records

Source: Accenture Survey, 2017
Examples of Observed Medical Device Cybersecurity Vulnerabilities

- Network-connected medical devices infected or disabled by malware
- Malware on hospital computers, smartphones/tablets, and other wireless mobile devices used to access patient data, monitoring systems, and implanted patient devices
- Uncontrolled distribution of passwords
- Security vulnerabilities in off-the-shelf software designed to prevent unauthorized device or network access
- Failure to provide timely security software updates and patches
CDRH Reorganization Goals

• Create an agile infrastructure that can adapt to future organizational, regulatory, and scientific needs.

• Facilitate information-sharing to help make better informed decisions.

• Ensure process and policy consistency.

• Minimize organizational layers of review and facilitate employee professional development, to achieve more efficient work processes and allow employees to leverage their knowledge of pre- and post-market information to optimize decision-making.
Proposed CDRH Reorganization - Office of Product Evaluation and Quality (OPEQ) Structure

- **Quality & Analytics Staff**
- **Clinical & Scientific Policy Staff**

**OPEQ Immediate Office**

**Strategic Initiatives Staff**

**Regulation, Policy & Guidance Staff**

**Operations Staff**

**Office of Regulatory Programs**
- Office of Clinical Evidence & Analysis
- Office of Health Technology 1 (Ophthalmic, Anesthesia, Respiratory, ENT & Dental Devices)
- Office of Health Technology 2 (Cardiovascular Devices)
- Office of Health Technology 3 (Reproductive, Gastro-Renal, Urological, General Hospital Device & Human Factors)
- Office of Health Technology 4 (Surgical & Infection Control Devices)
- Office of Health Technology 5 (Neurological & Physical Medicine Devices)
- Office of Health Technology 6 (Orthopedic Devices)
- Office of In Vitro Diagnostics and Radiological Health
21st Century Cures Implementation

- Establish Breakthrough Device Pathway
- Change HDE Limit to 8000 Patients
- Streamline Process for 510(k) Exemptions
- Modifications to Classification Panels
- Allow for Central IRBs
- Update CLIA Waiver Guidance
- Recognition of Standards
- Train and Audit Least Burdensome
- Clarify Medical Software Regulation
- Cleaning and Validation Data
Achieving Our Vision

CDRH Vision
Patients in the U.S. have access to high-quality, safe, and effective medical devices of public health importance first in the world.
Thank You

U.S. FOOD & DRUG ADMINISTRATION

& Devices
Session V: Patient Identification, Enrollment, & Retention
MDIC Early Feasibility Workshop
Patient Identification, Enrollment & Retention
Mar. 7, 2019
Patient ID, Enrollment & Retention:
*EFS Balancing Act*
Patient ID, Enrollment & Retention: 
An Early EFS Experience

Enrollment
(34 months)

Contributing Factors:
1. Breaking into new therapy-space & new procedure methods
2. Complicated patient assessments
3. Complex patient care pathway with multiple physician stakeholders
4. Screening to Enrollment ratios
5. Small company staged funding
Patient ID, Enrollment & Retention: Engage Site Teams Early

- Novel Device, New Therapy, New Procedure
  - Invest in benchtop simulations/models
  - Gather device, procedure and patient care feedback
- Flowchart patient’s procedure, follow-up process
  - Recognize difficult data collection points, study parameters that could frustrate or fatigue site personnel
  - Remove barriers – any unnecessary or burdensome steps
Patient Recruitment Flow

Identify ways patients may present to hospital/care system
“Who will see patient first”

Specialty Clinic
Current Patient Pool
Frequent Readmissions, Past Similar Experience
I & E Criteria Familiarity
Add to Study Team

Hospital Admission
ER Admissions familiar with Study
How to contact Study Personnel if patient seems like a good match

Surgical procedure
PI Reviews each Patient
Study Coordinator reviews all surgical procedure patients

ICU
Recognize patients with symptoms that match I&E

What to Know Study I&E
Who to Call Study Personnel
Patient Identified
Patient ID, Enrollment & Retention: 
Screening, Enrollment & I/E Criteria

• Closely Tracking Screen Failures
  • Overall difficulty in finding patients
  • I/E Criteria too tight
  • Site support needed
  • Use of screening committees

• Tailor Recruitment Programs to each Site’s needs
  • Grand Rounds, Database Searches, Referral Dinners, Pre-Screening
Patient ID, Enrollment & Retention: Sponsor Support

- Engage sites early to receive feedback
- Reduce study complexity and remove enrollment barriers
- Map potential recruitment sources
- Build awareness and partnerships across multiple site therapy specialties and patients’ “points of entry”
- Closely track screening to enrollment rates
- Submit expansions to Inclusion/Exclusion as appropriate
- Create individualized enrollment programs for each site
Patient Experience

Identification, Enrollment, & Retention

Necole Kell, RN
Baylor Scott & White Research Institute
The Heart Hospital Plano
Identification/Enrollment

Where are the subjects, and do they qualify?

**Early Feasibility**
- Many questions (unknown)
- Specific/smaller patient population
- Stringent I/E
- Knowledge of referring (Specialty)
- New science with limited data
- Little to no patient education provided
- Fear of “First in Human”
- Screening to screen
- Extra testing
- More “upfront” work
- Multiple amendments.

**Pivotal**
- I/E criteria fine tuned
- More information, more data, easier to explain to potential subject.
- Referring has probably heard about trial/technology = potential increased referrals
- More information = easier to market
- More marketing tools and patient education
- Less vigorous screening process
Retention
How do we keep them coming back?

Early Feasibility/Pivotal
• Length of follow up
• Age of subject
• Comorbidities
• Distance from main site
• SOC vs Research
Session VI: Coverage Determination & Site Budgets
Coverage Determinations & Site Budgets

Jill Trekell
Senior Director, Clinical Affairs
Edwards Lifesciences

jill_trekell@edwards.com
Trial Reimbursement

- **Category A**
  - CMS will pay for standard of care / routine procedures, and the implant procedure, but **NOT** the Device

- **Category B**
  - CMS will pay for standard of care / routine procedures, the implant procedure, and the Device

- **No Reimbursement**
  - Sponsor pays for everything, including the device and does not charge for the Device
Developing EFS Budgets

- Start with the protocol and determine what procedures are required by the protocol and which are standard of care (SOC)
- Establish Fair Market Value (FMV) for study procedure costs, SOC vs non-SOC items
  - FMV calculators – Grant Plan, Grant Manager, etc.
  - Establish FMV range from low to high

<table>
<thead>
<tr>
<th>Procedures (24)</th>
<th>United States</th>
<th>Sub-Study: All Budgets</th>
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<tbody>
<tr>
<td>Code</td>
<td>Procedure</td>
<td>Qty</td>
</tr>
<tr>
<td>1Q09</td>
<td>IQVIA Code: Medical History with Informed Consent (Formerly IQVIA code 99209)</td>
<td>8</td>
</tr>
<tr>
<td>500719</td>
<td>New York Heart Association Functional Classification (NYHA); clinician- or research-administered</td>
<td>8</td>
</tr>
<tr>
<td>99214</td>
<td>Detailed office or other outpatient examination; includes at least two of these three components - a detailed medical history, a detailed physical examination including vital signs, medical decision making of moderate complexity. Typically, 25 minutes are spent performing or supervising these services; visit (formerly code 92120, 92130)</td>
<td>9</td>
</tr>
</tbody>
</table>
Procedure Cost Estimation (non-CMS reimbursed)

- If sponsor *doesn’t* have CMS approval, Sponsor will pay for **all** procedures required by the protocol & hospitalization
  - To obtain implant procedure estimate, pull hospital data for CMS reimbursement for similar procedure and provides estimate and rationale
  - Fee is a one-time fixed payment which will cover everything during hospitalization
- Budget sent to site includes implant and hospitalization fee plus other FMV data required at study intervals
- Goal: Find middle ground with clinical sites within FMV range
Procedure Cost Estimation (non-CMS reimbursed)

- Find appropriate similar procedure DRG
- Estimate the occurrence of major cardiovascular complications and weighted average between reimbursement with or without MCCs
- Compare national average and local hospital reimbursement
- Add any additional costs
  - Hospital component: inpatient reimbursement
  - Physician component: payment for first/second device placement, TEE, etc.
- Medicare reimbursement assumes payment for device; deduct as applicable
- Resulting fee is basis for negotiation with hospital
Challenges with Negotiating Budgets Before CMS Determination

- Clinical sites want higher fees for the implant & hospitalization than what is considered FMV
  - Sites are unsure of the “unknowns” that may occur & don’t want to be left with a large bill
  - Sponsor can only pay within FMV due to kick-back concerns & the payment has to be fixed vs. open ended

- Budget negotiations without CMS determination can take 2x or 3x longer
Budget Negotiations

“Okay, so what number can we both be happy with?”
Common Challenges with MCTAs & CTAs

▪ Most disputed issues:
  – Who pays in the event of an injury?
  – Breach of confidentiality and damages – LOL Section
  – Indemnification
    ▪ Will we indemnify both the PI and his or her employer that hasn’t entered into the contract?
  – Publication on clinical trials.gov and other disclosure requirements

IT TAKES TIME & ONE ISSUE
ALONE CAN CAUSE DELAYS THAT LAST MONTHS!
Case Scenario A

- Hospital is a university hospital ultimately governed by state policies and regulations.
- Hospital claimed that under their university/state policies they may have to disclose all trials they were working on – no secrets as a public institution.
- Some EFS trials can be highly confidential & sponsor doesn’t always want to disclose trial information.
- Site insisted that it could not keep any information secret due to public disclosure requirement.
  - Site refused to take the risk of breaching confidentiality provisions.
- Impasse lasted months and several rounds of negotiation calls.

- In addition …
  - Required external review of SOW; >1 year delay (MDIC site).
Case Scenario B

- Hospital is a university hospital
- EFS program without CMS reimbursement where sponsor proposed FMV budget
- Hospital initially agreed to proposed FMV budget and signed statement of work, site activated to enroll
- Prior to first patient enrolled, site balked and requested increase in procedure cost reimbursement to 3x FMV rate
- Sponsor could not justify 3x FMV from a compliance perspective
  - It’s not always about the actual money, but about the risk sponsors run if they pay over FMV
- EFS was not able to move forward at this site unless the trial received CMS reimbursement