Clinical Trial Innovation and Reform (CTIR)
Speakers

• Susan Alpert, PhD, MD
  – SFA Consulting
  – Principal

• Karim Benali, MD, MSc
  – Abiomed
  – Vice President and Chief Medical Officer
Vision
Clinical trial innovation has the potential to improve the safety and effectiveness of products being introduced into the market, reduce clinical trial cycle times and costs, and yield earlier access to beneficial innovative technologies for U.S. patients.

Priorities
• Address the infrastructure, data collection and pre- and post-market data requirements necessary to restore US leadership in clinical excellence
• Providing tools and methods to facilitate early feasibility studies in the U.S.
MDIC Clinical Trial Innovation Priorities

What do you see as the top priority for Clinical Trial Innovation and Reform (CTIR) project? (Select up to 3)

<table>
<thead>
<tr>
<th>Priority</th>
<th>Series1</th>
<th>Series2</th>
<th>Series3</th>
<th>Series4</th>
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<th>Series7</th>
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<tr>
<td>Optimizing pre-submission interactions with FDA</td>
<td>36.8%</td>
<td>26.3%</td>
<td>31.6%</td>
<td>21.1%</td>
<td>31.6%</td>
<td>68.4%</td>
<td>0.0%</td>
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<td>Broader adoption of the benefit-risk assessment framework (FDA Guidance Document)</td>
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<td>Surrogate and intermediate endpoints, biomarkers, patient reported outcomes and other medical device development...</td>
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<td>Increasing first in human / early feasibility study activity in the US</td>
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<td>Optimizing clinical trial protocol design, including: Endpoints, Quantity of total data elements (Case Report Forms), Value and...</td>
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<td>Alternative clinical trial models, including: Large Simple Trials, Scalable research networks, Adaptive Design</td>
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<td>Study conduct, including: Site selection, Patient recruitment, BIMO audits</td>
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<td>Globalization of clinical research</td>
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<td>Rebalancing pre- and post-market data requirements</td>
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CTIR Steering Committee
Chair: Richard Kuntz, MD, MSc, Medtronic
Co-Chair: Jeff Popma, MD, Harvard Medical School
Karim Benali, MD, MSc, Abiomed
Michael Tarnoff, MD, Covidien
Kathryn M. O’Callaghan, FDA
Bram Zuckerman, MD, FDA
William D. Voorhees III, PhD, MED Institute, Inc.
Bill Murray, MDIC
Susan Alpert, PhD, MD, SFA Consulting

Early Feasibility working group
Chair: Karim Benali, Abiomed
Vicki Anastasi, Aptiv Solutions
Andrew Farb, FDA
Dorothy Abel, FDA
Chip Hance, Creganna
Jonathan Batiller, Johnson & Johnson
Nancy Drake, NAMSA
Petra Kaufman, NIH
Kip Ludwig, NIH
Stephanie Board, St. Jude
Ray Goodrich, TerumoBCT

Clinical Trial Design working group
Chair: Susan Alpert, SFA Consulting
Ken Stein, Boston Scientific
Xavier Lefebvre, Covidien
Chip Hance, Creganna
Liz Galle, CVRx
Katie O’Callaghan and Gerry Gray, FDA
Jeff Popma, Harvard
Mahtab Fatemi, Holaira
Bill Voorhees and Scott Snyder, MED Institute, Inc.
Rick Kuntz, Medtronic
Jennifer Mischke and Katie Schaaf, NAMSA
Mark Carlson, St. Jude

Clinical Trial Innovation and Reform: Team Structure
Differences between pharmaceuticals and medical technologies

- **Pharmaceuticals** are discovered, tested in animals, then tested in stages in humans.

- **Medical technologies** are designed to accomplish a particular action in or on the body; materials are selected based on location of use and duration of use; products are tested at the bench, then in animal models, and confirmed in human trials.

- FDA regulations governing these product types recognize the differences.
Product Regulation, Safety and Effectiveness

• Pharmaceuticals – chemistry and manufacturing controls, animal pharmacology testing, phases I-III in humans to identify risks and benefits

• Technologies - design and materials testing, bench testing, animal models, human trials to confirm extent of predicted efficacy and quantify the identified risks

• Device safety – that the probable benefits to health from use of the device for its intended uses and conditions of use, with adequate directions and warnings against unsafe use, outweigh any probable risks

• Device Effectiveness – that in a significant portion of the target population... will provide clinically significant results
Differences between novel technology and modifications to existing technology

- Across the Total Product Lifecycle different data is needed to support market entry
- Novel technology needs to establish safety and effectiveness
- Modifications elicit different needs for data to support continued safety and effectiveness
- New populations raise different questions than technological changes
- Pre-market requirements are different from post-market data needs
Which of the following best describes your current position on the quantity of data elements in the case report form?

- I have not found the number of data elements in the CRF overly burdensome. I am happy that I have the ability to define these elements based on my needs.

- I have not found the number of data elements in the CRF overly burdensome. I would favor standardization of the definitions of these data elements amongst all medical device trials in my class.

- I feel compelled to collect a large number of data elements in order to make certain that I collect enough information to satisfy all the questions that the FDA may ask during the evaluation of my medical device. I would like to substantially reduce the number of data elements in the CRF with mutual agreement of the FDA.

- I feel compelled to collect a large number of data elements in order to make certain that I collect enough information to satisfy all the questions that the FDA may ask during the evaluation of my medical device. However, if there were standardization of the data elements that were needed for evaluation of devices with the help of a guidance document, FDA-recognized consensus standard that were consistently applied to all medical devices in my class, I would not object to collecting them.

- Other
• One of CDRH’s 2014-2015 strategic priorities is to strengthen the clinical trial enterprise.

  –“CDRH is committed to improving U.S. patient access to new devices by strengthening and streamlining the clinical trial enterprise so that medical device clinical trials are conducted in the U.S. in an efficient and cost-effective manner, while maintaining appropriate patient protections.”

• The MDIC CTIR Clinical Trial Design working group’s goal is to examine the burden of current medical device trial design and explore possible alternatives that will still meet the regulatory needs of high quality data to demonstrate safety and efficacy of medical devices.

• Possible tools may include:
  – Case series of clinical trials
  – Menu of clinical trial options
  – Pilot projects
Clinical Trial Design Working Group

• Topics the group will consider
  – Simplify trials by reduction of data fields
    • Most data is never used
    • Stakeholder considerations to assure that agreed-upon reduced dataset is sufficient to demonstrate safety and efficacy
  – Application of alternative trial designs in selected trials to improve efficiencies where possible
Clinical Trial Design Project Progress

• There is a general understanding that medical device trials are too large, too complex, too expensive
• Working group members were asked to provide data from example trials within their organizations
  – Device type
  – Type of submission
  – Number of subjects
  – Number of data points
• Data from working group informed a broader survey of clinical trial data from MDIC member organizations
• Data will inform menu of clinical trial options
• Future case series
Survey of clinical trial data

- Survey of MDIC companies engaged in clinical trials
- Capturing the amount of data collected, the amount of data used and associated costs
- Data will inform our efforts on innovation in trial designs
Early Feasibility Working Group
Karim Benali, MD
Chairman
Outline

- Problem Statement
- The Opportunity
- The Proposed Roadmap
Problem Statement

• Companies and investors rely on an efficient, transparent and predictable device development ecosystem in order to make well informed decisions.

• In the current era of globalization, businesses can and will conduct research, clinical investigations and development overseas if the legal/regulatory/financial environment is more favorable.

• While the US remains the world’s leader in medical device innovation, the initial clinical testing of novel or “next generation” devices has moved to other continents in response to an increasingly more uncertain development/regulatory ecosystem in the US.

• As a consequence, US investigators fall increasingly behind the curve and American innovations are being made available to patients and physicians in other countries first.
Product Development Process

- Bench Tests
- Animal Pre-clinical Studies
- First-in-Man / Early Feasibility Study
- Traditional Feasibility Study
- Pivotal Study
- Post-market Study

*For Class III device
Challenges That Discourage Companies From Conducting Early Feasibility Studies in the US

• Regulatory process
• Ethics committee review cycle and processes
• Legal challenges (contracts, rights to patent)
• Cost (cost of insurance)
• Ethical / Safety evaluation: balance in risk/benefit determination
US Regulatory Timelines*: Submission to Decision

Agency meets or exceeds goals agreed to by FDA and industry under the Medical Device User Fee Amendments (MDUFA) for ~95% of the submissions reviewed each year.*

Average Time to 510(k) Decision*

Average Time to MDUFA Decision on PMA’s and Panel-Track Supplements (non-expedited)**

* Time from submission to clearance or approval. Regulatory Reform Series #5 – Jeff Shuren - FDA Medical Device Regulation: Impact on American Patients, Innovation and Jobs.
http://www.fda.gov/newsevents/testimony/ucm263491.htm

*Time may not add to total due to rounding
** 2009, 2010 cohort still open as of July 5, 2011: data may change
Most of the Burden Occurs Early

*It takes ~ 6.5 years and ~$36 Million in Investment Before the Start of the Pivotal Study*

![Average Time By Stage For a PMA Product](chart1)

![Average Monthly Expenditures By Stage for a PMA Product](chart2)

http://www.advamed.org/NR/rdonlyres/040E6C33-380B-4F6B-AB5B-9AB1C0A7A5CF/0/makowerreportfinal.pdf
Global Business Leaders Perception on The Regulatory Environment*

Outline

• Problem Statement

• The Opportunity

• The Proposed Roadmap
The Opportunity

• Initiatives have been proposed by US policy makers and patient advocate groups to reverse the current trends and incentivize early feasibility studies in the US.

• FDA CDRH has developed a new guidance and identified in their 2014-15 strategic priorities that they would like to see more early feasibility/first-in-human medical device studies in the US.

• Everyone (especially patients) would gain if industry leaders, FDA, NIH and patient advocate groups developed a shared understanding of a balanced approach that will ensure the safety of the patient while promoting early access to innovation.

• The MDIC CTIR Early Feasibility working group’s goal is to identify the barriers to early feasibility studies “ecosystem” in the U.S. and based on the barriers identified propose possible solutions/tools to facilitate bringing these studies back to the U.S.
The Opportunity is Real

Fields that are likely to benefit from early feasibility studies

There are several prominent fields where a number of feasibility studies are planned for the next 6-24 months:

• Leadless pacemakers
• Cardiac assist devices
• endovascular prostheses
• Structural Heart (New aortic and mitral valve devices, left atrial appendage, heart failure, tricuspid valve repair/replacement)
• Neurostimulation devices
• Orthopedic devices (ankles/extremity joints)
• Wearable artificial kidney
• Vestibular implants
• Ophthalmic devices (intraocular lenses & contact lenses)
FDA Has Taken The Lead and Offered New Guidance

• The agency recognizes the need for a cultural change to shift the focus from not only protecting public health but to also promoting public health.*

• The FDA guidance introduces new approaches to facilitate timely device and clinical protocol modifications during early feasibility studies*
  – Expanded application of 5-day notices
  – Contingent approval
  – Interactive review

• The medical device community has taken note of FDA’s efforts to stimulate the EFS process in US

*Andrew Farb & Dorothy Abel from FDA. 
Guidance For Early Feasibility Studies*

Sponsors welcome FDA new Guidance and Initiative but would like to see more...

Guidance does not go far enough: 43%
Guidance is a useful tool: 43%
Do not have experience with early feasibility study: 14%

*Survey conducted for the MDIC CMO workshop 01/07/2014. Response to question “Based on your experience with medical device development, what is your position on the Early Feasibility guidance published by the FDA?” (N=14 replies)
Companies Would Be Interested to Conduct Their Early Feasibility Studies in the US*

80% of responders would be interested “to test” the new regulatory path for US Early Feasibility Studies... But some relative skepticism remains.

- 34% Interested in US EFS but with increased clarity in guidance document
- 13% Would try EFS in the US but will pursue parallel path overseas
- 13% Interested to include 1+ site(s) in US as part of a study intended originally to be conducted OUS
- 7% Would like to see others document success before committing
- 13% Do not foresee their company participating in this initiative

* Survey conducted for the MDIC CMO workshop 01/07/2014 (N=15 replies)
Other Actions Taken By the FDA

• Dorothy Abel¹ and Andrew Farb² at FDA have been in charge of developing the early feasibility program ODE wide. Education of FDA staff and industry will be a principal goal for them. Industry should reach out to them with new ideas or guidance.

• Ms. Abel and Dr. Farb are actively working with a group of representatives from each review division (Early Feasibility Division Reps) to expand the available resources within and outside of CDRH to help in the preparation and evaluation of early feasibility study IDEs (contact info can be found in the appendix).

• ODE division directors are also interested in moving along with the early feasibility program. Industry also should contact the division directors.

¹Email: Dorothy.Abel@fda.hhs.gov
²Email: Andrew.Farb@fda.hhs.gov
Other Challenges Beyond Regulatory

• Ethics Committee (IRBs) Issues¹:
  – IRB concerned that the early feasibility IDE may place increased burden on IRBs to determine the level of risk for the patients. Will they be ready?
  – IRB may need to assume more responsibility in monitoring the study
  – IRB may be “out of the loop” if device/protocol can be changed with less constraints.

• Legal Issues:
  – Patent issuance
  – Cost of insurance

• Ethical/Safety Issues
  – Patient informed consent
  – Independent Data Monitoring Committee

¹Jeffrey Brinker, MD. Are US Sites and IRBs Ready for First In Human Studies? FDA Town Hall session at CRT 2012.
Outline

- Problem Statement
- The Opportunity
- The Proposed Roadmap
Early Feasibility / First in Human (FIH) Studies in the U.S. Working Group

Topics the group will consider

• Implications of a broad industry commitment to do more early feasibility in the US (Identify current barriers to early feasibility studies)

• FDA considerations for implementation of early feasibility guidance (Identify risks for rapid approval of early feasibility in the US)

• Develop standards for early feasibility studies in the US (Blueprint handbook on the “How to” conduct these studies in US)
## Proposed Short-term Roadmap

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<th>2014</th>
<th>2015</th>
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<tr>
<td><strong>Q2</strong></td>
<td><strong>Phase 1:</strong> Identify Deliverables And Actionable Measures</td>
<td><strong>Phase 3:</strong> Roll-out Phase (TBD)</td>
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<td></td>
<td>• “Build” the team</td>
<td>• Possible release of successful “tools”</td>
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<td>• Define operating mechanisms</td>
<td>• “Push” 4 or 5 new technologies (devices) through this program for validation</td>
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<td>• Define actions</td>
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<td>• Interview “key” MDIC FIH Members</td>
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<td>• Launch a survey to large audience of stakeholders</td>
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<td>• Develop “tools”</td>
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| **Q3** | **Phase 2:** Pilot Phase (TBD) |  |
|  | • Limited “roll-out” of proposal and tools |  |
|  | • Collect early feedback |  |
|  | • Fine-tune as necessary |  |

| **Q4** | 2015 |  |
|  | **Q1** |  |

### Phase 1:
- Identify Deliverables and Actionable Measures
- “Build” the team
- Define operating mechanisms
- Define actions
  - Interview “key” MDIC FIH Members
  - Launch a survey to large audience of stakeholders
  - Develop “tools”
Phase I: “Build” the Team

Team of 12 members representing different stakeholders

*Representation at the MDIC FIH committee
1 Consider adding more small companies to MDIC committee
2 Consider adding members for MDIC committee
Phase I: Interviews

Interviewees:

16 members representing Industry, VCs, FDA, NIH, CROs, IRBs were interviewed

Outcomes:

1. Gained consensual approach: Collected individual perspectives and expectations on the role of the working group and desirable possible achievements
2. Identified specific short term actions with measures of success
3. Collected actionable feedback on the goals/content of the survey
Phase I: Stakeholders Survey

1. Survey stakeholders (industry/sites/IRB in particular) to orient future possible actions of MDIC FIH working group and set some baseline measures (WIP).
2. Draft survey to be circulated among the MDIC Steering Committee Members
3. Release Survey in Q3 to Stakeholders
4. Results of the survey will help prioritize the next actions and define the “tools” the MDIC FIH group would propose
Conclusion and Future Perspectives

- FDA CDRH identified in their 2014-15 strategic priorities that they would like to see more early feasibility/first-in-human medical device studies in the US.

- The desire to bring back the EFS/FIH studies to the US is largely shared among the stakeholders. Fair skepticism remains. Success stories would need to be publicized and further encouragement will be needed.

- MDIC is committed to leverage existing opportunities and foster collaboration between different stakeholders to help remove (or reduce) barriers and facilitate bringing these studies back to the U.S to benefit patients.
Acknowledgments

MDIC Members
Stephanie Christopher, MDIC
Bill Murray, MDIC
Dorothy Abel, FDA
Andrew Farb, FDA
Kathryn O'Callaghan, FDA
Bram Zuckerman, FDA
Chip Hance, Creganna
Vicki Anastasi, Aptiv Solutions
Jonathan Batiller, Johnson & Johnson
Nancy Drake, NAMSA
Petra Kaufmann, NIH
Kip Ludwig, NIH
Stephanie Board, St. Jude
Ray Goodrich, TerumoBCT
Ross Jaffe, Versant Ventures

Institutional Review Board Members
Bette Bayne, Schulman Associates IRB
Patrick Turk, Schulman Associates IRB
Kathye Richards, Sterling IRB
Alison Alesi, Sterling IRB
Questions and Discussion

Twitter: @MDIConline
#MDIC2014
# Early Feasibility Studies Reps @ FDA

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<td>Joy Samuels-Reid</td>
<td>Tejashri Purohit-Sheth</td>
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