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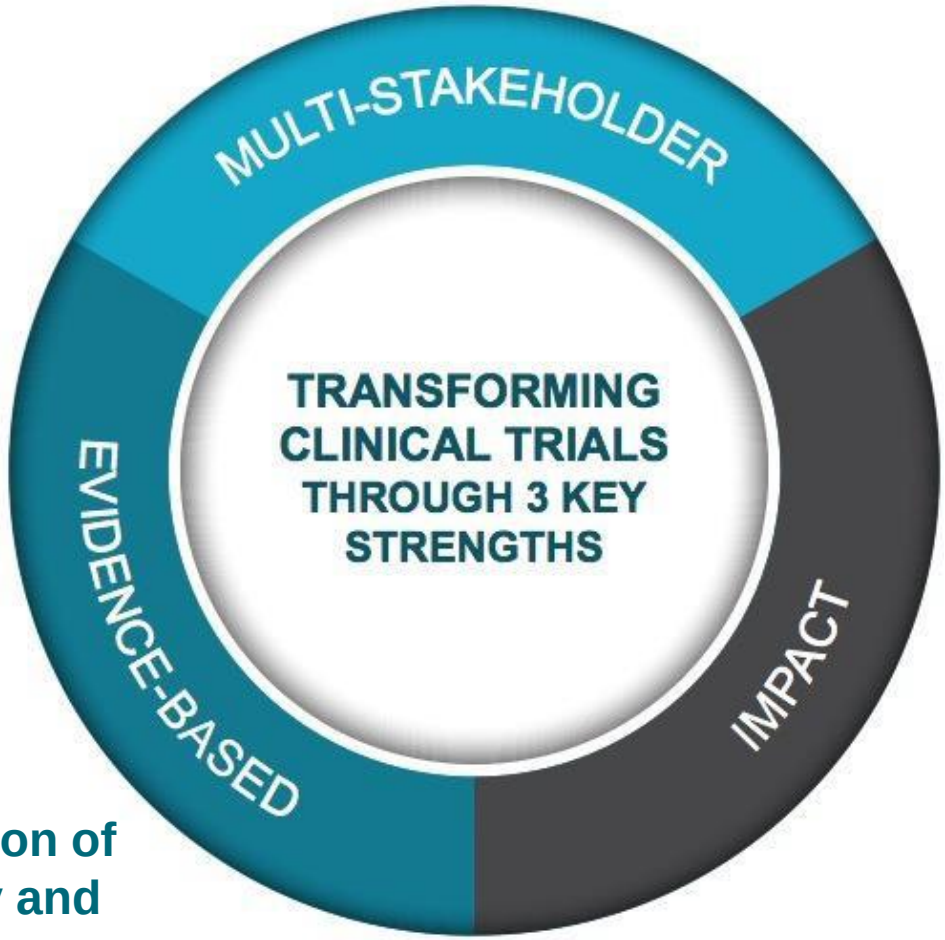
CLINICAL TRIALS TRANSFORMATION INITIATIVE

May 17, 2018

CTTI Overview

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

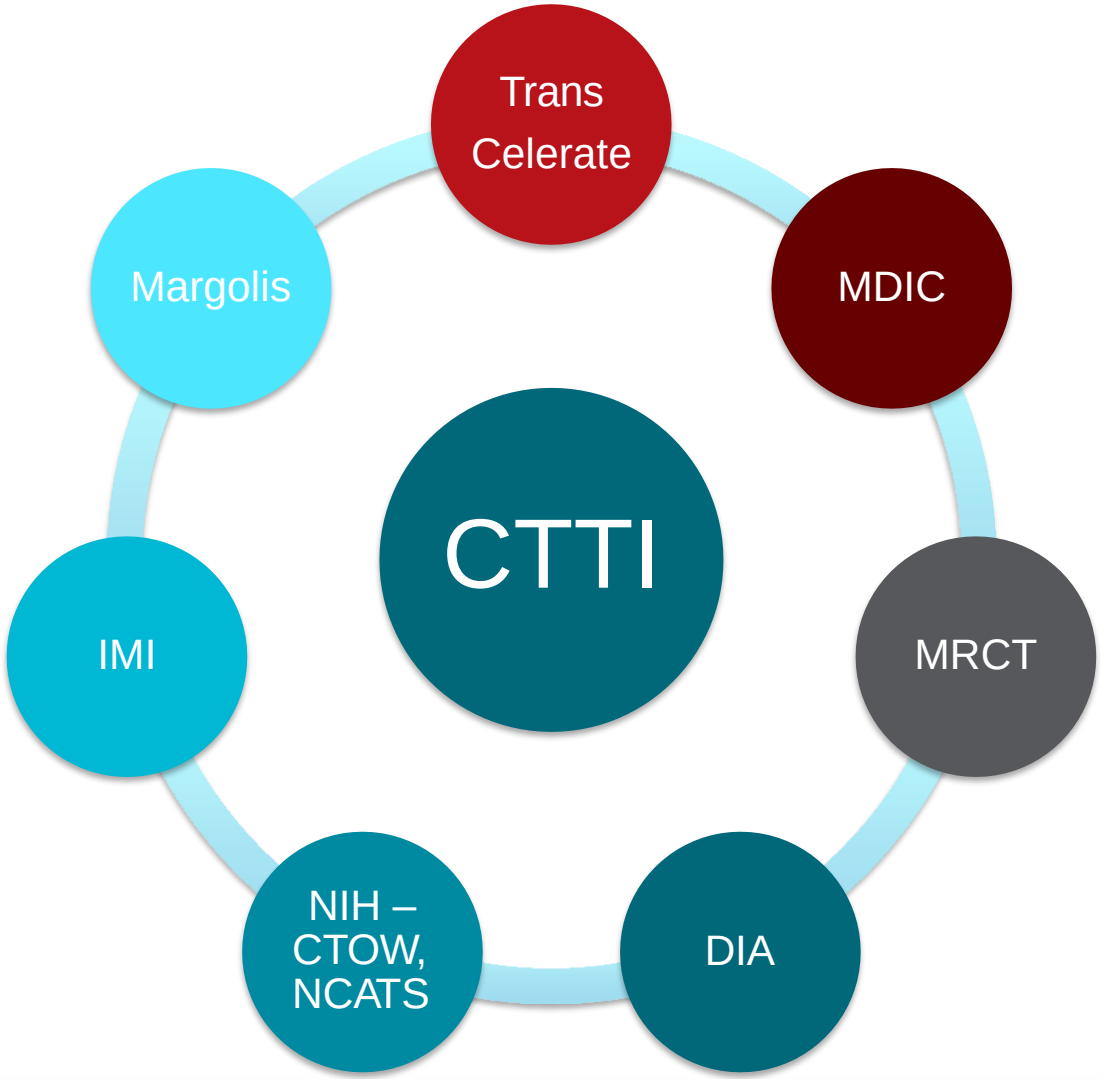


Public-Private Partnership
Co-founded by Duke University & FDA
Involves all stakeholders
80+ members

MISSION: To develop and drive adoption of practices that will increase the quality and efficiency of clinical trials

CTTI Membership

Related Efforts



CTTI & Related Efforts

- Initiatives have different scope and stakeholder make-up
- Regular communications
- Sometimes address similar topic, but different aspects
- Aim is to have complementary, not duplicative efforts

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

May 17, 2018

Medical Device Innovation Consortium

MDIC and CTTI: Synergies in Clinical Trials Efforts

Stephanie Christopher, MA, CCRC, FACRP, Program Director, MDIC

Dan Schwartz, Program Director (acting), MDIC

MDIC
MEDICAL DEVICE INNOVATION CONSORTIUM
Align › Achieve › Accelerate

Disclaimer

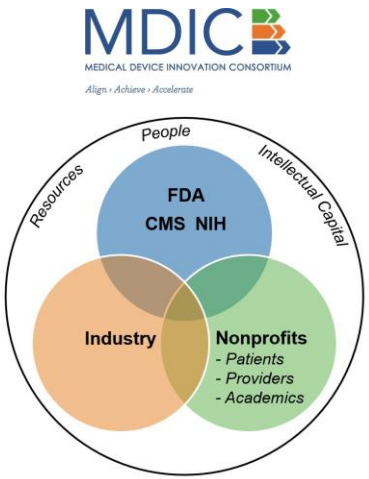
- The views and opinions expressed in this presentation are those of the individual presenter and do not necessarily reflect the views of the Clinical Trials Transformation Initiative.

Our agenda

- Introduction to MDIC
- MDIC Science of Patient Input Initiatives
  - Patient Input in Clinical Trials
- MDIC Clinical Trials Science Initiatives
- Questions

What is MDIC?

MDIC is a 501(c)(3) non-profit organization and is the first-ever public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit



Align Resources

Accelerate Progress

Achieve Results

WORKING COOPERATIVELY
to re-engineer pre-competitive technology innovation

REDUCING TIME
and resources needed for new technology development, assessment, and review

HELPING PATIENTS
gain access to new medical technologies sooner

MDIC HIGHLIGHTS

66 participating member organizations

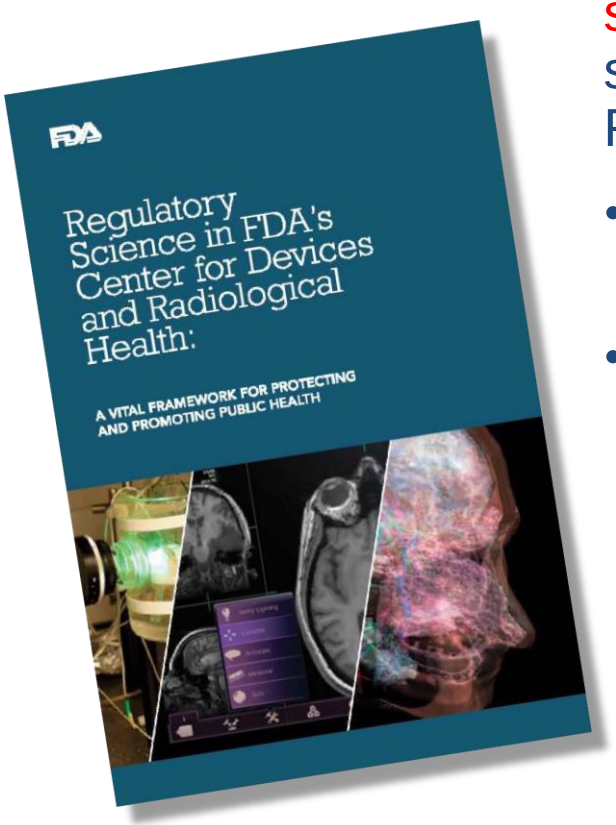
Leading resource on issues important to the Medtech innovation ecosystem

6 Projects have been initiated

Congressional testimony on modernizing clinical trials

Over $35M funding from grants and contracts for Program initiatives.

What is Regulatory Science?



FDA Strategic Plan, August 2011
Advancing Regulatory Science at FDA

The science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of FDA-regulated products

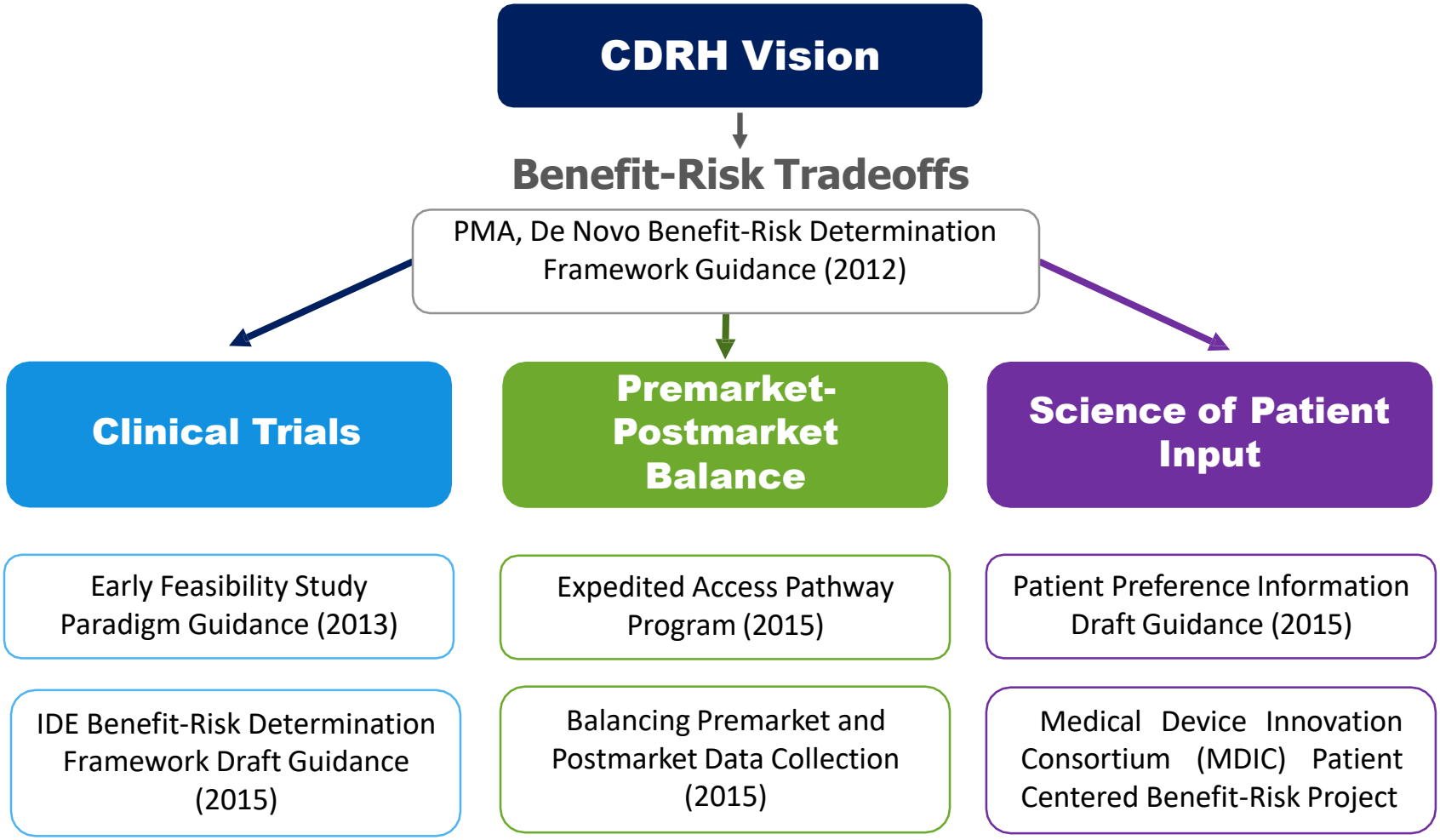
- Benefits patients by speeding the rate of important technologies reaching market
- Reduces time and resources needed for device development, assessment, and review. For example:
  - Can lead to quicker, more efficient device approvals
  - Can decrease the size and duration of pre-market clinical trials

Faster, Safer, More Cost-effective

MDIC is Aligned with CDRH Priorities

Flexible Regulatory Paradigms

Applied Across the Total Product Life Cycle



* Slide from Dr Shuren NEST Presentation May 2016

Using Patient Preferences to Inform Clinical Trials

Sculpting the fog…

A near impossible task…

Patient Preference Information – Voluntary Submission, Review in Premarket Approval Applications, Humanitarian Device Exemption Applications, and *De Novo* Requests, and Inclusion in Decision Summaries and Device Labeling

Guidance for Industry, Food and Drug Administration Staff, and Other Stakeholders

Document issued on August 24, 2016.
This document will be in effect as of October 23, 2016.

The draft of this document was issued on May 18, 2015.

For questions about this document regarding CDRH-regulated devices, contact the Office of the Center Director (CDRH) at 301-796-5900 or Anindita Saha at 301-796-2537 (Anindita.Saha@fda.hhs.gov)..

For questions about this document regarding CBER-regulated devices, contact the Office of Communication, Outreach, and Development (OCOD) at 1-800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration

Center for Devices and Radiological Health

Center for Biologics Evaluation and Research

But we did it!

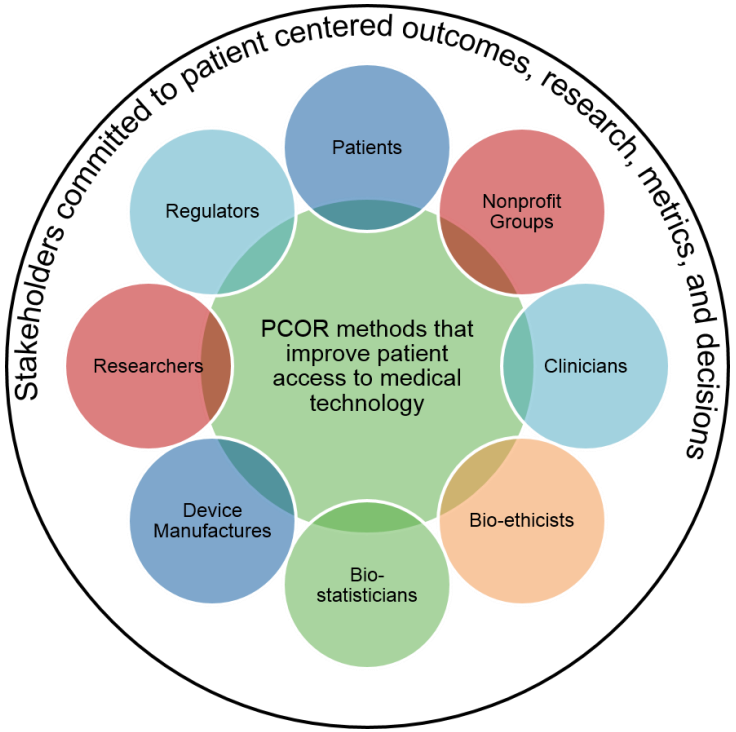
How did we do it?

An intriguing question

What if patients' **urgency for new therapeutic options** and **tolerance of uncertainty** were taken into account when designing and sizing clinical trials?

A New Collaboration to Move Clinical Trials from Generic p-value of 0.05 to Therapy-Specific Patient-Values

A new approach to designing and interpreting clinical trials



Developing and testing a method to incorporate Patient Perspectives on Benefit/Risk as an explicit means to set significance levels in clinical trial design

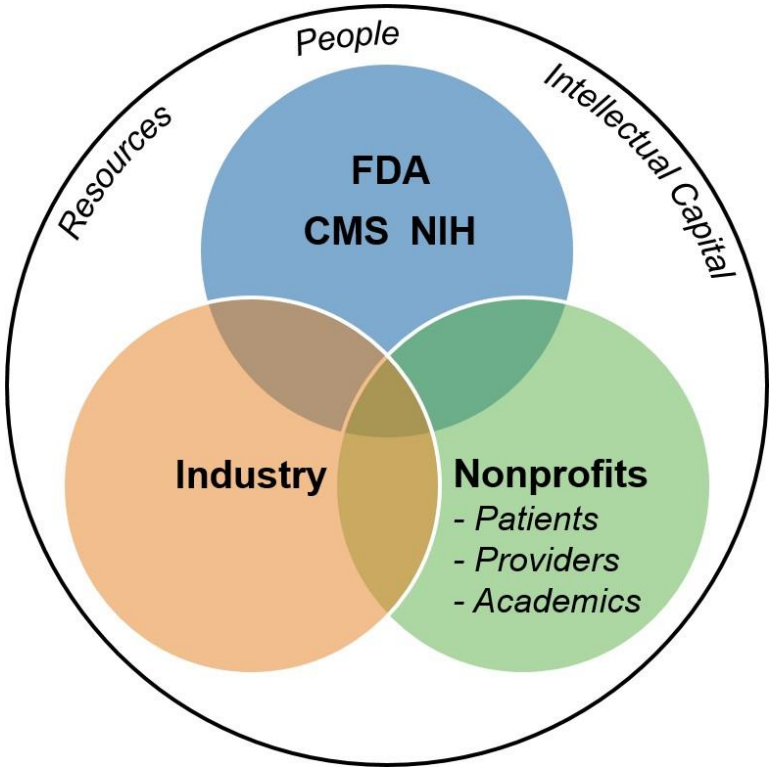
Investigative Partners: FDA, RTI, MIT, MDIC

Patient Partner: The Michael J. Fox Foundation for Parkinson's Research

Platform for real world patient data: Fox Insight – an online research study to gather the world's largest collection of data about life with Parkinson's.

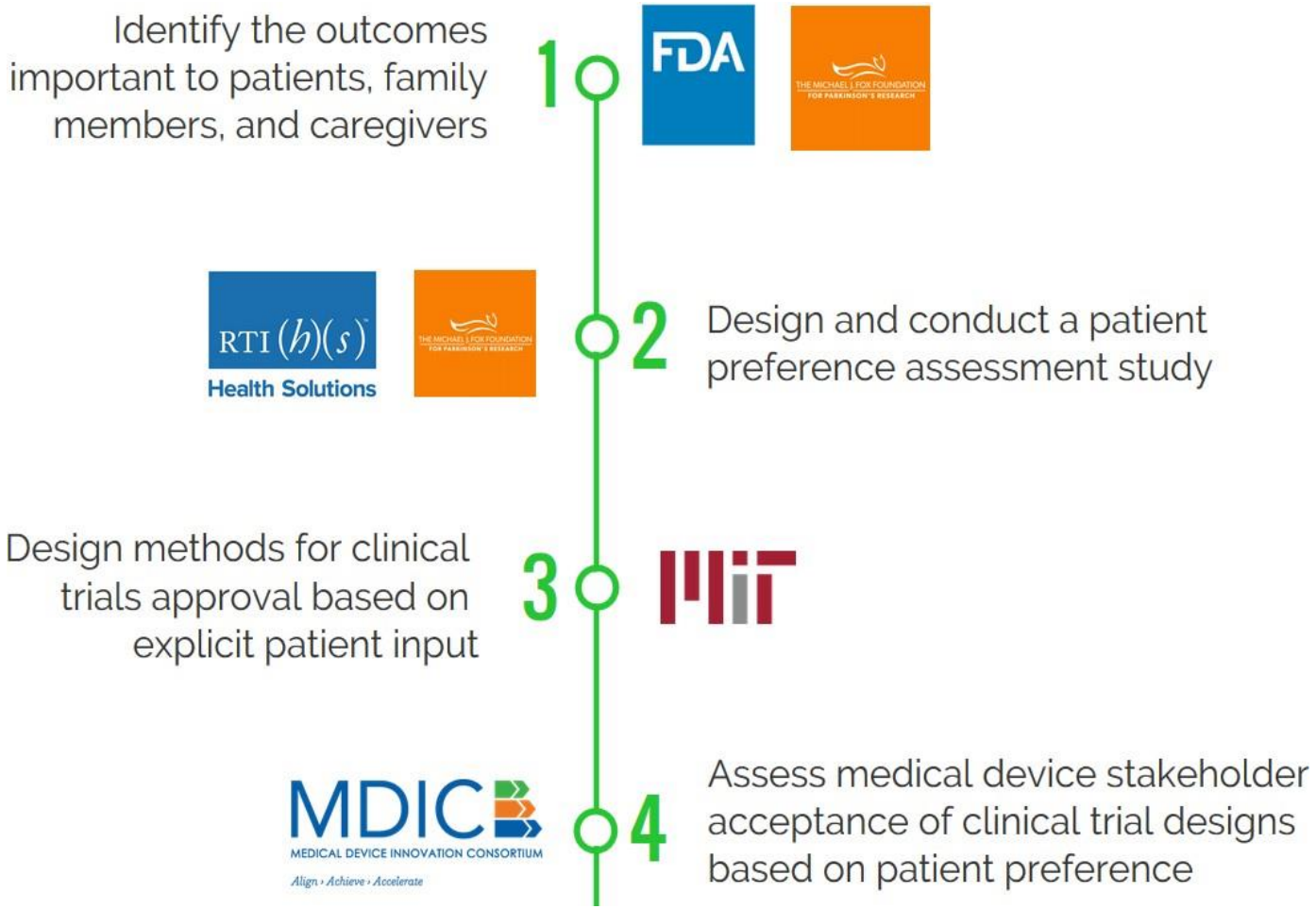
http://mdic.org/pcor

Why MDIC?



MDIC is a 501(c)(3) non-profit organization and is the first-ever public-private partnership created with the sole objective of advancing regulatory science of medical devices for patient benefit

Specific Aims



Results

- Aim 1 – Identify Important Device Outcomes
  - Interviews with 7 patients; ranking exercise completed by 29 patients
  - Consultation with CDRH reviewers and experts
  - Identified 10 important benefits, risks and other considerations for treatments for Parkinson's Disease
  - Used these outcomes to develop patient-preference survey
  - Manuscript describing Aim 1 currently under review at FDA
- Aim 2 – Survey Development
  - MDIC, FDA, the Michael J Fox Foundation, and RTI developed a patient preference survey
  - Conducted interviews to review survey with 20 patients identified by the Michael J Fox Foundation
  - The Michael J Fox Foundation, RTI, and Qualtrics programmed the online survey

Results

- Aim 2 – Survey Administration and Analysis
  - The Michael J Fox Foundation recruited patient participants through Fox Insight
    - As of January 2018, there are 16,000 people with PD and healthy controls enrolled in Fox Insight.
  - Survey was administered online Nov. 27, 2017 to Jan. 12, 2018
    - 11,288 individuals were sent an email invitation through Fox Insight
    - 4,203 respondents accessed the survey
    - 2,752 respondents were eligible and completed the survey
    - Sample reflects composition of the Fox Insight panel

What we asked

	~~Risks~~
Increase in daily “on time”	Risk of (worsening) depression or anxiety
Decrease in motor symptoms	Risk of serious adverse event (brain bleed)
Decrease in PD pain	Increase in 1-year mortality risk
Decrease in cognitive impairment	Increase in wait time (discounting)
Decrease in medication and side effect burden	

Discounting required for MIT model, so a modified time tradeoff exercise was included in the survey in addition to the benefit-risk thresholds

Results

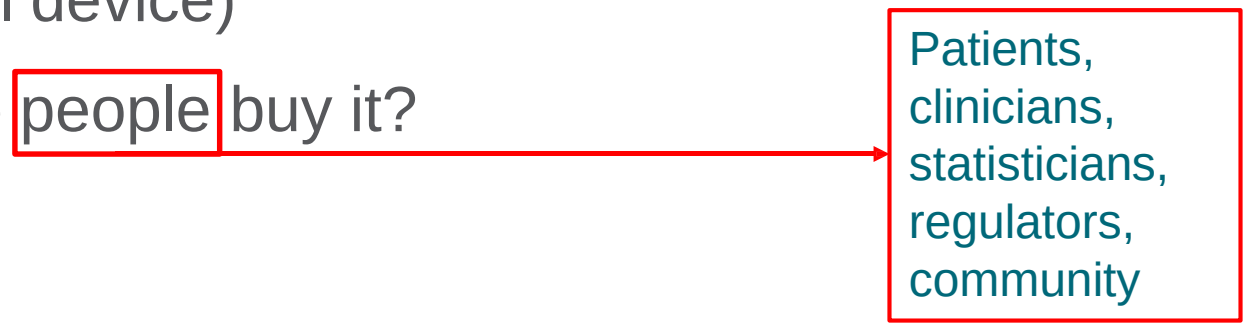
- Aim 2 – Results
  - Estimated tolerance for each risk in exchange for each benefit
    - Higher tolerance for risk in exchange for greater benefit
    - Risk tolerance has face validity
      - Highest tolerance for depression and anxiety
      - Lower tolerance for brain bleed
      - Lowest tolerance for death

Results

- Analysis process assisting CDRH in developing recommendations for good data management practices for preference surveys
- Risk-tolerance estimates being incorporated into MIT model for clinical trial design

Stakeholder engagement

- Not enough just to create a really cool new widget (or medical device)
- Will the people buy it?



- Transformative research requires transformative engagement

Why this matters to MDIC members (and more importantly, patients)

- Meeting patient needs
- CDRH commitment to advancing use of patient preference
- Efficiency and effectiveness in clinical trials

http://www.milkenreview.org/articles/p-values-vs-patient-values

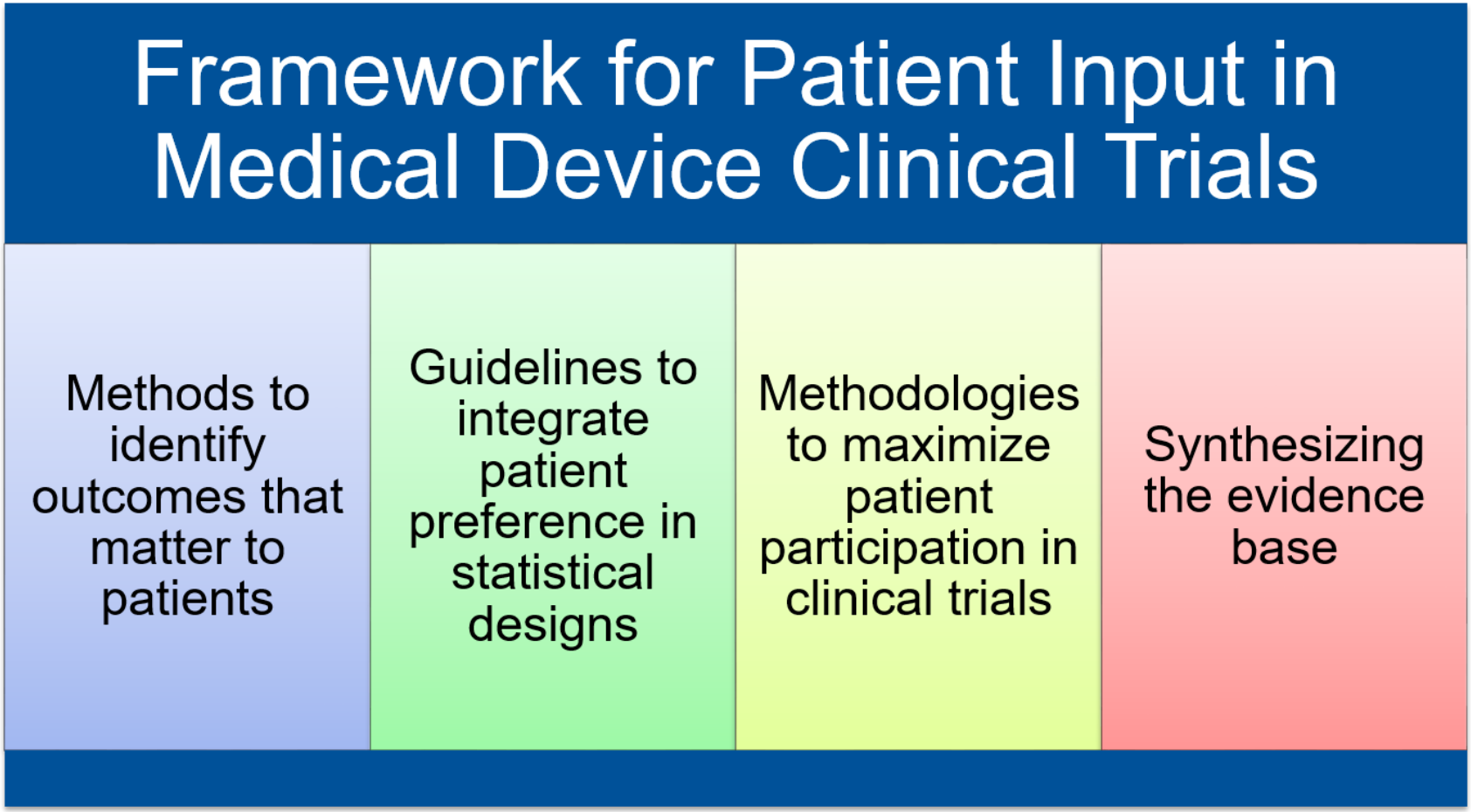
Join us May 18 to hear the final results of the project
http://mdic.org/spi/pcor/workshop

ISPOR panel – May 22, 3:45 p.m.
What is patient-centered and fit-for-purpose patient preference information?

CTTI

Building a Framework for Patient Input in Clinical Trials

MDIC Framework for Patient Input in Medical Device Clinical Trials



Objective

- The proposed project is to develop a Framework for Incorporating Patient Input in Medical Device Clinical Trials. The Framework will include four sub-projects: Methodologies to identify outcomes that matter to patients; guidelines for integrating patient preference into the design of trials; methodologies to maximize patient participation in clinical trials and a report summarizing and validating the evidence from the deliverables in this project.

Deliverables

1. A report for sponsors and CDRH staff to use when considering methodologies to prioritize clinical trial outcomes that matter most to patients, and determine how to establish these outcomes as primary or secondary endpoints for clinical studies
2. A set of guidelines for sponsors and CDRH staff to use when integrating patient preferences into the statistical design of clinical trials
3. A report with guidelines and a tool-kit for sponsors and CDRH staff to use when considering the need for methodologies to maximize patient participation in clinical trials
4. A report summarizing and validating the evidence base for the methodologies, guidelines, and framework developed under this project

Expectations

- Building on and synthesizing great work done in this space
- Two year initiative
- Living document
- Stakeholder engagement

MDIC Clinical Trial Science (CTS) initiatives

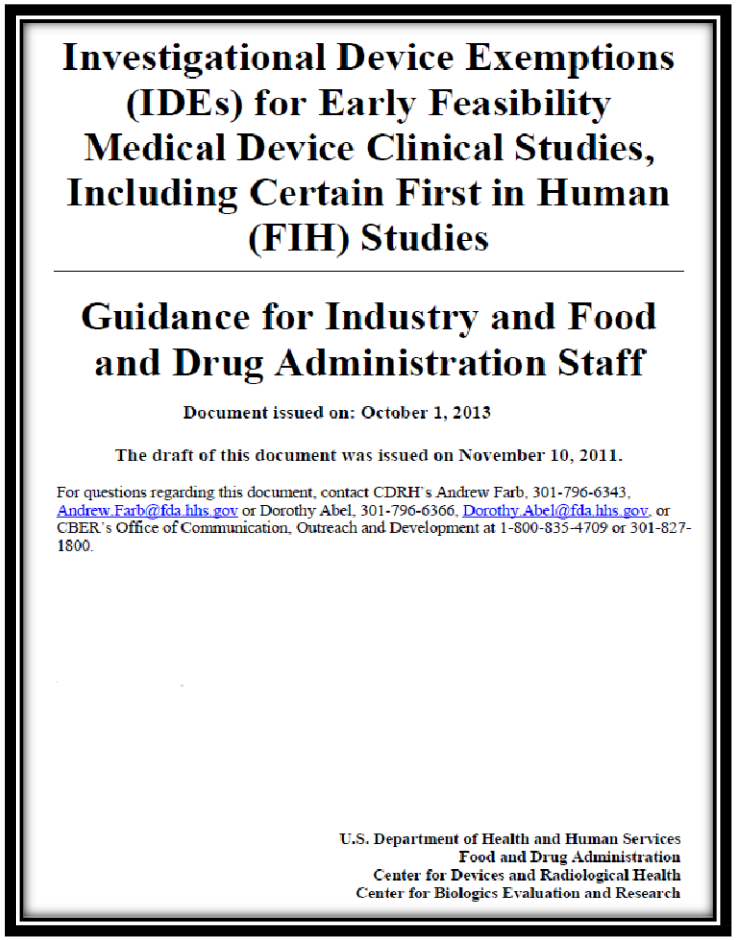
EFS: Historical Background

- Substantial outmigration of clinical studies for medical devices from the U.S.
- From 2004 to 2009 the percentage of clinical studies for medical technology products listed on clinical trials.gov in the U.S. decreased from 87% to 45%

Holmes DR et al: J Am Coll Cardiol 68:1908-15, 2016

FDA Response: EFS Guidance

- New program to facilitate early patient access to medical technology
- 2013: EFS Guidance Document
  - Why are Devices unique?
    - *Surgical approach* may change
    - Device *development is iterative*, and often custom made (one-off)
  - How to Address?
    - Pre-Pivotal *testing expansion* (does not replace Pivotal)
    - IDE may be based on more *alternative data* to clinical: bench testing, animal models, etc.



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.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health
Center for Biologics Evaluation and Research

FDA Guidance: Investigational Device Exemptions (IDEs) for Early Feasibility Medical Device Clinical Studies

EFS Ecosystem Stakeholders: Manuscript & Executive Committee

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

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

ABSTRACT

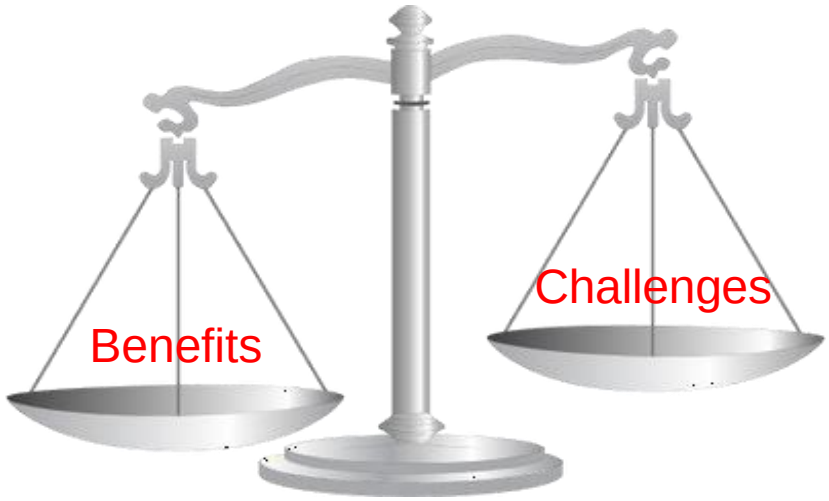
Initial clinical studies of new medical technologies involve a complex balance of research participant benefits versus risks and costs of uncertainty when novel concepts are tested. The Food and Drug Administration Center for Devices and Radiological Health has recently introduced the Early Feasibility 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)

Source: Journal of the American College of Cardiology, October 25, 2016

EFS Executive Committee

- David Holmes (Chair/Mayo)
- Karen Alexander (Duke)
- Dan Burkhoff (CRF)
- Joseph Chin (CMS)
- Chip Hance (MDIC/Industry)
- Aaron V. Kaplan (Dartmouth)
- Martin Leon (CRF/Columbia)
- Michael Mack (Baylor)
- Jeff Shuren (CDRH/FDA)
- Tamara Syrek-Jensen (CMS)
- Bram Zuckerman (CDRH/FDA)

EFS: Benefits and Challenges



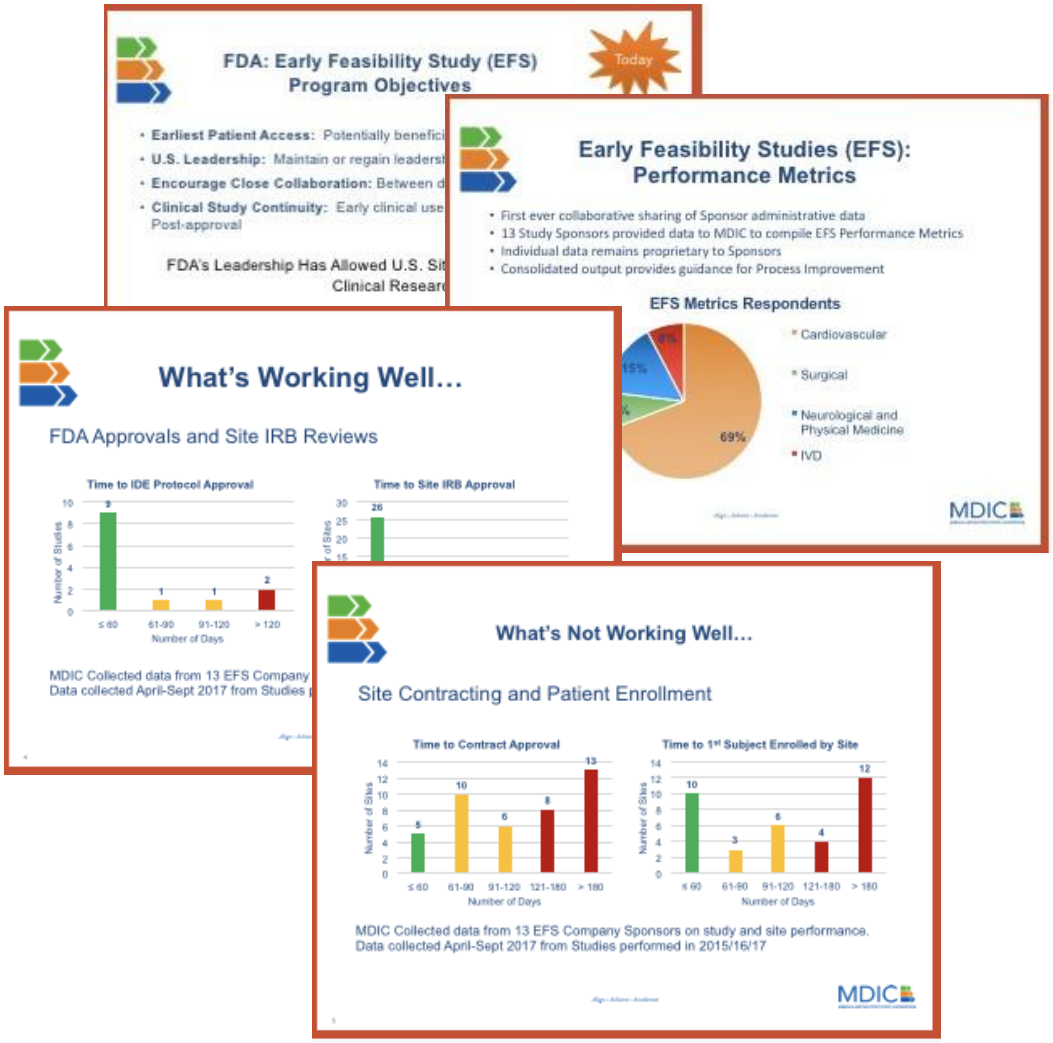
- **EFS Ecosystem Stakeholders**
  - Called for shared responsibility across the stakeholder
  - Recognized the need for concessions across regulators, sponsors, payers, IRB's, sites and investigators

- **Benefits: Patients, Physicians, Sites and Payers**
  - Early exposure to medical technologies addressing unmet clinical needs
  - Offer the newest treatment options
  - Promote training and education of all site personnel,
  - Support research program growth
  - Provide easier transition to pivotal studies
  - Early feedback on new device risks and benefits and comparative effectiveness

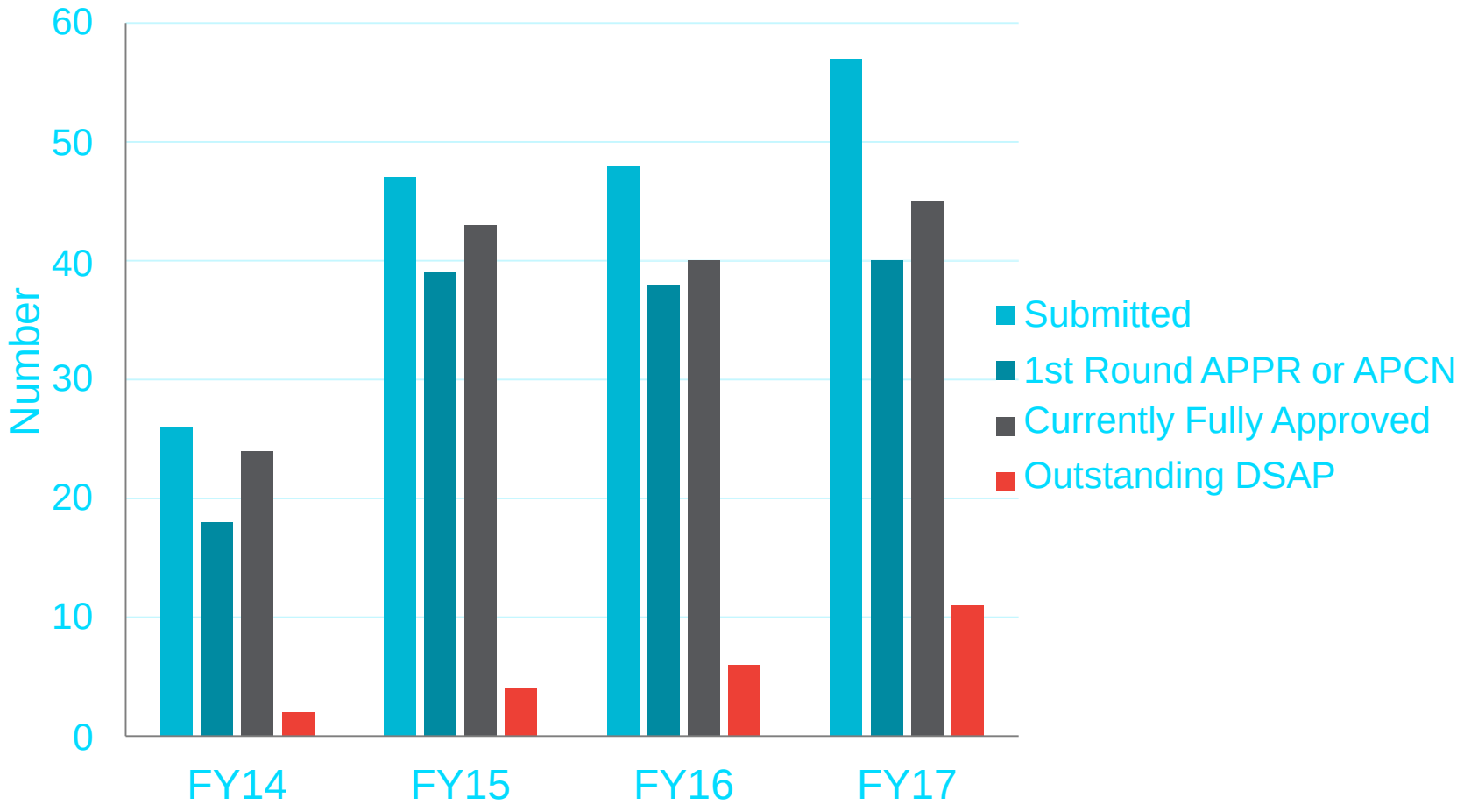
- **Challenges**
  - Unknown risks and benefits
  - Patient protections
  - Contract considerations
  - Coverage Reimbursement questions
  - Clinical site qualifications

EFS Initiative: MDIC Background

- FDA EFS program has had positive impact on earliest patient access
- EFS leadership team launched with Clinicians, FDA/CDRH, CMS, and MDIC to drive efficiencies
- EFS contracting and enrollment identified as greatest barriers to success
- **Vision:** Establish a voluntary, open research network of clinical sites committed to high-quality and efficient EFS that supports “First-in-World” U.S. patient access
- **First step: demonstrate feasibility of tools, methods, and structure**

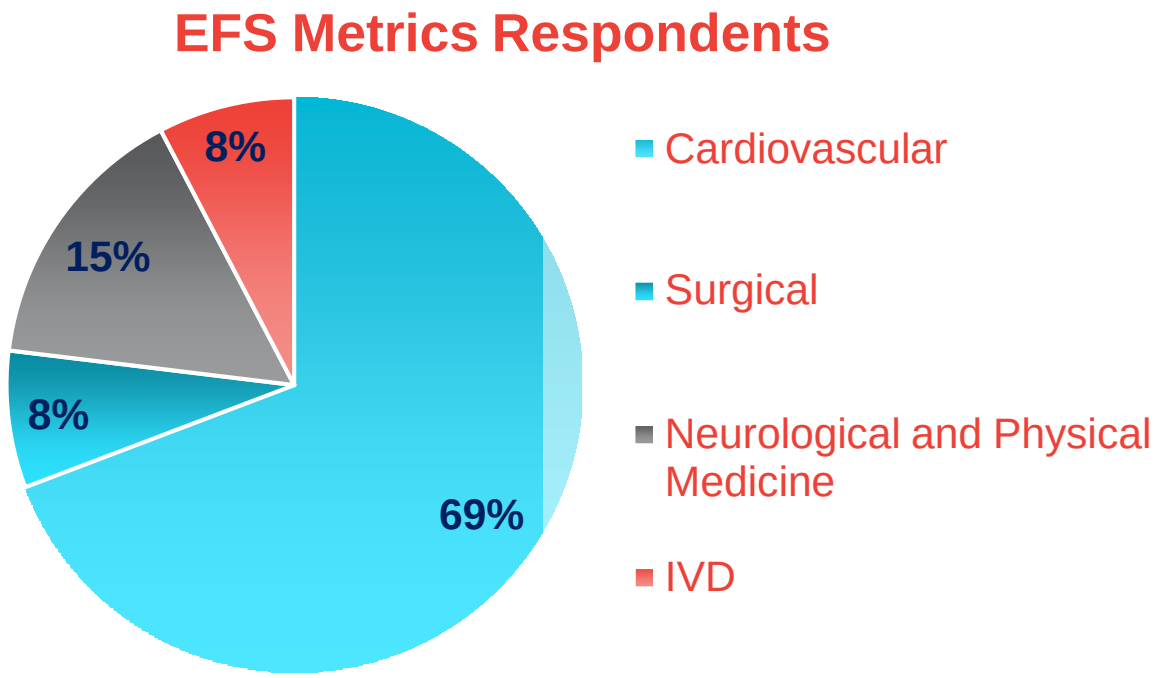


EFS: IDE Submission & Decision Trends



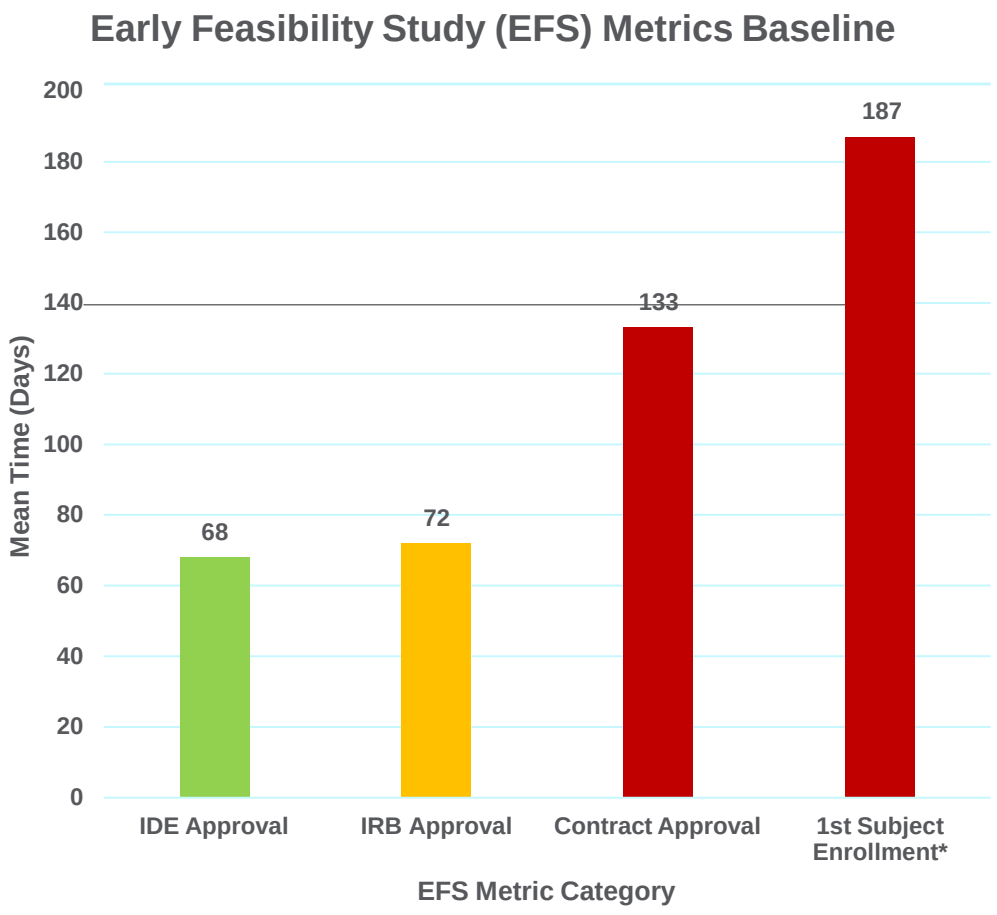
EFS Performance Metrics: Respondents

- First ever collaborative sharing of Sponsor administrative data
- 13 Study Sponsors provided data to MDIC to compile EFS Performance Metrics
- Individual data remains proprietary to Sponsors
- Consolidated output provides guidance for Process Improvement

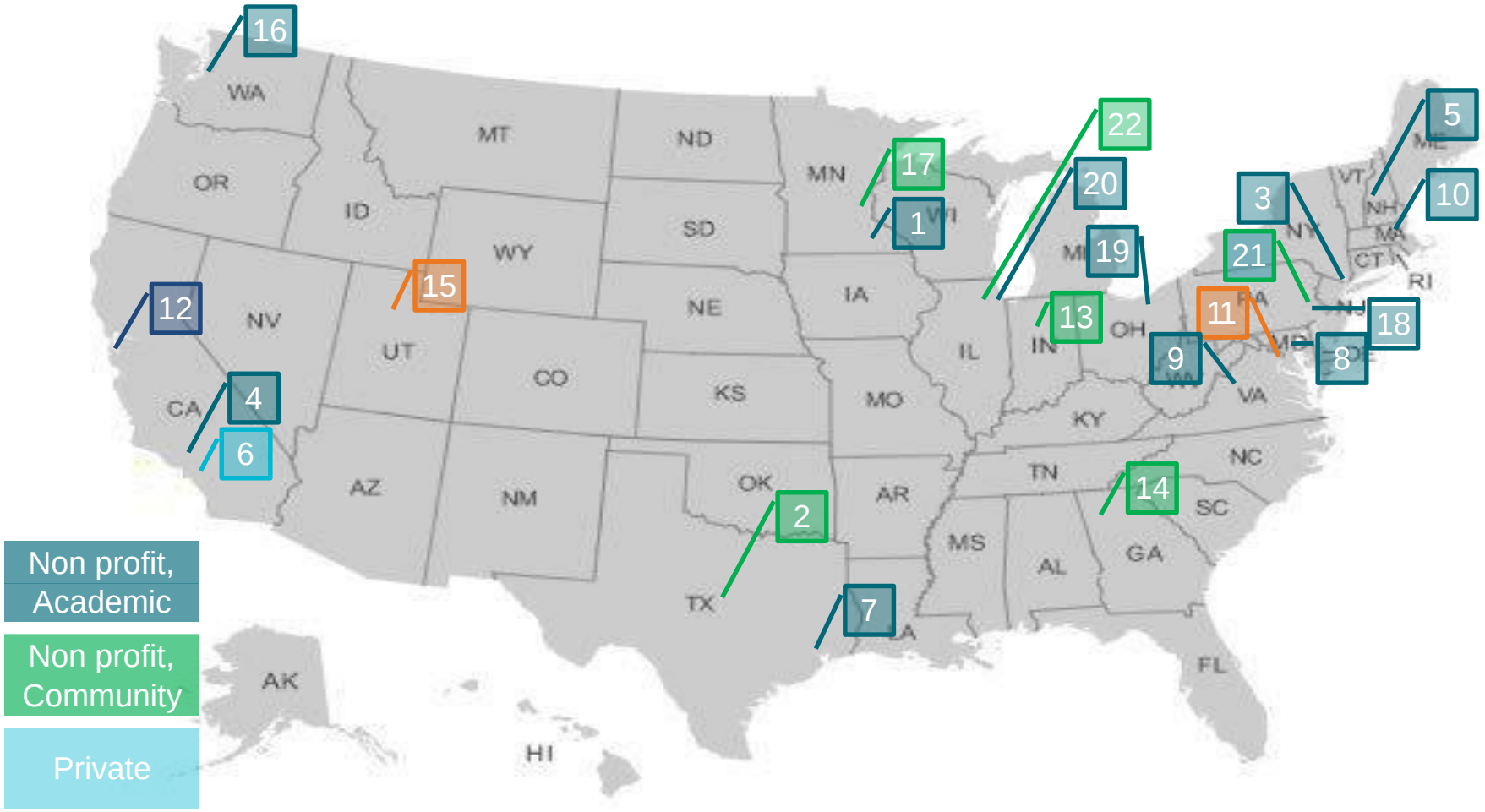


Early Feasibility Study (EFS) Metrics

- MDIC collected metrics on 22.8% of all industry IDEs submitted through the EFS program between 2015 to 2017.
- These metrics reflect 12 industry sponsors and 50 clinical sites
- IDE Cycle Time Mode: One round
- IDE Cycle Time Mean: Two rounds
- *First Subject Enrollment: Measured from last to occur among site IRB or Contract approval
- Suggested Goals of 60/60/60
  - 60 Days for IRB Approval
  - 60 Days for Contract Execution
  - 60 Days for first subject Enrollment



CV EFS Pilot: Site Demographics*



Non profit, Academic

Non profit, Community

Private

*Indicates Possible Sites – Selections TBD

EFS Legal Roundtable: Master Clinical Trial Agreement

- Contracting identified as an improvement opportunity, averaging 133 days and often exceeding 180 days
- The MDIC EFS Contracts working group, Chaired by Jamie Walkowiak from Baylor Scott & White, publishes an EFS Language Library (2017)
- Ecosystem leadership recognized an opportunity to further streamline contracting through development of an EFS Master Clinical Trial Agreement (CTA)

Key Deliverables:

- Development and public release of an EFS-specific Master CTA for sponsors and sites
- Implementation of Master CTA to:
  - Pre-specify those EFS contract clauses the most resource-intense to negotiate:
    - Focus individual EFS trial negotiations on the clinical indication with trial Statements of Work (SOW)s.
    - Parallel Projects: A Clinical Site Demonstration project in Partnership with Industry Could Carry On and Measure Process Improvements

EFS: IRB and Patient Advocacy

- **Lead Authors:**

- Karen Alexander, MD: Co-Director, Integrated Clinical Events and Safety Surveillance (ICE-SS); Faculty Leader for Safety Surveillance; Professor of Medicine, Cardiology

- Dan Burkhoff, MD, PhD: Director of Heart Failure, Hemodynamics and Circulatory Support in the CRF Clinical Trials Center (CTC)

Introduction to Consent for Early Feasibility Studies

You are eligible to participate in an Early Feasibility Study (EFS) of a device to treat your current cardiovascular medical problem The information below provides a background related to such studies in the US and offers points to keep in mind when considering participation in this study.

Key Points

- Early Feasibility Studies (EFS) are focused on devices that have limited or no experience with use in humans with your or other cardiovascular problems
- This means we do not know the benefits or possible harms or whether agreeing to participate will improve your health condition
- Participation in an EFS study means you may gain access to a new device option for your specific problem
- Participation in an EFS study can advance the care for others
- Protections for participants include careful patient selection, monitoring, and oversight by the Food and Drug Agency (FDA)

MDIC – CTTI Opportunity: IRB

	Site Investigators, coordinators, other study staff	Ease frustration/confusion over new process
	Relying Human Research Protection Programs (HRPP)	Uniform applications to reduce duplicative information collection
	Relying Research Institutions	Provide clear instructions to stop requests for unnecessary or inappropriate IC modifications
	HRPP Staff and Review Board(s)	Prepare staff for new process, streamline existing processes
	Sponsors, investigators, Regulators, Patients	Determine if goals of single IRB review are being met
	Single IRB, local HRPP, local institution, study personnel	Clear procedures to maintain participant protections and comply with reporting requirements
	Institution, IRBs	

Adaptation from CTTI Single IRB Driving Adoption Committee

EFS Takeaways:

- EFS Program critically important in facilitating patient access of innovative medical technologies
- Opportunities to engage with MDIC on the EFS Pilot
- Ability for MDIC – CTTI to collaboratively leverage each others tools and programs to drive best practices in clinical research

THANK YOU.

CLINICAL TRIALS **TRANSFORMATION** INITIATIVE

MDIC
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Align › Achieve › Accelerate

Stephanie schristopher@mdic.org

Dan dschwartz@mdic.org

www.ctti-clinicaltrials.org