Issues in Clinical Trial Designs for Devices

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FDA Clinical Investigator Training Course
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What is a Medical Device?

The Section 201(h) of the Food, Drugs and Cosmetics Act defines a medical device as any healthcare product that does not achieve its principal intended purposes by chemical action or by being metabolized.

- As simple as a tongue depressor or a thermometer
- As complex robotic surgery devices
Medical Device Classification

- **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]

  - "Substantial Equivalence"
    - 10-15% have clinical data

  - "Reasonable Assurance of Safety and Effectiveness"
    - Bench-Animal-Clinical
Stages of review for PMA device

Pre-Sub
- Discuss: Device design
- Bench testing
- Animal testing
- Clinical trial

IDE
- Request approval for clinical trial

PMA
- Request market approval

PMA-S
- Request approval for device change or upgrade (which may require a new IDE)
Today’s focus:

Pre-Sub → IDE → PMA → PMA-S

Discuss:
- Device design
- Bench testing
- Animal testing
- Clinical trial

Request approval for clinical trial

Request market approval

Request approval for device change or upgrade (which may require a new IDE)
What is an Investigational Device Exemption (IDE)?

FDA approval of an IDE is required for US human study of a significant risk device which is not approved for the indication being studied.
Types of IDEs

• Feasibility study
  – May provide support for a future pivotal study or may be used to answer basic research questions
  – Not intended to be the primary support for a marketing application
  – Endpoints and sample size generally not statistically driven
  – Generally ~10-40 patients but may be larger
  – FDA review is primarily focused on safety and whether the potential benefit or value of the data justifies risk
  – Early Feasibility Studies (EFS) program supports research early in device development (generally < 15 subjects)
Types of IDEs

• Pivotal study
  – Generally intended as the primary clinical support for a marketing application
  – Designed to demonstrate a “reasonable assurance of safety and effectiveness”
  – Endpoints and sample size statistically driven
  – Designed to assess both safety and effectiveness
  – FDA review is much more complex
Primary Endpoint Design

• Should evaluate the safety and effectiveness of the device in the population expected to be indicated.

• Generally divided into
  – 1 or more “safety” endpoints
  – 1 or more “effectiveness” endpoints

• A study would be considered successful if both the safety and effectiveness endpoints are met.
Sample Size & Follow-Up

• Driven by either:
  – Primary safety endpoint
  – Primary effectiveness endpoint

• Minimum number of patients and/or minimum duration of follow-up may be required depending on:
  – Understanding of the safety and effectiveness of the device
  – Concerns regarding durability of device safety or effectiveness
Device Trials are Unique

Challenges in medical product development are different for drugs and devices

- Use of many devices is highly dependent on clinician knowledge, experience, and skill
- Devices and techniques iteratively and rapidly improve (sometimes even during a trial)
- Gold-standard RCT often not practical
Considerations for device trials

- Device trials tend to enroll fewer participants
- Many assess iterative improvements
- Device design/procedure may be modified during trial
- Adaptive designs increasingly common
- Existing data can substitute for prospective trial data
# Recent PMA Approvals

<table>
<thead>
<tr>
<th>Device</th>
<th>Study Design</th>
<th>N</th>
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<tbody>
<tr>
<td>BioMimics 3D Vascular Stent System (Cardiovascular 10/24/2018)$^1$</td>
<td>Prospective, multi-center, single-arm study with performance goal</td>
<td>271</td>
</tr>
<tr>
<td>Hydrus Microstent (Ophthalmic 8/10/2018)$^3$</td>
<td>Prospective, multi-center, randomized (2:1) superiority study</td>
<td>556</td>
</tr>
<tr>
<td>Magtrace and Sentimag Magnetic Localization System (Surgical 7/24/2018)$^2$</td>
<td>prospective, multicenter, paired comparison, non-inferiority study</td>
<td>160 (+ OUS data)</td>
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</table>

$^1$P180003, $^2$P160053, $^3$P170034
Unique Examples

Leveraging Non-Clinical Data
• Revo MRI PMA approved based on modeling data with confirmatory clinical study of 464 subjects

Leveraging Registry Data
• Edwards Sapien Transcatheter Heart Valve expanded indication based in part on data from the Transcatheter Valve Therapy (TVT) registry
Towards our vision

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

CDRH Vision Statement
CDRH 2014-2015 Strategic Priorities

Strengthen the Clinical Trial Enterprise
- Improve efficiency of IDE review
- Increase number of Early Feasibility Studies

Strike the Right Pre/Post-Market Balance

Provide Excellent Customer Service
Strengthen the Clinical Trials Enterprise

>90% Reduction in Time to IDE Approval

Median number of days to full IDE approval

<table>
<thead>
<tr>
<th>Fiscal Year</th>
<th>Days</th>
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<tr>
<td>2011</td>
<td>442</td>
</tr>
<tr>
<td>2013</td>
<td>215</td>
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<tr>
<td>2014</td>
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<td>2015</td>
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<tr>
<td>2016</td>
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Flexible Approaches

The Least Burdensome Provisions of the FDA Modernization Act of 1997: Concept and Principles; Final Guidance for FDA and Industry

Amended by Food and Drug Safety and Innovation Act and 21st Century Cures

Factors to Consider When Making Benefit-Risk Determinations for Medical Device Investigational Device Exemptions
Early Feasibility Studies

- 17 EFS in FY2013
- 40 EFS in FY2016
Adaptive Designs

Adjust sample size during study
Stop early for futility or success
Modify population during the study

Adaptive Designs for Medical Device Clinical Studies
Guidance for Industry and Food and Drug Administration Staff

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

For questions regarding this document that relate to devices regulated by CDRH, contact Dr. Gery Gray (CDRH) at 301-796-5750 or by e-mail at Gery.Gray@fda.hhs.gov.

For questions regarding this document that relate to devices regulated by CBER, contact the Office of Communication, Outreach and Development (CBER) at 1-800-825-4708 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
Philosophies For Success

- Benefit-Risk
- Patient Focused
- Interactive
- Quality
- Efficiency
Subtitle F—Medical Device Innovations

SEC. 3051. BREAKTHROUGH DEVICES.

(a) IN GENERAL.—Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351 et seq.) is amended by inserting after section 515B, as added by section 3034(b), the following:

“SEC. 515C. BREAKTHROUGH DEVICES.

Expedited Access Pathway -> Breakthrough Devices
“(B) take steps to ensure that the design of clinical trials is as efficient and flexible as practicable, when scientifically appropriate;

“(C) facilitate, when scientifically appropriate, expedited and efficient development and review of the device through utilization of timely postmarket data collection with regard to application for approval under section 515(e); and
CDRH 2016-2017 Strategic Priorities

Establish a National Evaluation System for Medical Devices
• Access and use of real-world data in decisions

Partner with Patients
• Patient input in regulatory decisions
• Trial design and PROs

Promote a Culture of Quality and Organizational Excellence
Evidence in Regulatory Decisions

- Pre-Clinical Testing + IDE
- Clinical Study
  Defines Constraints for Device Claims
- Pre-Market Application
  Indications for Use
- Post-Market
Evidence in Regulatory Decisions

Pre-Clinical Testing + IDE ➔ Clinical Study ➔ Pre-Market Application ➔ Post-Market

Real-World Device Use Physician and Patient Experience

Healthcare Information:
- Claim Databases
- Laboratory Tests
- Pharmacy Data
- Social Media
- Electronic Health Records
- Patient Reported Outcomes
- Registries
- Hospital Visits

Healthcare Information

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Evidence in Regulatory Decisions

Pre-Clinical Testing + IDE → Clinical Study → Pre-Market Application → Post-Market

Hypothesis Generation
Device Innovation

Informed Clinical Decision Making

Real-World Device Use
Physician and Patient Experience

Healthcare Information
- Claims Databases
- Laboratory Tests
- Pharmacy Data
- Social Media
- Electronic Health Records
- Registries
- Patient Reported Outcomes
- Hospital Visits
Evidence in Regulatory Decisions

Pre-Clinical Testing + IDE → Clinical Study → Pre-Market Application → Post-Market

Hypothesis Generation Device Innovation

Informed Clinical Decision Making

Real-World Device Use Physician and Patient Experience

Non-Traditional Evidence Generation

Healthcare Information
- Pharmacy Data
- Social Media
- Electronic Health Records
- Hospital Visits
- Registries
- Patient Reported Outcomes
- Laboratory Tests
- Claims Databases
Some Regulatory Uses for RWE

- Control arm for pivotal clinical study
- New indications for approved devices
- Studying new improvements to devices
- Replacing post approval study
- Adverse event reporting
- Shifts to pre-postmarket balance
Use of Real-World Evidence to Support Regulatory Decision-Making for Medical Devices

Guidance for Industry and Food and Drug Administration Staff


The draft of this document was issued on July 27, 2016

For questions about this document regarding CDER-regulated devices, contact the Office of Surveillance and Biometrics (OSBE) at 301-796-5997 or CDERClinicalEvidence@fdac.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
National Evaluation System for Health Technologies (NEST)

- Provide governance, coordination, and standardization
- Expand access to and use of data from clinical practice

www.fda.gov
Needs for NEST

- Strategic approach for collecting data
- Establishing core data sets
- Establishing common definitions
- Facilitating transfer and linking among interoperable data sources
- Embed research data collection into routine clinical workflow and participating patients’ daily activities
Partner with Patients
Patient Perspective Information: Fit for purpose

- Patient-reported outcomes
- High-quality surveys
- Focus groups
- Patient organization engagement
- Carepartner engagement
- Medical professional engagement

Patient-preference information
Clinical Trial Design Innovation: What can it mean?

- Highly Interactive and Flexible Engagement of Stakeholders
- Special Programs to Address Needs (Breakthrough, EFS)
- Adaptive Designs to Optimize Trial Size and Duration
- More Efficient, Simpler Trials
- Better Leveraging of Real World Data
- Strike the Right Premarket – Postmarket Balance
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