Issues in Clinical Trial Designs for Devices

Adam Donat
Deputy Director, Division of Clinical Science and Quality
Office of Clinical Evidence and Analysis
Office of Product Evaluation and Quality
CDRH | Food and Drug Administration

Clinical Investigator Training Course
November 12, 2019
Learning Objectives

• Understand the medical device review process
• Identify unique aspects of device trials
• Review CDRH’s strategic priorities and how they impact device studies
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

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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
### Device Study Design Examples

<table>
<thead>
<tr>
<th>Device</th>
<th>Study Design</th>
<th>N</th>
</tr>
</thead>
<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>
</tr>
</tbody>
</table>

\(^{1}\text{P180003, }^{2}\text{P160053, }^{3}\text{P170034}\)
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
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>2011</th>
<th>2013</th>
<th>2014</th>
<th>2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days</td>
<td>442</td>
<td>215</td>
<td>101</td>
<td>30</td>
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</table>
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
• 53 EFS in FY2018
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. Gayy Grzy (CDRH) at 301-796-5730 or by e-mail at Gayy.Grzy@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 1-800-835-4709 or 240-402-8010.

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

www.fda.gov
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
21st Century Cures Act – Breakthrough Devices

FDA shall:

“(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

• Vision for refining oversight of device safety throughout the Total Product Life Cycle (TPLC)

• 5 Focal Areas:
  1. Establish a robust medical device patient safety net in the US
  2. Explore regulatory options to streamline and modernize timely implementation of postmarket mitigations
  3. Spur innovation towards safer medical devices
  4. Advance medical device cybersecurity
  5. Integrate CDRH's premarket and postmarket offices and activities to advance the use of a TPLC approach to device safety
Safer Technologies Program (STeP)

• STeP Draft Guidance Issued September 19, 2019*

• Voluntary program for medical devices and device-led combination products that provide for more effective treatment or diagnosis of life-threatening or irreversibly debilitating diseases or conditions.

• Intended to help patients and health care providers have more timely access to these medical devices

• Key Program Principles:
  – Expedite device development and review
  – Opportunities for interaction to efficiently support device development
  – Increased opportunity for senior management involvement

*https://www.fda.gov/media/130815/download
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

Pre-Market Application

Post-Market

Indicates for Use

Defines Constraints for Device Claims

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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
- 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

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

Informed Clinical Decision Making

Real-World Device Use
Physician and Patient Experience

Non-Traditional Evidence Generation
Some Regulatory Uses for RWE

<table>
<thead>
<tr>
<th>Control arm for pivotal clinical study</th>
<th>New indications for approved devices</th>
<th>Studying new improvements to devices</th>
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<td>Replacing post approval study</td>
<td>Adverse event reporting</td>
<td>Shifts to pre-postmarket balance</td>
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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 CDRH-regulated devices, contact the Office of Surveillance and Biometrics (OSB) at 202-636-5997 or CDRHClinicalEvidence@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
National Evaluation System for Health Technologies (NEST)

• Provide governance, coordination, and standardization
• Expand access to and use of data from clinical practice
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
CDRH 2018-2020 Strategic Priorities

- Employee Engagement, Opportunity, and Success
- Simplicity
- Collaborative Communities
Clinical Trials and Simplicity

• In applying an approach of simplicity, we must tackle the extent of uncertainty encountered.

• Uncertainty is almost always present.

• Uncertainty cannot be a reason for unnecessary delays or requirements.
Clinical Trials and Simplicity

• Simplicity considerations in trial design
  – Typically won’t know full benefit-risk profile before device is widely used
  – Even very large trials might not truly reflect benefits and risks
    • Large trials may impose unreasonable costs and time delays that ultimately adversely affect patients.
  – CDRH must balance an appropriate level of uncertainty as one of several factors in decision making.
    • Desire for certainty vs. patient access and unmet clinical needs
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
Challenge Question

• Which of the following statements about device trials is FALSE:
  – They tend to enroll fewer subjects than drug trials.
  – They are more likely to be blinded or randomized than drug trials.
  – Many assess iterative improvements to devices.
  – The device design may be modified during the trial.
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