FDA and the Medical Device Clinical Trial Enterprise

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Faculty Disclosure

In compliance with ACCME Guidelines, I hereby declare:

I do not have financial or other relationships with the manufacturer(s) of any commercial services(s) discussed in this educational activity.

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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
Device Classification

• Class I
  – General Controls
  – Most exempt from premarket submission

• Class II
  – Special Controls
  – Premarket Notification [510(k)]

• Class III
  – Require Premarket Application [PMA]
510(k) Premarket Notification

• Substantial equivalence
• 10-15% require clinical data
• Usually confirmatory
• Type of study dictated by:
  – Ability of bench and animal testing to answer questions
  – Amount of difference between subject device and predicate
De Novo Process

• Low to moderate risk devices
• No predicate for substantial equivalence assessment
• General and special controls can be used to provide reasonable assurance of safety and effectiveness
• In many cases, clinical data are required to support granting of the de novo
Premarket Approval Application (PMA)

• Class III – highest risk devices (heart valves, pacemakers, coronary stents)
• Life sustaining or life supporting; or
• Substantial importance in preventing impairment of human health; or
• Present major risk of illness or injury
• Establish reasonable assurance of safety and effectiveness
  • Bench testing, animal studies, clinical data
  • Pre-approval manufacturing inspection
  • May require post-approval studies
Stages of review for PMA device

Pre-Sub → IDE → PMA → PMA-S

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

Request:
- Approval for clinical trial
- Market approval
- Approval for device change or upgrade (which may require a new IDE)
Investigational Device Exemption (IDE)

• Established in 21 CFR Part 812
• 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.
• Exempts sponsor from certain provisions of FD&C Act
• Requirements for informed consent, labeling, monitoring of the study, records/reporting
• Requires approval by Institutional Review Board (IRB)
Types of device studies

• Feasibility Studies
  – Intended to gather preliminary information regarding
    • Safety profile and potential for effectiveness
    • Refinements to device or future study
  – Not intended to provide primary support for marketing
  – Generally not statistically driven (n ≈1-40 subjects)
  – FDA’s review focused on safety
  – Early feasibility studies (discussed later)
Types of device studies

• Pivotal Studies
  – Intended to provide the primary clinical data in support of a future marketing application
  – Statistically driven sample size and hypotheses
  – FDA’s review focused on safety and study design
Types of device studies

• Postmarket Studies & Registries
  – Often required as a condition of PMA approval
  – May be required for reimbursement purposes
  – Allows for gathering longer term data that may be more representative of real-world clinical use
Device studies are unique

- Trials tend to be smaller than drug trials
- Some novel, many “me-too”
- Many not blinded, randomized, controlled
- Adaptive designs increasingly common
- Endpoints highly diverse
- Typically, single pivotal trial follows feasibility stage(s)
- Designed to demonstrate a “reasonable assurance of safety and effectiveness” for the marketing application
IDE Review Decisions

• Approval
  – Approves the trial for a specified number of patients and investigational center. Trial may begin upon IRB approval

• Approval with Conditions
  – Allows sponsor to begin the trial if the sponsor agrees to address the conditions (deficiencies) from the conditional approval letter within 45 days

• Disapproval
  – Trial may not start until sponsor addresses the deficiencies from the letter, submits this information to FDA, and receives approval
IDE decision making

• IDE Disapproval is appropriate when:
  – Probable risks to the subjects are not outweighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained
  – Study does not pose a reasonable scientific question and/or is not designed to collect data related to that scientific question

• Concerns regarding the study design that are not related to protecting study subjects are not the basis for a disapproval
Strategic Goal: Strengthening the Clinical Trial Enterprise

• Goal: Reduce the time and cost of conducting clinical studies in the US while assuring robust evidence generation and adequate patient protections.
Strategic Goal: Strengthening the Clinical Trial Enterprise

• Goal: Improve the efficiency, consistency, and predictability of the IDE process to reduce the time and number of cycles needed to reach appropriate IDE full approval for medical devices, in general, and for devices of public health importance, in particular.

• Goal: Increase the number of early feasibility/first-in-human IDE studies submitted to FDA and conducted in the U.S.
The IDE Challenge

• The IDE review process is an important part to protecting subjects in investigational device studies.
• We also recognize, the sooner an IDE is approved, the sooner a potentially important technology can be available to US patients.
• The IDE process has at times led to avoidable bottlenecks in the process.
• We can and should look for ways to improve the process of FDA’s decision making for IDEs.

Survey link: https://www.research.net/s/fdamdct
What is CDRH doing?

• Established Clinical Trials Program and Clinical Trials Director (CTD)
• Established broader oversight for:
  • Ensuring CDRH is “in the right place”
  • Ensuring flexibility is applied where appropriate
  • Increased communication with sponsors
• Established Early Feasibility Study (EFS) coordinators within Clinical Trials Program
Median Days to Full IDE Study Approval

FY11: 442
FY13: 215
FY14: 101
FY15: 30
Early Feasibility Study (EFS) Program

- **Intent** - To facilitate US EFS under the IDE regulations

- **Scope** - Elements that define an early feasibility study:
  - Small number of subjects
  - Device that may be early in development, typically before the device design has been finalized
Why focus on EFS?

- EFS is often a critical step in device innovation and development
- When EFS are conducted in the US, important new technologies may become available to US patients sooner.
The Right Testing at the Right Time

- Comprehensive testing during early phases of device development may add cost without significant return
- It may be acceptable to defer some nonclinical testing until the device design has been finalized
- An early feasibility study incorporates enhanced risk mitigation strategies and patient protection measures as compared to a pivotal study
FY2015 EFS Goal and Results

By June 30, 2015, compared to FY13 performance, CDRH sought to increase the number of early feasibility/first-in-human IDE studies submitted to each premarket Division.

- Result: goal met in 6 of 7 ODE Divisions
- 50% increase in EFS submissions for CDRH
- Over 100% increase in EFS approvals for CDRH
- Many EFS currently under presubmission discussion
Challenges to successful study initiation and execution

• Site contracting
• Local IRB approval
• Subject recruitment and continued participation
• Study complexity and burden
• High overhead at academic centers
• Study reimbursement
Where might we be headed?

• Simpler, more efficient studies
• Better use of observational data for regulatory and clinical decision making
  – Registries
  – Electronic health records
• Better incorporation of patient perspective in regulatory decision making
Exciting partnerships

• Medical Device Innovation Consortium (MDIC)
• Clinical Trials Transformation Initiative (CTTI)
Conclusions

• Strengthening the Clinical Trial Enterprise is a high priority for CDRH.
• We have made major progress
• However, much work remains and future progress will be a joint effort between FDA and our external stakeholders.
Important Guidance Documents

- FDA Decisions for IDE Clinical Investigations

- IDEs for Early Feasibility Medical Device Clinical Studies

- Design Considerations for Pivotal Clinical Investigations for Medical Devices

- Factors to Consider When Making Benefit Risk Determinations for Medical Device IDEs (DRAFT)