Successful Clinical Strategies

FDA Small Business
Regulatory Education for Industry (REdI)
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Poll Question

Do you plan to start a device Clinical Investigation in the near future?

a) Within the next 6 months

b) Within the next year

c) Within the next 2 years

d) No, but I'd like to learn how

Learning Objectives

- Define an Investigational Device Exemption (IDE)
- Describe what should be included in an IDE
- Describe interactions with FDA
- Identify study pitfalls and strategies for a successful submission

I. What is an IDE?

What is an Investigational Device Exemption (IDE)

- *Temporary* **exemption** from Food, Drug, and Cosmetic Act *for the purposes of conducting Clinical research*:
  - 510(k) and PMA requirements
  - Registration & Listing
  - Quality System *except* Design Controls (21 CFR 820.30)
- *A*llows for *collection of Safety and Effectiveness data*
- Must have FDA and/or IRB approval ***prior*** to study initiation (unless Exempt)

Who is Involved?

(21 CFR 812.3)

- **Subject** - the patient
- **Sponsor** - a person located in the United States who initiates, but who does not actually conduct the investigation
- **Investigational Review Board (IRB)** - group formally designated by an institution to review biomedical research involving subjects
- **Investigator** - an individual who conducts a clinical investigation
- **Sponsor-Investigator** - an individual who may or may not be affiliated with original Sponsor that both initiates and conducts an investigation. Obligations are as *both* Sponsor and Investigator

II. Content of an IDE

Application

(21 CFR 812.20)

- Names, addresses of Sponsor, Investigator(s), and IRB(s)
- Complete Report of Prior Investigations
- Methods, facilities, controls, and manufacturing (processing, packaging, storage, etc.)
- Example and Certification of Agreements for Investigators

Benefit-Risk Assessment

- Early-stage device development typically associated with greater uncertainty
- Risk Analysis
  - Harms
    - How harm may lead to clinical sequelae, including length of time and potential residual effect
  - Likelihood
    - Focus on severity of risk and probability of sequelae
  - Residual Risk and completeness of risk control
    - Residual risk outweighs anticipated benefits

Factors to Consider When Making Benefit-Risk Determination for Medical Device Investigational Device Exemptions
www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM451440.pdf

Investigational Plan

(21 CFR 812.25)

- Protocol - Objectives, Endpoints, and Hypotheses
- Description of device
- Monitoring procedures, summary flowchart or table
- Data collection & statistics, Risk & Mitigations
- Labeling & Packaging
- Study Personnel, Subjects, Protections & Informed Consent
- Other Institutions

eCopy

- *One **Paper** and one **eCopy*** (FDASIA Section 1136) - electronic duplicate of paper submission

- eCopy should include all required information for review, whereas the paper copy can include a placeholder cross-referencing information in the eCopy (statistical analysis programs, videos, x-rays)

- eCopy Decision
  - eCopy accepted: submission proceeds to review division
  - eCopy Hold: sponsor receives written notification identifying eCopy issues

III. Interactions with FDA

Pre-Submission Meetings

To obtain FDA feedback prior to Study start or for Supplements & Amendments

- Risk Determination
  - Exempt, Significant vs. Non-Significant Risk
- Non-clinical testing design
  - Types of appropriate animal, “bench,” or other forms of testing
- Clinical study design
  - Types of appropriate Clinical Testing, focusing on trial design

Progress Report

21 CFR 812.150(b)(5)

- At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's and FDA

- Include:
  - Study Progress
    - Report data collected from beginning of the study, unless otherwise indicated
  - Risk Analysis
    - Identify any new adverse information
    - Supply reprints of any articles published from study data

Final Report

(21 CFR 812.150(b)(7))

- Sponsor must notify IRB and/or FDA within ***30 working days*** of study completion
- Final Report must be submitted to IRB and/or FDA ***within 6 months*** of study completion
- Often sent to FDA along with Premarket Submission

IV. Study Pitfalls and Strategies For a Successful Submission

Common Deficiencies: Prior Reports of Laboratory Studies

- Inadequate description of methods
- Inadequate/lack of summary or conclusion
- Conclusions not supported by data

Common Deficiencies: Prior Reports of Animal Studies

- No rationale for animal selection
- No scientific justification for number of animals selected
- Inappropriate duration or follow-up
- Failure to address compliance with Good Laboratory Practices for Nonclinical Studies, 21 CFR 58

Common Deficiencies: Investigational Plan

- Failure to clearly develop or define study objectives
- Inadequate description of protocol
- Failure to identify all risks
- Study subjects exposed to unacceptable probable risks
- Lack of proper monitoring procedures
- Inadequate informed consent documents

Quality

Low **Quality** directly impacts Submission

Examples

- Poorly organized/written, not cohesive, inconsistent
- Lacks scientific rigor
- Missing information (e.g., failure to communicate with Manufacturer – *especially Sponsor-Investigators*)
- Doesn't "tell the Sponsor's story"

Impact of Low Quality

- Slows/impairs decision-making process
- Delays interaction and review cycles
  - take longer to understand study details
- Neglect urgent, specific questions

Cohesive Narrative

"Tell Your Story"

Clarify:

- Background/history
- Device version being tested
- Previous testing and *rationale*

Describe:

- Key operating principle(s)/characteristic(s)
- New/innovative technologies, components/materials
- *Objectives*, test conditions

Provide:

- Success criteria
- Reports, Summaries, & Results
- Adverse Events

Cohesive Narrative

Strategies

- ***Show*** but *don't forget* to ***tell***
- Be ***thorough*** *and* ***educate*** reader
- Can I ***follow*** and ***understand*** the *entire* Submission, and is it ***complete***?

Contents of the Final Report

- ***Cover Letter***
- Executive Summary
- Table of contents, accurate numbering
- Complete sections, figures, appendices, references
- ***Benefit-Risk Assessment*** & Mitigations
- Deviations

Writing the Final Report

The Body

- Device name
- Intended/Indicated Use(s), principles & key characteristics
- Materials, technologies, components
- Specifications & Performance, Plan changes (21 CFR 812.35)
- Diagrams, tables & charts, videos & pictures
- Related products, Combination Products, other Submissions

Writing the Final Report

Testing & Data

- Is testing sufficient? Complete? Relevant?
- Guidances & Recognized Consensus Standards, other standards
- Design History (Safety & Effectiveness)
- Limitations and anomalies, Unanticipated Adverse Device Effects

Writing the Final Report

Strategies

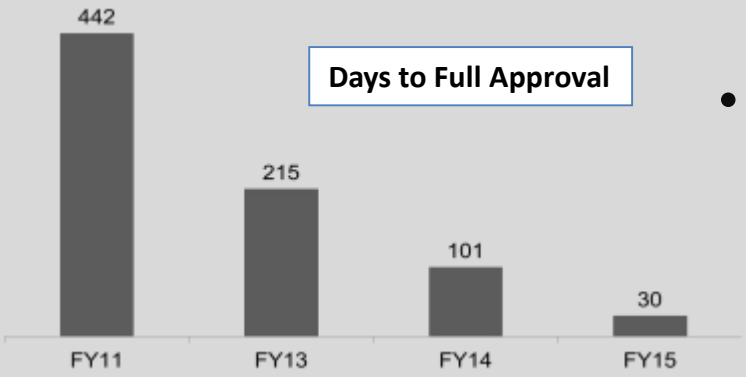
- ***Prioritize*** – organize information by importance
- ***Key information*** up-front, summarized and consistent
- Can "***story***" be followed? Additional descriptions or explanations?
- ***Innovative features*** addressed and quantified

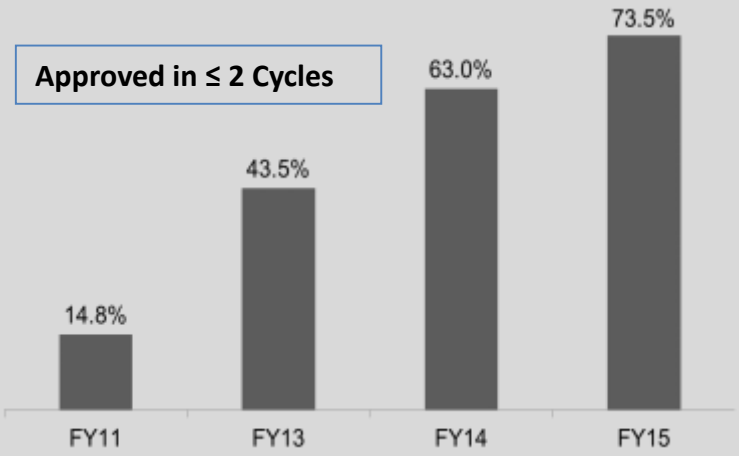
Writing the Final Report

Strategies

- ***Guide*** the reader
- **Summaries**
- ***Clear, concise*** tables and graphs of key data, testing, results
- Quick comparisons or contrasts

Benefits of a Quality Application





- ***Interactions*** *throughout process:*
  - *Interactive, tailored approaches*
  - "right information at the right time"
  - Leveraged data from other countries

- Result: ***Decreased*** **IDE Approval time**

blogs.fda.gov/fdavoice/index.php/2015/09/strengthening-the-clinical-trial-enterprise-for-medical-devices-an-fdacdrh-strategic-priority-update/

V. Summary

Successful Strategies - Summary

- Be ***thorough***: ***educate*** and ***guide*** the reader
- ***Prioritize*** important information, data/results; clear & concise tables, comparison-contrasts
- Put yourself in FDA's position - can I ***follow*** and ***understand*** the *entire* Submission, and is it ***complete***?

Useful Information

- **IDE Policies and Procedures**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf
- **FDA Decisions for Clinical Investigations**
  www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm279107.pdf
- **Significant Risk and Nonsignificant Risk Medical Device Studies**
  www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126418.pdf
- **Factors to Consider For Benefit-Risk Determinations**
  www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm451440.pdf
- **Design Considerations for Pivotal Clinical Investigations**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM373766.pdf
- **Early Feasibility and First in Human Clinical Studies**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM279103.pdf
- **IDE Refuse to Accept Policy**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM081312.pdf
- **IDE Application Cover Letter**
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080274.htm
- **CDRH Learn – IDEs**
  www.fda.gov/Training/CDRHLearn/default.htm

Other Helpful Links

- **Pre-Submissions**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM311176.pdf
- **(Electronic) Clinical Data for Premarket Submissions**
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/PremarketSubmissions/ucm136377.htm
- **eCopy**
  www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM313794.pdf
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/ucm370895.htm
- **Refuse to Accept (RTA) Policy for 510(k)s**
  www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm315014.pdf
- **Information Sheet Guidance For IRBs, Clinical Investigators, and Sponsors**
  www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/GuidancesInformationSheetsandNotices/ucm113709.htm
- **FAQs about IDE (at Device Advice)**
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051480.htm
- **IDE Enforcement of Good Clinical Practices (GCP) Regulations**
  www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/HowtoMarketYourDevice/InvestigationalDeviceExemptionIDE/ucm051363.htm

Questions?

Please evaluate this session:

surveymonkey.com/r/DEV-D1S02

Your Call to Action

1. Write to **educate** **and** **guide** **– explain**.
2. Write for **understanding** and **clarity**.
3. Write for the reader – **summarize**. Can they **follow** and **understand**?
4. Ultimate test of your Final Report – **have someone else read it**.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