Clinical trials for medical devices: FDA and the IDE process

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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

Medical Device Classes

- **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]
510(k) Premarket Notification

- Substantial equivalence
- 10-15% require clinical data
- Performance testing
- Usually confirmatory
- Type of study dictated by:
  - Ability of bench and animal testing to answer questions
  - Amount of difference between subject device and predicate
PMA
Premarket Approval Application

• Establish reasonable assurance of safety and effectiveness
• Bench-Animal-Human
• Clinical Studies
  – Feasibility and pivotal
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-IDE
  - 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)
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.
Device trials are unique

- Trials tend to be smaller than drug trials
- Some novel, many “me-too”
- Many difficult to blind, randomize, control
- Many depend on physician technique
- Device modifications occur during trial
- Endpoints highly diverse
- Typically, single pivotal trial follows feasibility stage(s)
- Designed to support a “reasonable assurance of safety and effectiveness” for the marketing application
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
  – Often required by FDA prior to pivotal study to assess basic safety and potential for effectiveness
  – 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
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
FDA’s Feasibility IDE Review

• Focused on safety
• Critical issues
  – Reasonable study conceptually?
  – Adequate preclinical validation of device?
    • Why is clinical really the next necessary step?
  – Appropriate mitigation of potential risks?
  – Appropriate enrollment criteria?
  – Patients adequately informed?
  – Sample size appropriate?
FDA’s Pivotal IDE Review

• Focused on safety and plan for collecting and evaluating study data

• Additional critical issues
  – Trial endpoints
  – Randomization, blinding, follow-up, etc
  – Study conduct and monitoring
  – Statistical analysis plan
Basic Submission Elements

• Background of medical issue, the study goals, and why this study will further the science
• Detailed description of the device under study
• Previous studies (preclinical and clinical)
  – Summary of available data
  – Why is a clinical study needed at this stage?
  – What evidence supports the safety of this study/device and the potential for the study data to be meaningful?
  – Are there outstanding safety questions that should be addressed with preclinical data?
Basic Submission Elements

- Risk analysis
  - What are the potential risks to the patient?
  - Does the study mitigate the risks where possible?
  - Are the risks outweighed by the potential for benefit and/or value of the study

- Patient monitoring and follow-up plan
- Inclusion and exclusion criteria
- Informed consent document
- Sample size and number of investigational centers, with justification
Submission Elements, Pivotal IDEs

• Primary and secondary endpoints
  – Discussion of appropriateness of endpoint parameters, hypotheses, and success criteria

• Basic trial design
  – Controlled? If not, why not?
  – Randomized? If not, why not?
  – Blinded? If not, why not?
Submission Elements, Pivotal IDEs

• Trial conduct and study monitoring
  – Data handling and adjudication process
  – Sponsor blinding
  – Independent committees
  – Case report forms
    • Is the right information being gathered to support the study endpoints and are investigators adequately prompted to report adverse events?
Submission Elements, Pivotal IDEs

• Statistical analysis plan
  – Clearly defined S & E hypotheses
  – Type-1 error and multiplicity
  – Missing data handling
  – Sample size calculations and assumptions
  – Assessment of critical covariates
  – Adaptive design plans
  – Interim analyses and early stopping rules
  – Data handling
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.
Primary Endpoint Design

• The clinical protocol should clearly and prospectively detail:
  – Methods for obtaining endpoint data
  – Definitions for what will be counted as a primary event in the analysis
  – Situations in which patient data will be excluded
  – How missing data will be handled
  – How the impact of covariates will be assessed
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
Secondary Endpoints

- Generally used to evaluate additional meaningful claims
- Generally only considered if primary endpoints are successful
- Should be used to provide further insight into the device effects and mechanisms of action
- Definitions and analysis methods should be clearly detailed prospectively
- Not considered "statistically significant" unless a pre-specified alpha allocation plan is in the protocol, even if the p-value is < 0.05
Submission Elements, Pivotal IDEs

Provide enough detail to avoid ambiguity once the trial has started.
FDA’s IDE Review Decisions

• Approval
  – Approves the trial for a specified number of patients and investigational centers

• 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
FDA shall not disapprove an IDE because:

- the investigation may not support a substantial equivalence or de novo classification determination or approval of a device;
- the investigation may not meet a requirement, including a data requirement, relating to the approval or clearance of a device; or an additional or different investigation may be necessary to support clearance or approval of the device.
Recent Revision to FD&C Act

This means that an IDE cannot be disapproved on the basis of FDA’s belief that the study design is inadequate to support a future PMA, 510(k), HDE, or de novo classification.
Does study failure imply PMA disapproval?

- Often but not always.
- PMA approval is based on a Benefit-Risk assessment
- FDA is always willing to review all available data to determine whether there is a reasonable assurance that the device safe and effective.
Does study failure imply device disapproval?

• **Alternatives**
  - Unexpected safety concerns are outweighed by stronger than expected benefit
  - Inconclusive study result is supplemented by other clinical or non-clinical data
  - Device is safe and effective for some limited indication or patient population
  - All of these alternatives may raise serious type-1 error concerns. FDA is therefore very conservative in its consideration of these alternatives.
Does study success imply device approval?

- Often but not always
- Sometimes the primary endpoints do not capture a serious unexpected safety concern that is observed in the trial.
- Other clinical or non-clinical data may conflict with the study result.
- Can result in:
  - Device disapproval
  - Requirement for more data
  - Limited indication
Some Generic Case Examples
Cardiovascular Devices

- LVADs
- Pacemakers, ICDs, leads
- Cardiac resynchronization therapy
- Ablation catheters and generators
- Cardiac monitoring devices
- Heart valves
- Stents
- Cardiac occluders
Example 1: Novel heart failure device study

• Novel implantable stimulation device to treat heart failure

• Key characteristics
  – Implant has serious risks
  – Device is programmable
  – Benefit may be symptomatic/functional
  – Patients can feel the stimulation

• Previous data
  – Feasibility data promising but single-arm
Study Considerations

• Safety
  – Require long-term follow-up
  – Safety success criteria should be rigorous to balance symptomatic benefit

• Effectiveness
  – Must be randomized to assess benefit
  – Symptomatic/functional benefit requires blinding
  – But how does one blind this study?
Company Proposal

- Implant device in all subjects
- Randomize to on vs. sham stimulation
- 6-month follow-up, after which device may be turned on or off in any subject
- Safety: all subjects pooled, compared to objective performance criterion (OPC)
- Effectiveness: Responder’s analysis of quality of life (QOL) and six minute walk distance
Problems with this plan

• 6-month follow-up
  – What if effect is short-lived?
  – What if long-term safety concerns arise?

• Sham stimulation
  – Is there enough data to know how to design true sham?
  – Will blinding truly be maintained?
Problems with this plan

- **Safety**
  - Endpoint evaluates only procedure and presence of the device, not effect of the therapy

- **Effectiveness**
  - 6MW and QOL highly placebo sensitive
  - Even if demonstrated, will benefit in these endpoints result in appropriate risk-benefit?
FDA’s advice

• 12 month follow-up
• Multiple, rigorous safety endpoints
• If sham, more data needed to support blinding
• More objective effectiveness endpoints
  – Mortality/hospitalization composite
  – VO2 max or ventilatory threshold
• Show reasonable risk-benefit profile
Example 2: MRI Conditional Pacemaker

- Concerns
  - Proper device function
  - Thermal or arrhythmogenic injury from MRI
- Design: Device implanted in all subjects, randomization to MRI or No-MRI.
- Safety/Effectiveness
  - MRI Adverse events
  - Pacing parameter changes (indicative of injury)
- Additional restrictions
  - At least 200 subjects to receive MRI
Example 2: MRI Conditional Pacemaker

• Limitations
  – Study not designed to assess basic device performance
  – Study not powered to detect low rate (but meaningful) safety issues
  – Clinical study considered confirmatory to comprehensive preclinical data

• Review focus
  – Trial design important, but...
  – Preclinical issues present the larger obstacle before FDA would allow proceeding to clinical
Example 3: Heart Valve

- **Design:** single-arm
- **Effectiveness**
  - Stenosis, leakage, and orifice area
  - Compared to normal published values
- **Safety**
  - 30-day and intermediate (1-year) complication rate
  - Compared to OPC
- **Additional restrictions**
  - 800 patient-years
  - At least 300 patients for at least 1 year
Conclusions

• One size does not fit all for device trials
• Pivotal studies should be designed to evaluate whether there is a “reasonable assurance of safety and effectiveness.”
• PMA approvability is based upon a Benefit-Risk assessment which strongly considers outcome of primary safety and effectiveness endpoints.
Conclusions

• Secondary endpoints are generally used to support claims if the primary endpoints are successful.

• All endpoint analyses and definitions should be clearly pre-specified in the approved clinical protocol.

• Trial design is challenging. We recommend talking to FDA early through the pre-submission process.
Online Resources

• CDRH Learn – Online Regulatory Training Tool
  – Over 50 Medical device and Radiological Health modules
  – Video and PowerPoint presentations available 24/7
  – Certificate of completion upon passing post-tests
  – Many modules are translated into Chinese and Spanish
  – http://www.fda.gov/Training/CDRHLearn/

• Device Advice – Online Regulatory Information
  – Searchable by topic
  – http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/

• Division of Small Manufacturers, International, and Consumer Assistance (DSMICA) – Live Regulatory Assistance
  – Technical Assistance for the Medical Device Industry
  – Available 8:00 am – 5:00 pm EST
  – 800-638-2041 or 301-796-7100
  – DSMICA@fda.hhs.gov