U.S. Food and Drug Administration
Department of Health and Human Services
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

Regulatory Perspectives Of Clinical Trials: What Core Elements does FDA look for?

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Disclosure Statement of Financial Interest

I, Heather Agler, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.

Clinical Trials for Medical Devices and FDA

- Trials submitted to FDA are conducted for multiple reasons:
  - Feasibility/proof of principle
  - Pivotal studies to support marketing approval
  - Sponsor-investigator studies
  - Postmarket/postapproval studies
  - Studies of device iterations
- FDA's review is always comprehensive, but focus may differ depending on the reason for the trial.

Device Approval Process

- IDE – Investigational Device Exemption
  - Allows distribution for clinical study
  - Required for all significant risk studies performed in U.S.
  - 30 day review time
  - Pre-IDE process encouraged for informal feedback prior to formal IDE submission

First Steps

- Intended use statement
  - What disease or condition is the device intended to treat or diagnose?
  - In what patient population?
- Clinical background and unmet need (if applicable)
  - Why was the device designed in this way?
- Summary of prior nonclinical and clinical studies
  - May affect design of clinical study (endpoints, length of follow-up, monitoring for adverse events)
  - Appropriate non-clinical safety testing is necessary to begin IDE

Development of a Protocol

- Objective (e.g., feasibility, pivotal study, confirmatory for iterations)
  - Scope of the trial
- Patient population (e.g., disease, anatomical factors)
  - Inclusion/exclusion criteria
- Questions to be answered (e.g., safety and effectiveness, longer-term outcomes)
  - Selection of primary and major secondary endpoints
  - Duration of follow-up

Development of a Protocol

- Trial design – minimize bias and confounding
  - Randomized
  - Single-arm
  - Type of control
    - Nonconcurrent
    - Historical
    - OPC/performance goal
  - Blinding (single, double, sham)
- Choice of control treatment – standard of care
  - Available device alternative
  - Surgical treatment
  - Medical therapy

Critical Elements

- Meaningful outcome measures
  - Can be measured reproducibly
  - Are well understood by physician and patient (if possible)
  - Clinically meaningful differences can be defined
- Clearly written hypotheses
  - In words and as mathematical expression
  - If superiority, specify clinically meaningful (not just statistical) difference
  - If non-inferiority, selection of appropriate margin
- Follow-up schedule
  - Appropriate to evaluate outcomes of interest
  - Reasonably close to standard practice (applicability to real world)
- Case report forms – clear and complete

Critical Elements

- Patient selection
  - Broad enough such that results are generalizable to large proportion of patient population
  - Narrow enough to facilitate interpretation of study results
  - For postmarket studies, inclusion of more “real world” patient population may be desired
- If enrolling sites in multiple geographies, understand and evaluate factors that potentially impact outcome
  - Demographics
  - Clinical practice patterns
  - Reimbursement issues

Critical Elements

- Prospective Statistical analysis plan
  - Appropriate test selection to evaluate hypotheses
  - Preservation of Type I error if multiple hypotheses to be tested
  - Adjustments for covariate differences in treatment and control groups, especially if nonconcurrent control
  - Plans to address missing data (e.g., sensitivity analyses)
- Appropriate informed consent document
- Plans for postmarket studies, if appropriate

Investigational Studies

We strongly recommend use of an independent:

- Data and Safety Monitoring Board (DSMB)
- Clinical Events Committee (CEC) adjudication
- Use of core labs for independent analysis (angiography, IVUS, ECG)

Reporting and Interpretation of Results

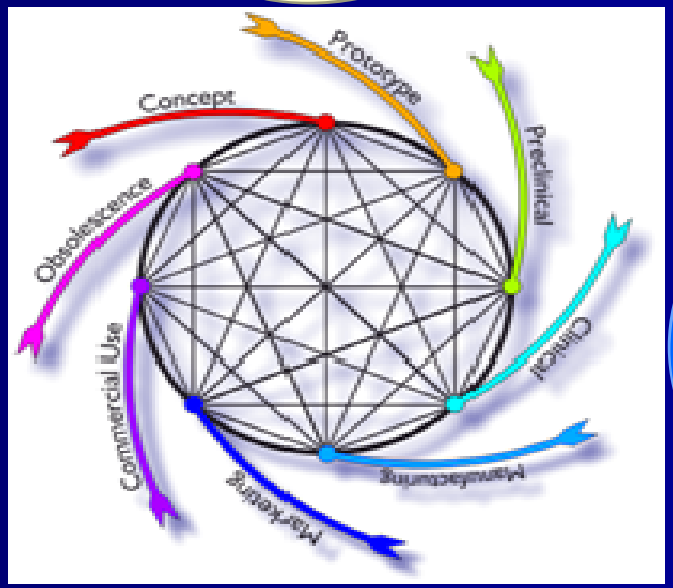
- Primary analysis is test of pre-specified hypotheses
  - Other analyses may be supportive, but are limited, considered hypothesis-generating
- Report all data, not just the positive subsets
  - Discuss any unexpected results, why results do not indicate a safety or effectiveness concern
  - Provide narratives for significant adverse events

Reporting and Interpretation of Results

- FDA review is not limited to whether primary endpoint is met or not
  - Consideration of components of composite endpoint
  - Overall review of safety issues – adverse events, device malfunctions
  - Clinical judgment applied to totality of data
- Accurate representation of results in labeling

Total Product Life Cycle Vision

Efficient, Effective, and Predictable Product Development



Ensuring the Safety of Marketed Medical Devices

Enabling Technology and Innovation

DHHS/FDA

Use of Foreign (OUS) Study Data

From the perspective of the FDA, the most important issue to determine if OUS data can be considered for review, and in what context such data can be reviewed, is the following:

21 CFR part 814 (d)(1) The foreign clinical data are applicable to the U.S. Population and U.S. Medical Practice

Use of OUS clinical data

- OUS (foreign) clinical data can be used to support approval of CV devices in the US
- Generalizability of OUS study results to the patient population in the US is a key issue.
- Sponsor must address the factors that may affect generalizability and justify why results are applicable to the US.
  - Patient demographic and clinical characteristics, geographic differences in medical practice, and differences in study protocol.

Case Study: Drug Eluting Stents
How new is your DES?

	DES "A"	DES "B"	DES "C"
Drug	NME	Approved for systemic indication	Paclitaxel or -Limus
Stent	New stent material	316L, CoCr, nitinol platform	Approved stent platform
Drug release	Novel drug release mechanism	Similar drug release profile	Same drug release mechanism / profile as approved DES

Entirely New Product → New and old technologies → Serial Iteration of existing DES

Case Study: DES Type of Trial

- RCT recommended for initial marketing approval
  - Patient demographics can affect outcome
  - Difficult to assess all covariates in single-arm setting
- Single-arm studies may be appropriate for
  - Minor product modifications
  - Addition of new stent sizes, lengths
  - Some indication expansion

Case Study: DES Trial Design Aspects

- Choice of control
- Superiority vs. non-inferiority
- Given prevalence of DES use, non-inferiority studies using active DES controls are the current paradigm of study design
  - Choice of “delta” for equivalency must be clinically meaningful
  - Concern for “outcome drift” in successive non-inferiority studies

Case Study: DES Choice of Endpoints

- Primary endpoint
  - Clinical composite endpoint of safety and effectiveness
    - Target lesion failure: CV death, target vessel MI, target lesion revascularization
- Angiographic endpoints
  - Provide important mechanistic insights
  - Not adequate to demonstrate safety

Case Study: DES Sample Size

- Sample size considerations driven by safety
- Ability to detect catastrophic safety events that occur at a 1% rate with an upper 95% confidence bound of 1.4%
  - Corresponds to at least 2000 patients for DES containing an NME or novel drug delivery system
- Not all patients need to be part of a randomized trial
- Can use multiple trials (both US and OUS) to demonstrate safety

Case Study: DES Length of Follow-up

- Current recommendations:
  - 12 month primary endpoint collection
  - 5 years follow-up
- Recommendations may change for:
  - Biodegradable polymer or totally bioabsorbable stents
  - Drug that elutes over longer period of time or stays resident in arterial tissue for longer period

Relevant Guidance

Draft Guidance for Industry: Coronary Drug-Eluting Stents - Nonclinical and Clinical Studies

Main document + companion document
published March 27, 2008

Available at:
http://www.fda.gov/cdrh/ode/guidance/6255.pdf
and
http://www.fda.gov/cdrh/ode/guidance/6255comp.pdf

Harmonization by Doing (HBD)

- **HBD is a "hands-on" approach to harmonization between the US and Japan**
  - The intent of HBD is not simply to create guidance and discuss policy but to develop common protocols for investigational clinical studies that would allow safe and effective "breakthrough" (especially cardiovascular) technologies to benefit patients worldwide
- **The objective is to try to eliminate redundancies, added costs, and time delays inherent in duplicative trials**

HBD: Where Can I Find Out More?

- General information and updates on future meetings
  - HBD West Think Tank Meeting July 15-17 2009, FDA White Oak Facility, Maryland

  http://www.fda.gov/cdrh/International/hbdpilot.html#1

- HBD East Think Tank Meeting (2008): http://www.jfmda.gr.jp/hbd/e/index.html

Conclusions

- Talk to FDA before trials begin (even OUS)
  - US/OUS
  - Feasibility/pivotal/postmarket/device iterations
- Successful protocol is complete, with prespecified analysis plan
- Interpretation of totality of data critical to FDA decision-making (i.e., p values aren't everything)

Thank you!

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