



FDA Guidance: “Design Considerations for Pivotal Clinical Investigations for Medical Devices”

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Design Considerations for Pivotal Clinical Investigations

- <http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm373750.htm>
- Draft issued Aug. 15, 2011; Final issued Nov. 7, 2013.
- It is guidance for industry, clinical investigators, institutional review boards and FDA staff.

Design Considerations for Pivotal Clinical Investigations

- **Guidance should help manufacturers select appropriate trial design.**
- **Better trial design and improve the quality of data that may better support the safety and effectiveness of a device.**
- **Better quality data may lead to timelier FDA approval or clearance of premarket submissions and speed U.S. patient access to new devices.**

Outline

- **Regulatory Considerations**
- **Principles for the Choice of Clinical Study Design**
- **Clinical Outcome Studies**
 - RCTs
 - Controls
 - Non-Randomized Controls
 - Observational Uncontrolled One-Arm Studies
 - OPCs and Performance Goals
 - Diagnostic Clinical Outcome Studies
- **Diagnostic Clinical Performance Studies**
- **Sustaining the Level of Evidence of Studies**
- **Protocol and Statistical Analysis Plan**
- **Closing Remarks**

Stages of Medical Device Clinical Studies

- 1) **Exploratory Stage** - first-in-human and feasibility/pilot studies, iterative learning and product development.
- 2) **Pivotal Stage** - definitive study to support the safety and effectiveness evaluation of the medical device for its intended use.
- 3) **Postmarket Stage** - includes studies intended to better understand the long-term effectiveness and safety of the device, including rare adverse events.

Not all products will go through all stages.

Importance of Exploratory Studies in Device Development

- Exploratory stage evaluation helps better understand how the device may perform, its intended use, and how to select an appropriate pivotal study design.

Kinds of Devices

- **Therapeutic Devices** - Intended to treat a specific condition or disease
- **Aesthetic Devices** - Provide a desired change in a subject's appearance through physical modification of the structure of the body
- **Diagnostic Devices** - Provides information when used alone or in the context of other information to help assess a subject's condition

Unique Features for Some Medical Devices

- Device complexity
- User skill level and training
- Learning curve
- Human factor considerations

Valid Scientific Evidence for PMAs

- **Statutory directive:**
 - valid scientific evidence to determine whether there is reasonable assurance that the device is safe and effective.
- **Valid scientific evidence comes from:**
 - well controlled studies
 - partially controlled studies
 - objective trials without matched controls
 - well documented case histories
 - reports of significant human experience (21 CFR 860.7)

Valid Scientific Evidence for PMAs

The valid scientific evidence used to determine the effectiveness of a device shall consist principally of well-controlled investigations.

21 CFR 860.7(e)(2)

Principles for Designing a Clinical Study

- Types of Device Studies
- Bias and Variance
- Study Objectives
- Subject Selection
- Stratification for Subject Selection
- Site Selection
- Comparative Study Designs

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Types of Device Studies

- **Clinical outcome**
 - All therapeutic and aesthetic devices and some diagnostic devices
- **Diagnostic clinical performance**
 - Some diagnostic devices

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Bias and Variance

- **Bias -- Systematic (non-random) error in the estimate of a treatment effect**
 - One objective of a clinical study: eliminate, reduce or estimate the bias, so as to characterize in an accurate manner the safety and effectiveness of the device
- **Variance can be reduced by a more efficient design or by a larger sample size.**

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Comparative Study Designs

- Parallel
- Paired
- Crossover

Clinical Outcome Study Designs

- Double-masked (blinded), randomized, controlled, multi-center clinical trials (RCTs) are the “gold standard” for clinical outcome studies (but not necessarily for diagnostic clinical performance studies). Such studies tend to minimize bias.
- But these studies may be impractical, unethical or infeasible in certain situations. For example, there are some devices where it is impossible to mask anyone to the treatment.
- Manufacturers should talk to FDA before finalizing a study design and provide a rationale for the proposed study design.

What if RCT is not Masked?

- Without masking, bias needs to be addressed.
- Usually bias occurs if the control is no treatment.
- This bias is usually very difficult to estimate and can be quite large and extend over a long period of time, even if the endpoints are “hard”.
- When the study is not doubly masked, the influence of the patient or the investigator can be subconscious or unconscious.

Controls

- **Concurrent Control (Randomized Clinical Trial)**
 - Placebo
 - Active
 - No treatment
 - Non-randomized Concurrent Control (Observational Study)
- **Historical Control (Observational Study)**
- **Patient as Own Control**

Placebo Effect and Choice of Control

- Placebo control—a totally ineffective treatment but almost always masked.
- Placebo controls (sometimes called “shams”) for devices can sometimes be much more difficult to devise than placebo pills.
- Placebo effect is well-known for endpoints of pain or function and can be long-lasting.
- Enhanced placebo effects for devices (vs. drugs)

Kaptchuk TJ et al. *J Clin Epidemiol.* 2000 53:786-792.

The Placebo Effect

- **Sources of the placebo effect**
 - Expectation of benefit
 - Regression to the mean
 - Showering of (medical) attention (Hawthorne effect)
- **It exists for objective as well as subjective endpoints and can be very long lasting.**
- **The sponsor should consider asking the subject and physician during the study which arm they think that subject is in.**

Control of No Treatment

- Called Standard of Care or Best Medical Management.
- Study is unmasked; patients get no experimental treatment. There is often a bias if they know they did not receive a treatment, whereas in the experimental arm there is the expectation of benefit.
- Further, in the experimental arm there is the expectation of benefit, for the controls there is no such expectation.
- For unmasked trials where there is a measurable difference between placebo and no treatment, usually based on patients' expectation of therapy, this is not a preferred control.

Non-Randomized Controls

- **Two types:**
 - use of a concurrent, non-randomized control.
 - historically controlled studies
- **There is a concern about how comparable the groups are without randomization. Even if comparable, is there the same expectation of benefit?**
- **Such studies are observational and comparative statistical inference is compromised.**
- **Example: some early hip studies**

Non-randomized Controls

- From a scientific standpoint, the randomized controlled trial (RCT) offers the strongest form of evidence, the least amount of bias and is generally preferred.
- It may be possible to match the non-concurrent control group to the investigational arm in all observed measures but there is no assurance for any unobserved ones. In contrast, randomization balances for observed as well as unobserved measures.
- Historical controls can be especially problematic due to temporal bias.

Historical Controls

- A one-arm study is an observational study—not a clinical trial or an experiment.
- Since there is no randomization, all comparative statistical inference is compromised.
- It may be possible to match the historical control group to the current study in all observed measures but there is no assurance for any unobserved ones.
- In contrast, randomization balances for observed as well as unobserved measures.
- Statistical techniques such as propensity scores can be used to investigate comparability and perform analysis,

One-arm Studies

- **Objective Performance Criteria (OPC)**
 - Usually a very well-described and publicly available control used to set the criterion.
 - Examples in CDRH:
 - IOLs, heart valves
- **Performance Goals**

In some instances, the OPC or PG may be based on the upper (or lower) bound of the confidence interval of an effectiveness (or safety) endpoint.

Objective Performance Criteria

- **An OPC is a numerical target value derived from historical data from clinical studies and/or registries which may be use for comparison with safety or effectiveness endpoints.**
- **Currently very few OPCs since device technology needs to be fairly mature.**
- **An OPC can be carefully constructed from all available patient-level data on a particular type of device. This is usually not done by FDA nor a particular company.**

Performance Goals

- A Performance Goal (PG) is a numerical value (point estimate) that is considered sufficient by FDA for use as a comparison for a safety or effectiveness endpoint.
- Generally PGs are inferior level of evidence to OPCs.
- It is recommended that (like OPCs) that PGs not originate from a particular sponsor nor from the FDA. It is often helpful if it is recommended by a scientific or medical society.
- A fundamental regulatory question is: When a device passes an effectiveness (safety) PG (or an OPC), does that provide evidence that the device is effective (safe)?

Diagnostic Clinical Outcome Studies

- Here the intervention is the outcome of the diagnostic test and the primary endpoints are clinical.
- It is usually always unmasked to the investigator but hopefully not the third party evaluator.

Diagnostic Clinical Performance Studies

- **Object:**
 - to characterize the performance of the diagnostic device based on the test results from the subjects
 - to provide evidence to be used in the assessment of the benefit risk associated with the use of the diagnostic device for the intended population.

Diagnostic Clinical Performance Studies

- **Consideration of Intended Use**
- **Study Population**
- **Study Planning, Subject Selection and Specimen Collection**
- **Comparison Studies using the Clinical Reference Standard**
- **Masking**
- **Skill and Behavior of Persons Interacting with the Device (Total Test Concept)**
- **Other Sources of Bias**

Sustaining Quality of Clinical Studies

- **Handling Clinical Data**
- **Study Conduct**
- **Study Analysis**
- **Anticipating Changes to the Pivotal Study**

The Protocol

- **Scientific rationale (and hypotheses if approp.)**
- **Definition of subject populations**
- **Proposed intended use**
- **Listing of study endpoints**
- **Statistical Analysis Plan**

Statistical Analysis Plan

- **As much detail as possible at the protocol stage**
- **Should include the statistical analysis for the primary endpoint on which the sample size is based, anticipate if the assumptions are not valid and plan for missing data.**
- **Final detailed Statistical Analysis Plan needs to be submitted before any outcome data are available or unmasked**
 - For non-masked (open label) studies this means before any patient reaches an outcome.

Closing Remarks

- **Device studies allow for a broad range of designs (much broader than the pharmaceutical world).**
- **Companies are encouraged to meet with the FDA in the planning phase for a pre-submission meeting or IDE meeting.**



Questions?