

Practical Issues with Adaptive Trial Design: An FDA Division of Cardiovascular Devices (DCD) Perspective

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Introduction

Today's goals:

- **Talk about Cardiovascular Device Trials at CDRH**
- **Indicate some current challenges for regulators**

CV Device Trials at CDRH

- Many instances where preclinical engineering data is most informative (e.g., mechanical heart valves)
- Usually proceed from feasibility stage to pivotal trial
- Unblinded trials are frequently performed
- Physician technique can have a major impact on device trial results
- Rapid iterative change from one device model to the next (e.g. stents)
- Many pivotal device trials employ nonrandomized design

CV Device Trials at CDRH

- Many small companies with innovative device designs (e.g., percutaneous heart valves)
- Limited resources of small firms frequently results in overoptimistic expectations
- As a consequence we see too many examples of non-prospectively planned attempts at adaptive design
 - An adaptive design should be adaptive by “design”, not a remedy for poor planning.

Challenges for use of Adaptive Design in Drug or Device Trials

- Who will perform the interim analysis?
- How broad should the data examination be?
- Who will have the authority to decide what type of design change is needed?
- Should there be any Sponsor involvement in the adaptive decision? How much involvement?
- How will the Sponsor ensure that interim results are not widely known?
- How is a recommended adaptation implemented so that the trial continues to run smoothly?

Challenges for use of Adaptive Design in Drug or Device Trials

- **What are suitable analyses to perform at the end of the trial to demonstrate that trial results remain valid even though an adaptation has been implemented?**
- **Possible role of information bias (assessment/referral) needs to be examined**
 - Effects on patient enrollment
 - Differential dropouts in favor of one treatment
 - Crossover to the other treatment
 - Protocol deviation due to additional medications/treatments
 - Differential assessment of the treatments