When is a Randomized Clinical Trial Appropriate vs. a Historical Control vs. a Performance Goal?

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My subspecialty is adult cardiology
Basis for Medical Device
Approval by FDA

PMA - Reasonable assurance that the device is safe and effective for the proposed intended use

HDE - Reasonable assurance that the device is safe and provides probable benefit for the proposed intended use
Achieving a Reasonable Assurance
Valid Scientific Evidence Required

Hierarchy of Medical Scientific Evidence

Randomized Controlled Trial
Observational Trial
  - Case-control
  - Cohort
Descriptive study
  - Physiologic study
  - Case series
  - Expert opinion
Why Clinical Trial Results May Be Erroneous

- The trial may have been biased in some predictable fashion
- The trial may have been biased by an unpredictable factor
- The result may have occurred by the play of chance
Confounding: A bias that distorts the treatment effect due to an imbalance between treatment groups of a variable associated with the outcome.

Randomization: The most effective way to prevent confounding.

- Randomization should result in the balanced distribution of all potential confounders (known or unknown) across all treatment groups at baseline.
  - Level playing field

Well-designed and executed RCT’s allow one to infer causation rather than only association.
Randomized Controlled Trials Used for FDA Approval of Cardiac Devices to Treat Congenital Heart Disease
**RCT Challenges**

- Expensive, labor-intensive, and time consuming
- Issue of generalizability (external validity)
  - To reduce variability, RCT’s use inclusion and exclusion criteria that may be quite restrictive
  - Subjects are carefully monitored and more adherent to treatment and follow-up than real-world patients
  - Raises question whether RCT results can be extrapolated to the community
**RCT Challenges**

**Enrollment**

- Requires clinical equipoise with an acceptable control (standard of care) treatment
  - An acceptable medical therapy or an alternative surgical or approved device intervention may not exist
  - Superiority or non-inferiority to an ineffective control is clinically meaningless
- Patients may refuse to be randomized
- Patients may drop out immediately if randomized to the control or drop out later before study completion if an alternative approved or off-label device intervention is available
Non-RCT’s

An alternative approach when a RCT is not feasible

Examples

- Non-randomized concurrent control
- Historical control
- Case-control study
Requirements for Valid Historical Control

- A recent study with the same treatment
- Same eligibility criteria, workup, and evaluations
- Prognostic factors completely known and are the same in both treatment groups
- No unexplained factors leading one to expect different results
- Differences in prognostic factors do not explain observed differences in outcome

Pocock SJ. J Chronic Dis 1976; 29:175–188
Disadvantages of Non-RCT's

- Most serious shortcoming is selection bias
- Can lead to biased estimates of treatment effects when patient characteristics are related to study outcomes (confounding)
- Unobserved differences in patient characteristics pose the greatest risk of selection bias
- Unobserved differences can neither be controlled for nor can their impact be measured
Examples of Discordance Between RCT’s and Non-RCT’s

- Hormone replacement therapy in post-menopausal women
- Beta carotene
- Vitamin E
- CABG vs. PCI
**Controlling for Selection Bias**

- **Risk adjustment methods**
  - Logistic regression models for short-term outcomes
  - Proportional hazards model for longer term outcomes

- **Propensity score analysis**

- **Characteristics and quality of the control database**
  - Are there matching inclusion/exclusion criteria?
  - Are all known variables associated with outcomes included?
  - Are methods of outcome evaluation appropriate?
  - Are missing data a problem?
Additional Trial Design Challenges for Evaluating Pediatric Devices

- Relatively small number of children affected
  - Small potential market - financial disincentives
- Large range of device size often required
- Devices may need to accommodate child’s growth
- Highly durable devices needed
- Off-label use of available adult devices
  - Not subjected to rigorous evaluation for pediatric use
  - Stifles development of novel pediatric devices
- Parental consent and (when appropriate) child assent to randomization

Examples of Non-Randomized Controlled Trials Used for Cardiac Device Approval

- **AGA Amplatzer Atrial Septal Occluder**
  - Non-randomized prospective and limited retrospective controlled study
  - Cox proportional hazards regression model

- **W.L. Gore HELEX Atrial Septal Occluder**
  - Non-randomized prospective and limited retrospective controlled study
  - Propensity score analysis
What About Single Arm Trials and the Use of OPC and PG’s?

- Objective and meaningful standards
- Usually a rate
- Surrogate for control groups
- Benchmark for minimally acceptable values
Objective Performance Criteria

- Rigorous compilation of patient-level complete datasets from multiple studies
- Uniformity of inclusion/exclusion, evaluation, and treatments
- All relevant baseline covariates and clinical outcomes included
- Statistical adjustments for baseline differences
Performance Goals
Sources of Data for Development

Less rigorous than OPC

- Developed when less historical information is available
  - Patient level data not available
  - Fewer studies or only smaller studies available
  - Summary of major endpoints in published studies with well-defined patient populations and definitions of events with similar devices
  - Clinical judgment may also be utilized in formulating a PG when data are limited
Advantages of OPC and PG’s

- Smaller sample size
- Standard value for all sponsors
- Saves time and money
- Easier to execute
- May be “least burdensome”
Disadvantages of OPC and PG’s

- **All the problems associated with non-RCT’s**
  - Problems with validity of data & analysis
  - Potential for selection bias

- **Sets a minimum standard - *no superiority claims!***
  - Upper or lower bound of 95% CI either meets or does not meet OPC or PG

- **OPC and PG’s may not reflect contemporary medical practice**
  - Outdated data can comprise OPC and PG’s unless they are updated
Examples of PG’s and OPC Used in Cardiac Device Single Arm Trials in Children Leading to PMA or HUD Approval

Performance goals
- AGA Amplatzer Muscular VSD Occluder (PMA)
- NMT CardioSEAL Septal (Muscular VSD) Occluder (PMA)
- Medtronic Melody Transcatheter Pulmonary Valve (HDE)

Objective performance criteria
- AGA Amplatzer Duct (PDA) Occluder (PMA)
The development of cardiovascular devices specifically to treat children remains an unmet need, and device trials pose many regulatory challenges. Although RCT’s should always be considered first in evaluation new cardiovascular devices, this type of trial is often not feasible in pediatric patients.
Non-randomized controlled two arm trials and single arm trials that utilize OPC or PG’s may be acceptable alternatives to RCT’s for pediatric CV devices.

- Close scrutiny of control data required to adjust for baseline covariates.

OPC and PG’s offer potential efficiencies but both:

- Are time and resource-intensive to develop.
- Require rigorous and scientifically valid methodologies.

Consultation with FDA to discuss trial designs strongly recommended.
Thank you

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Back-ups
Other Advantages of RCT’s

- Can utilize enrollment stratification to further ensure that patients are well-balanced across treatment groups
  - E.g., Age, body weight, BSA, severity of disease
  - May be particularly important in small sample size RCT’s, which are prone to imbalances despite randomization
- Blinding – Although patient and investigator blinding in device trials may not be possible, RCT’s allow for blinding of study personal performing follow-up evaluations, core labs, and CEC’s
  - Enhances internal validity of clinical trial
When Objective Performance Criteria May Be Considered

- Much known about disease natural history
- Patient population well described
- Extensive experience with the intervention (device)
- Stable and well known standard of care
- Stable ancillary technology and treatments
- No significant new questions of safety & effectiveness
- Consensus among FDA, industry, clinical, academic and patient communities
- Expectation of significant positive treatment effect
Other Potential Uses for Single-Arm Trials

- Evaluation of device iterations that raise questions that cannot be addressed by pre-clinical testing
- Potential for expansion of device indications for use
  - In specific patient populations or specific lesion subsets not adequately represented in pre-approval clinical trials