Effectiveness Studies: Considerations for Design, Conduct, Analysis, and Reporting

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General Principles

- Collaboration and early communication
- Clinicians should involve their statisticians
  - early in the planning process
  - whenever possible changes are discussed
- Contact CVM (reviewers, statisticians etc) if questions/problems arise
- Flexibility – general approaches work in most cases, but flexibility is important for novel therapies or indications

Outline

- Designing the (clinical) field study
- Study conduct
- Data management and statistical analysis
- Final study report
Target Population

- Identify the target animal population
- Population to be tested (entrance criteria) should match the intended patient population
- Consider important subgroups (e.g., disease etiology, severity)
  - Varying response to treatment or treatment outcome
  - Consider stratification
  - Effect on labeling
- Likelihood of detecting treatment differences in chosen target population

Experimental Design Concepts

- Experimental unit (EU) is the smallest unit in an experiment to which a treatment can be assigned, and whose response is independent of the responses of other units (Petrie and Watson, 1999)
- Randomization involves randomly allocating the EUs to treatment groups. It minimizes treatment selection bias by equalizing other factors that have not been accounted for in the experimental design
- Bias is any process or effect in a study that produces results or conclusions that differ systematically from the truth.

Adequate and Well-Controlled Studies

21 CFR 514.117(a) and (b)

“The primary purpose of conducting adequate and well-controlled studies […] is to distinguish the effect of the new animal drug from other influences […]. One or more adequate and well-controlled studies are required to establish, by substantial evidence, that a new animal drug is effective.”

One of the characteristics of an adequate and well-controlled study is that the study should use “…a design that permits a valid comparison with one or more controls to provide a quantitative evaluation of drug effects.”
Study Design

**Choice of Control Group**

Appropriate control groups [21 CFR 514.117(b)(4)]
- Placebo concurrent control
  - inactive preparation designed to resemble the new drug
- Untreated concurrent control
  - absence of treatment
- Active treatment concurrent control
  - compared to known effective therapy
- Historical control
  - historically derived experience

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**Ethical Considerations**

- For placebo control
  "...when there is no serious harm, it is generally considered ethical to ask patients to participate in a placebo-controlled trial, even if they may experience discomfort..."

  ... rescue treatment clause ensures "the prompt removal of subjects whose clinical status worsens or fails to improve... [The rescue criteria ...] should be well specified, and the timing of measurements should ensure that patients will not remain untreated [...] while their disease is poorly controlled."

ICH E10
Ethical Considerations

- For active control
  - Generally preferred when there is known effective therapy for the condition

  "Active controlled trials are generally considered to pose fewer ethical and practical problems than placebo-controlled trials because all subjects receive active treatment" - ICH E10

Trial Logistics

- Placebo control
  - Generally requires smaller sample sizes
  - Bias minimization
    - Easier to maintain masking in drug administration
    - Known adverse events may reveal group assignment

- Active control
  - Recruitment is likely to be easier
  - Better subject retention in long trials

Effectiveness Evaluation

- Placebo control
  - New treatment should demonstrate superiority
  - Can choose a new clinical endpoint
  - Quality of inference: statistical superiority may not imply clinical relevance
Evaluating Effectiveness

- **Active control**
  - New treatment can show effectiveness using non-inferiority (NI) to a proven regimen
  - If the active control is not approved for the indication, effectiveness can be shown via superiority of the new treatment over the active control
  - Quality of inference from NI trial comes with many caveats

Requirements for Non-inferiority Studies

21 CFR 514.117 (4) (iii) on active controlled studies:

- Similarity of the new animal drug and the active control drug can mean either that both drugs were effective or that neither was effective. The study report should assess the ability of the study to have detected a difference between treatments. The evaluation of the study should explain why the new animal drugs should be considered effective in the study, for example, by reference to results in previous placebo-controlled studies of the active control.

Historical Control Group

- The results of treatment with the new animal drug are quantitatively compared with experience historically derived from (a) adequately documented natural history of disease or condition (b) regimen (therapeutic, prophylactic, diagnostic) whose effectiveness is established
- “Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances.”
- Examples
  - diseases with high and predictable mortality
  - predictable morbidity

[21 CFR 514.117 (b) (4) (iv)]
Choice of Control Group

Considerations
- Ethical issues
- Trial logistics
- Test for effectiveness (superiority, NI) and quality of inference
- Others

Experimental Design

- Power and sample size
  - Check that study is adequately powered
  - For multi-site trials, consider the balance between number of sites vs number of subjects in each site
- Bias minimization is important
  - Randomization
  - Masking/blinding

Related Guidance

- ICH E10: Choice of Control Group and Related Issues in Clinical Trials (2001)
- Draft CDER GFI: Non-inferiority Clinical Trials (2010)
- CDER GFI: Antibacterial Drug Products: Use of Noninferiority Studies to Support Approval
**Study Endpoints**

Define the pivotal effectiveness outcome
- Match the proposed claim
- Clinically/biologically relevant, easy to interpret
- Should be precisely and consistently measured
  - How and when to measure, who will measure
  - Establish procedures to minimize missing data
  - prospectively define outcomes for missing observations
- Sloppy trial conduct tends to obscure treatment effect
  - harder to show a difference (in a superiority comparison)
  - raises questions on quality of trial and interpretability (in NI comparison)

**Study Endpoints: Statistical vs Biological Relevance**

- Statistical significance is a "significant" difference based on current data
- Biological importance relates to
  - magnitude of the response
  - associated clinical benefit
  - consistency with which it can be demonstrated
- Need to establish both statistical and biological relevance and show that the inference is applicable to the target population

**Aspects of Clinical Trial Design**

<table>
<thead>
<tr>
<th>Statistical</th>
<th>Ethical</th>
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<tbody>
<tr>
<td>• Target population</td>
<td>• Overall safety</td>
</tr>
<tr>
<td>• Control group</td>
<td>• Minimize treatment failures</td>
</tr>
<tr>
<td>• Endpoints</td>
<td></td>
</tr>
<tr>
<td>• Randomization</td>
<td></td>
</tr>
<tr>
<td>• Masking</td>
<td></td>
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<tr>
<td>• Precision</td>
<td></td>
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<tr>
<td>• Power</td>
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</tbody>
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<thead>
<tr>
<th>Logistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Recruitment</td>
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<tr>
<td>• Study cost</td>
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<td>• Study duration</td>
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Statistical Analysis

- The pivotal analysis should match the primary clinical hypothesis
- Model should match the study design (including blocks, strata, other randomization restrictions)
- Describe the principal features of the proposed pivotal analysis of the effectiveness variables
  - Statistical model, including fixed/random design factors
  - Analysis details (e.g. covariance structures)
  - Plan for unexpected analysis problems (e.g., missing data, non-convergence issues)

Statistical Analysis

Describe any planned adaptations to study conduct or analysis
- Interim analysis
  - for sample size recalculation
  - stopping for futility or remarkable efficacy
- Adaptive study designs
  - Draft CDER GFI: Adaptive Design Clinical Trials for Drugs and Biologics
- Data safety monitoring committee decisions
- Adding/dropping/combining sites

The Final Study Report

The data submission
- Data
  - Raw data (case report forms, laboratory report)
  - Electronic versions of all data captured in CRFs
  - Analysis data sets (data sets actually analyzed)
- Statistical programs
  - Convert raw electronic data to analysis-ready data
  - Perform the statistical analysis
- CVM GFI #197: Documenting Statistical Analysis Programs and Data Files
Recap: General Principles

- Collaboration and early communication
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Thank you very much!
Questions?

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