Key Elements of Statistical Analyses for Studies with Small Populations (Pediatrics)

Pediatric Clinical Investigator Training

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Why am I, an industry statistician, speaking on what FDA reviews?

I was…

- **An FDA statistical reviewer for 24+ years**
- **Member of the Pediatric Review Committee**

I reviewed study protocols, statistical analysis plans, and completed studies for

- **Pediatrics**
- **Rare diseases**

So, I am speaking from the viewpoint of a FDA statistical reviewer with a bit of industry experience (departed FDA in February 2014)

What do FDA statisticians review?

1. **Study protocol**
   - Study hypothesis
   - Assessments and endpoints
   - Primary endpoint
   - Sample size calculations
   - Statistical analysis section

2. **Special Topics**
   - Missing data
   - Ages of enrolled subjects
   - Adaptive designs
   - Historical controls

Study protocol

Study protocol

Study hypothesis

- The hypothesis needs to include very specific language
  - Drug X will improve distance walked
  - Drug X will improve the distance walked as assessed by the six minute walk test (6MWT) – more precise
  - Subjects randomized to Drug X will walk further than those randomized to Placebo as assessed by the 6MWT -- better
- The hypothesis needs to be achievable
- The hypothesis needs to be clinically relevant

Study protocol

Assessments and endpoints

Assessments and endpoints are not the same concept.

- **Assessment – what you are measuring or instrument you are using to measure; for example,**
  - **Blood pressure**
  - **Bayley Scales of Infant Development (need to convert raw scores to usable scores)**

- **Endpoint – how assessment is used in analysis; for example,**
  - **Responder (does change exceed a threshold)**
  - **Change from baseline**
  - **Survival time**

Study protocol

Primary endpoint

- The primary endpoint results provide the primary evidence for evaluating the study hypothesis.

- The primary endpoint must be stated very precisely.

- Define at the level of the subject, not at the level of the group.
  - Did subject respond? (not proportions who responded)
  - What was subject's change from baseline (not the mean change from baseline within treatment group)
  - Did subject survive? (not the proportion who survived nor the mean time to survival within the group).

- The subject-level results are aggregated to the group-level for the statistical analyses

Study protocol

Sample size calculations

- Usually for the primary endpoint but could be for other endpoints as well.
- Calculation needs to be consistent with the primary analysis objective; for example,
  - Compare proportions who respond
  - Compare mean change from baseline
  - Compare survival curves
- The protocol needs to include all assumptions so the estimates can be reproduced.
- These assumptions include:
  - Power – e.g., 80%, 90%
  - Type I error rate – .05 (2-sided)
  - Expected difference between experimental arm and control
  - Standard deviation of expected difference

Study protocol

Sample size calculations

- Provide evidence of the expected difference and its standard deviation. The evidence can be published literature or results from other studies, for example.
- Sample size assumptions need to be realistic.
- But assumptions are often optimistic, because
  - Lack of data on assessments and endpoints in pediatric populations
  - Few patients available for study
- A well-conducted study will minimize random noise and increase ability to detect a difference.
- Sample size re-estimation can be useful in certain situations (more later).
- How do sample size calculations account for missing data?

Study protocol

Statistical analysis section

Role of statistical analysis section:

- **Statisticians need to understand the analyses that will be done. Analyses need to be pre-specified to avoid data-dredging (or the appearance of).**
- **The statistical analysis section can be high level. The statistical analysis plan (SAP) will explain the exact details on how to implement the analyses.**
- **Speak with FDA statisticians and the medical division to reach agreement on assessments, endpoints, and analyses.**

Study protocol

Statistical analysis section

- **Define the analysis data set to be used for the primary analysis.**

  For example,
  - **All subjects with at least one dose of study treatment**
  - **All subjects with a baseline assessment and one post-baseline assessment**

- **A data set consisting of only those who complete the study generally is not appropriate for the primary analysis.**

- ***Note:*** **Data sets should follow standards to enable the reviewer to use the data and to reproduce your analyses.**

Study protocol

Statistical analysis section

More on analyses of completers …

- **Generally, not primary**
- **Need to *include data from all subjects* in an intent to treat analysis**
- **Characterize and describe those who did not complete the study**
  - **Informative missing data**
  - **Demographics**
  - **Reasons, for example …**
    - **Toxicities**
    - **Drug not working**

Study protocol

Statistical analysis section

- **Describe the analysis that will assess evidence of efficacy as measured by the primary endpoint**

- **Say more than 'appropriate statistical methods will be used'**

- **For example,**
  - **An analysis of covariance will compare the change from baseline among those randomized to placebo with the change from baseline among those randomized to treatment. The covariates will include age and disease status at baseline.**

  - **A Cochran-Mantel-Haenszel test, stratified by age categories and disease status at baseline, will compare the proportion of responders among those randomized to placebo with the proportion of responders among those randomized to treatment.**

Study protocol

Statistical analysis section

- Statistical analyses need to be pre-specified.
  - Avoids ‘data dredging’, ‘cherry picking’
  - Exploratory analyses are reserved for hypothesis generation
- Describe how missing data will be handled in the analysis.
- Subgroup analyses
  - Required for:
    - Race
    - Age
    - Sex
  - Pre-specify other subgroups
  - Describe analysis

Special topics

Missing Data
Every subject counts!

- Every subject needs to be included in analyses, whether or not the subject has data

- What do you do if subject has missing data due to, for example,
  - Missing laboratory values
  - Missing visits
  - Discontinuation from study

- Approvals are based on a risk benefit analysis.

- If a ‘low amount’ of missing data, ‘huge treatment effect’, and a good safety profile then missing data likely doesn’t matter much.

- But, if ‘large amount’ of missing data, ‘small treatment effect’, and a safety signal, then missing data matters a lot.

Missing Data
Every subject counts!

Example 1:

Let's say we have 100 subjects per treatment arm.

Endpoint is response (yes/no)

20% response rate among subjects randomized to treatment.
10% response rate among subjects randomized to placebo.

	Treatment	Placebo
# randomized	100	100
# without endpoint	0	0
Response rate	20%	10%

High confidence in 10% difference between groups

Missing Data
Every subject counts!

Example 2:

20% response rate among subjects randomized to treatment.
10% response rate among subjects randomized to placebo.

But now 10% of those randomized to treatment don't have an endpoint. Why are they missing? Toxicity? Something else? How do we count those subjects? As non-responders?

Missing endpoints counted as non-responders

	Treatment	Placebo
# randomized	100	100
# without endpoint	10	0
Response rate	10%	10%

Missing Data
Every subject counts!

This report changed the landscape:

"The Prevention and Treatment of Missing Data in Clinical Trials", Panel on Handling Missing Data in Clinical Trials Committee on National Statistics, Division of Behavioral and Social Sciences and Education, National Research Council of the National Academies, The National Academies Press, Washington, D.C., 2010. **www.nap.edu**

Ages of enrolled subjects
Assessment, endpoint and analysis challenges

- **Ages can cover a broad range**
  - **Neonates**
  - **0 – 4 years**
  - **5 – 12 years**
  - **Adolescents**

- **Consider age ranges when selecting assessments, defining the study endpoints, and planning the analyses.**

- **Assessments and endpoints used for adult studies may not be appropriate for pediatric studies.**

Ages of enrolled subjects
Assessment, endpoint and analysis challenges

- **Assessments can depend on age of subject**
  - **Neuro-developmental**
  - **Laboratory values**
  - **Growth tables**

- **Verbal skills and cognitive development need to be considered**
  - **Ability to articulate and verbalize**
  - **Reporter at different developmental stages (example, pain)**
    - **Parent**
    - **Child**

Adaptive designs

What is an adaptive design?

"…an adaptive design clinical study is defined as a study that includes a prospectively planned opportunity for modification of one or more specified aspects of the study design and hypotheses based on analysis of data (usually interim data) from subjects in the study."

Possible adaptations particularly relevant for pediatric studies:

- **Treatment regimens of the different study groups (e.g., dose level, schedule, duration)**
- **Total sample size of the study (including early termination)**

Source: FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics
http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf

Adaptive Designs

A recommended overview of adaptive designs

Chris Coffey, Ph.D., "Adaptive Designs and Small Clinical Trials", presented at "Accelerating Therapies for Rare Diseases Workshop" (October 2010) http://rarediseases.info.nih.gov/files/Coffey.pdf

Adaptive Designs

Sample size re-estimation and dose selection

- Sample size re-estimation
  - Used if
    - Low confidence in assumptions for initial sample size estimate calculations
    - Small numbers of patients are available for study enrollment
  - Usually, the variance is re-estimated
  - Prefer the use of data pooled across treatment groups without knowledge of treatment assignments. In other words, 'blinded' sample size re-estimation is preferred.

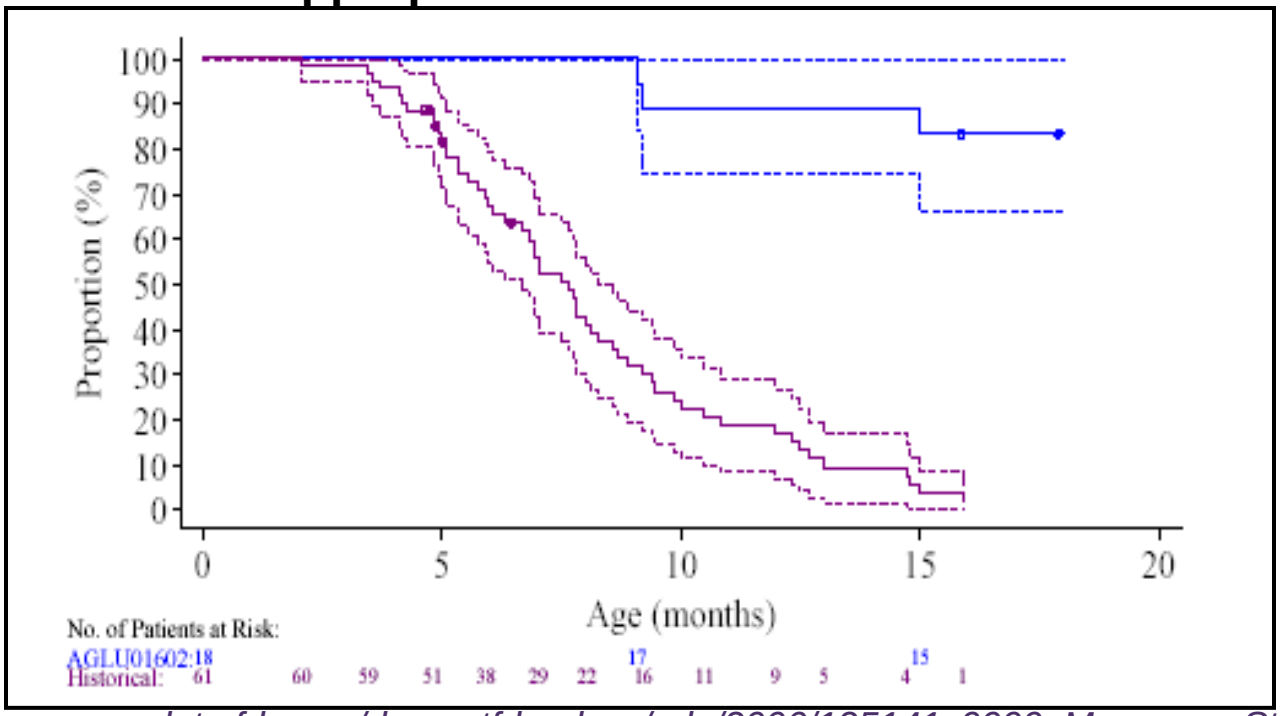
- Dose selection: Optimal design

  Goal: *Minimize the expected sample size* if Stage 1 suggests the proportion of responders is low. Stop study after first stage if data don't support expected response rate. (R. Simon, "Optimal Two-Stage Designs for Phase II Clinical Trials", Controlled Clinical Trials, 1989)

Historical Controls

Example: Myozyme

- Subjects needed to survive long enough to enter the study (median: 5.7 months, range: 1.2 to 7.3 months). Controls did not.
- Exaggerated treatment difference
- Statistical tests not appropriate



Source: www.accessdata.fda.gov/drugsatfda_docs/nda/2006/125141s0000_Myozyme_StatR.pdf

Summary

Careful and thoughtful planning are musts!

- Protocol and statistical analysis plans must be written precisely and with enough information for a reviewer to understand what you will be doing

- Distinguish between assessments and endpoints

- Define primary endpoint at the level of the subject; aggregate results for statistical tests

- Think about subject ages when selecting assessments and defining endpoints

- Sample size calculations need to be aligned with primary objective. Include details!

Summary

Careful and thoughtful planning are musts!

- Data sets need to be usable and allow reproduction of analyses. Follow standards.
- Adaptive designs: sample size re-estimation, two-stage studies
- Historical controls: not recommended. Many statistical challenges.
- Missing data: every subject counts!
- Consult your friendly statistician.

References

Where to find FDA reviews of pediatric studies

Drugs@FDA – all approved products (e.g., Myozyme):
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/

FDASIA (2012):
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm316937.htm

FDAAA:*(2007)*
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049872.htm

References
Overview and missing data

Overview of pediatric studies:

Susan Devine, Ramzi N. Dagher, Karen D. Weiss and Victor M Santana. "Good Clinical Practice and the Conduct of Clinical Studies in Pediatric Oncology", Pediatric Clinics of North America, 2008.

Missing data:

"The Prevention and Treatment of Missing Data in Clinical Trials", Panel on Handling Missing Data in Clinical Trials Committee on National Statistics, Division of Behavioral and Social Sciences and Education, National Research Council of the National Academies, The National Academies Press, Washington, D.C., 2010. **www.nap.edu**

References

Adaptive designs

FDA Draft Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics
http://www.fda.gov/downloads/Drugs/Guidances/ucm201790.pdf

R. Simon, "Optimal Two-Stage Designs for Phase II Clinical Trials", Controlled Clinical Trials, 1989

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