Session II: Preparation for Clinical Trials Workshops
Clinical Trial Issues and Methodology
"The Essentials"

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Presentation Outline

Introduction to Research Designs
- Stages of a Clinical Trial

Stage 1 - Development
- Traditional Clinical Trial Design Decisions
- Maximizing Validity of Research Conclusions

Stage 2 - Execution
- Medical Monitoring
- Interim Analyses: Safety and Efficacy Monitoring

Stage 3 - Analysis, Interpretation and Reporting

Role of Quantitative Scientists in Clinical Research

Learning Objectives and Key Messages
Presentation Outline

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Learning Objectives and Key Messages
Background:
Research Design Process

Research Design:

◆ **Critical** to research success

◆ **Partnership** (internal and/or external):
  – Scientists (Clinical, Quantitative, Regulatory)
  – Operations Specialists (e.g., Data Management, Supplies)
  – Research Partners and Customers

◆ **Dynamic** process

Goal:

Maximize the validity of research conclusions that endure scientific peer review and ensure research conclusions that shape evidence-based public health policy and provide value to patients, providers and payers

Key Guiding Principles:

◆ Design based on achieving specific research conclusions

◆ Spending time on design quality will enable effective execution

**“The Essentials”**
Message #1
### Background – “Research Design 101”: Clinical Research Design Tool Box

#### OBSERVATIONAL

- **Descriptive**
  - Case history/case studies
  - Cross-sectional
- **Analytic**
  - Prospective cohort
  - Retrospective Case-control

#### INTERVENTIONAL

- **Single group**
- **Two or more groups**
  - Non-randomized
  - Randomized
Background: Evidence-Based Medicine* - Qualification of Evidence
U.S. Preventive Services Task Force

Ranking Evidence:

◆ **Level I:** Evidence obtained from at least one properly designed randomized controlled trial

◆ **Level II-1:** Evidence obtained from well-designed controlled trials without randomization

◆ **Level II-2:** Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group

◆ **Level II-3:** Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence

◆ **Level III:** Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

* http://en.wikipedia.org/wiki/Evidence-based_medicine
Clinical Trial [Level II-1]

- “…a prospective study comparing the effect and value of intervention(s) against a control in human subjects”

Ideal Clinical Trial [Level I]

- “…the ideal clinical trial is one that is randomized and double-blinded.”

[Friedman, Furberg and DeMets, 1996]
Understand the strengths and weaknesses of randomized controlled trials (Level I) and observational studies (Level II-2):

- Randomized trials offer one kind of knowledge but prevent us from seeing other properties of a medical intervention

- Observational studies can help elucidate those properties but may introduce new blind spots

- To understand everything we should know about a medical intervention, we must do both kinds of research with rigor and humility

[Avorn, 2007]
Stages of a Clinical Trial
[Decision Making Process*]

**DEVELOP**

*Framing the Issues*
- Study design
- Preparation: (e.g., site selection, manuals/SOPs, CRFs, training)

**EXECUTE**

*Gathering Intelligence*
- Enroll
- Follow-up
- Monitor (e.g., data review, safety review, medical monitoring, interim analyses)

**REPORT**

*Coming to Conclusions/Learning from Experience*
- Data lock
- Planned and unplanned analyses
- Interpretation
- Regulatory submission
- Publication and presentation
- Data base archiving

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Learning Objectives and Key Messages
The Research Statement

This study demonstrated a significant improvement in ____________________ among participants with ______________ who received ______________ as compared to participants who received ______________.

Basic Research Design Decisions (What is the Question?”)

To evaluate the efficacy/safety of ________________________________

intervention regimen v. control regimen

In participants with ______________

eligibility criteria

as assessed by _____________________.

primary outcome measurement
Development – Traditional CT Design Decisions: Number/Types of Intervention Groups

“To evaluate the efficacy/safety of ___________________________ … intervention regimen v. control regimen

Intervention Group(s) v. Control Group(s)

- Protocol procedures
- Treatment schedule
- Multiple regimens (e.g., dose ranging, factorial designs, …)

- Placebo Control
- Active Control
- Background Control (“add-on” trial)

- Add Standard of Care to both!!
Development – Traditional CT Design Decisions: Eligibility Criteria

Inclusion Criteria
- Defines target population
  - Disease
  - Demographics
  - History

Note: Eligibility Criteria Changes by Development Phase

Exclusion Criteria
- Eliminate subsets of target population
  - Non-compliance with treatment/follow-up
  - Potentially harmed by intervention
  - Intervention potentially ineffective

... in participants with ____________________ ...

eligibility criteria

Note: Eligibility Criteria Changes by Development Phase

As an intervention regimen progresses from early phase clinical trials (e.g., pilot or proof of concept trials) through later phase clinical trials (e.g., pivotal or registration trials) the eligibility criteria (especially the exclusion criteria) tends to change from exclusive criteria to more inclusive criteria
Development – Traditional CT Design Decisions: Primary and Secondary Outcomes

Types of outcomes

- Ultimate (e.g., major morbidity, mortality)
- Staging of severity (e.g., Change in a functional outcome)
- Functional (e.g., BP, glucose)

Primary/Secondary outcomes:

- Clinically relevant and compelling
- Responsive to treatment
- Measured precisely, reliably
Development – Traditional CT Design Decisions: Research Objectives and Hypotheses

**Basic Research Design Decisions (What is the Question?”)

To evaluate the efficacy of ________________________________

*intervention regimen v. control regimen*

In participants with ______________

*eligibility criteria*

as assessed by ________________________________.

*primary outcome measurement*

**Research Objectives**
- General goals to evaluate intervention effects

**Research Hypotheses**
- Specific, testable statements addressing objectives
- Success criteria pre-defined
- Types:
  - Superiority
  - Non-inferiority
Development – Traditional CT Design Decisions:
Additional Decisions

- Intervention regimen v. Control regimen
- Inclusion criteria
- Primary outcome measurement
- Sample size and statistical power
- Follow-up schedules
- Randomization procedure
- Quality control procedures
- Policy (e.g., publication)
- Timetable
- Statistical analysis strategy (e.g., analysis models, interim analysis, subgroup analysis)
- Masking of treatment/outcomes
- Patient management and unmasking
- masking of the intervention procedure

PROTOCOL

- Patient management and unmasking

Intervention regimen

Inclusion criteria

Primary outcome measurement

Sample size and statistical power

Follow-up schedules

Randomization procedure

Quality control procedures

Policy (e.g., publication)

Timetable

Statistical analysis strategy (e.g., analysis models, interim analysis, subgroup analysis)

Masking of treatment/outcomes

Patient management and unmasking

Quality control procedures

Policy (e.g., publication)

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Patient management and unmasking

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Development – “Research Design 101”: Maximize Validity of Research Conclusions

**MINIMIZE the following:**

- **Chance**  
  (False Positive and False Negative Conclusions)  
  - Design (e.g., Sample Size Determination)  
  - Analysis (e.g., Control of False Positive Rate)

- **Bias**  
  - Selection (e.g., Intention-to-Treat Design/Analysis)  
  - Information (e.g., Masking of Interventions/Outcomes)

- **Confounding**  
  - Baseline (e.g., Randomization)
Development – Maximize Validity of Research Conclusions
Minimize Chance During the Design

DEFINITIONS:

- **False Positive**: Concluding that a specified relationship *does exist* between an intervention and outcome when in reality such a relationship *does not exist* (Type I error)
- **False Negative**: Concluding that a specified relationship *does not exist* between an intervention and outcome when in reality such a relationship *does exist* (Type II error)
- **Statistical Power** (True Positive Rate) = 1 - False Negative Rate

GOAL:
During the design stage, minimize the potential for False Positives and False Negatives

“Clinical trials should have sufficient statistical power to detect differences between groups considered to be of clinical interest. Therefore, calculation of sample size… is an essential part of planning.”

[Friedman, Furberg and DeMets, 1996]
DEFINITION:
Selection Bias

◆ Distortion in the relationship of intervention and outcome due to evaluation of a biased subset of participants and/or their outcomes (“informative censoring”).

◆ Differential selection of participants and/or their outcomes results in under- or over-estimation of relationship

GOAL:
Participants contributing to the results provide an unbiased assessment of the intervention and outcome relationship

Example:
Intention-to-treat analysis and design: All participant’s followed without regard to follow-up events (e.g., compliance, AEs) until the scheduled end of follow-up.
DEFINITION:

Information Bias

- Distortion in relationship of the intervention and outcome due to biased assessment of the intervention and/or outcome
- Biased assessment results in under- or over-estimation of the intervention and outcome relationship

GOAL:

Avoid/minimize during design/execution

Examples:
- Mask the intervention to patient, provider and sponsor
- Mask the outcome to the provider and sponsor
- Mask the intervention to those adjudicating outcomes
Development – Maximize Validity of Research Conclusions
Minimize Confounding

DEFINITION:

Confounding:

- Distortion in the intervention and outcome relationship due to a third factor (i.e., confounder)
  - Associated with intervention (not a consequence)
  - Associated with outcome
- Results in under- or over-estimation of the intervention and outcome relationship

GOAL:

Avoid/minimize during design

Example:
Random assignment in intervention studies
Peer Review Process:

- Involves peers of the research design process partners
  - Scientists, Ops Specialists, Partners, Customers
- Levels of Peer Review:
  - Protocol Development Team
  - Scientific Advisory Committee
  - Protocol Review Committee

Goals – Peer Review Process:

- Ensure appropriateness of the individual research design decisions (functional expertise)
- Ensure alignment among research design decisions (clinical trialist and/or cross-functional expertise)
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Learning Objectives and Key Messages
Stages of a Clinical Trial

DEVELOP
- Study design
- Preparation (e.g., site selection, manuals/SOPs, CRFs, Training)

EXECUTE
- Enroll
- Follow-up
- Monitor (e.g., data review, safety review, medical monitoring, interim analyses)

REPORT
- Data lock
- Planned and unplanned analyses
- Interpretation
- Regulatory submission
- Publication and presentation
- Data base archiving
Execution:
Medical Monitoring

In Pharmaco-Epidemiology:

“…to understand the Drug,
   it is necessary to understand the disease.”

[Guess, Jacobsen, Girman, et al., 1995]

Goals of medical monitoring:

“…to understand the tables/figures generated during final analysis and reporting of a clinical trial,
   it is necessary to understand the data base that generated the tables/figures.”

To understand the data, do not wait for the final data base; start understanding the information generated as a result of the protocol’s research design as soon as feasible
Ongoing review of accumulating, masked, aggregated clinical/laboratory data:

- Ensuring patient safety and study integrity
- Understanding the accumulating safety and efficacy data base before final analysis/reporting

Patient safety enhanced by looking at safety data in aggregate to spot trends of concern (vs. visual inspection of stream of individual patient data)

Study integrity enhanced by the clinical research team learning and understanding their accumulating (masked) safety and efficacy data before final analysis/reporting; and taking appropriate action, if needed
Execution: Interim Analyses – Safety and Efficacy Monitoring

- Ongoing review of accumulating, unmasked, aggregated clinical/laboratory data:
  - Ensure patient safety
  - Ensure efficacy objectives are achievable
  - Enabled by independent Data Monitoring Committee (DMC):
    - Pivotal trial: external DMC
    - Non-Pivotal trial: internal DMC

- Patient safety enhanced by looking at safety data by treatment group to spot trends of concern and modify protocol, if needed.

- Interim analysis of efficacy data:
  - Futility used to discontinue ineffective interventions
  - Early “very good” efficacy findings may be realistic
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Role of Quantitative Scientists in Clinical Research
Learning Objectives and Key Messages
Analysis, Interpretation and Reporting:

The final analysis, interpretation and reporting of information collected during a research study is impacted by decisions made during the design stage and by the performance and modification of the research design during the execution stage.

“One fundamental principle is that statistical analysis of results, no matter how cleverly done, can never rescue a poorly designed <or executed> study.”

- Stuart Pocock (1983)
Stages of a Clinical Trial

**DEVELOP**
- Study design
- Preparation (e.g., site selection, manuals/SOPs, CRFs, training)

**EXECUTE**
- Enroll
- Follow-up
- Monitor (e.g., data review, safety review, medical monitoring, interim analyses)

**REPORT**
- Data lock
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Analysis, Interpretation and Reporting: Final Analysis - Planned v. Unplanned Analyses

**Planned Analyses (Statistical Analysis Strategy):**

- Analysis strategy is driven by the research design decisions
- Detailed analysis strategy is documented in an approved protocol’s “Statistical Analysis Plan” section

**Unplanned (Post Hoc) Analyses:**

**Reasons:**
- Explain conclusions based on the planned analyses
- Generate new hypotheses
- Informative in designing new research protocols

**Caution:** Unplanned analyses increase false positive rate
False Positive:

◆ Concluding that a specified relationship does exist between an intervention and outcome when in reality such a relationship does not exist (Type I error)

Issue: “Torture data enough, it will tell you anything.”

Sources of potential inflation of false positive error rate:

– Multiple outcomes
– Multiple interventions
– Multiple time points
– Subgroups

*This “multiplicity” must be addressed scientifically (e.g., protocol-specified multiple comparison procedures) or must be clearly articulated during the interpretation of the research results.*
**Chances of Getting a False Positive**

Assuming Intervention and Control Regimen Are Equal

[Each test performed at 5% level of significance]

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</table>
“The investigator has an obligation to review critically the study and its findings and to present sufficient information so that readers can properly evaluate the trial”

[Friedman, Furberg and DeMets, 1996]

What was done compared to what we (they) said we (they) were going to do…

Know the strengths and weaknesses of the research design selected including its execution
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Learning Objectives and Key Messages
Clinical Trials Workshops: Clinical Trial Research Team

**Clinical Scientists** (subject matter experts)  Fellows

**Regulatory Scientists**  NICHD Staff

**Quantitative Scientists**  Liz and Ray

**Operation Specialists** (project, data, site, …)

**External Scientific Advisors**  Faculty

**Others** (ethicist, patient advocates, …)
Quantitative Scientists: Proactive Partners During Design, Execution, Analysis and Interpretation of Scientific Investigations

**Biostatisticians:**
- Clinical research (in addition to basic and pre-clinical research)
- Research design options and risk mitigation
- Execution stage quality and change control, and risk mitigation
- Analysis and interpretation including strengths/weaknesses
- Presentation and publication development including graphics

**Epidemiologists:**
- Experts in observational/data base studies and outcomes research
- Define disease including effected population & burden of illness
- Assist with clinical trial protocol development decisions
- Execution stage quality and risk mitigation

**Health Economists:**
- Experts in burden of illness, cost-benefit modeling and outcomes research
- Assist with clinical trial protocol development decisions

**Scientific Programmers:**
- Programming support for quantitative scientists
- Research design programming (e.g., trial simulation)
- Enable regulatory- and publication-based analysis and reporting
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Innovative Clinical Trial Designs
- Adaptive Designs

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Learning Objectives and Key Messages
Learning Objectives and Key Messages

Research Design

✦ Customer-driven collaborative process with peer review that:
  – Maximizes the validity of research conclusions that endure scientific community scrutiny
  – Ensures evidence-based conclusions that shape public health policy
  – Provides value to patients, providers and payers

✦ The right design for the right “knowledge” base!
✦ Design with the end in mind!
✦ Design takes time!
Learning Objectives and Key Messages

Final Analysis of Research Results

 Impacted by decisions made during the design stage
 Impacted by performance and modification of the research design during the execution stage

"One fundamental principle is that statistical analysis of results, no matter how cleverly done, can never rescue a poorly designed <or executed> study"

– Stuart Pocock (1983)

 Design/execution of a research study eats the final analysis of results for lunch!
 Reward researchers for participant retention during execution; not just participant recruitment
 A "clever" analysis of data obtained is more satisfying then a "clever" assumption about missing data
Learning Objectives and Key Messages

Interpretation and Reporting

- Requires a clear understanding of the strengths and weaknesses of each stage during a clinical trial including:
  - Research design developed including its numerous options
  - Execution of the research design
  - Statistical analysis of results

"The investigator has an obligation to review critically the study and its findings and to present sufficient information so that readers can properly evaluate the trial"

– Friedman, Furberg and DeMets (1996)
References: