



**Session II:**  
**Preparation for Clinical Trial Workshops and  
 Mock Study Sections**  
**Clinical Trial Issues and Methodology**  
**"The Essentials"**

**23<sup>rd</sup> NICHD Conference on Maternal-Fetal-Neonatal-Reproductive Medicine**  
 Eaglewood Resort  
 Itasca, Illinois  
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 Global Clinical Development & Regulatory Affairs  
 Merck Research Laboratories




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**Presentation Outline**

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**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**




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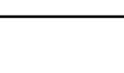
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**Background:  
Research Design Process**

**"The Essentials"  
Message #1**

**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**



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**Background – "Research Design 101":  
Clinical Research Design Tool Box**

**OBSERVATIONAL**

- |                             |                              |
|-----------------------------|------------------------------|
| ◆ <b>Descriptive</b>        | ◆ <b>Analytic</b>            |
| • Case history/case studies | • Prospective cohort         |
| • Cross-sectional           | • Retrospective Case-control |

**INTERVENTIONAL**

- |                       |                             |
|-----------------------|-----------------------------|
| ◆ <b>Single group</b> | ◆ <b>Two or more groups</b> |
|                       | • Non-randomized            |
|                       | • Randomized                |



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**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](http://en.wikipedia.org/wiki/Evidence-based_medicine)



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**Background: Clinical Trial Design Example -  
Interventional with Two or More Groups**

**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]



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**Background:  
Qualification of Evidence**

**"The Essentials"  
Message #2**

**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]



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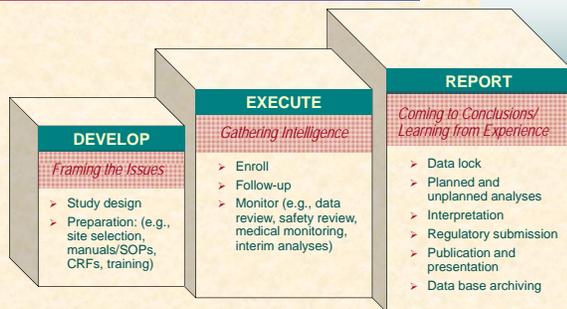
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**Stages of a Clinical Trial  
[Decision Making Process\*]**



\* Russo JE, Schoemaker PJ. (2002)



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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

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## Development – Traditional CT Design Decisions: Framing the Question

### The Research Statement

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

*primary outcome measurement*      *eligibility criteria*  
*intervention regimen*      *control regimen*

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

To evaluate the efficacy/safety of \_\_\_\_\_

*intervention regimen v. control regimen*

In participants with \_\_\_\_\_ as assessed by \_\_\_\_\_.

*eligibility criteria*      *primary outcome measurement*

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## 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!

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### Development – Traditional CT Design Decisions: Eligibility Criteria

... in participants with \_\_\_\_\_ eligibility criteria ...



#### Inclusion Criteria

- ◆ Defines target population
  - Disease
  - Demographics
  - History



#### Exclusion Criteria

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

#### 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

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### Development – Traditional CT Design Decisions: Primary and Secondary Outcomes

...as assessed by \_\_\_\_\_ outcome measurement ...

#### 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

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### 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

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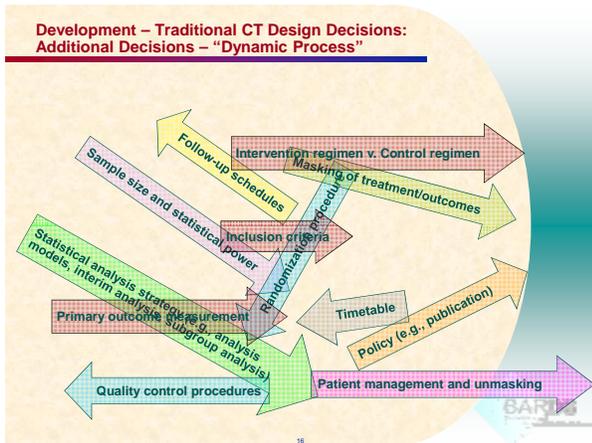
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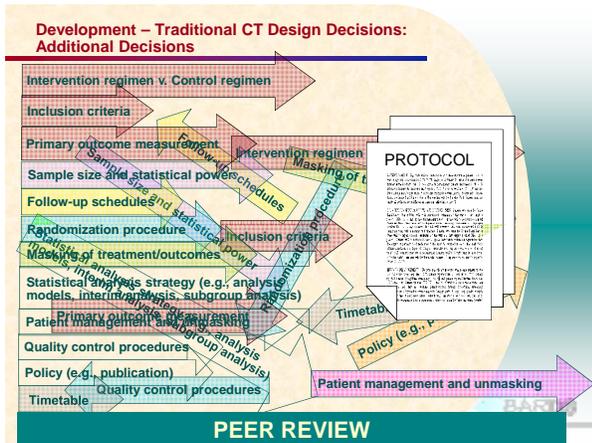
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**Presentation Outline**

- 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
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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)



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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]*



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Development – Maximize Validity of Research Conclusions  
Minimize Selection Bias

**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.



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**Development – Maximize Validity of Research Conclusions  
Minimize Information Bias**

**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



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**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



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**Development:  
Peer Review of a Customer-Driven Research Design**

**“The Essentials”  
Message #3**

**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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### Role of Quantitative Scientists in Clinical Research

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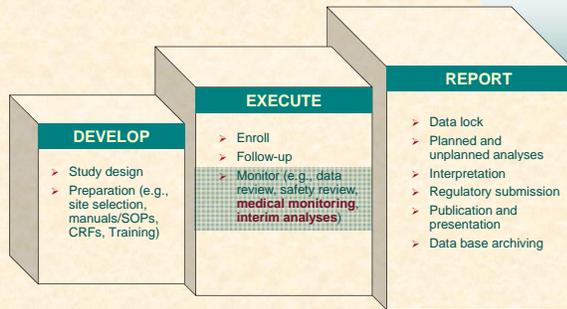
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## Stages of a Clinical Trial



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## 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

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**Execution:**  
**Medical Monitoring**

- ◆ 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



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**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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**Analysis, Interpretation and Reporting:**

**"The Essentials"**  
Message #4

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)



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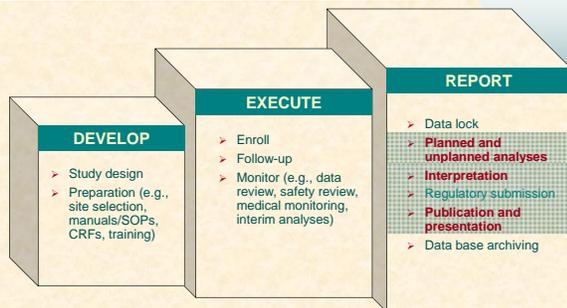
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**Stages of a Clinical Trial**



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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**



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**Analysis, Interpretation and Reporting:  
Minimize Chance During Planned and Unplanned Analyses**

**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.*



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**Analysis, Interpretation and Reporting:  
How Big a Problem is "Multiplicity"??**

**Chances of Getting a False Positive**

Assuming Intervention and Control Regimen Are Equal

[Each test performed at 5% level of significance]

# of Tests	Chances of 1+ False Positive
1	0.0500
2	0.0975
3	0.1426
4	0.1855
...	...
10	0.4013
...	...
50	0.9231



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**Analysis, Interpretation and Reporting:  
Publication and Presentation of Research Conclusions**

**"The Essentials"  
Message #5**

*"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

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## Clinical Trials Workshops: Clinical Trial Research Team

<u>Clinical Scientists</u> (subject matter experts)	Fellows
<u>Regulatory Scientists</u>	NICHHD Staff
<u>Quantitative Scientists</u>	Liz and Ray
<u>Operation Specialists</u> (project, data, site, ...)	
<u>External Scientific Advisors</u>	Faculty
<u>Others</u> (ethicist, patient advocates, ...)	

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## 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

### Role of Quantitative Scientists in Clinical Research

### Learning Objectives and Key Messages

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## 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!**

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## 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 than a “clever” assumption about missing data

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## 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)

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