

# *Practice-Based Evidence Study Design*

## **Patent Foramen Ovale and Stroke Prevention: Going Beyond the Holy Grail of Randomized Controlled Trials**

**Presentation to Heart and Brain Symposium 2009  
May 2, 2009**

**Susan D. Horn, PhD**

**shorn@isisicor.com**

**Institute for Clinical Outcomes Research**

**699 E. South Temple, Suite 100**

**Salt Lake City, Utah 84102-1282**

**801-466-5595 (T) 801-466-6685 (F)**

# Alternative Study Designs

## Randomized Controlled Trials-RCTs

---

### Advantages

- Gold standard for evidence (holy grail)
- Highest level of control – ideal patients
- Minimize bias by random allocation
- Double or triple blind – however, problematic for some treatments

### Disadvantages

- Costly
- Ignore individual patient differences
- Need consent – hard to recruit
- Not generalize to every-day practice

# Alternative Study Designs

## Cohort Studies

---

### Advantages

- Longitudinal studies of cohorts defined by some characteristic, e.g., PFO
- Repeated observations over time
- Minimal restriction on participation

### Disadvantages

- Prone to attrition
- Sometimes costly
- Vulnerable to selection bias

# Alternative Study Designs

## Practice-based Evidence Studies

---

### Advantages

- All patients with study condition are included
- Use data from existing records
- New prospective data collection does not interfere with practice
- Handle individual differences using statistical control for patient factors and other treatment influences

### Disadvantages

- Need large sample size
- Require careful analysis for causal inferences

# Presentation Overview

- **Describe practice-based evidence (PBE) study methodology and compare to RCT for comparative effectiveness of treatments**
- **Understand how to conduct PBE studies**
  - **Incorporate clinical heterogeneity**
  - **Incorporate treatment heterogeneity**
  - **Incorporate many clinical outcomes**
  - **Incorporate patient reported outcomes**
- **Discuss examples of PBE study findings**

# Why PBE?

**PBE offers a way to assess comparative effectiveness of specific treatment processes**

- **More detailed patient, process, and outcome evaluation than is possible with administrative data, CQI, and RCTs**
- **Permits examination of highly variable practices where patient, process, and outcome data are recorded, carefully defined for analysis, and compared**
- **Provides viable method to study comparative effectiveness of interventions when used in clinical practice by many providers, overcoming some limitations of RCTs**

# Practice-Based Evidence Study Design

*Improve/Standardize:*

## ***Process Factors***

- Management Strategies
- Interventions
- Medications

*Control for:*

## ***Patient Factors***

- Psychosocial/demographic Factors
- Disease(s)
- Severity of Disease(s)
  - › physiologic signs and symptoms
- Multiple Points in Time

*Measure:*

## ***Outcomes***

- Clinical
- Health Status
- Functional
- Cost/LOS/Encounters

# Practice-Based Evidence Study Design

Analyzes the *content and timing* of individual steps of a health care process, in order to determine how to achieve:

- *superior medical outcomes* for the
- *least necessary cost* over the
- *continuum* of a patient's care

# **Efficacy vs. Effectiveness**

---

- ***Efficacy*** is concerned with the question of whether a treatment works under ideal conditions.
- ***Effectiveness*** is concerned with the question of whether a treatment works under usual conditions of care.

# Efficacy Studies

---

- **Seek to maximize likelihood of correctly identifying an effect**
  - » **Homogeneous patient population**
  - » **Detailed assessments of one or two outcomes**
  - » **Placebo comparison**
  - » **Random assignment of treatments**
- **Most appropriate research design:**
  - » **Randomized Controlled Trial (RCT)**

# Effectiveness Studies

- **Seek to identify effects correctly under conditions of routine clinical care**
  - » **Heterogeneous populations-clinical heterogeneity**
  - » **Multiple clinically relevant outcomes**
  - » **Comparisons to other active treatments (comparative effectiveness)**
- **Most appropriate research design:**
  - » **Practice-Based Evidence for Clinical Practice Improvement (PBE-CPI)**

# Practice-Based Evidence (PBE)

---

## PBE Studies—7 Signature Features

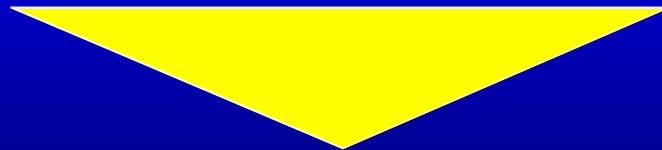
- 1. Hypotheses can be focused or broad*
- 2. All interventions considered to determine relative contribution of each.*
- 3. Minimal patient selection criteria to maximize generalizability and external validity*
- 4. Detailed characterization of the patient by robust measures of patient severity and functional status*

# Practice-Based Evidence (PBE)

---

## PBE Studies—7 Signature Features

5. *Patient differences controlled statistically* rather than through randomization.
6. *Facility and clinical/patient buy-in* through use of trans-disciplinary Clinical Practice Team.
7. *High level of transparency* for all stakeholders.



Findings more generalizable and transportable than RCTs'

# Practice-Based Evidence (PBE)

---

## PBE Studies—7 Signature Features

2. *All interventions considered* to determine relative contribution of each. This requires:
  - **A detailed characterization of the care process through a well-designed point-of-care (POC) documentation system**
    - **User-defined and user friendly**
    - **Time sensitive characterization of all interventions**

# Practice-Based Evidence (PBE)

## PBE Studies—7 Signature Features

4. *Detailed characterization of the patient* by robust measures of individual severity and functional status
  - Includes Comprehensive Severity Index (CSI<sup>®</sup>)
    - Over 2,200 condition-specific signs, symptoms, and physical findings
    - Continuous score: 0 → ∞
    - Admission, discharge, maximum during stay, visit
  - Includes Functional Independence Measure (FIM) and/or other measures of functional status

# Practice-based Evidence Study Design compared to Randomized Controlled Trial

## PBE

I. Select Key Conditions  
to Study

## RCT

I. Define Study

# Practice-based Evidence Study Design compared to Randomized Controlled Trial

## PBE

### II. Data Collection

#### A. Patient Variables

- Patient eligibility and stratification factors
- Use severity of illness to measure:
  - comorbidities
  - disease severity
- All patients qualify

## RCT

### II. Data Collection

#### A. Patient Variables

- Patient eligibility and stratification factors
- Eliminate patients who could bias results:
  - comorbidities
  - more serious disease
- ~ 15% of patients qualify

# Practice-based Evidence Study Design compared to Randomized Controlled Trial

## PBE

### II. Data Collection

#### B. Process Variables

- Methods for Stabilization
  - Measure all processes and use analysis findings to develop protocol associated with better outcomes

## RCT

### II. Data Collection

#### B. Process Variables

- Treatment Protocol
  - Specify explicitly every important element of the process of care for both treatment and control arms

# Practice-based Evidence Study Design compared to Randomized Controlled Trial

## PBE

### III. Data Analysis

#### Outcome Variables

- Dynamic improvement based on combinations of interventions

### IV. Result

- Effectiveness research

## RCT

### III. Data Analysis

#### Outcome Variables

- Change based on one protocol

### IV. Result

- Efficacy research

# Strength of Evidence

- **RCT** – Immediate level 1 evidence based on strength of design, but limited applicability due to all confounders being eliminated.
- **PBE** – Strength of evidence built through research process
  - No added confounders cause the significant association to disappear
  - A change in outcomes follows a change in treatment as predicted by the PBE model
  - Repeated studies on the same topic yield the same findings

# PBE Hallmarks

---

- **Non-experimental**: Follows outcomes of treatments actually prescribed
- **Inclusive**: Uses patient populations undergoing routine clinical care
- **Pragmatic**: Uses actual clinical outcomes
- **Lower Cost** than RCTs
- **Faster** than RCTs

# PBE and RCT Compared

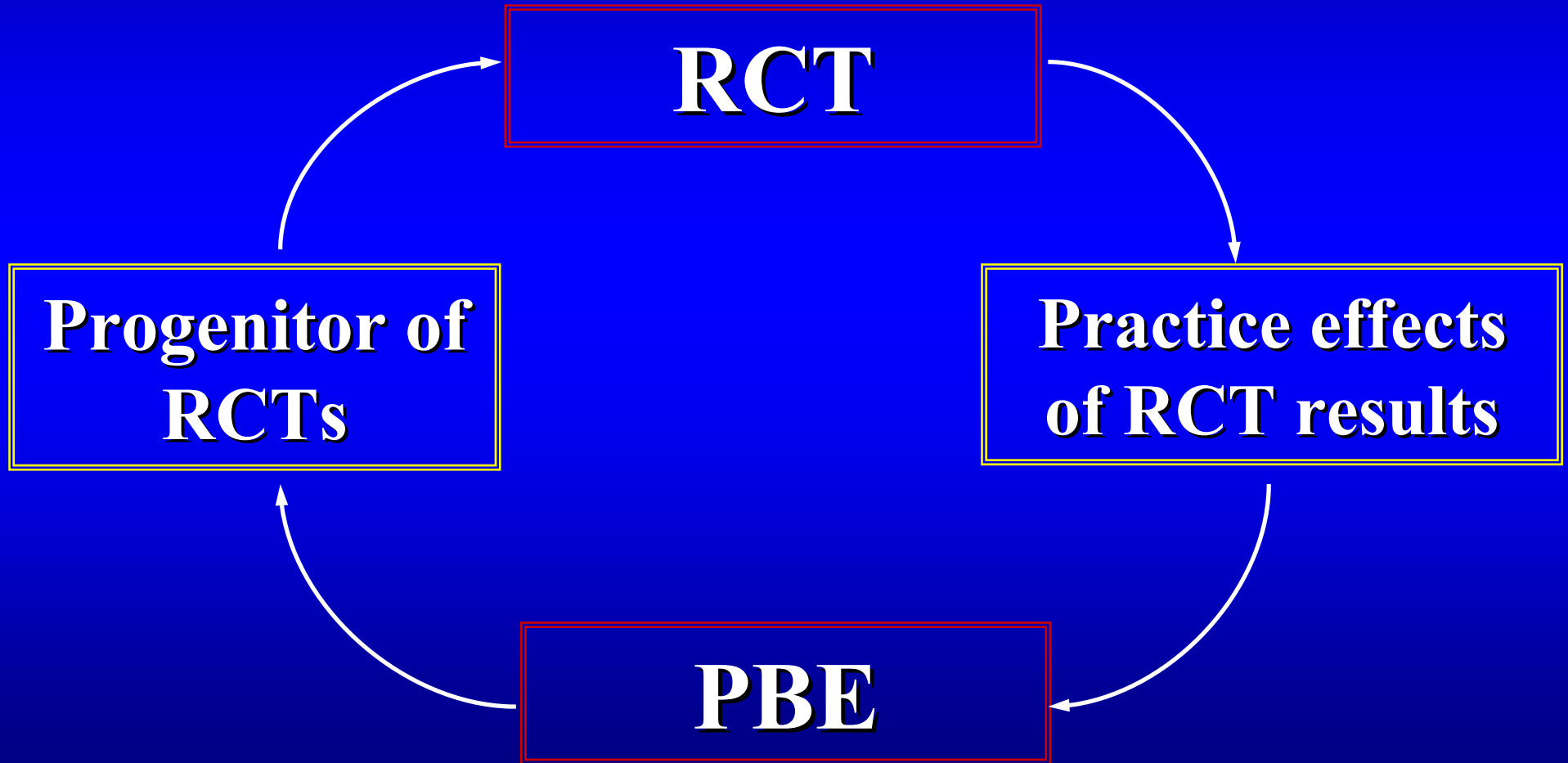
---

**“What is efficacious in randomized clinical trials is not always effective in real world of day-to-day practice...**

**Practice-based research provides the laboratory that will help generate new knowledge and bridge the chasm between recommended care and improved care.”**

- **JM Westfall, *et al.* “Practice-based Research—’Blue Highways’ on the NIH Roadmap.” *JAMA* (January 24/31, Vol 297, No. 4, 2007: 403-410.**

# PBE and RCT



# PBE & RCT Compared

<b>Dimension</b>	<b>PBE</b>	<b>RCT</b>
<b>Type of study</b>	<b>Observational Study</b>	<b>Randomized Controlled Trial</b>
<b>Intervention</b>	<b>All interventions deemed relevant</b>	<b>1 or 2 discrete interventions</b>
<b>Hypotheses</b>	<b>Focused or broad</b>	<b>Well-specified</b>
<b>Selection criteria</b>	<b>Minimal</b>	<b>Extensive</b>
<b>Sample size</b>	<b>As large as desired</b>	<b>Typically small</b>
<b>Control for participant differences</b>	<b>Detailed characterization and statistical control</b>	<b>Randomization</b>

# PBE & RCT Compared

<b>Dimension</b>	<b>PBE</b>	<b>RCT</b>
<b>Blinding</b>	<b>No</b>	<b>Single, double, triple</b>
<b>Outcomes</b>	<b>Many</b>	<b>Few</b>
<b>Effect size</b>	<b>Often large</b>	<b>Often small</b>
<b>Confounders</b>	<b>Affect outcomes and are interesting</b>	<b>Not interesting; exclude them</b>
<b>Validity</b>	<b>High external</b>	<b>High internal</b>
<b>Causality</b>	<b>Assumed</b>	<b>Assigned</b>
<b>Ability to examine subgroups</b>	<b>Yes—large and heterogeneous sample</b>	<b>Limited—small and homogeneous sample</b>

# PBE & RCT Compared

<b>Dimension</b>	<b>PBE</b>	<b>RCT</b>
<b>Cost</b>	<b>Moderate</b>	<b>High</b>
<b>Culture (1)</b>	<b>High transparency</b>	<b>Top-down; blinding</b>
<b>Culture (2)</b>	<b>Local knowledge contributes, valued</b>	<b>Local knowledge excluded</b>
<b>Knowledge translation</b>	<b>High level of buy in; findings transportable</b>	<b>Far less buy in</b>
<b>Science of ....</b>	<b>Discovery &amp; innovation</b>	<b>Confirmation</b>
<b>Science of ....</b>	<b>Effectiveness</b>	<b>Efficacy</b>

# PBE Study

---

- **Connects outcomes with detailed process steps**
- **Adjusts for severity of illness to control for patient differences/selection bias**

# Criteria to Select a Severity Indexing System to Control for Patient Differences/Bias

---

- **Disease-specific**
- **Independent of treatments**
- **Comprehensive (all diseases)**
- **Clinically credible**
- **Able to measure severity at multiple points in the care process**
- **Statistically valid in explaining costs/outcomes**

# Comprehensive Severity Index CSI®

- **Over 2,200 individual criteria subdivided into more than 5,500 disease-specific groups**
- **No treatments used as criteria**
- **Computes disease-specific and overall severity levels on a continuous scale**
- **Fixed times for inpatient reviews**
  - **Admission review--first 24 hours**
  - **Maximum review--any time during stay**
  - **Discharge review--last 24 hours**
  - **Each visit**

# Coronary Artery Disease - IHD

Disease codes 411-411.89, 413-414.05, 414.8-414.9

Category	Indicator	1	2	3	4
Cardiovascular	*Heart Blocks	No or 1 <sup>st</sup> degree	2 <sup>nd</sup> or 3 <sup>rd</sup> degree		Severe (4+)
	*Mitral/Aortic Regurgitation	No or mild (1+)	Moderate (2+-3+)		
	*Lowest Ejection Fraction	>=35 %	20-34 %	<=19 %	
	*Left Main Stenosis	<= 90 % left main	> 90 % left main		
	*Stenosis >50% in Arterial Lesions	None or >50% in 1-3 lesions	>50% in >=4 lesions		
Lab – Chemistry	*Highest BUN	<=23 mg/dl	24-70 mg/dl	71-100 mg/dl	>=101 mg/dl
	Highest Creatinine	<=1.2 mg/dl	1.3-3.0 mg/dl	3.1-7.0 mg/dl	>=7.1 mg/dl
Lab – Hematology	*Highest WBC	<=11.0 K/cu mm	11.1-20.0 K/cu mm	20.1-99.9 K/cu mm	>=100.0 K/cu mm
Pain	*Chest Pain	Chest pain on 1 <sup>st</sup> day	Single episode ≥2days	Multiple episodes ≥ 2days	

# Coronary Artery Disease - IHD

Disease codes 411-411.89, 413-414.05, 414.8-414.9

Category	Indicator	1	2	3	4
Vitals	*Highest Systolic BP	<=180 mm Hg	181-219 mm Hg	>=220 mm Hg	
	Highest Diastolic BP	<=99 mm Hg	100-109 mm Hg	>=110 mm Hg	
	*Lowest Systolic BP	>=90 mm Hg	80-89 mm Hg	61-79 mm Hg	<=60 mm Hg
	*Highest Pulse Rate	<=99 beats/min	100-129 beats/min	>=130 beats/min	
	EKG Rhythm		>=6 PVCs/min, SVT		Runs V-Tach
	*Lowest Pulse Rate	>=51 beats/min	41-50 beats/min	31-40 beats/min	<=30 beats/min
	*Lowest Cardiac Output	>=4.6 L/min	3.0-4.5 L/min	1.8-2.9 L/min	<=1.7 L/min
	Lowest Cardiac Index	>=2.1 L/min/m2	1.4-2.0 L/min/m2	0.9-1.3 L/min/m2	<=0.8 L/min/m2
	Highest AVO2 Difference	<=6.0 ml/dl	6.1-9.0 ml/dl	9.1-10.0 ml/dl	>=10.1 ml/dl
	*Highest Temperature	<=100.4 OralF	100.5-102.0 OralF	102.1-103.9 OralF	>=104.0 OralF
Respiratory	*Dyspnea	None	On exertion	At rest	Apnea
	Rales	None	<=50%/<3 lobes	>50%/>3 lobes	
	Breath Sounds	None	Decreased <=50%/>=3 lobes	Decreased >50%/>=3 lobes	Absent >50%/>=3 lobes

# PBE Data Sources

---

- **Medical record**
  - » Patient characteristics and medical procedures
- **Point-of-care documentation**
  - » Treatment process details not in the record

# **Post-Stroke Rehabilitation Study**

## **2001 - 2003**

---

### **Patient Characteristics**

**1,161 U.S. Patients**

**52% Male; 58% White, 26% Black**

**Age range: 18.6 - 95.5 yrs**

# **Post-Stroke Rehabilitation Study**

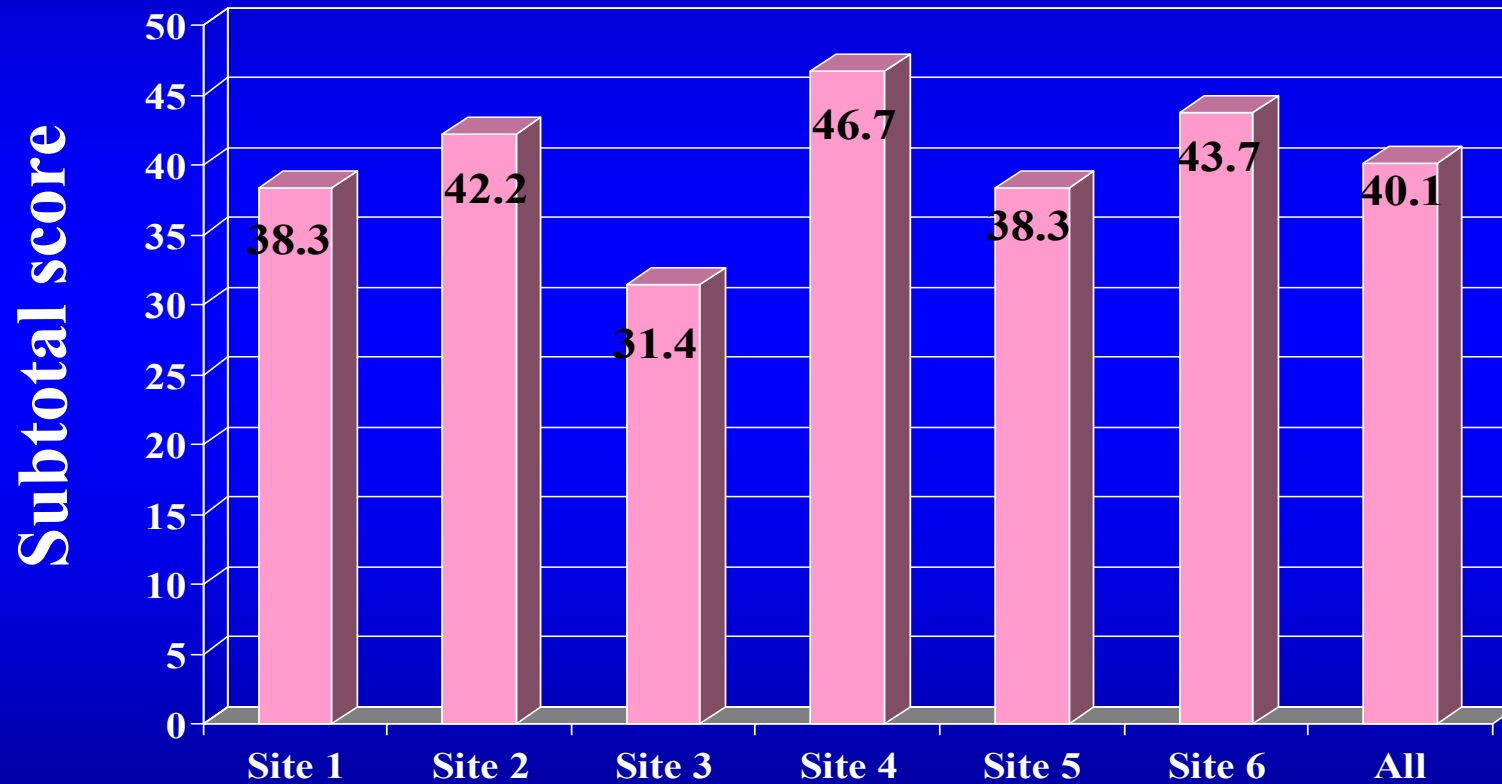
## **Significant Site Variation**

---

### **Patient Variables**

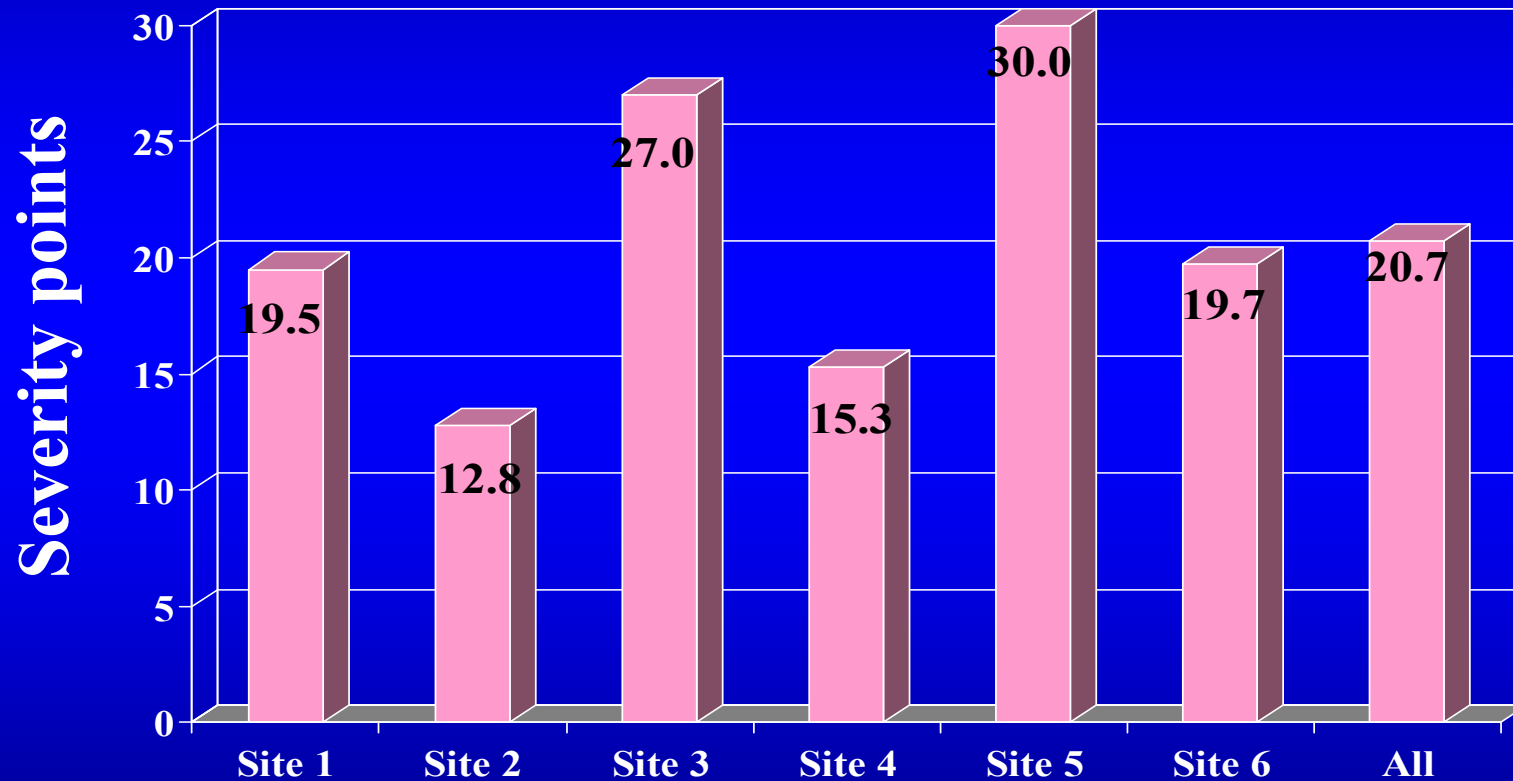
- **Race**
- **Payer**
- **Stroke risk factors**
- **Type and side of stroke**
- **Functional Independence Measure (FIM) scores**
- **Severity of illness scores**
- **Case Mix Groups**

# Significant Site Variation - Stroke Admission Motor FIM



ANOVA,  $p < .001$

# Significant Site Variation - Stroke Admission Severity of Illness score



ANOVA,  $p < .001$

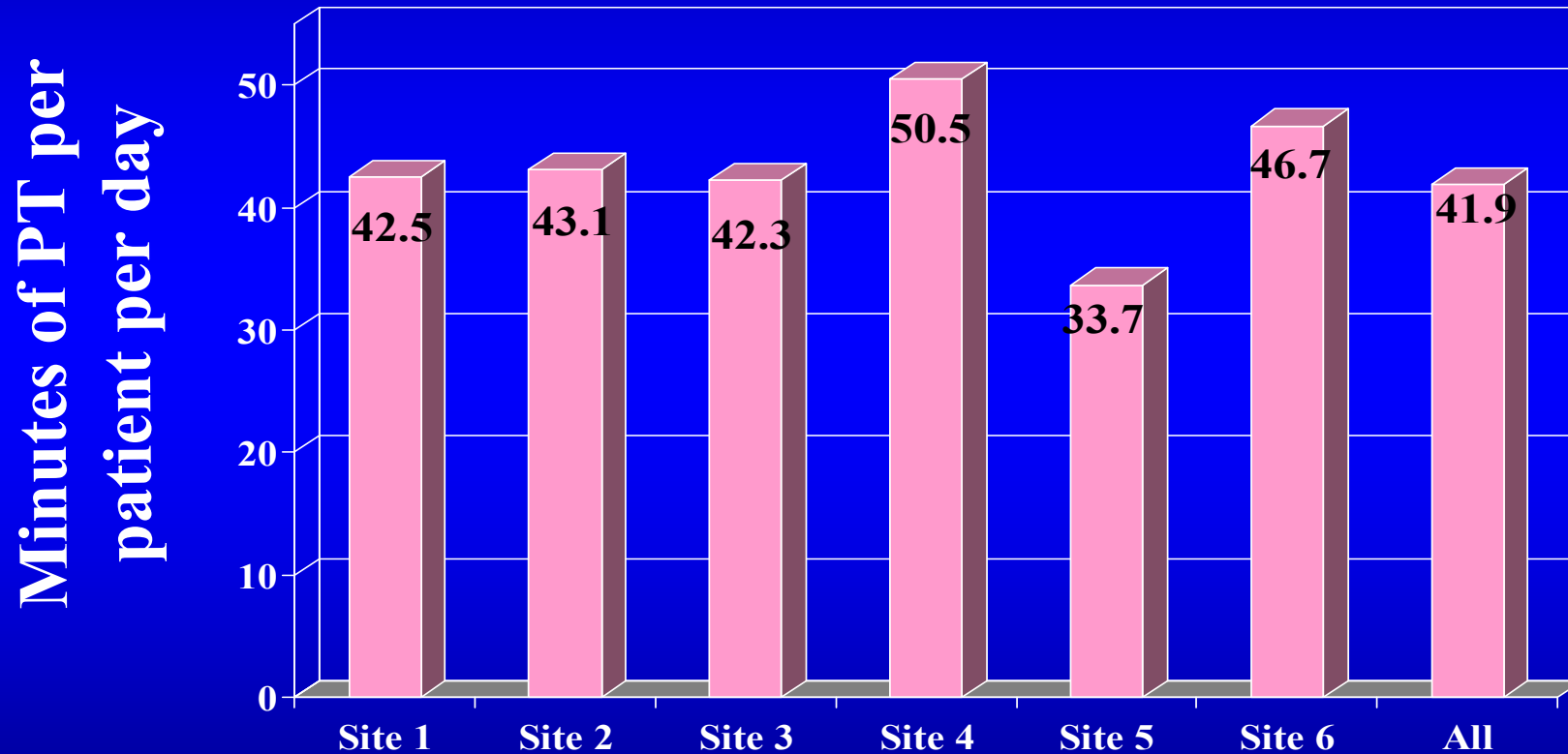
# Post-Stroke Rehabilitation Study

## Significant Site Variation

### Process Variables

- **Rehab LOS**
- **Intensity of PT**
- **Intensity of OT**
- **Intensity of SLP**
- **Tube Feeding Use**
- **Medication use**
  - » **Antidepressants**
  - » **Antipsychotics**
  - » **Opioid analgesics**
  - » **Anti-seizure meds**

# Significant Site Variation Physical Therapy (Severe Stroke)



ANOVA,  $p < .001$

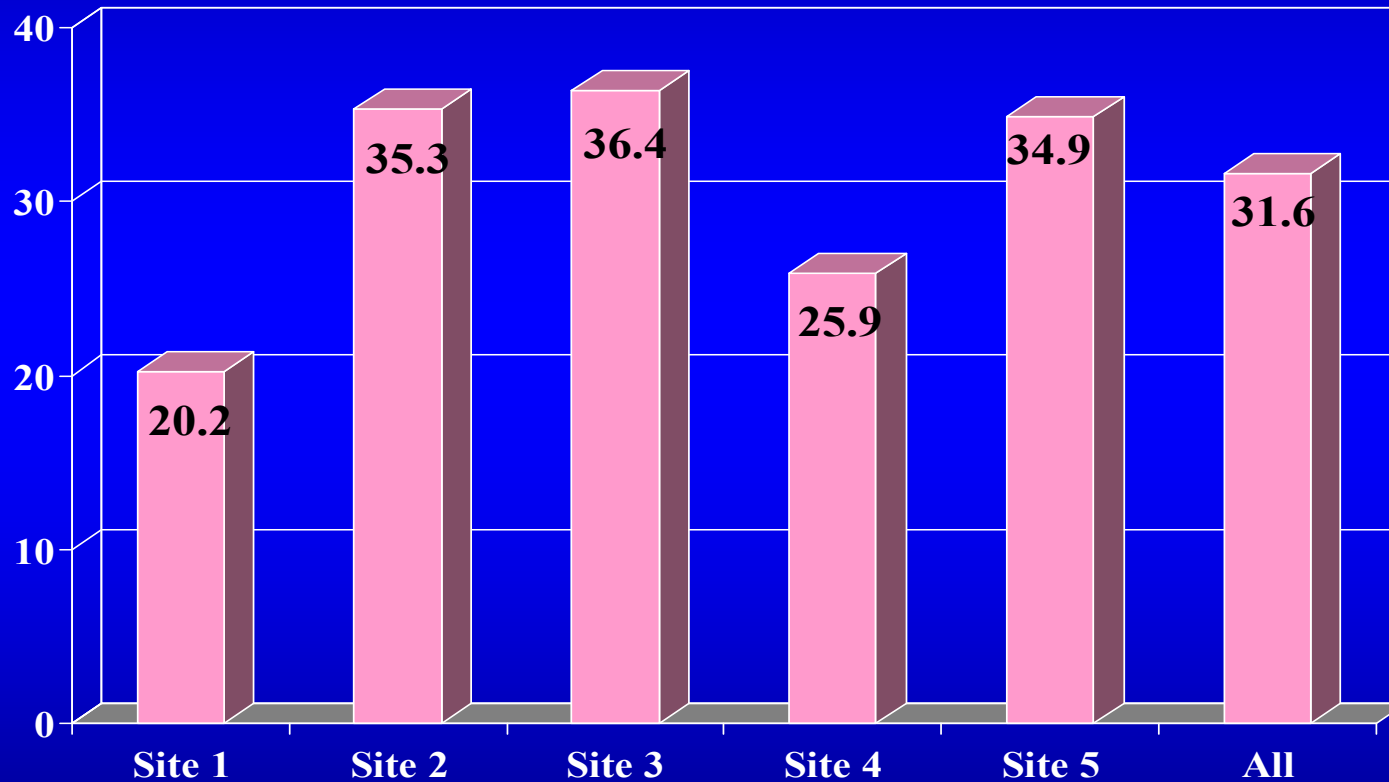
# Significant Site Variation Occupational Therapy (Severe Stroke)



ANOVA,  $p < .001$

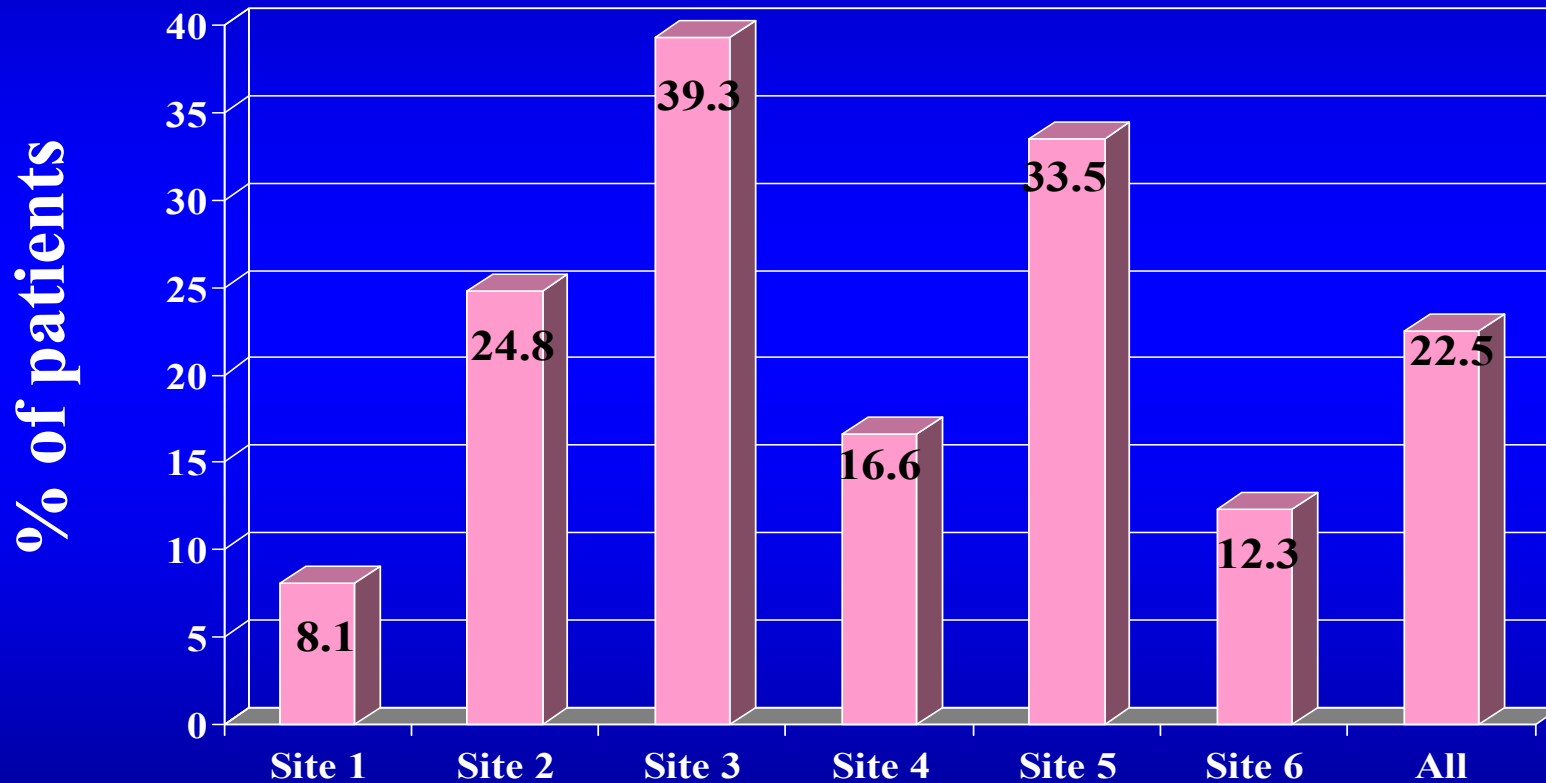
# Significant Site Variation Speech Therapy (Severe Stroke)

Minutes of SLP per  
patient per day



ANOVA,  $p < .001$

# Significant Site Variation - Stroke Opioid Pain Medication Use



Chi-Square,  $p < .001$

# Outcome: Discharge Motor FIM

## Severe Stroke (CMGs 108-114) – Full Stay

### General Assessment

- Age
- Black race
- + Mild motor impairment
- + Admission Motor FIM
- + Admission Cognitive FIM

### General Interventions

- Days onset to rehab
- + Enteral feeding

### PT Interventions

- Formal assessment
- Bed mobility
- + Gait
- + Advanced gait

### OT Interventions

- + Home management

### Medications

- Anti-Parkinsons
- Modafinil
- Old SSRIs
- + Atypical antipsychotics

### SLP Interventions

- Swallowing
- Orientation
- + Reading comprehension

# Outcome: Discharge Motor FIM

## Severe Stroke—1<sup>st</sup> 3 hour Therapy block only

### General Assessment

- Age
- Severe motor impairment
- + Admission Motor FIM
- + Admission Cog. FIM
- + No Dysphagia
- + Neurotropic Impairments treated with meds

### PT Interventions

- Bed mobility time in 1<sup>st</sup> 3 hrs
- + Gait time in 1<sup>st</sup> 3 hrs
- + Advanced gait time in 1<sup>st</sup> 3 hrs

### General Interventions

- Days onset to rehab
- + LOS
- + Enteral feeding

### OT Interventions

- + Home management

### SLP Interventions

### Medications

- Other Antidepressant
- Old SSRIs
- + Atypical antipsychotics

# What Makes PBE Study Design Different?

---

- Ability to characterize the patient more fully
- Ability to characterize interventions/treatments/process of care more fully
- Not able to achieve through use of administrative databases or patient record review alone
- Involves front-line clinicians
- Adds clinical validity
- Helps identify what happens in actual practice

# Discover Best Practices using PBE

- **Manufacturers**: PBE studies show comparative effectiveness of products and are less expensive to conduct than RCTs
- **Practitioners**: PBE data allow investigation of effects of combinations of treatments on outcomes, controlling for patient differences
- **Payers**: PBE data allow discovery of practices associated with better functional and clinical outcomes at lower cost