MINIMIZING VARIABILITY IN TRIALS THAT USE CLINICIAN-ASSESSED OUTCOME MEASURES

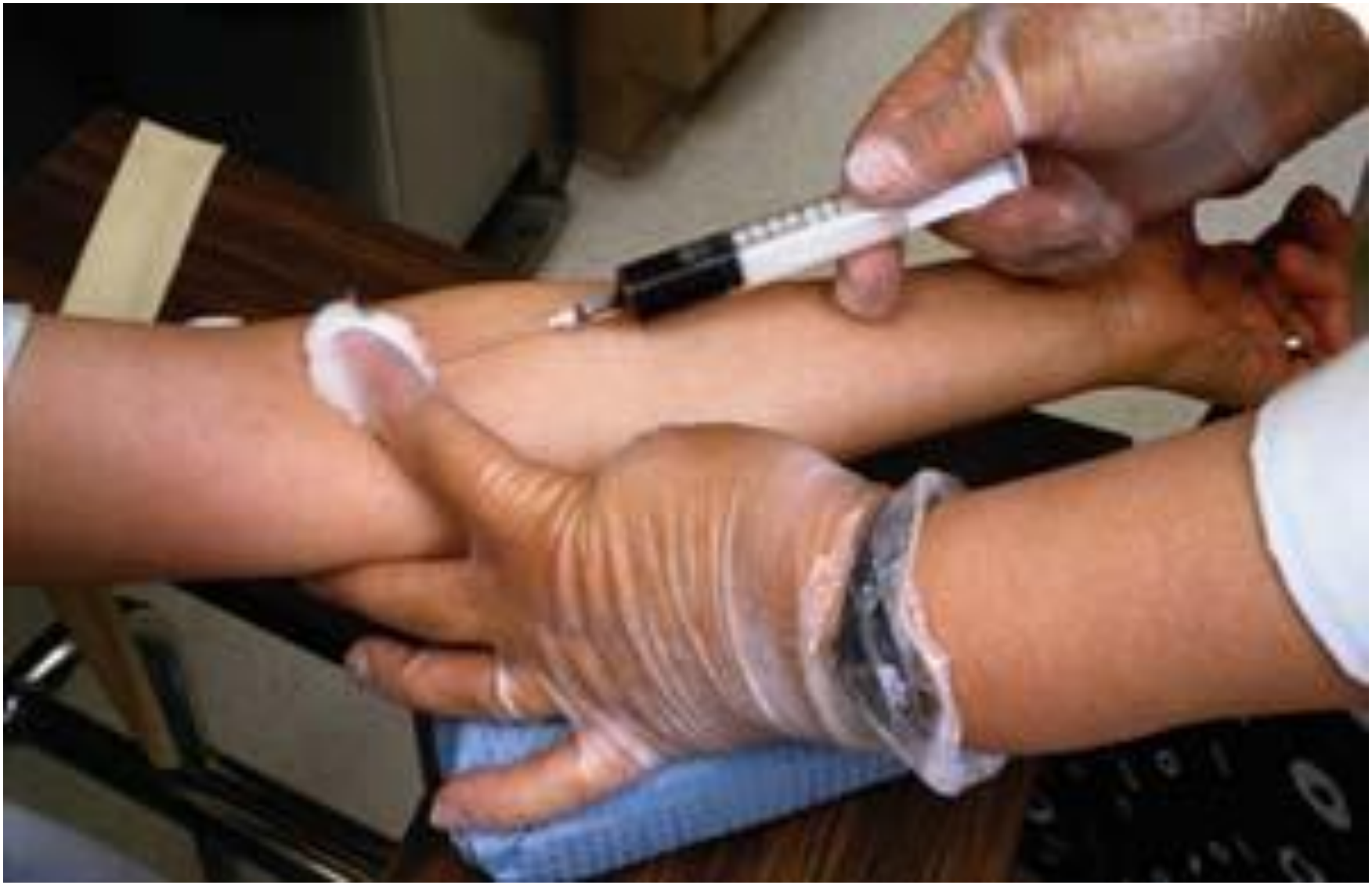
Harry Barnett

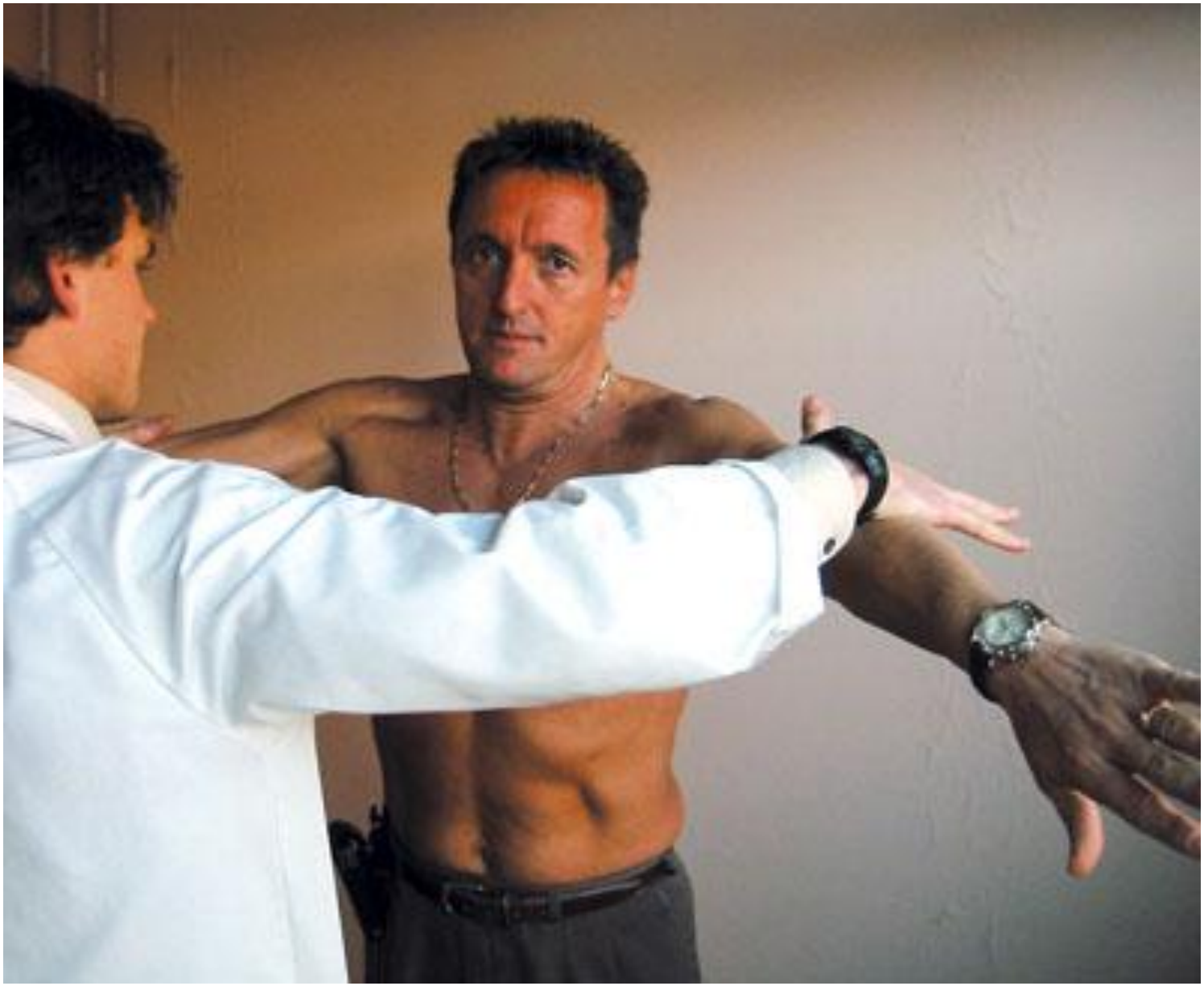
Managing Partner

Clinical Assistance Programs, LLC

What I Will Discuss Today

1. Introduce and roughly define clinician-assessed outcome measures
2. Explain why variability is a problem
3. Introduce and describe a process for minimizing variability - Outcomes Training
4. Offer a case study with findings





Clinical Trial Outcome Measures

1. Surrogate markers of disease
2. Imaging or histological endpoints
3. Clinician (and subject)-dependent assessments

Outcome Measures: Surrogate Markers of Disease

- Typically laboratory derived
- Quantitative
- Easily standardized (centralized lab)
- Examples: neutrophil count, PSA, cytokine levels

Outcome Measures: Imaging or Histological Endpoints

- Based on established measurements of accuracy
- Require standardization of techniques and criteria
- Can centralize reading and interpretation
- Examples: tumor response measured by MRI, cytology, radiologic endpoints, etc.

Outcome Measures: Clinician-Dependent Assessments

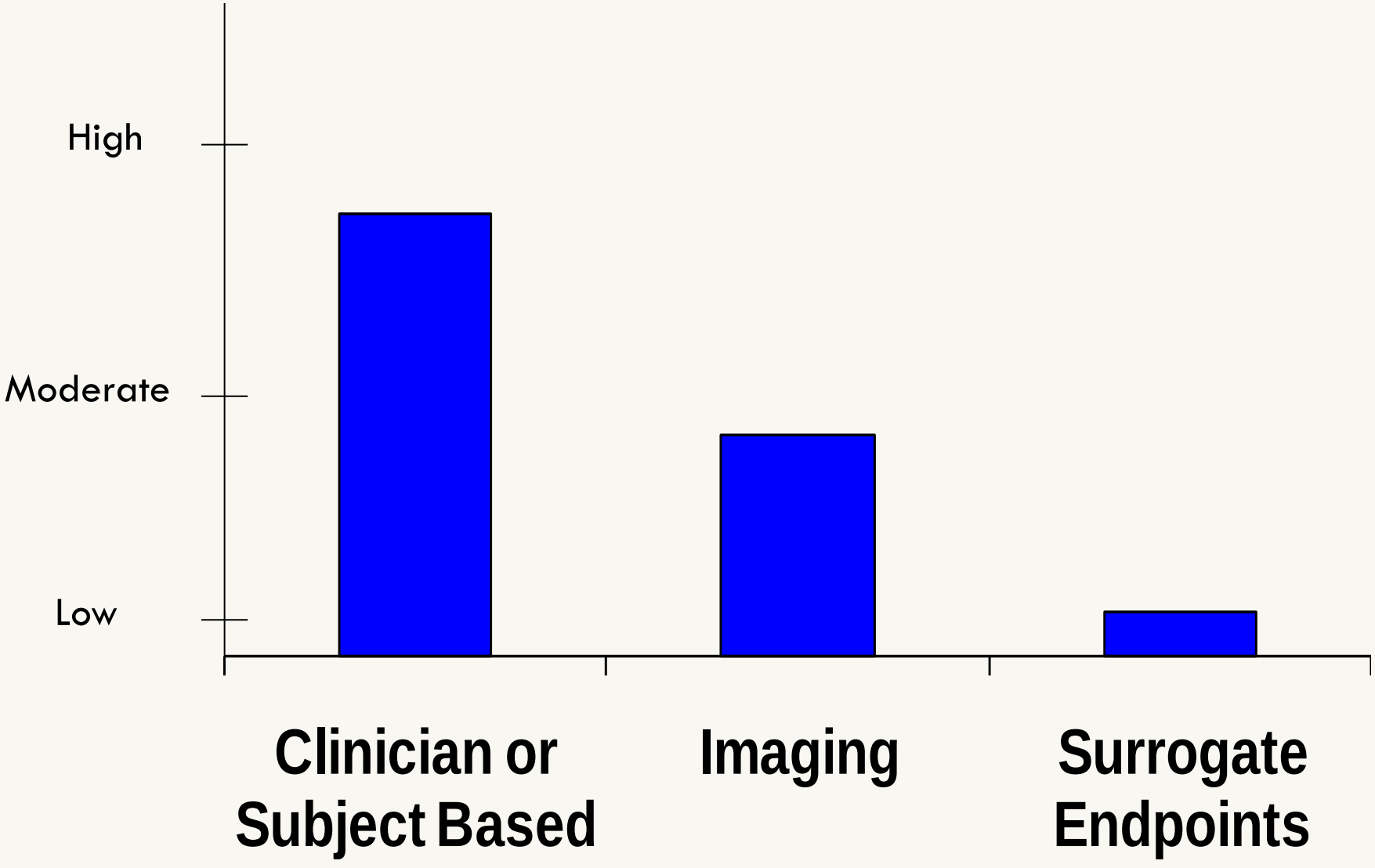
- Meaningful to patient status
- Often based on validated scales
- Applicable to a wide-range of indications
- Subjective and inconsistently applied
- Examples: neurological testing, rash or wound severity, arthritis range of motion, depression, xerostomia, visual acuity, etc.

Outcome Measures: Clinician-Dependent Assessments

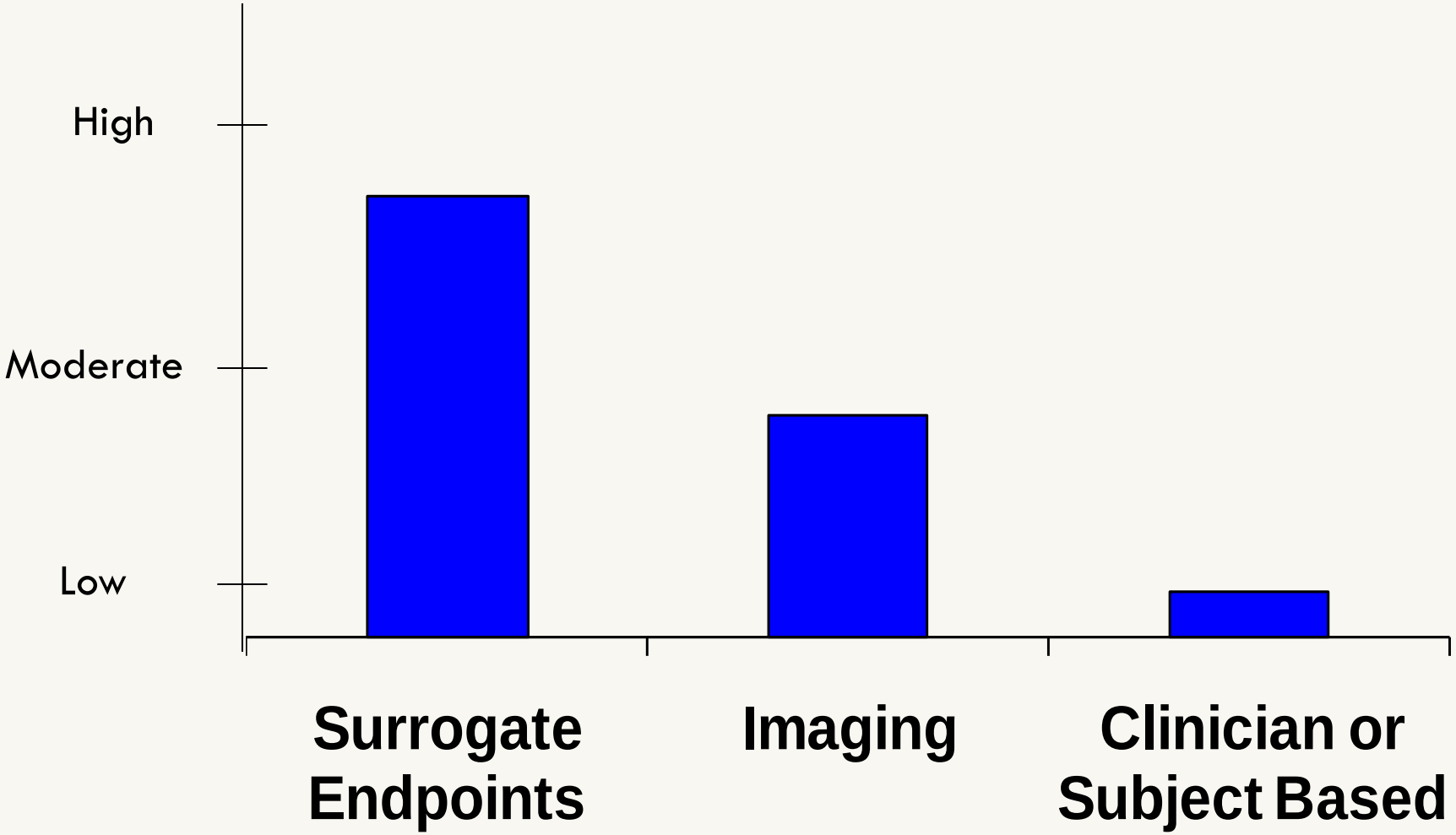
Increasing regulatory focus on functional/QOL outcome measures which are clinician-/subject-based

- Biochemical, physiologic and other effects must be accompanied by improvement in function or quality of life
- Examples: emphysema, spinal cord injury, arthritis

Frequency of Use in Efficacy Studies



Outcome Measure Accuracy



Factors that Contribute to Lack of Accuracy for Clinician-Dependent Outcome Measures

- Many outcome measures are not designed for clinical trials
- Protocol wiggle-room
- Subjective interpretations (how red is red?)
- Regional variability
- Inconsistencies using multiple scoring systems
- Multiple sites and assessors
- Assessor/site arrogance ("I/we know best")
- Standard outcome-related source documentation is not designed for clinical trials

Specialized Outcomes Training

What is it?

Why is it necessary?

“You ask for miracles. I give you….
the FDA”

FDA "Guidance"

The FDA maintains that comprehensive, consistently applied training is necessary to standardize trial conduct.

The Traditional Standard: Investigator Meeting

Reliance on Outcomes Training at Investigator Meetings is a Failed Strategy

- Multiple topics discussed in compressed format
- Attendees at the IM are often not the people who will perform the outcome assessments
- Changes in the PI (principal investigator) or other site personnel
- IMs often occur well in advance of site activation and first patient accrual – the learning curve plummets
- Training typically occurs at the end of the meeting when people are less attentive

The Starbucks Approach

The Endpoint: Café Latte

Café Latte Recipes on Google

236,000!!!

Consistency and Uniformity

How Do They Do It?

- Select a clear, measurable, meaningful endpoint
- Define and standardize ingredients, utensils, and appliances
- Rigorous training on how to perform functions
- Constant QA and feedback

The Starbucks Approach for Clinical Trials

- Optimize study design/endpoint selection
- Standardize essential tools and equipment
- Onsite Assessor screening, training, and competency assessment
- Develop clinician-friendly source data capture instruments – source document worksheets
- Real-time data review and analysis – clinical reality check

Ideal Clinical Endpoint

- Accurately reflects severity and course of objective and subjective clinical changes
- Easy to teach and use
- Does not require complex measurements
- Sensitive enough to discriminate treatment efficacy
- Clinically meaningful and easily interpretable endpoints for clinicians, patients, sponsors, and FDA
- Balances regulatory/medical/business interests

Greg Jay, M.D.

BROWN

Standardizing Essential Tools and Equipment

- Consider everything
- Be proactive
- Regional variability

Onsite Assessor Training - Trainers

- Trainers must be clinically qualified, credible and highly respected
- Trainers must be trained on each study protocol
- Trainers must remember that the training is all about the study data quality

Onsite Assessor Training

- Important to standardize the assessment methodology and grading criteria
- Assessors should be trained to assess using the same technique, same standards, same equipment, same order, same time frame, same source documents, etc.
- Training *without* competency evaluation and continuous feedback is of reduced value

Collecting the Endpoint: Source Worksheets

- Protocol-specific
- Provide sites with source documentation for the endpoint assessments
- Enable the tracking of subjects throughout the study
- Assist in ensuring that the assessments occur in the proper order (e.g., patient-reported *then* examination)
- Minimizes data collection and calculation errors

Neurological Level

	R	L
Sensory	☐	☐
Motor	☐	☐

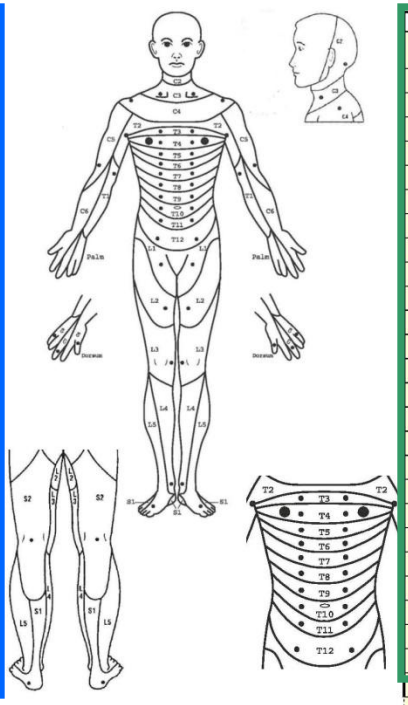
Single Neurological Level ☐

SENSORY CLINICAL EXAM

0	1	2	NT
Absent	Impaired (hyperesthesia or hypoesthesia)	Normal	Not Testable

** Please note that the Right and Left sides are grouped! Record your light touch and pin prick scores carefully **

Right Side		
Light Touch		Pin Prick
	C2	
	C3	
	C4	
	C5	
	C6	
	C7	
	C8	
	T1	
	T2	
	T3	
	T4	
	T5	
	T6	
	T7	
	T8	
	T9	
	T10	
	T11	
	T12	
	L1	
	L2	
	L3	
	L4	
	L5	
	S1	
	S2	
Light Touch Right Sub-total (A)		Pin Prick Right Sub-total (B)

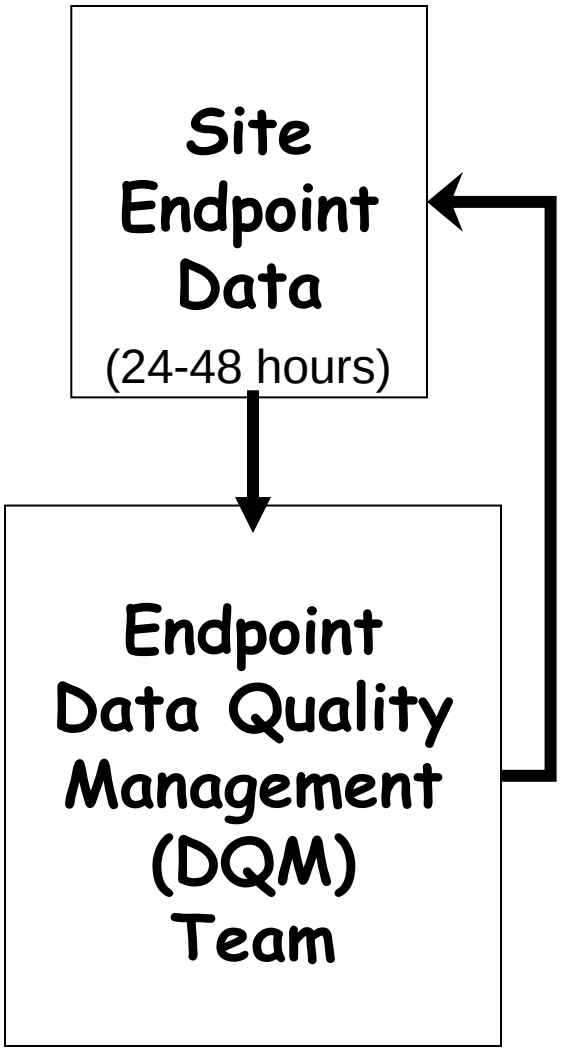


Left Side		
Light Touch		Pin Prick
	C2	
	C3	
	C4	
	C5	
	C6	
	C7	
	C8	
	T1	
	T2	
	T3	
	T4	
	T5	
	T6	
	T7	
	T8	
	T9	
	T10	
	T11	
	T12	
	L1	
	L2	
	L3	
	L4	
	L5	
	S1	
	S2	
Light Touch Left Sub-total (C)		Pin Prick Left Sub-total (D)

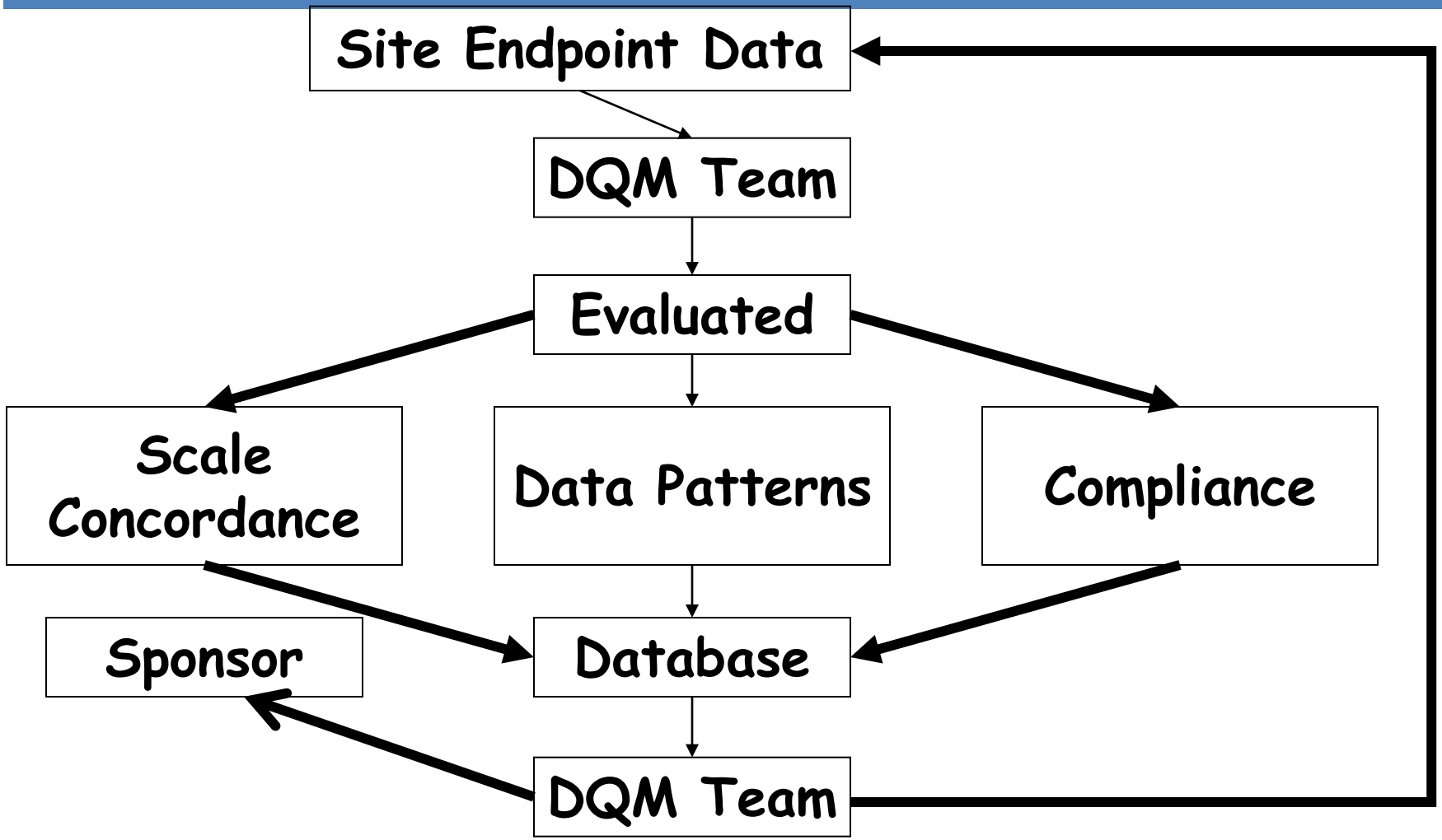
Data Quality Review: The Traditional Standard

- Collect data on traditional or electronic CRFs during entire study
- Transfer data to sponsor's data management group
- Lock database at the end of study – often many years after study commencement
- Analyze data
- Discover problems

The New Paradigm: Real-Time Data Quality Review



Real Time Data Quality Review: Feedback Loop



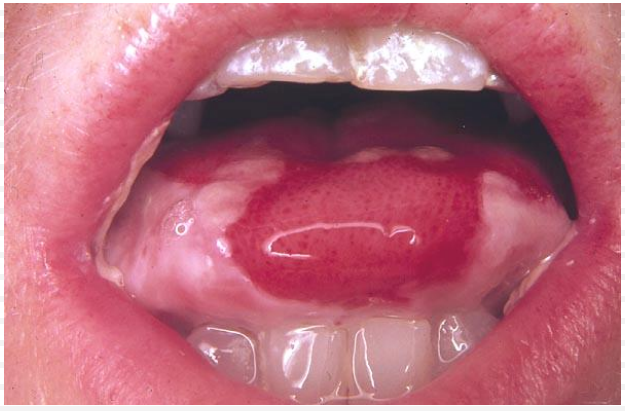
Benefits of Real-Time Data Quality Review

- Confirms findings during onsite training and identifies deficiencies
- Provides valuable, independent, expert analysis of outcomes data during study
- Identifies systemic problems, toxicities, dosing compliance, formulation tolerability, etc.
- Permits data modeling and trend assessment
- Facilitate the collection of quality data specifically related to the efficacy endpoints
- Provide continuous data review and communication with the sponsor and study sites

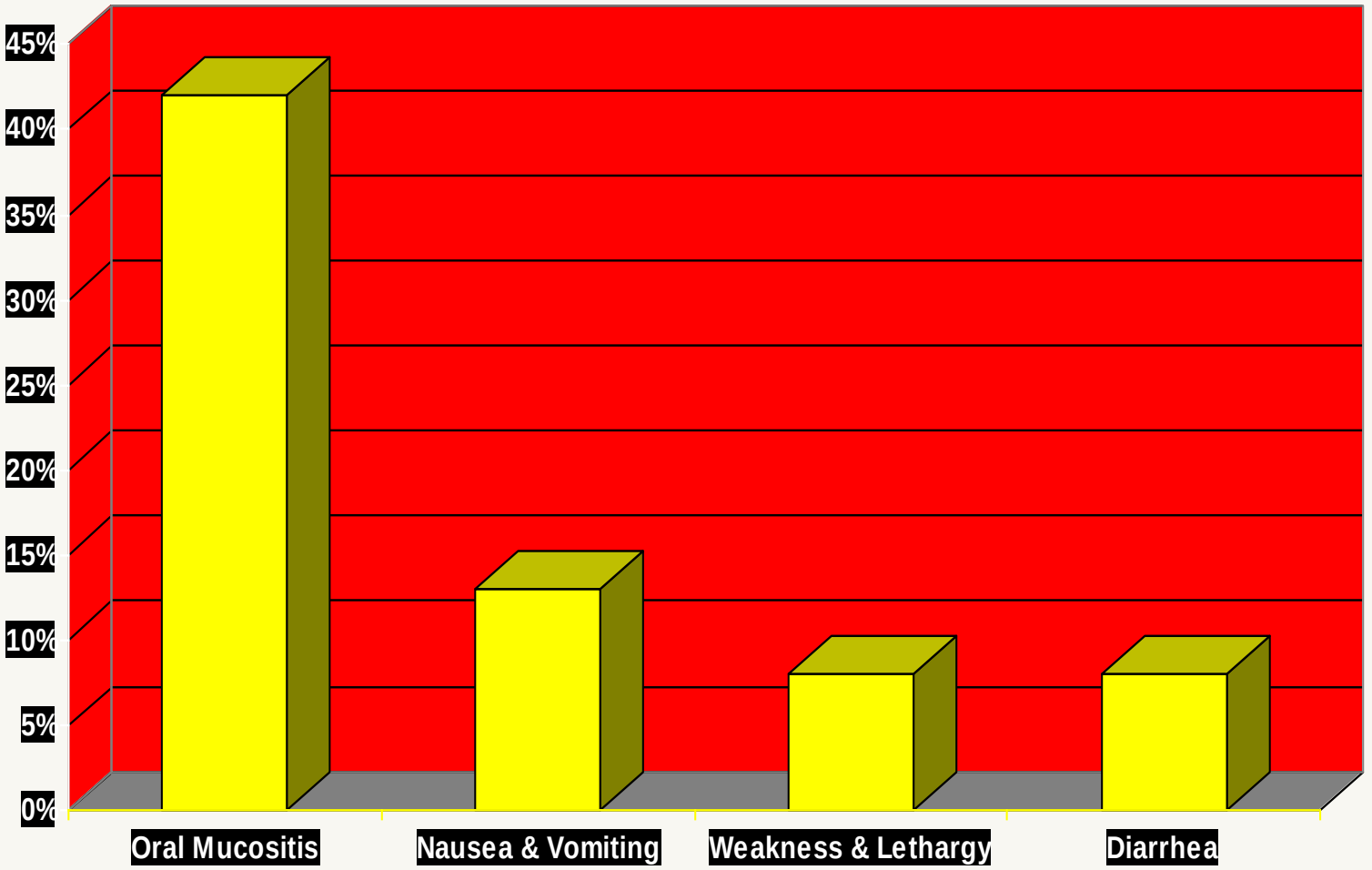
Real-time Data Quality Review: The Family Oral Care Analogy

Case Study

Amgen's Phase 3 Study of Kepivance® for Oral Mucositis

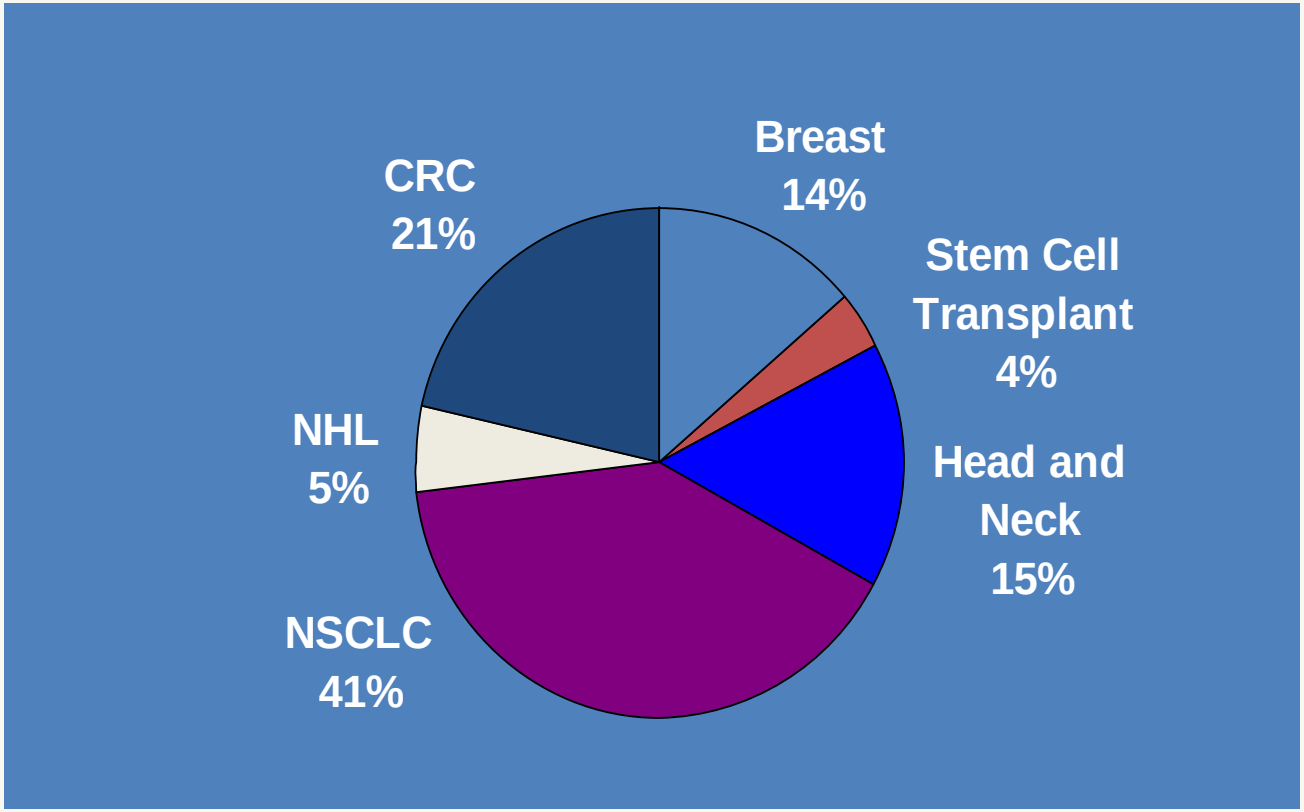


Oral Mucositis: Worst Complication of Ablative Chemotherapy



Adapted from Bell LA, Epstein JB, Rose-Ped A, Martin P, Fuchs HJ. Support Care Cancer. 2000;8:33-39.

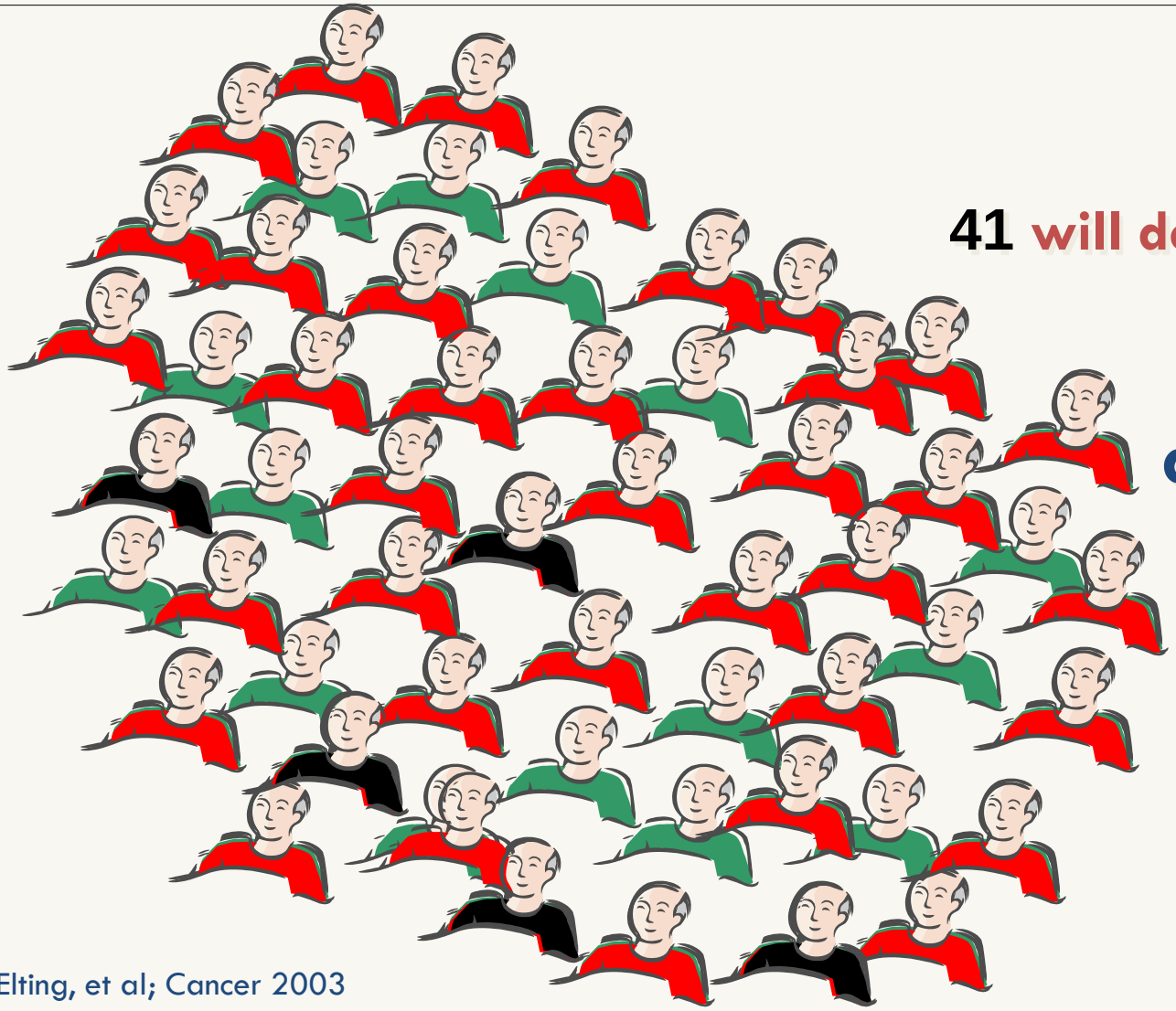
Close to 450,000 Patients Per Year Suffer from Mucositis During Cancer Therapy



- Stem cell transplant and radiation +/- chemotherapy for solid tumor (head and neck cancer, non-small-cell lung cancer) patients have the highest risk for severe mucositis
  - Mild, moderate, and severe mucositis can have serious clinical and economic consequences

Source: Mattson, Jack. Database 2003; NCI; Note: 400,000 patients in the US; CRC = colorectal cancer; NHL = Non-Hodgkin's lymphoma

For Every 55 Patients with Grade 3-4 Mucositis and Myelosuppression…



41 will develop infection …

and 5 will die.

Elting, et al; Cancer 2003

Case Study – Kepivance®

Overview

- Kepivance (KGF) was being tested in cancer patients receiving autologous BMT for ability to treat or prevent OM
- Previous studies had been confounded by inter-observer and inter-site variability
- Previous studies had operational issues that went uncorrected until nearly the end of the study
- No successful Phase III in the indication (many failures)

Case Study – Kepivance®

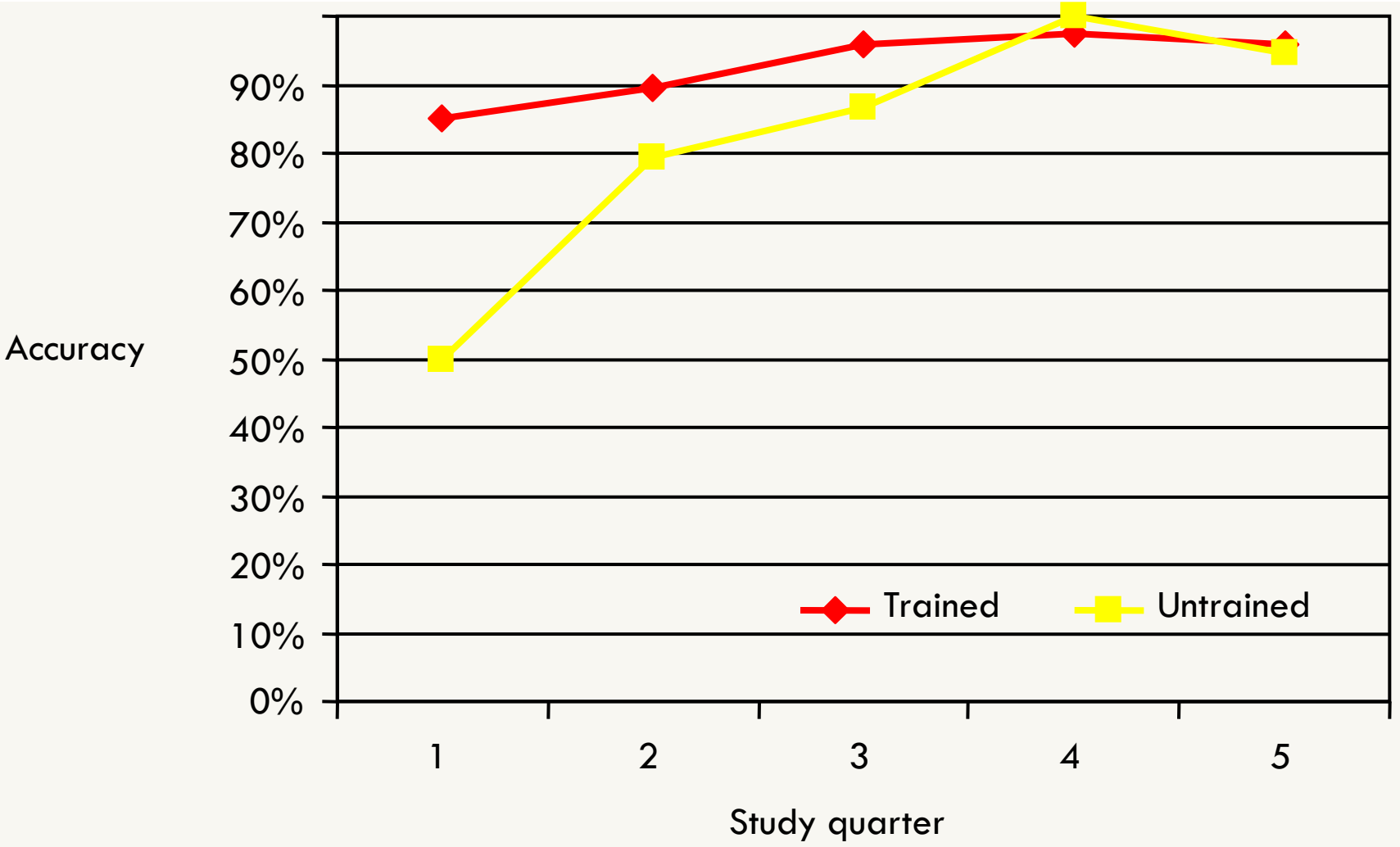
Actions

- Standardize method of examinations and scoring including use of source worksheets
- On-site training required at time of site initiation
- Continuous data review for abnormal trends and consistency
- Early recognition of, and intervention to address, site/investigator issues
- Immediate feedback provided to the sites
- Real-time inquiries fielded regarding study assessments
- Refresher training provided throughout the study

Accuracy Comparison

- Overall accuracy with IM training alone: 62.87%
- Overall accuracy with on-site training: 87.95%

Accuracy: Trained and Untrained



Recap: Learning Objectives

- Selecting outcome measures in the design of clinical studies that will help get drugs to market faster
- Minimizing variability in clinical research involving the assessment of subjective clinical outcomes
- Improving the accuracy and consistency of outcomes data during a clinical study

THANKS AND QUESTIONS

THANKS TO:

- Steven T. Sonis, DMD, DMSc
- Charlotte Harrison