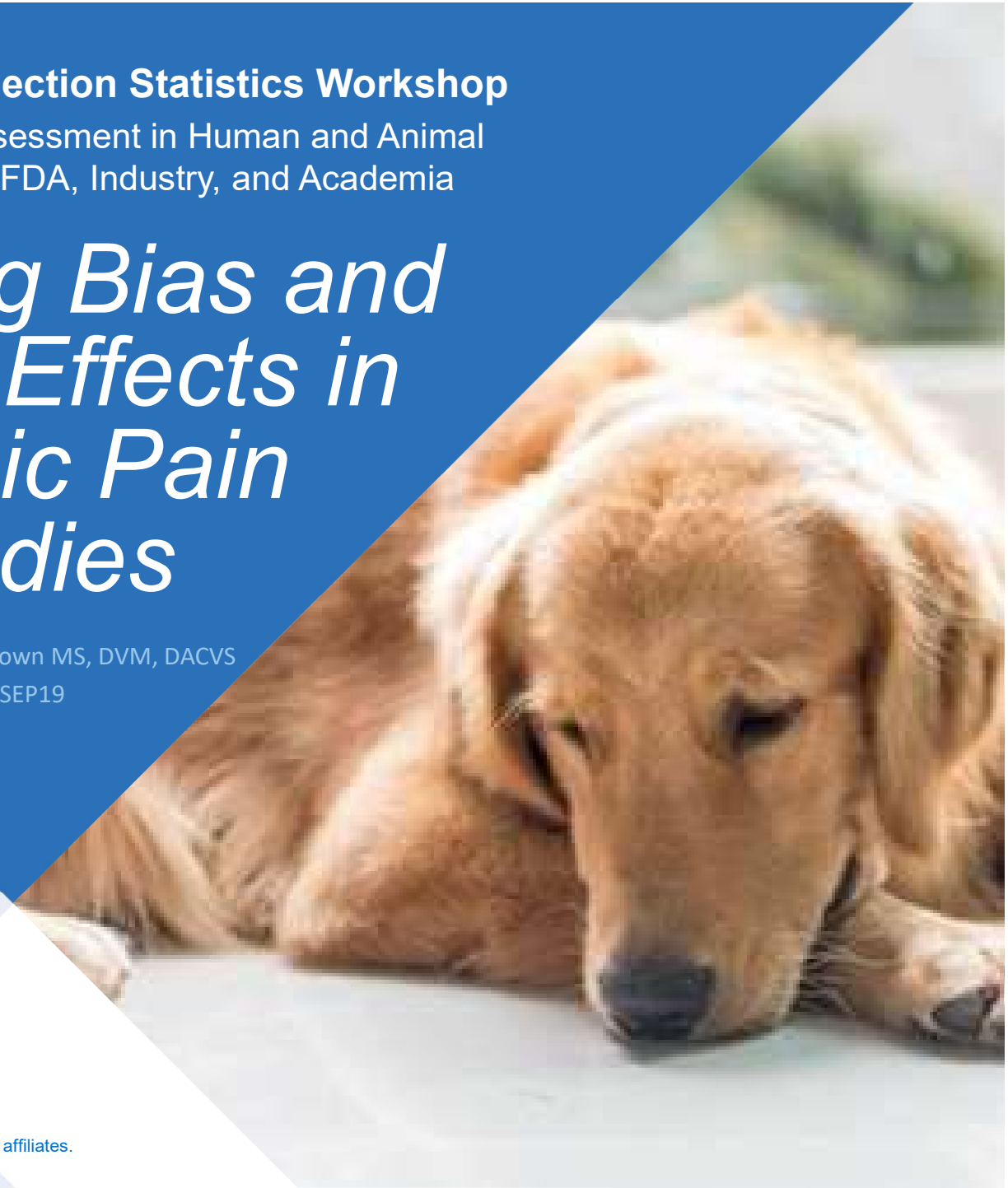
ASA Biopharmaceutical Section Statistics Workshop

PS6f - Challenges in Pain Assessment in Human and Animal Studies: Perspectives from FDA, Industry, and Academia

Minimizing Bias and Placebo Effects in Chronic Pain Studies

Dorothy Cimino Brown MS, DVM, DACVS

25SEP19



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Systematic versus Random Error

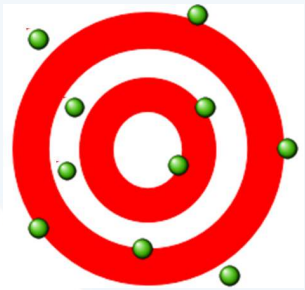
Random Error

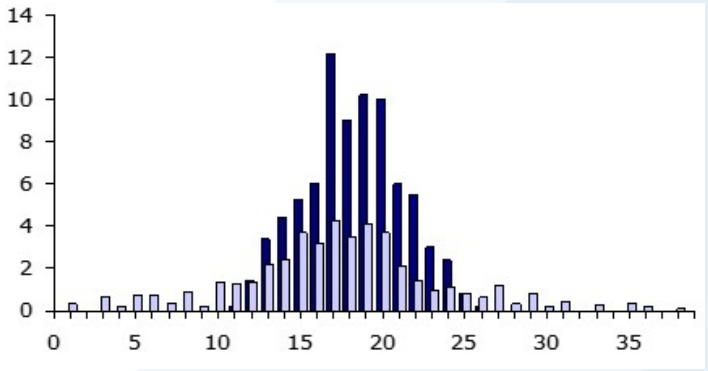
Chance leads to imprecise results

As more data is collected:

Average value approaches true value

Average error decreases





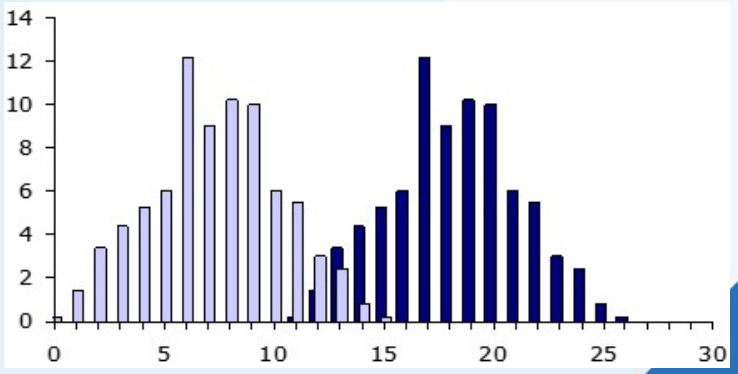
Systematic Error

Bias leads to inaccurate results

As more data is collected:

Average value does not approach true value

Average error stays the same



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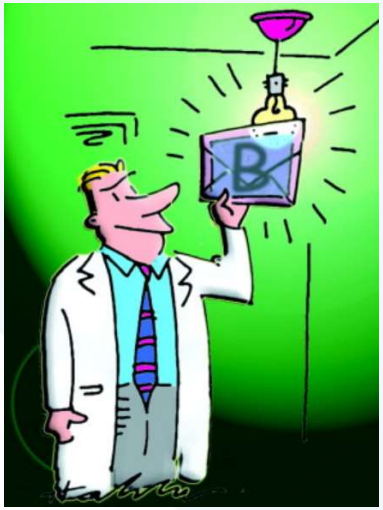
Selection vs Observation Bias

Allocation Concealment



THE LANCET • Vol 359 • February 16, 2002 • www.thelancet.com

Blinding (Masking)

Figure 2: **The authors blinded and masked**

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Randomization

Screening

Outcome Assessment

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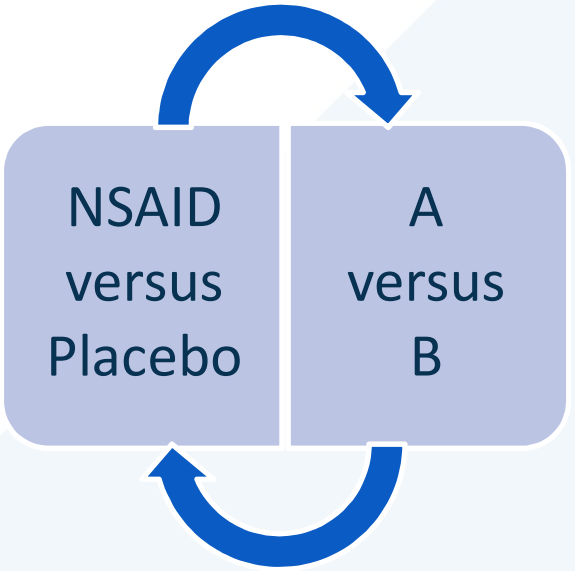
Allocation Concealment



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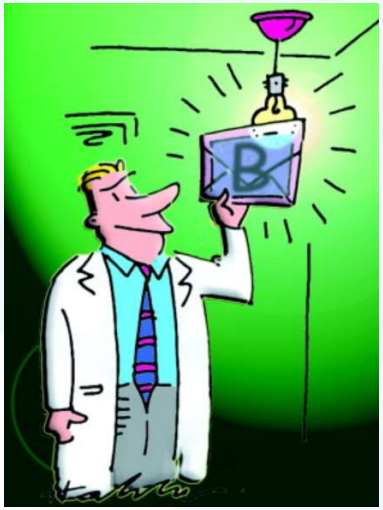
Selection vs Observation Bias

Allocation Concealment



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Randomization

Screening

Analysis

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Selection vs Observation Bias

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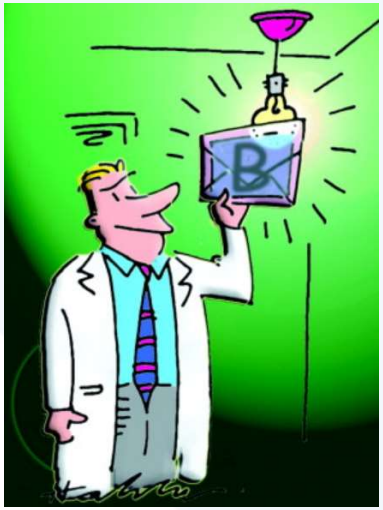

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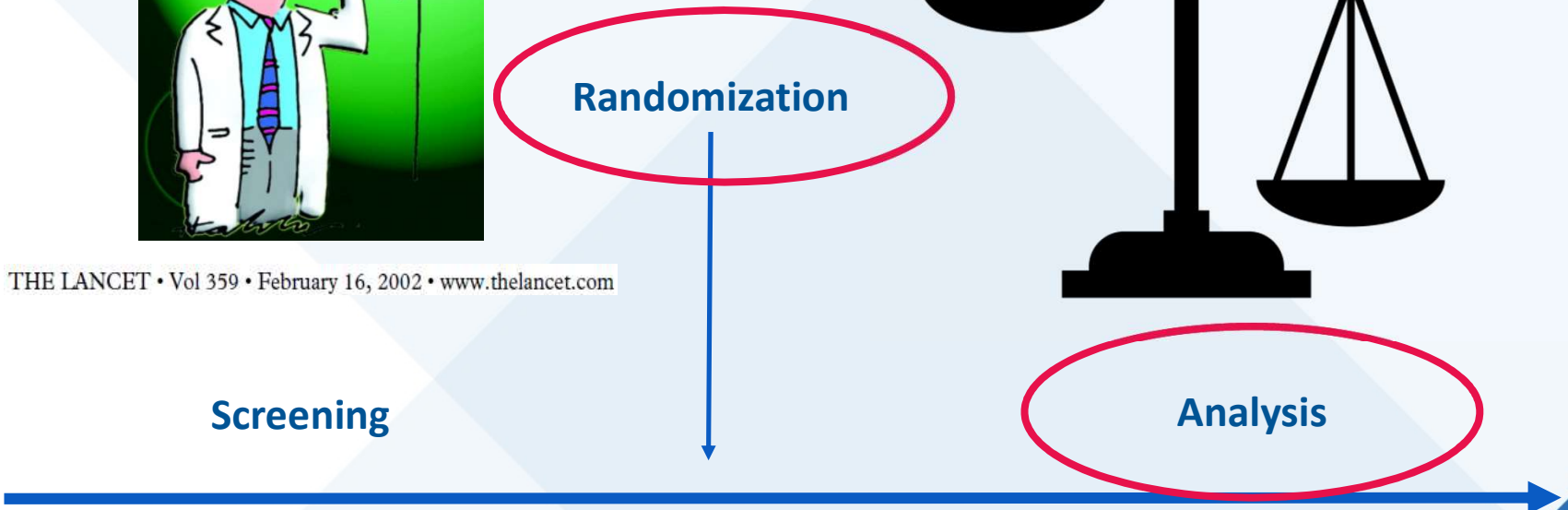

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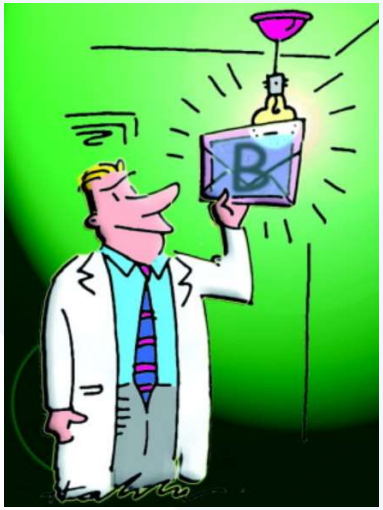
Always Possible

Allocation Concealment



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Randomization

Screening

Outcome Assessment

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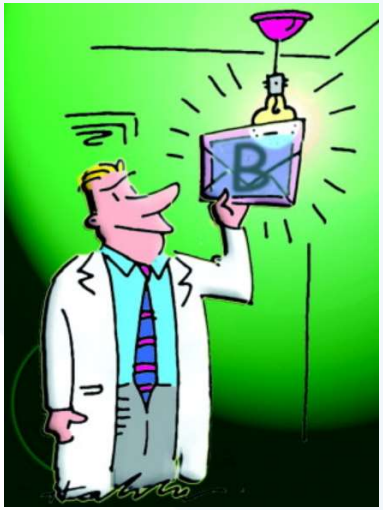
Always critical in chronic pain studies

Allocation Concealment



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Randomization

Screening

Outcome Assessment

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Blinding for Outcome Assessment

Subjective

Owner completed behavior based scoring systems

Veterinarian completed gait and palpation based scoring

Objective

Kinetic & kinematic gait analysis

Activity monitoring

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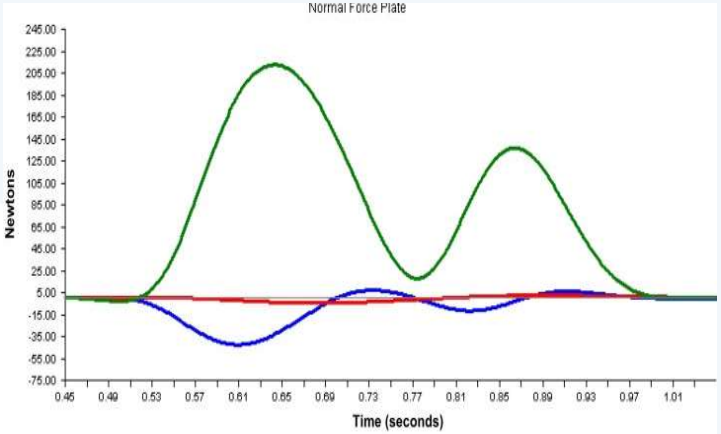
The Subjectivity of the Objective Outcomes



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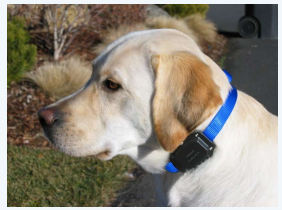
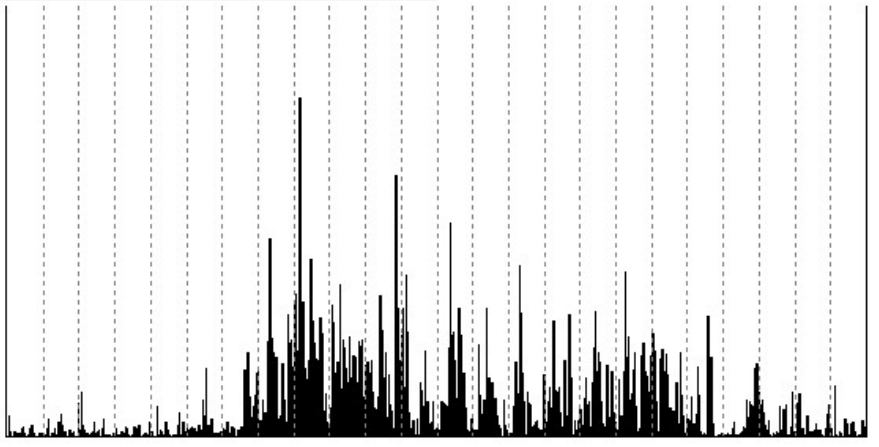
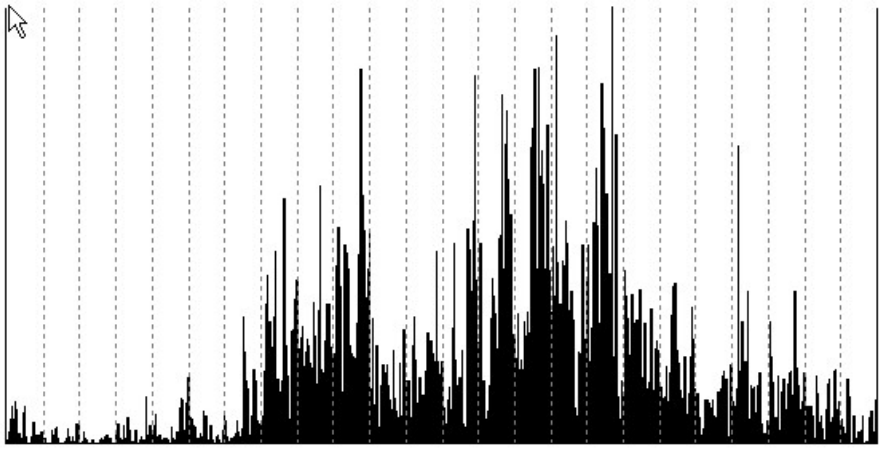
The Subjectivity of the Objective Outcomes



Before NSAIDs



Treated with NSAIDs



Date Stam	Time Stam	Activity Data:
10-Jun-04	5:45:00	0
10-Jun-04	5:46:00	0
10-Jun-04	5:47:00	0
10-Jun-04	5:48:00	0
10-Jun-04	5:49:00	0
10-Jun-04	5:50:00	0
10-Jun-04	5:51:00	0
10-Jun-04	5:52:00	0
10-Jun-04	5:53:00	0
10-Jun-04	5:54:00	0
10-Jun-04	5:55:00	0
10-Jun-04	5:56:00	0
10-Jun-04	5:57:00	0
10-Jun-04	5:58:00	0
10-Jun-04	5:59:00	0
10-Jun-04	6:00:00	11
10-Jun-04	6:01:00	1355
10-Jun-04	6:02:00	249
10-Jun-04	6:03:00	316
10-Jun-04	6:04:00	569
10-Jun-04	6:05:00	665
10-Jun-04	6:06:00	1159
10-Jun-04	6:07:00	102
10-Jun-04	6:08:00	305
10-Jun-04	6:09:00	206
10-Jun-04	6:10:00	305

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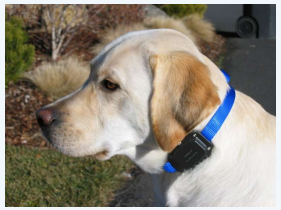
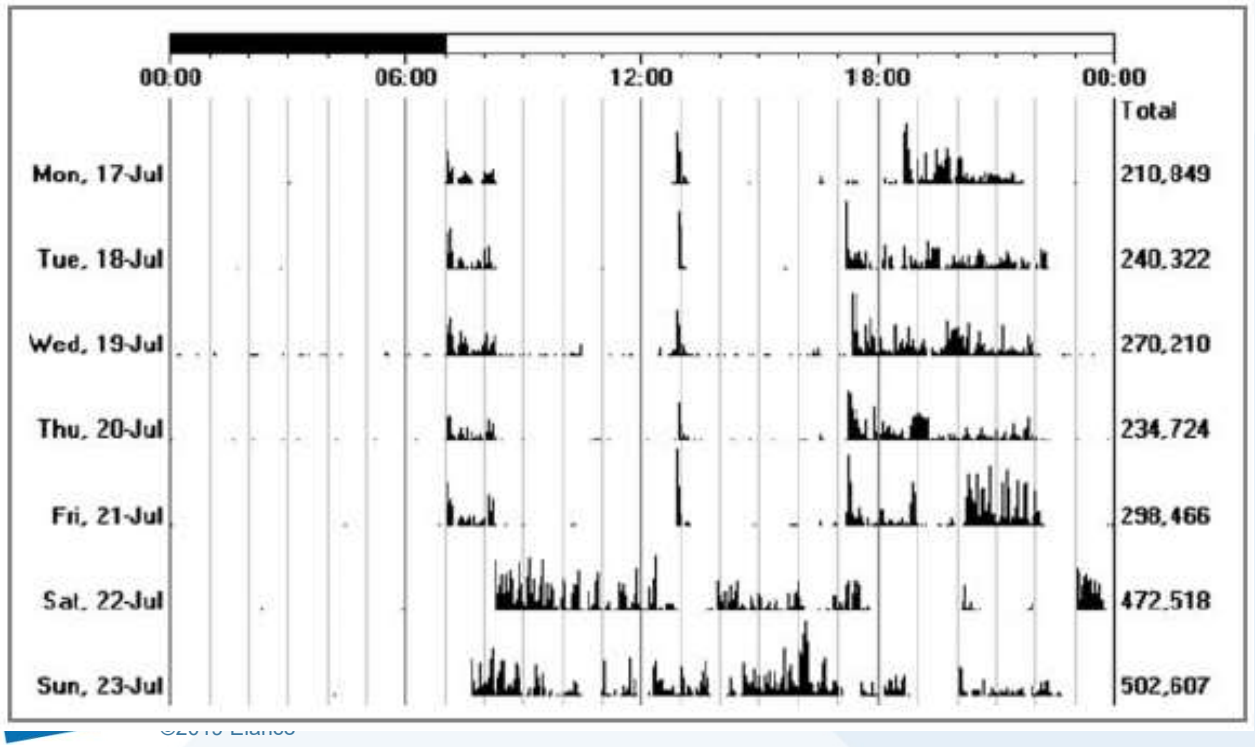
The Subjectivity of the Objective Outcomes



Day	Activity count
Mondays	182,076 (58,495 – 635,145)
Tuesdays	179,281 (62,268 – 767,268)
Wednesdays	187,478 (57,254 – 833,070)
Thursdays	174,696 (52,440 – 708,213)
Fridays	204,961 (52,760 – 750,630)
Saturdays	216,147 (57,338 – 827,354)
Sundays	231,335 (64,276 – 588,536)



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10-Jun-04	5:51:00	0
10-Jun-04	5:52:00	0
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10-Jun-04	5:55:00	0
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10-Jun-04	5:59:00	0
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10-Jun-04	6:07:00	102
10-Jun-04	6:08:00	305
10-Jun-04	6:09:00	206
10-Jun-04	6:10:00	305

What are Placebo Effects?

Animals in the placebo control arm of a study improve

Treatment Arm

Pain/Lameness

Placebo Arm

Pain/Lameness

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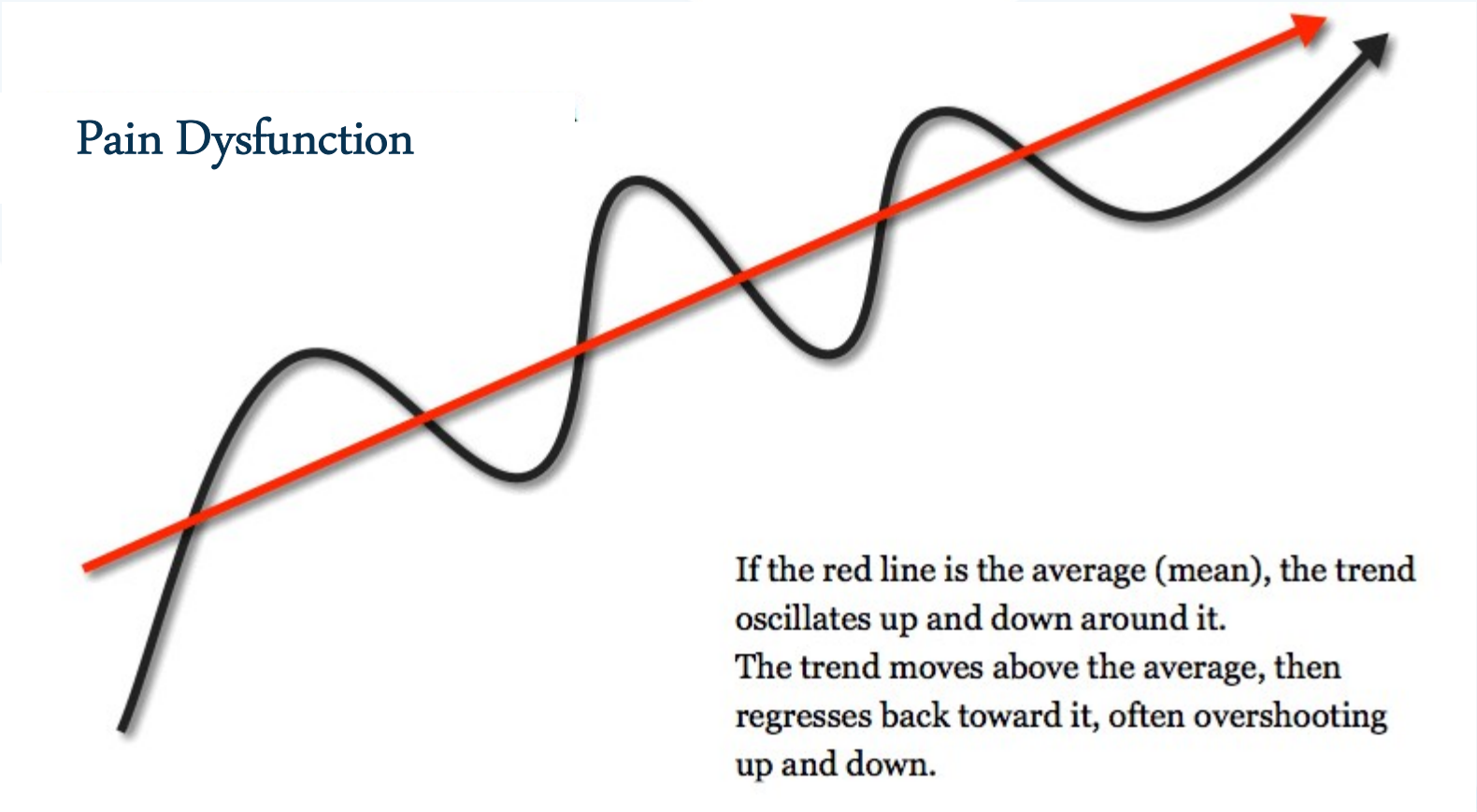
Expectation vs. Actual Improvement

Regression-to-the-Mean



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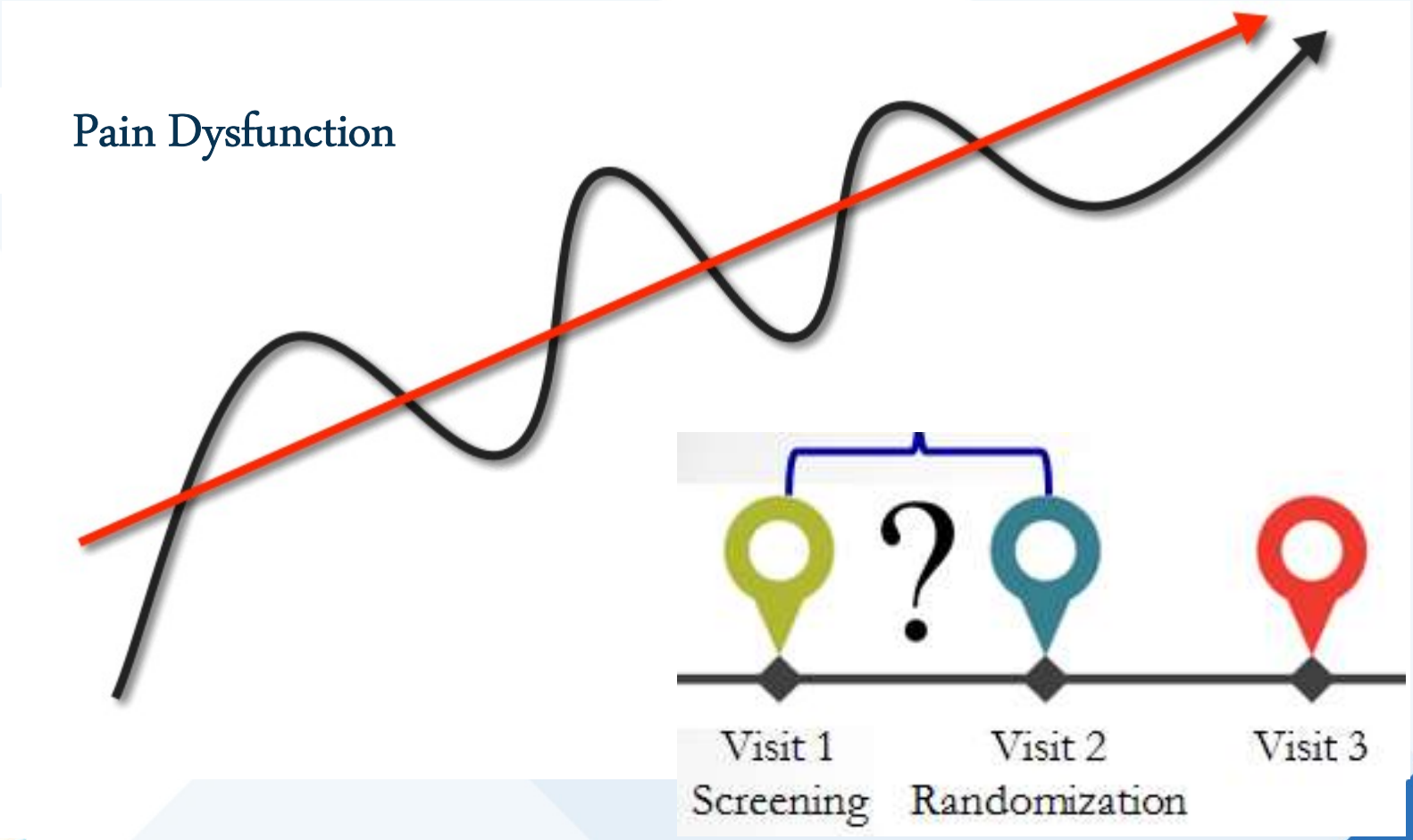
Minimizing Regression-to-the-Mean



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Minimizing Baseline Inflation

- Minimum score required for a responders analysis
- Awareness of the cut-off for enrollment can consciously/unconsciously and directly/indirectly affect the baseline score

Owners communicating cut-offs

Site pressures

- Timelines
- Owner satisfaction
- Site financial incentives

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Minimizing Baseline Inflation

- Randomizing all patients but specifying the primary efficacy analysis will only include dogs with a minimum baseline score
- Keeping investigators, data collectors, and owners blinded to specific baseline inclusion criteria
  - A lot of dogs are failing at their screening visit
  - Unblinded phone screener – fewer dogs fail at the blinded in-hospital screening
- Scripted owner and study personnel interactions

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Limiting Baseline Variability

- Including only patients with <25% variation in daily scores during a 7 day baseline period

- Using an average of daily scoring as opposed to retrospective weekly (or longer) assessment

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PAIN® 155 (2014) 1622–1631

PAIN®

www.elsevier.com/locate/pain

Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: An ACTTION study

A higher variability in the patient-reported baseline 7-day pain diary identified patients with a greater likelihood of response in the placebo group, without affecting the likelihood of having a response to the active medication treatment

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‘Expectation’ Placebo Effects

- Expectation for + effect increases
  - With an active control arm in the study
  - As the number of study arms increases

- Consider the type of intervention

Annals of Internal Medicine

REVIEW

Effectiveness and Implications of Alternative Placebo Treatments

A Systematic Review and Network Meta-analysis of Osteoarthritis Trials

Raveendhara R. Bannuru, MD, PhD; Timothy E. McAlindon, MD; Matthew C. Sullivan, BA; John B. Wong, MD; David M. Kent, MD; and Christopher H. Schmid, PhD

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Placebo Responders

Research Paper

PAIN®

Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials

- Patient age +
- Baseline pain +
- Discontinuation due to AEs +
- Opioid trials +

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PAIN®

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Unmeasured variables

?

Consent form wording

AEs

IVP description

Individual patient characteristics

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Placebo Run-in Periods

- Single blind
- Double blind, variable duration

- “Placebo responders” removed from study/analysis
- Decrease placebo response
- Increase assay sensitivity

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Placebo Run-in Periods

0271-0749/01/2106-0561/0
Journal of Clinical Psychopharmacology
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The Double-Blind Variable Placebo Lead-in Period: Results From Two Antidepressant Clinical Trials

Contemporary Clinical Trials
www.elsevier.com/locate/conclintrial

Psychiatry Research, 30:191-199
Elsevier

Enriched analgesic efficacy studies: An assessment by clinical trial simulation☆

The Introductory Placebo Washout: A Retrospective Evaluation

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Center for Veterinary Medicine (CVM)

Public Meeting: Incorporating Alternative Approaches in Clinical Investigations for New Animal Drugs

Johns Hopkins University – Montgomery County
9601 Medical Center Drive, Rockville, MD 20850

July 16, 2019

AGENDA

9:00 a.m.	**Session 1: Complex adaptive and other novel investigation designs**
10:45 a.m.	**Session 2: Real world evidence**
1:30 p.m.	**Session 3: Biomarkers and surrogate endpoints**
3:15 p.m.	**Session 4: Data from foreign countries**

Adaptive Designs for Clinical Trials of Drugs and Biologics

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

September 2018

F. Adaptations to Endpoint Selection

This is a design that allows adaptive modification to the choice of primary endpoint based on comparative interim results. Such a design might be motivated by uncertainty about the treatment effect sizes on multiple patient outcomes that would be considered acceptable primary endpoints by FDA. As with other adaptive designs, the adaptation rule should be prespecified, and statistical hypothesis testing methods should account for the adaptive endpoint selection. Because endpoint selection involves important clinical considerations, early discussion with the FDA review division is recommended when such designs are being considered.

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