From Statistician to Trusted Drug Development Leader

Statistics, Strategy, and Scientific Judgment

Gary A. Cline, PhD · Cline Consulting, LLC · November 2, 2026

ABOUT THE SPEAKER

25+ years from biostatistician to drug development leader

Industry

ClinTrials, Procter & Gamble, ICON Clinical Research, Celgene and AstraZeneca — teams and governance committees

Leadership

Data science and AI, strategic research and innovation, biostatistics, decision science, programming and data management

Today

Cline Consulting, LLC: legal expert and drug development consulting; Washington Statistical Society Board

Education

PhD Statistics, University of Kentucky; MS Mathematics, Eastern Kentucky University

THE THESIS

Technical expertise is necessary — but not sufficient

1 Methodological breadth

Choose the method that answers the question, not the one that is most familiar.

2 Effective communication

Make the complex actionable for clinicians, regulators, payers and executives.

3 Scientific judgment

Know the disease, the data and the limits of what an analysis can claim.

4 Decisions under uncertainty

Help multidisciplinary teams make informed choices when the data are incomplete.

THE ROAD MAP

Preparing early, middle and late in a career

Early

University of Kentucky · ClinTrials

- Study design and randomization
- Sample-size determination
- Programming and data quality
- Statistical logic and methodology
- Reproducible

Mid

Procter & Gamble · ICON

- Hone the core skills
- Broaden across functions
- Apply early insights to regulators, payers and partners
- Lead teams and standards

Late

Celgene · AstraZeneca · Consulting

- Integrate across development stages
- Integrate across therapeutic areas
- Govern investment decisions
- Serve as independent expert

PART 1 OF 3

Early career

Eastern Kentucky University · University of Kentucky · ClinTrials

Build the foundation: study design, randomization, sample size, programming, data quality, statistical logic and reproducible documentation.



Yes, there will be math in the finals..This is math class.

EARLY CAREER

What teaching undergraduate math teaches you

Translation
Explaining math to people who don’t think like you

Understanding
You don’t truly know a topic until you teach it

Reading the room
Spotting confusion and adjusting in real time

Composure
Handling the question you can’t answer, honestly

Empathy
Delivery shapes whether people can take it in

Structure
Building a session around a few key points

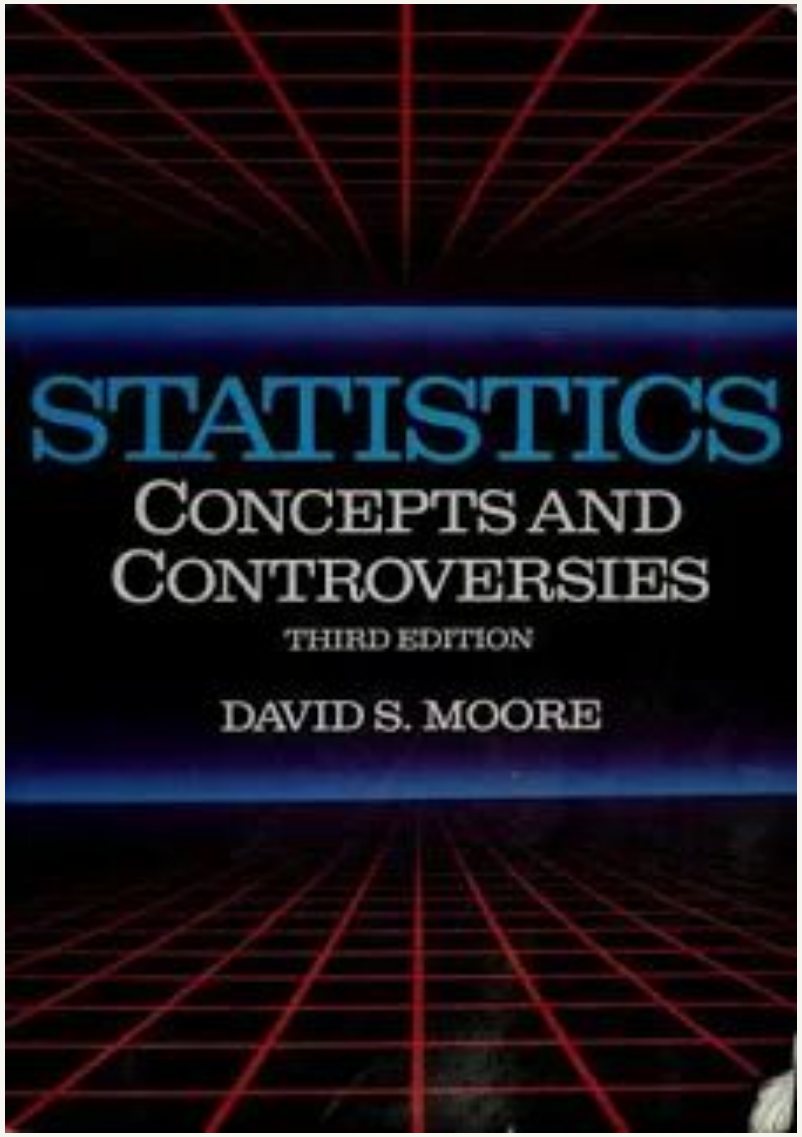
Judgment
Fair decisions and uncomfortable conversations

Prioritization
Balancing teaching, coursework and research

Takeaway: teaching turns a technical expert into a communicator.

Understand and Explain the Basics

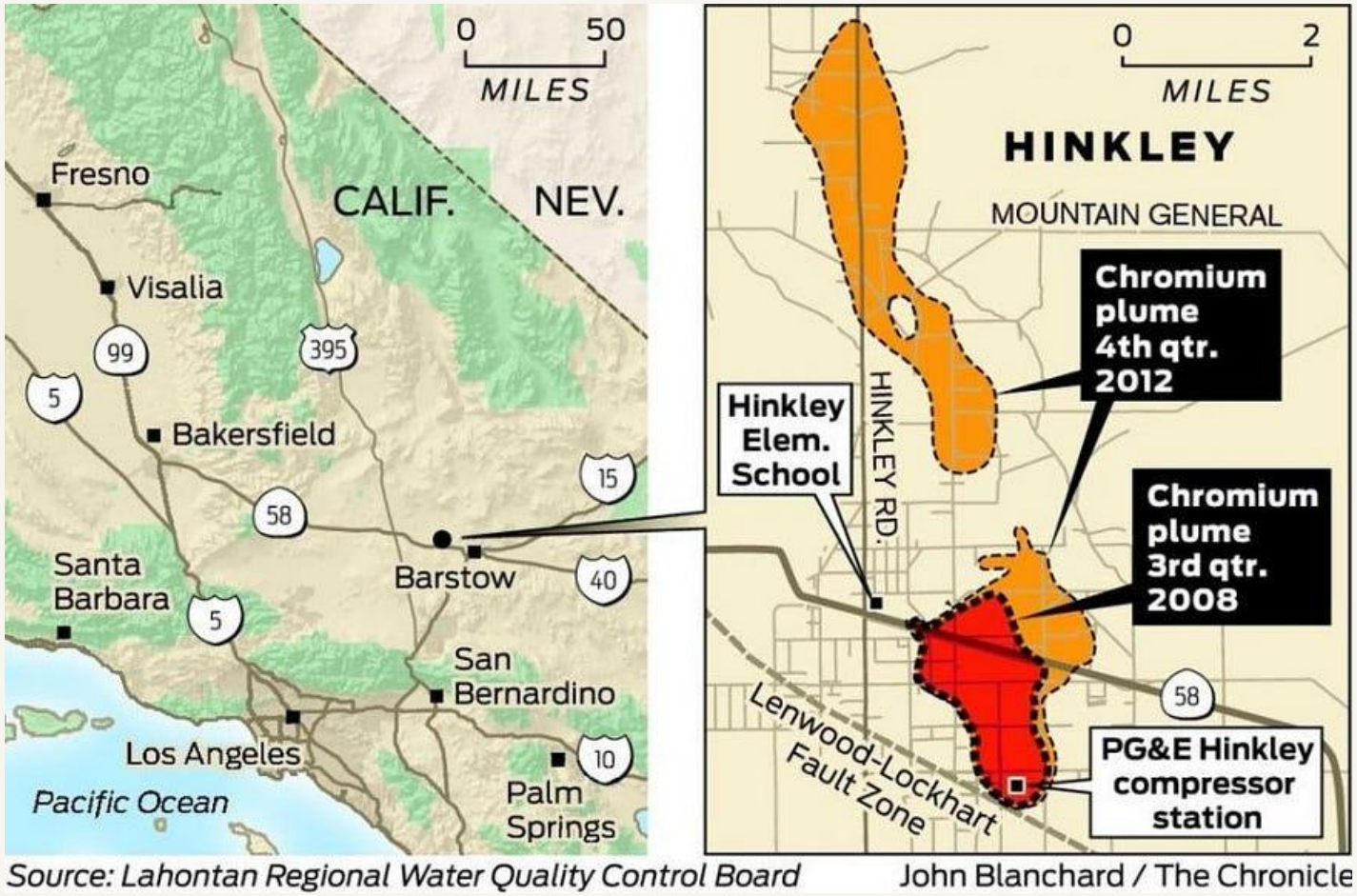
- How to interpret the information around us
- What assumptions were made in the interpretation





Frontline: "Who's Killing Calvert City?" (PBS, June 20, 1989). [1, 2]

Between 1952 and 1964, hexavalent chromium, Cr(VI), was released into groundwater from the Pacific Gas and Electric Company (PG&E)





1993 action led to a movie in 2000

EARLY CAREER · UNIVERSITY OF KENTUCKY

Cancer near the factories: is it real?

The problem

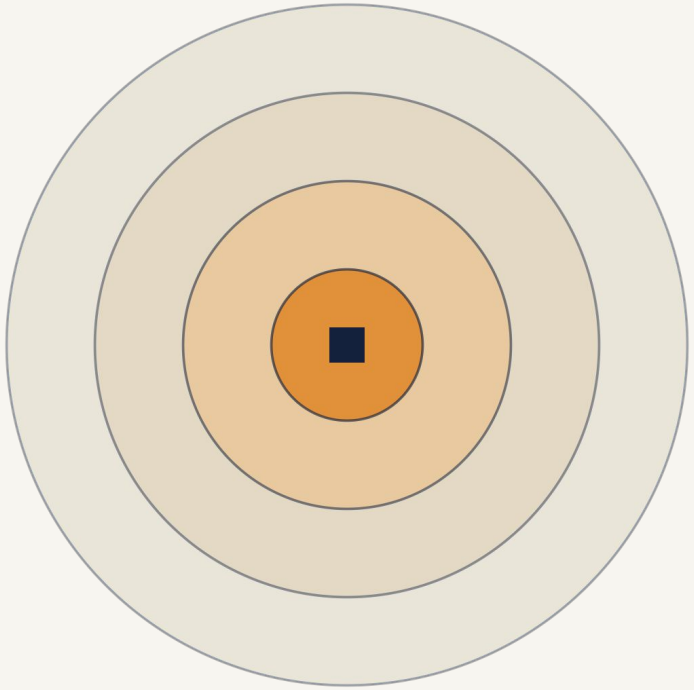
A rise in certain cancers around industrial plants in Calvert City, Kentucky.

The solution

Putative-source statistics on Kentucky Cancer Registry data: concentric distance bands, testing whether risk falls with distance, following Stone's approach (Statistics in Medicine, 7, 649-660 (1988))

Learning

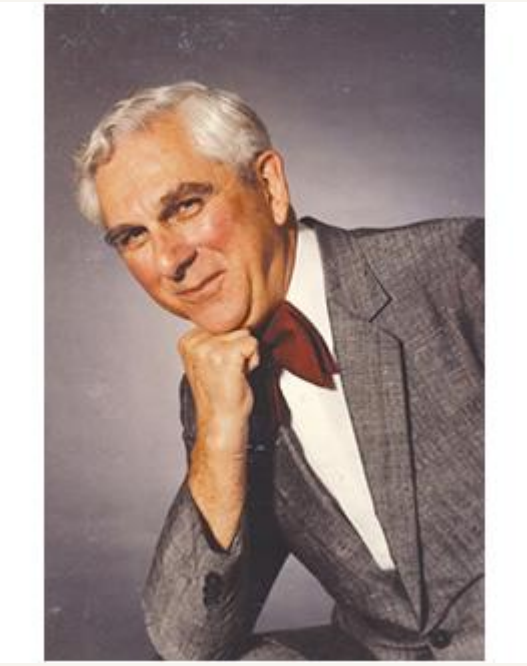
- Establishes association not causation … consider extraneous variables
- Reproduce results independently



Schematic: distance bands around one source

Dr. Richard L. Anderson (1915–2003)

- Founding chair of UK Statistics (1967–79) after helping build NC State's program with Gertrude Cox
- WWII Statistical Research Group at Princeton; coauthored *Statistical Theory in Research*
- Influenced early statistical software: SAS, BMDP, IMSL
- Co-founded Statistical Consultants of Lexington (1978), which later merged into ClinTrials; retired 1998
- ASA President (1982) and Founder's Award (1992): "the success of his students was his legacy"
- **Question Everything!**



EARLY CAREER · CLINTRIALS · STATISTICAL LOGIC

What should we do?

Topic	Why it mattered
Type III sums of squares	In unbalanced multicenter data, Type I results depend on term order; Type III tests each effect adjusted for all others.
ICH E9 implications	Pre-specify the model, the handling of center and interaction, and the primary hypothesis.
Adjust for site and interactions	Accounting for site effects and efficiency
Interpret interactions and when to do them	Differential treatment effects
Understanding type 1 error via simulation	Deeper distribution understanding
Permutation tests always?	Not always
Conservative approaches	When in doubt, choose the analysis a skeptical reviewer cannot undo.
Assumptions and standardization	Check them, document them and apply them the same way every

Original Contribution

FREE

Diaspirin Cross-Linked Hemoglobin (DCLHb) in the Treatment of Severe Traumatic Hemorrhagic Shock

A Randomized Controlled Efficacy Trial

Cite Permissions Metrics

JAMA
Published Online: November 17, 1999
1999;282;(19):1857-1864.
doi:10.1001/jama.282.19.1857

- An exception to informed consent was used when necessary.
- Early neutropenia signal by DSMB
- How to share with sponsor and follow E9 and SOPs?
- At 28 days, 24 **(46%)** of the 52 patients infused with **DCLHb died**, and 8 (**17%**) of the 46 patients infused with the **saline solution died** ($P = .003$).
- At 48 hours, 20 (38%) of the 52 patients infused with DCLHb died and 7 (15%) of the 46 patients infused with the saline solution died ($P = .01$).

The efficacy and safety of Dermagraft in improving the healing of chronic diabetic foot ulcers: results of a prospective randomized trial

FDA

- **"a modified (after the interim analysis) statistical plan specified** that (1) the effectiveness analyses would be based **only on the patients with ulcers greater than 6 weeks in duration at the time of the screening visit** and (2) the **primary endpoint would be analyzed using Bayesian statistical methods**."

Challenge

- During the advisory panel review, FDA review teams challenged the sponsor's application of a **one-sided Pocock boundary significance level of 0.0294**….

Publication

- The final publication p-value= 0.023 calculation is the **a result of the post-hoc protocol changes.**

William A. Marston, Jason Hanft, Paul Norwood, Richard Pollak, for the Dermagraft Diabetic Foot Ulcer Study Group; The Efficacy and Safety of Dermagraft in Improving the Healing of Chronic Diabetic Foot Ulcers: **Results of a prospective randomized trial**. *Diabetes Care* 1 June 2003; 26 (6): 1701–1705. https://doi.org/10.2337/diacare.26.6.1701

PART 2 OF 3

Mid career

Procter & Gamble Pharmaceuticals · ICON Clinical Research

Hone the core skills while broadening — and apply early insights to regulators, payers, partners and new industries.

Actonel for Otseoarthritis

Will it work?

MID CAREER · P&G · RISEDRONATE IN OSTEOARTHRITIS

Designing the Phase III OA program

UK Phase II: BRISK → Endpoint plans to regulators → Phase III: KOSTAR

What to learn from MRI

Quantitative cartilage volume and bone lesions, before they show on X-ray.

What to learn from imaging

Minimum medial joint space width as the structural endpoint, continuous or not? Meta-analyses

What to learn from biomarkers

Bone and cartilage degradation markers as early signals.

Preclinical to phase 3

Preclinical evidence

Dosing

UK objection

Biology

Meniscal extrusions

Bone involvement

MID CAREER · P&G · RISEDRONATE IN OSTEOARTHRITIS

Is joint space narrowing clinically relevant?

1

How to measure

Compared fixed-flexion, semi-flexed and MTP knee views; tested technologist reproducibility across countries.

2

Pool the evidence

Link joint structure to what patients feel: pain, function and joint replacement.

3

Support from Phase II

Use BRISK to anchor the Phase III assumptions.

Outcome: in KOSTAR, risedronate lowered cartilage-degradation markers but did not reduce symptoms or slow radiographic progression. A well-measured negative is still an answer.

Arthritis & Rheumatology

AN OFFICIAL JOURNAL OF THE AMERICAN COLLEGE OF RHEUMATOLOGY

American College of Rheumatology
Empowering Rheumatology Professionals

Research Article

Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: Results of the two-year multinational knee osteoarthritis structural arthritis study

Clifton O. Bingham III ✉, J. Chris Buckland-Wright, Patrick Garnero, Stanley B. Cohen, Maxime Dougados, Silvano Adami, Daniel J. Clauw, Timothy D. Spector, Jean-Pierre Pelletier, Jean-Pierre Raynauld, Vibeke Strand, Lee S. Simon, Joan M. Meyer, Gary A. Cline, John F. Beary ... See fewer authors

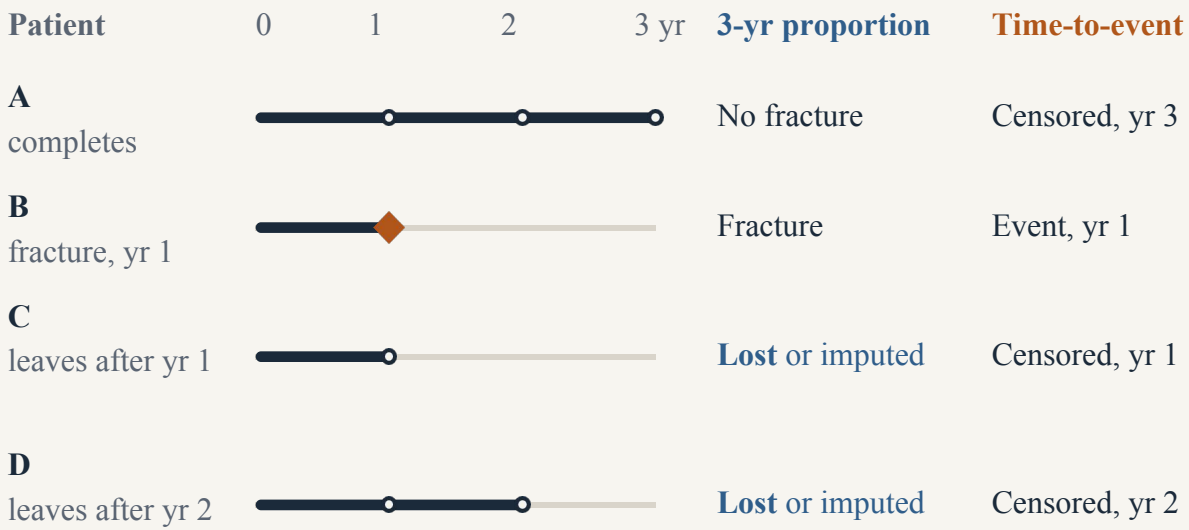
First published: 30 October 2006 | https://doi.org/10.1002/art.22160 | VIEW METRICS

Actonel for Otseoporosis

Get it approved and communicate the benefit!

STATISTICS AS STRATEGY · PRIMARY ENDPOINT ANALYSIS

Why Actonel’s primary analysis was time-to-event



Fosamax (FIT, 1996): spine films only at 24 and 36 months, obtained for 98% of survivors, so a 3-year proportion lost little: 8.0% vs 15.0% with ≥1 new fracture (RR 0.53).

Uses every randomized patient

Dropouts count up to their last X-ray. In VERT-NA only 450 placebo and 489 risedronate 5 mg patients completed all 3 years.

Fits annual X-rays

Films at years 1, 2 and 3 give each fracture a time; a single 3-year yes/no throws that timing away.

Shows when benefit starts

Year 1: 2.4% vs 6.4%, a 65% reduction. Year 3: 11.3% vs 16.3% cumulative incidence, a 41% reduction.

Patients A–D are a schematic, not trial data. Sources: Black et al., Lancet 1996 (FIT); Harris et al., JAMA 1999 (VERT-NA).

Who stole my inch?

Analyses of height loss as a surrogate for vertebral fracture led to Canadian diagnosis method changes and a US commercial product.

Then came the question of insurance coverage.



Osteoporos Int. 2005 Apr;16(4):403-10. doi: 10.1007/s00198-004-1709-z. Epub 2004 Aug 11.

Accuracy of height loss during prospective monitoring for detection of incident vertebral fractures

K Siminoski [1], G Jiang, J D Adachi, D A Hanley, G Cline, G Ioannidis, A Hodsman, R G Josse, D Kendler, W P Olszynski, L-G Ste Marie, R Eastell

Affiliations + expand

PMID: 15309381 DOI: 10.1007/s00198-004-1709-z

Who Stole That Inch?







PR PROGRAM







TV

Awareness into Action

In 2004, Actonel was introduced to consumers.
We needed to grow share quickly!

Motivate a complacent consumer

Give Women 50+ a wake-up call about osteoporosis...
Actonel can prevent fractures caused by the disease!

Make an invisible disease visible

- Multi-media strategy to reach "information seeking" target
- Broad reach increased awareness 200%
- National PR increased exposure on news venues
- Inspired action and a sense of community

Awareness into Action yields success

- Became the #2 drug in the category
- Share of total osteoporosis prescriptions increased 12%
- An increase valued of over $80 million



PRINT



ON-LINE

MID CAREER · P&G · ACTONEL FOR OSTEOPOROSIS

Who stole my 50M?

Competitor claimed higher efficacy for nonvertebral fractures …

- Consider the complement
- Consider claims data
- Interpret in the customers language – Delphi method, clinical impact
- Create robustness analyses – tipping point, missing data

$50M

a year in sales, lost overnight with a managed-care coverage change

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Combining real-world evidence with clinical trial data reinstated it — and moved the competition to a lower tier.

MID CAREER · P&G · DUE DILIGENCE

Close discovery, move to licensing and acquisition

Close internal discovery → Move to L&A

HOW

- **Immersion**
- **Learn all you can from the data**
- **Recreate the analysis data**
- **Model within class**

CASE STUDY · ASSET REPURPOSING

Encaleret: one molecule, two fates

An oral calcium-sensing receptor (CaSR) antagonist that Merck in-licensed from Japan Tobacco for osteoporosis, later revived by BridgeBio for ADH1

OSTEOPOROSIS

2008

Merck licenses JTT-305

Worldwide rights ex-Japan to an oral osteoanabolic agent, then in Phase 2 in Japan

OSTEOPOROSIS

2011

Merck exits; JT stops

PTH stayed up ~4 h, not a brief spike; BMD fell vs. alendronate; **dose-related hypercalcemia**

ADH1

2019–25

BridgeBio revives it

Calcilytix (CLTX-305): NIH Phase 2b, then Phase 3 CALIBRATE met all primary and key secondary endpoints

ADH1

2026

Under FDA review

NDA accepted with Priority Review; PDUFA date May 8, 2027. **Phase 3 in chronic hypoparathyroidism started**

DILIGENCE METHODOLOGY – Model hypercalcemia from other preclinical and clinical data available

Same mechanism, different population. Raising PTH by blocking CaSR wasn't enough to build bone, but it targets the root cause of ADH1, where a gain-of-function CaSR variant suppresses PTH.

Sources: Merck/JT press (2008, 2011); Osteoporos Int 2016 (MK-5442 Ph2); NCT05735015; BridgeBio releases (2025–26)

WORKED EXAMPLE · PREDICTING A SAFETY SIGNAL FROM PRIOR EVIDENCE

Predicting encaleret's hypercalcemia in 2008

1 · PUBLISHED BY 2008

Forteo 20 µg (humans; Neer 2001, label): PTH back to baseline within 3 h ($t_{½}$ ≈ 1 h). Serum Ca peaks 4–6 h post-dose, median +0.4 mg/dL. Hypercalcemia 11.1% vs 1.5% placebo; on consecutive draws 3% vs 0.2%.

PTH(1-84) (humans; PaTH, JCEM 2007): serum Ca >10.5 mg/dL in 14%. Risk rose with baseline Ca (HR 1.9 per 0.5 mg/dL) and 1,25$(OH)_2$D.

NPS 2143 calcilytic (OVX rats; JCI 2000): PTH stayed up ≥4 h, vs back to baseline by 2 h after PTH injection. Turnover rose, with no net bone gain.

Encaleret Phase 1 PTH curve (JT data): PTH peak and duration by dose, the bridge from the drug class to this molecule.

2 · MODEL

Hypercalcemia risk as a function of PTH exposure (excess × hours elevated), adjusted for baseline Ca. Forteo anchors the short-pulse end; sustained-PTH data set the slope. Fit as a Bayesian logistic model with priors from these sources.

3 · 2008 PREDICTION

If encaleret holds PTH up for hours, like NPS 2143, expect hypercalcemia **above Forteo's 11% and rising with dose**. Draw Ca 4–6 h post-dose, screen or stratify on baseline Ca, and set dose-level stopping rules.

4 · WHAT MERCK'S PHASE 2 SHOWED

PTH 3–6× baseline at 1 h, still 2–3× at 4 h. Hypercalcemia rose with dose, and BMD fell vs alendronate. **The prediction's direction held.**

Sources: Forteo USPI; Neer, NEJM 2001; Antoniucci, JCEM 2007; JCI 2000 (NPS 2143); Osteoporos Int 2016 (MK-5442)

MID CAREER · P&G · CONFERENCES

Why statisticians belong at the podium

Education

Keep learning, and teach what you learn.

Statistical community

Organized OA statisticians from industry, academia and regulators.

Bone and rheumatology

Abstracts, posters and work with KOLs.

Competition and science

Know the competitors and the disease.

MID CAREER · P&G · TRY SOMETHING DIFFERENT

Marketing? Same statistics, new customers

NEWCASTLE UPON TYNE, UK

Fabric and Home Care R&D

- Dishwashing
- Design of Experiments (DOX: formulation, storage, cleaning
- Drivers of purchasing
- Dosing of product

PROCTER & GAMBLE

Paper Products R&D

- Can paper towels improve life?
- Lawsuits
- Mobility with diapers

MID CAREER · STANDARDIZATION

Standardization is how one good analysis becomes a thousand.

At P&G: standards for data capture and reporting, with standard tables produced within 48 hours of database lock.

MID CAREER

An SAE imbalance: real signal or detection bias?

OBSERVATION

A difference in one SAE that leads to death

An imbalance between arms across multiple studies raised a safety question.

QUESTION

How to prove detection bias?

Were events in one arm simply more likely to be found?

ANSWER

National Death Index

Real World Data provides greater follow-up and showed no difference between treatment groups

MID CAREER · ICON CLINICAL RESEARCH

Many clients, many needs, one standard

Various projects across sponsors	Reorganize US and India statistics	Grow India and China; a 24-hour operation
Randomization and adaptive design	Business development and innovation	Staffing, budget and billable hours
Statistical quality	One global programming group: ~200 people	Prepare small biotechs for due diligence

MID CAREER · ACTIONS TO TAKE

Hone the core, then broaden it

Action	Where we saw it
Learn the disease and the measurement	Joint space width methods for OA & Osteoporosis
Translate for MDs, regulators and payers	Time-to-event; 1 inch diagnosis, $50M reinstated
Evaluate other people's data	Due diligence for licensing
Build a community outside your company	Conferences and the OA statisticians group
Try something different	Fabric and Home Care; Paper Products
Standardize so quality can scale	48-hour tables; one global ICON group

PART 3 OF 3

Late career

Celgene · AstraZeneca · Cline Consulting, LLC

Integrate insights across stages of development and therapeutic areas — and bring them to the decision table.

LATE CAREER · CELGENE · OTEZLA

Can an uncontrolled Integrated Summary of Efficacy analysis be included in labeling?

THE LABEL LANGUAGE

"Treatment with OTEZLA resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis."

The challenge

An integrated summary of efficacy, without a controlled comparison.

The answer

Yes — when the analysis is clinically relevant, credible and clearly framed.

LATE CAREER · CELGENE · Hematology and Oncology

Innovation

From 3+3 designs to Bayesian dose finding

Move a rule-based tradition to model-based decisions.

Stem Cell Research

CAR-T Research

Recruiting

Abraxane labeling

LATE CAREER · CELGENE · RECEPTOS AND ZEPOSIA

From statistics to every function: integrating an acquisition

$7.4B

Receptos acquisition, bringing Zeposia in late-stage development

First corporate executive onsite full time to guide post-acquisition activities

Matrixed leadership across manufacturing, discovery, development and commercialization

Advanced the pipeline: Zeposia submission and lifecycle studies in MS, UC and Crohn's disease

LATE CAREER · CELGENE · ZEPOSIA

Using what we already know to design better trials - ZEPOSIA

MS

Disproportionate drug metabolite

Surprise finding right before submission

MS

Predicting the Phase 3 disability endpoint

Combine drug-class data with Phase 2 results.

GI

Predicting power ranges

Use pooled, blinded incidence rates while the trial runs.

KEY POINTS

From siponimod exposure to ozanimod disability progression

1 **Siponimod: dose → absolute lymphocyte count (ALC)**
Phase 2 dose-ranging study (BOLD, 0.25–10 mg): lymphocyte count falls with dose; 2 mg lowers ALC by ~70–75%

2 **Prediction model for confirmed disability progression (CDP), built on 2016 data**
EXPAND trial, siponimod 2 mg vs placebo: 3-month CDP hazard ratio (HR) 0.79; log-HR scaled by each dose's share of the 2 mg lymphocyte effect

3 **Ozanimod Phase 2 plugged in → predicted 3-month CDP HR vs placebo**
Lymphocyte count ↓ ~50% at 0.5 mg and ~60% at 1 mg

0.5 mg	1 mg
0.85	**0.82**

4 **Ozanimod Phase 3 observed after unblinding (vs interferon beta-1a)**

Study	3-month CDP, 0.5 mg	3-month CDP, 1 mg	6-month CDP, 1 mg
SUNBEAM (≥12 months)	3.9% vs 4.5%	3.0% vs 4.5%	Not reported separately
RADIANCE Part B (24 months)	HR 0.80 (0.53–1.21)	HR 1.05 (0.71–1.54)	HR 1.44 (0.89–2.31)
Pooled	Not available	HR 0.95 (0.68–1.33)	HR 1.41 (0.92–2.17)

Predicted HRs are vs placebo; observed results are vs active interferon beta-1a, so the two are not directly comparable. No observed difference was significant.

LATE CAREER · ASTRAZENECA · BUILDING INNOVATION

The first master protocol and platform study

One master protocol

Multiple populations and interventions sharing a single control group

25–50%

reductions in sample size and timelines

- Sub-study A
- Sub-study B
- Sub-study C
- New arms added over time

Add Bayesian approaches ….

LATE CAREER · ASTRAZENECA · BUILDING INNOVATION

Making innovation repeatable

Team of ~100 · Member of governance for ~$2B of investment decisions and development plans

Master protocols

Shared control, multiple populations

Bayesian approaches

Historical data expected to cut trial time ~25–50%

Precision medicine

Optimal dose and population

Decision science

Quantified choices for governance

Decentralized components

Trials closer to patients

Automated analysis

Standard macros reused across areas

LATE CAREER · CLINE CONSULTING, LLC

The independent expert

Legal

litigation, statistical expert witness

- **Biometrics leadership** for drug development projects
- **Short-term engagements** for medicines and devices
- **Giving back:** Washington Statistical Society Board, 2025–2027

The Kentucky lesson comes full circle: be ready before the testimony.

CASE STUDY

KBP v. Novo Nordisk: statistics on trial

The case, from the public record

Oct 2023

Novo Nordisk acquires ocedurenone from KBP in a deal worth up to $1.3B

Jun 2024

At a prespecified interim analysis, the IDMC finds CLARION-CKD futile; Novo stops the trial

Feb 2025

Novo alleges KBP withheld Phase 2 interim analyses and a site's anomalous results; seeks $830M

2025–26

KBP cites a corrected analysis: 4.3 mmHg vs placebo (futility bar 5), p = 0.002. Final step: ICC arbitration or settlement

The questions are statistical

Interim data: did Phase 2 signal failure?

One site: anomaly or ordinary noise?

Futility: is one of two criteria enough?

Being the expert witness

Independent — same opinion for either side

Reproducible — every number from raw data

Plain-spoken — explain it to a tribunal

In your lane — statistics, not intent

Novo Nordisk; SICC and SGCA rulings; Fierce Biotech; pharmaphorum · Allegations unproven; arbitration pending

LATE CAREER · ACTIONS TO TAKE

Integrate across stages and therapeutic areas

Action	Where we saw it
Turn pooled evidence into labeling	Otezla dactylitis and enthesitis
Design with prior and class data	Bayesian dose finding; Zeposia predictions
Lead integrations across functions	Receptos; MedImmune; ICON
Build innovation that scales	Master protocols; reusable macros
Take a seat at the decision table	Governance of ~$2B in investments
Serve as the independent expert	$1.3B litigation

BRINGING IT TOGETHER

How a statistician becomes a trusted leader

IMPACT

EARLY

Be right

Rigorous design, clean data, reproducible work.

MID

Be useful

Translate for every audience and broaden your reach.

LATE

Be trusted

Integrate across stages and areas, and judge under uncertainty.

THANK YOU

Questions?

Gary A. Cline, PhD · Cline Consulting, LLC

linkedin.com/in/gary-cline · clinestatconsulting.com