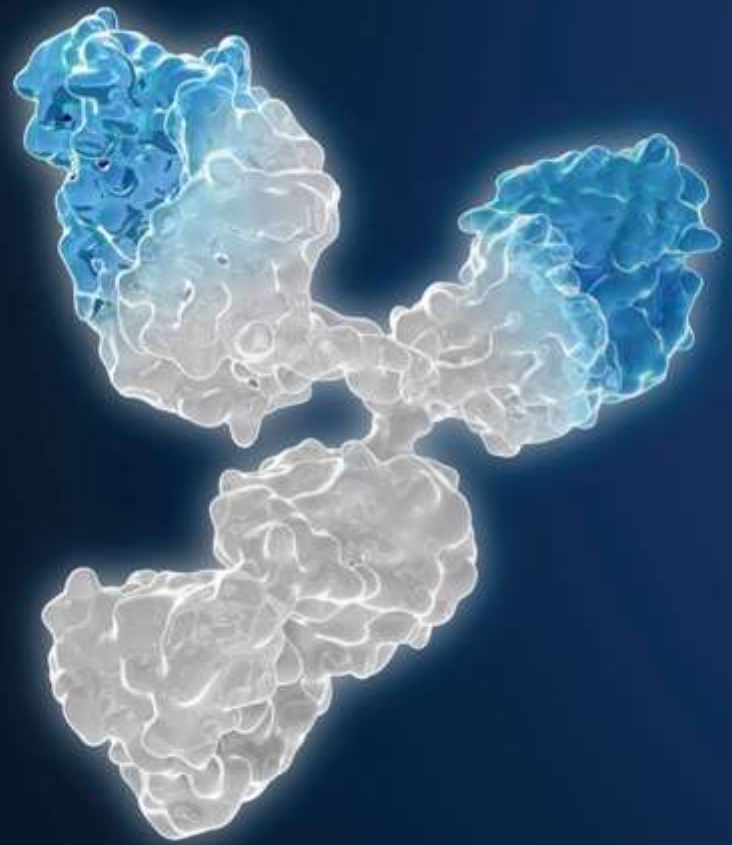

THIS ISN'T PEEWEE SOCCER: BUILDING TEAMWORK BETWEEN STATISTICIANS AND PHARMACOMETRICIANS

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ICSA

REGENERON

SCIENCE TO MEDICINE®

PEEWEE SOCCER?

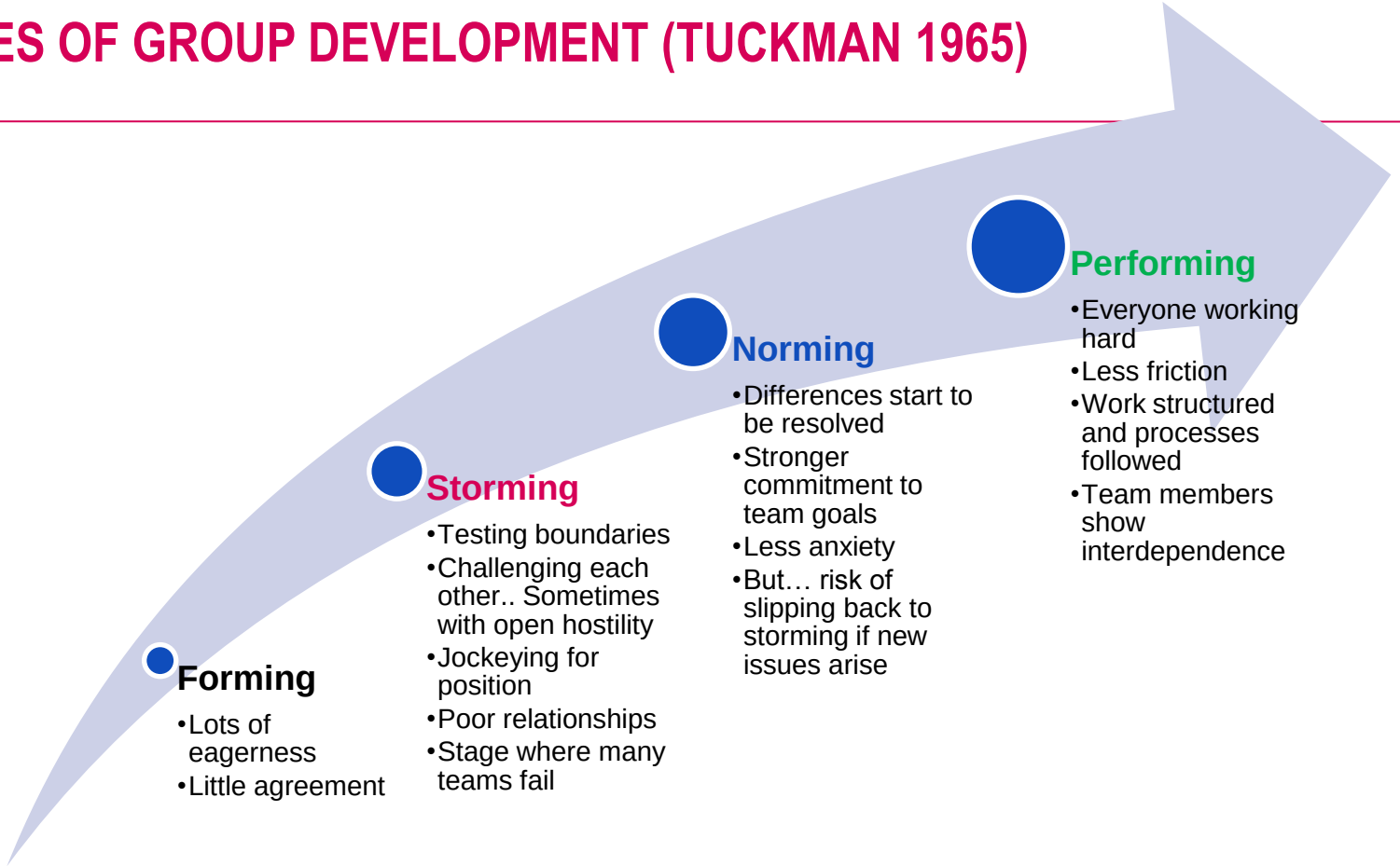
- How can we think about the maturity of a discipline, an organization or a team?

- Soccer maturity model
  - Peewee soccer – kids all chase the ball… even the goalie
  - Pro soccer – focused on position and strategy, passing the ball and working as a team

- Human maturity
  - Early childhood – “parallel play” (interrupted only when one child steals the other’s toys)
  - Adolescence – period of independence (even if it means rejecting a few good ideas)
  - Adulthood – seeing each other’s strengths and working together

- Tuckman model of team development – forming, storming, norming, performing

STAGES OF GROUP DEVELOPMENT (TUCKMAN 1965)



Forming

- Lots of eagerness
- Little agreement

Storming

- Testing boundaries
- Challenging each other.. Sometimes with open hostility
- Jockeying for position
- Poor relationships
- Stage where many teams fail

Norming

- Differences start to be resolved
- Stronger commitment to team goals
- Less anxiety
- But… risk of slipping back to storming if new issues arise

Performing

- Everyone working hard
- Less friction
- Work structured and processes followed
- Team members show interdependence

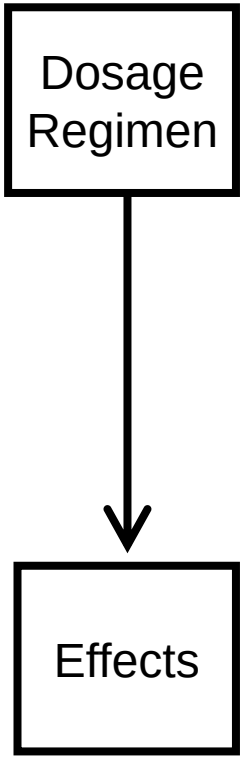
THE FORMING STAGE: BIRTH OF TWO DISCIPLINES

- *Statistics* is a long-standing field – Royal Statistical Society formed in 1834, ASA in 1836
  - In the US, Salk polio vaccine trial in 1955 was a major milestone in application of RCT and use of Statistics in drug development
  - Kefauver-Harris Amendment in 1962 required proof of effectiveness and safety for new drugs, and era of RCT began
  - Biopharm (sub)section of ASA formed in 1968
  - Initial focus for Statistics was confirmatory clinical trials and manufacturing quality / process control, where attention to detail, accuracy, elimination of bias, and need to generate overwhelming evidence were of paramount importance
  - Statisticians earned a reputation for being excessively conservative…. They were guardians of scientific process, ensuring medicines developed properly and with high quality, but at a cost of being viewed as inflexible and sometimes a hindrance to scientific discovery

- *Pharmacometrics* was born in the 1970s as physicians wanted to use quantitative methods to make better decisions on how to dose patients, to understand drug action, and to design better clinical trials
  - Pharmacometrics was born from both the good and bad sides of Statistics…. Focused on individual patients rather than group-level statistics…. often using statistical methods but shunning the conservative empiricism born from the regulatory agenda
  - First PAGE conference held 1992, ASOP/ISOP formed in 2011
  - Over last 30 years, has strived to become “required” while also being strategic

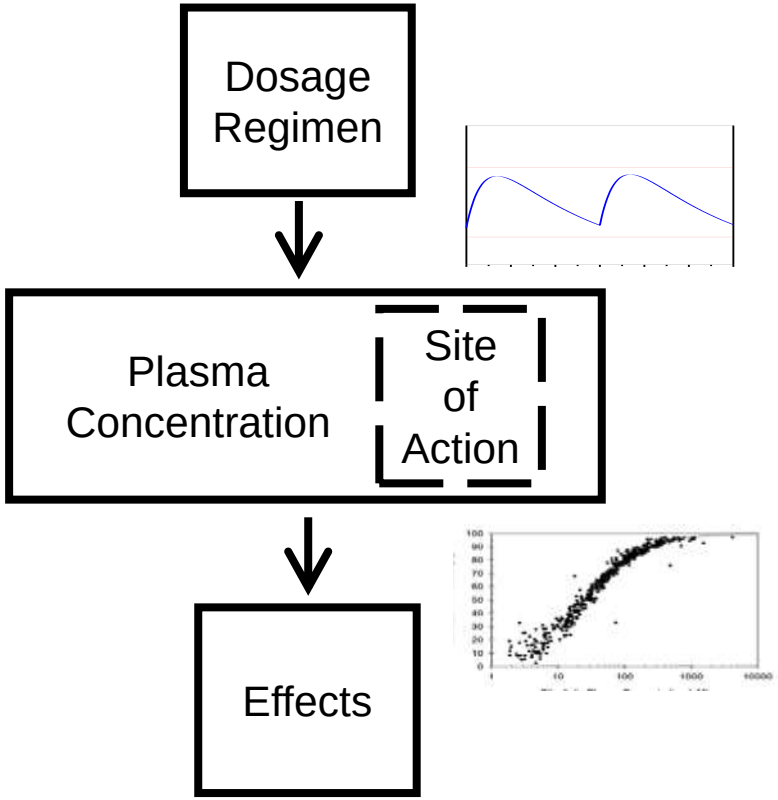
EXAMPLE OF HOW STATISTICIANS AND PHARMACOMETRICIANS THINK DIFFERENTLY: DOSE RESPONSE VS EXPOSURE RESPONSE

- Dose: What a patient is supposed to get when prescribed a drug
- Response: Measure of pharmacological effect of a drug
- Statistical analysis typically straightforward: within-group estimates and pairwise comparisons between dose-groups
  - Trend tests often performed
  - Continuous models for dose-response (e.g. regression line, hill equation / Emax model) less commonly fit
- Baseline patient characteristics are typically assessed, but D-R analyses do not distinguish where in the causal pathways any differences arise
- Dose-response modeling gives a straightforward way to answer what happens when patients get a medication
  - Power of the approach relies on the simplicity, e.g. facilitates ITT assessment



EXAMPLE OF HOW STATISTICIANS AND PHARMACOMETRICIANS THINK DIFFERENTLY: DOSE RESPONSE VS EXPOSURE RESPONSE

- Exposure: measures of acute or integrated drug concentration (e.g. average, maximum or minimum concentration)
- Response: Measure of pharmacological effect of a drug
- Modeling typically broken into two steps: modeling of *dose* to *exposure*, then modeling of *exposure* to *response*
  - Patient characteristics can effect either or both relationships
  - Either step involves individual patient variation; modeling the two relationships can drive to an understanding of why a given dose may work differently in different people
  - Allows for a more mechanistic approach to thinking about dose selection
- Statistical analyses often utilize non-linear models that focus on estimating parameters that define the curve, rather than group-level estimates
- Requires more measurements to get the data for the modeling; need to assess exposure in patients in the study
- Also, often exposure-response modeling will utilize biomarkers instead of, or in addition to, the ultimate clinical endpoint – possibly with additional models linking the biomarkers to the clinical endpoint



EXAMPLE OF HOW STATISTICIANS AND PHARMACOMETRICIANS THINK DIFFERENTLY: DOSE RESPONSE VS EXPOSURE RESPONSE

Attributes of Dose-Response

- Dosage regimen is “fixed” – assigned by study design – instead of being a measurement
- Agnostic to *why* patient characteristics cause different responses – variability in exposure becomes part of the variability in response
- Easy to implement intention-to-treat analyses, survival analyses – just need dose and outcome
- Easier to utilize ‘dose’ in adaptive designs than PK

Is one way right and the other way wrong?

NO

They are different and each brings something unique.

Does this mean people won’t be dogmatic about “their” approach??

Attributes of Exposure-Response

- Between-subject variability in disposition means that dose really isn’t “fixed” when thinking about what drives response
- Drives one more level of understanding in how the drug works – can understand complexities such as
  - Nonlinear relationship between dose and exposure
  - Time lags between dose administration and acute pharmacodynamic effects
  - Differential impact of patient characteristics on D-E vs E-R
- Greater understanding can drive decisions in changing dosing forms or regimen, switching populations

THE STORMING STAGE: TWO DISCIPLINES, SQUABBLING LIKE SIBLINGS

- Clinical Statisticians were often their own worst enemy
  - Started as “required” – Statisticians were “number crunchers,” invited to be involved when “necessary” by regulation, called in for sample size calculations and multiplicity concerns (and often this is still the case…)
  - For the enlightened Statistician, sample size was a ticket to start the real discussion on design and strategy… but many prided themselves on being keepers of the p-value, enforcers of the ITT principle, or simply arbiters of what was “right” or “wrong”
  - When introduced with the new field of PK/PD modeling, attitude was to either ignore it, dismiss it… but a few embraced it
  - Ego and attitude was real, even if not universal, and many prominent statisticians argued otherwise
    - "An approximate answer to the right problem is worth a good deal more than an exact answer to an approximate problem."
      -- John Tukey

- Pharmacometrics purposefully pushed backed against this excessive dogmatism of Statistics and Statisticians
  - “What is wrong is that a particular statistical practice….has become almost mandatory, to be applied willy-nilly to drug trials, regardless of the purposes they are meant to serve.”
    -- Lewis Sheiner (1991)
  - Statisticians pushed back too:
    “We have to trust the scientific judgement of the scientists who ran the study. Statistics should be their handmaiden, not their jailer.”
    -- D. Salsburg (1990)
  - Nick Holford was a vocal opponent against naïve statistical thinking

STORMING, AS SEEN IN BIG PHARMA
BEST OF TIMES RESEMBLED "PEEWEE SOCCER"

- The storming phase in the scientific community was reflected inside of companies

- Examples include
  - Dueling analyses: Dose-response versus exposure-response to choose a Ph3 dose… each analysis suggesting a different dose. Management ended up choosing BOTH doses for Ph3.
  - Preventing access to data… lack of trust and understanding led Statistics department to deny Modeling department to have access to data.

    (Which prompted Modeling department tried to write their own SOP with a scope broader than their department giving them the right to access data)
  - Disregarding statistical thinking… Pharmacometrician initiates a cross-functional working group (excluding Stats) to determine how to assess BE studies, only to reinvent confidence intervals.
  - Disregarding statisticians… to help with trust issues, Modeling department invited comments on modeling plans from Statistics but then didn't listen to the feedback when provided.

THE NORMING STAGE: STATISTICS EVOLVES, PHARMACOMETRICS MATURES

- Statistics is becoming less dogmatic and more strategic
  - Statistical innovations – e.g. adaptive design – facilitated by greater computing power, become more responsive to addressing real problems in drug development…. Facilitated by PDUFA VI which encourages simulation-based design
  - Statisticians taking on more modeling – although not always driven by pharmacology
  - ASA's statement on overreliance on p-values reflects changing attitudes with statistical community… or perhaps a return to original statistical thinking
    - "It has been widely felt, probably for thirty years and more, that significance tests are overemphasized…. " (Cox 1986)

- Pharmacometrics is maturing as a field
  - FDA's 2003 guidance on exposure-response has set expectations for contributions of PMX to regulatory submission
  - Papers on Model Informed Drug Development (MIDD) reflect maturing framework of what defines PMX – and part of the work on MIDD discusses model qualification and validation, two issues of particular concern to statisticians working in the regulatory arena
  - PDUFA VI includes initiative on exposure-based Model-Informed Drug Development
  - PMX groups becoming more standardized – developing their own SOP frameworks

CURRENT STATE: “PARALLEL PLAY”

- Today, Stats and PMX departments are working together, but still many aspects of “parallel play”
- Both have SOPs…. But they’re separate SOPs
- Both have analysis plans…. But they’re written separately (maybe some cross-review?)
- Both have programming groups… But working in silos (at least many share the same SDTM files)
- Many PMX groups will have a couple of statisticians… But few/no Stat departments will hire a PMX

FROM NORMING TO PERFORMING

Lewis Sheiner (1991) said, as a critique of the dogmatic application of statistics,

> *"Restore intellectual primacy to the questions we ask, not the methods by which we answer them"*

However, the quote equally applies to the field of Pharmacometrics and to those who shun statistical thinking.

And do not forget the classic proverb:

> *"If you want to go quickly, go alone. If you want to go far, go together."*

FROM NORMING TO PERFORMING: WORKING AS A TEAM

- SOPs are role-based not department-based
  - Same submission reporting standards applied to both Statistics and Pharmacometrics groups
  - Neither group encumbered by burdensome SOPs for exploratory work
  - Data files programmed to the same standards
- Analysis plans are integrated
  - Strengths of different approaches explicitly recognized and planned – no dueling analyses
  - Especially important in Ph1-2 space
- Statistics and Pharmacometrics colleagues look out for each other on teams
  - Each recognizes the role of the other, and ensures teams include the other
- Departments can be separate, but cross-pollinated
  - Organizational structure doesn't matter – open minds and organized science are what matters
  - Shared interviewing of candidates – ensure an openness to alternative approaches
  - Rotational assignments between disciplines
- Critical resources are shared
  - Computing platforms, data access/storage

FROM NORMING TO PERFORMING: LEVERAGE COMMONALITY AND EXPLOIT DIVERSITY

- Cross-train Statisticians and Pharmacometricians
  - Offer (require?) rotational assignments between the groups
  - Bring in short-courses and offer to both groups
- Initiate true collaborative research efforts
  - Work on methods that truly unify the disciplines – pharmacology-driven and statistically appropriate
- Integrate analysis plans
  - Studies have a single set of objectives, so there shouldn't be two analysis/modeling plans – avoid dueling models
  - Have discussions before the data are revealed about which analyses are best addressed by an empirical approach and which addressed by a modeling approach, considering overall modeling efforts and strength of prior information
- Build a vibrant joint professional community
  - ASA/ISOP Statistics and Pharmacometrics Special Interest Group is part of the solution

Statistics and Pharmacometrics Interest Group (SxP)

ASA AMERICAN STATISTICAL ASSOCIATION
Promoting the Practice and Profession of Statistics

ISOP INTERNATIONAL SOCIETY OF PHARMACOMETRICS

- SxP Special Interest Group co-sponsored by ASA and ISOP created in 2016
- Goals:
  - Promote collaboration between Statisticians and Pharmacometricians
  - To enable each discipline to learn and grow from the other
  - To develop innovative approaches to model informed drug development
- Membership open to everyone
- Join http://community.amstat.org/sxp/home

SIG Activities

- Sponsoring technical sessions at Statistics and PMX conferences
  - ASCPT, ACOP
  - MBSW, ICSA, JSM, Biopharm/Industry
- Discussion forum
- Learning resources in development (incl glossary of discrepant terms)
- Promoting technical working groups