Quantitative Safety Evaluation at CDER

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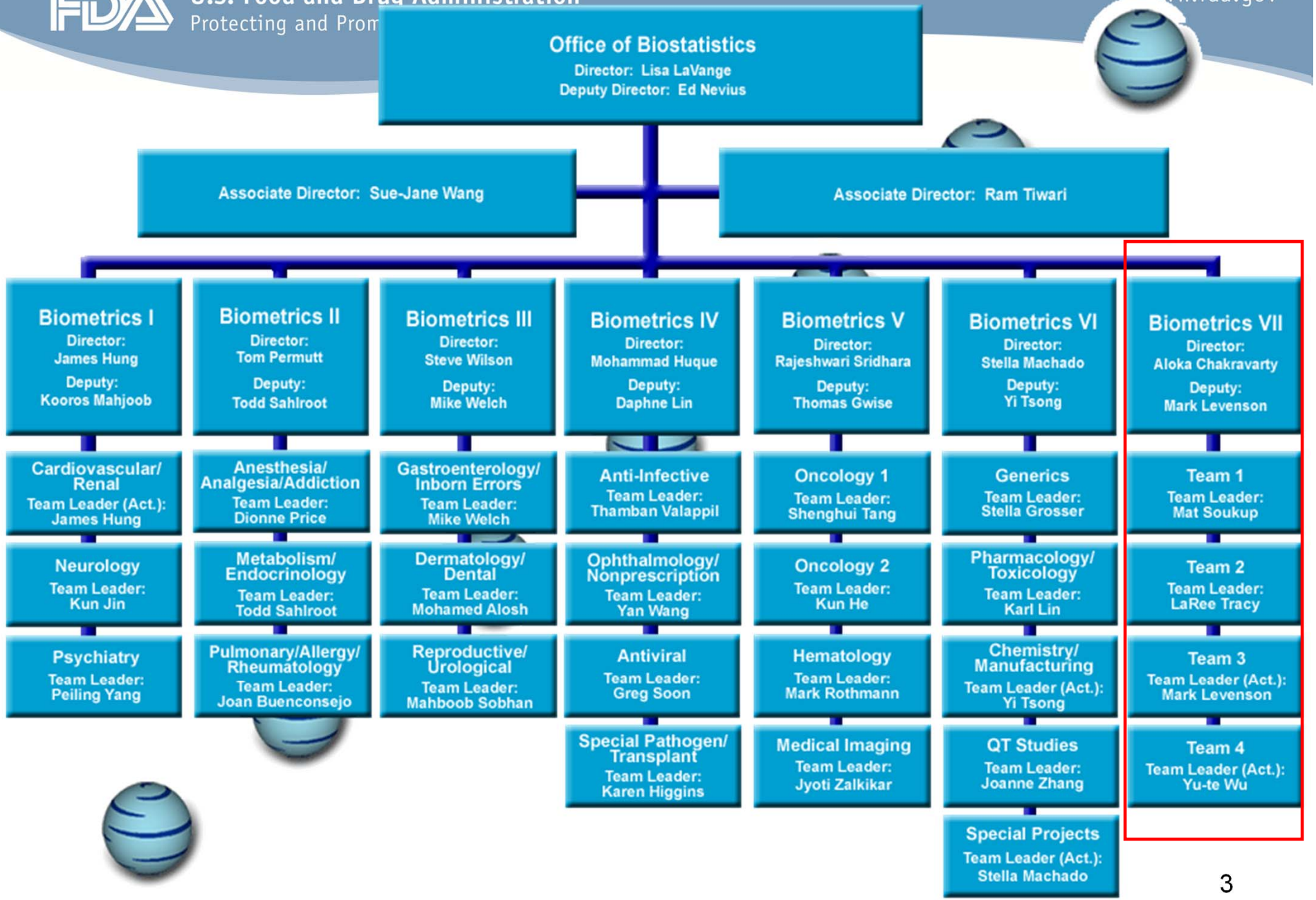
Outline

- Background and Organizational History
- Statistical Support
  - Pre-marketing and post-marketing
- Statistical Issues in Safety Trials
- Graphical Display of Safety Data
- Sentinel Initiative
- Concluding Remarks


Office of Biostatistics
Director: Lisa LaVange
Deputy Director: Ed Nevius
Associate Director: Sue-Jane Wang
Associate Director: Ram Tiwari
Biometrics I
Director: James Hung
Deputy: Kooros Mahjoob
Cardiovascular/ Renal
Team Leader (Act.): James Hung
Neurology
Team Leader: Kun Jin
Psychiatry
Team Leader: Peiling Yang
Biometrics II
Director: Tom Permutt
Deputy: Todd Sahlroot
Anesthesia/ Analgesia/Addiction
Team Leader: Dionne Price
Metabolism/ Endocrinology
Team Leader: Todd Sahlroot
Pulmonary/Allergy/ Rheumatology
Team Leader: Joan Buenconsejo
Biometrics III
Director: Steve Wilson
Deputy: Mike Welch
Gastroenterology/ Inborn Errors
Team Leader: Mike Welch
Dermatology/ Dental
Team Leader: Mohamed Alosh
Reproductive/ Urological
Team Leader: Mahboob Sobhan
Biometrics IV
Director: Mohammad Huque
Deputy: Daphne Lin
Anti-Infective
Team Leader: Thamban Valappil
Ophthalmology/ Nonprescription
Team Leader: Yan Wang
Antiviral
Team Leader: Greg Soon
Special Pathogen/ Transplant
Team Leader: Karen Higgins
Biometrics V
Director: Rajeshwari Sridhara
Deputy: Thomas Gwise
Oncology 1
Team Leader: Shenghui Tang
Oncology 2
Team Leader: Kun He
Hematology
Team Leader: Mark Rothmann
Medical Imaging
Team Leader: Jyoti Zalkikar
Biometrics VI
Director: Stella Machado
Deputy: Yi Tsong
Generics
Team Leader: Stella Grosser
Pharmacology/ Toxicology
Team Leader: Karl Lin
Chemistry/ Manufacturing
Team Leader (Act.): Yi Tsong
QT Studies
Team Leader: Joanne Zhang
Special Projects
Team Leader (Act.): Stella Machado
Biometrics VII
Director: Aloka Chakravarty
Deputy: Mark Levenson
Team 1
Team Leader: Mat Soukup
Team 2
Team Leader: LaRee Tracy
Team 3
Team Leader (Act.): Mark Levenson
Team 4
Team Leader (Act.): Yu-te Wu

Background

- Provides consultation, advice, and support for quantitative safety evaluation
  - for the Office of New Drugs (OND), Office of Surveillance and Epidemiology (OSE) and other CDER offices/units
  - unique expertise in statistical and epidemiological methods relevant to safety evaluation
- Full lifecycle safety evaluation support
- New Division within OB formed in October 2009
  - Provides safety evaluation to all 17 therapeutic areas
  - Currently 21 statisticians in four teams

Some Areas of Expertise

- Randomized trials designed primarily to evaluate safety
- Design and analysis of observational studies (including propensity score and marginal structural models expertise)
- Meta-analyses
- Signal detection
- Survey methodology
- Time series analysis
- Graphical and computational methods
- Analyses of registry and health care databases

Office of New Drug Support

- What
  - Clinical trials designed primarily for safety
  - Epidemiologic methods/observational studies
  - Registries
  - Format and content of safety data
  - Development of safety studies as part of PMRs
  - Meta-analyses of drug classes for safety
- When
  - EOP2, pre-NDA, NDA filing meetings, new safety issue in post-marketing
- Who
  - Statistical Team Leaders collaboratively determines if a focused safety evaluation is needed

OSE Support: Spectrum

- Sponsor protocol or study review
- Intramural study design and analysis support
- Sentinel and Safe Rx support
- Contract study support
- Guidance development (e.g. Pharmaco-epi using electronic databases)
- Support roles
  - Review of design or analysis developed by sponsor / collaborator /contractor
  - Collaboration on the development of study protocol with the design developed by DBVII reviewers
  - Conducting of analysis
  - Coauthoring of study report

Statistical Issues in Quantitative Safety Evaluation

Current Landscape

- Greater focus on safety assessment throughout product life cycle
  - Planning for safety begins in the earliest stages of product development, goal is to provide a framework for risk-benefit
- Varying degrees of risk tolerance based on indication, yet safety issues often unobserved until post-marketing
- Update knowledge of risks based on active or passive safety surveillance systems
- Learn and refine from post-market experience
  - Medication errors and 'near misses'
  - Use of similar products: intended or unlabeled use
  - New populations (e.g. pediatrics, high risk)
  - Emerging safety issues identified in the literature
  - Epidemiological and post-market clinical studies (FDAAA, 2007)

Frequent Safety Questions

- Pre-market safety signals - real or due to chance?
  - Increased hypersensitivity reactions - Is there a immunogenicity concern and how does it correlate to clinical outcome?
  - Increased mean BP - Does this suggest a long-term CV risk?
- Any differences and impact of shifts from normal in key laboratory parameters?
- If a RCT shows a trend of more events in the new treatment arm v. control but the trial is underpowered for that outcome
  - How large and long should a future trial be to show a difference, should one exist?
- Published observational studies suggest an association between exposure and safety outcome
  - How does this finding compare with findings from RCTs?

Challenges in answering them

- Safety endpoints often not precisely measured or adjudicated
  - Impacts the estimate sensitivity/specificity
  - Exposure time may be critical to onset of events
- Safety events may occur after withdrawal from exposure
  - On-treatment analysis will ignore these events
  - On-trial analysis includes events but comparison might be confounded by intervention after treatment discontinuation
- Multiplicity of events, recurrent events and multiple different events per subject
- Unexpected signal from non-systematically collected data
- Trial design complicates comparative assessment (e.g. cross-over design, limited data collected after endpoint, etc.)

Observational v. Experimental

- Observational: cohorts, registries, case-control
  - Less expensive and generally more efficient
  - Suffer from lack of internal validity due to the lack of randomization
  - Adjustment methods cannot control for unmeasured confounding
  - Results vary by analysis performed
  - **Need for a prospective SAP**

- Experimental: Randomized Clinical Trials (RCTs)
  - Less bias due to randomization
  - Often suffer from lack of external validity due to restrictive I/E criteria (results may differ from observational study)
  - Large safety trial can be more inclusive but also more messy
  - Costly, time consuming, may be difficult to enroll subjects

Analytical Approaches in Safety

Safety Analytical Methods What We Often Do ….

- Estimates of event rates: Proportion (%) with event
- Estimates of relative and absolute estimates
- Events per unit of time (e.g. rate per 100 person years)
- Hazard rate, hazard ratios for an event or composite
- Cumulative incidence
- Risk factor modification of hazard
- Composite vs. individual endpoint contributions for time to event (delayed) and for acute outcome
- Univariate, time independent summaries
- Combine data from patients with different durations of exposure and ignoring the role of hazard rates of adverse events

In Safety Analytical Methods We Could Be….

- Placing greater emphasis on time-to-event analyses
  - Multiple failure-time data or multivariate survival data
  - Consideration of ordered and unordered events
- Assessing the following when estimating rates
  - If the constancy assumption holds
  - If not, then stop focusing on events per person time
- Analyzing composite endpoints by assessing
  - The relative contribution of each component
  - The time dependencies of each component
    - Not all events are created equal!
  - Additional analyses excluding less severe events
- Analyzing multiple events per patient more precisely

Population for Analysis

- Intent-to-Treat who received at least one dose of treatment and had at least one follow-up visit
  - could be a biased population if exposure time differs between treatment groups
- On-Treatment v. On-Trial
  - Ignoring data after treatment discontinuation may lead to underestimate of risk
  - Considering all on-trial data may lead be difficulty in interpretation

Missing Data

- As much of a problem for safety as it is for efficacy analyses
- Discordance in missing may favor arm with greater amount of missing
  - Missing assumed to be no event/toxicity in safety
- Imputation for missing not straightforward
  - Might over-estimate true risk
- Need to fully understand reason for missing
- May impact ability to rule-out specific risk (when pre-specified)

Premature Treatment Discontinuation

- Extent of data collection after treatment discontinuation varies across trials
  - Lack of laboratory assessment off-treatment
  - Less detailed/frequent data collection
  - Need for specification in protocol
  - Follow true ITT principle for data collection
- Protocol allowed treatment switches/cross-over
  - Negatively impacts ability for comparative safety
  - Trade-off between efficacy and safety evaluation should be heavily considered during protocol development

Graphical Display of Safety Data

Why Graphics for Safety?

- Safety information is often times presented in the form of tables and line listings
- But tables and line listings *may not* be the most effective means for conveying information
  - When understanding variable relationships
  - When there is information overload
  - When data summaries do not capture the full extent of the data
  - When integrating information over time
  - When presenting multivariate information for a single subject

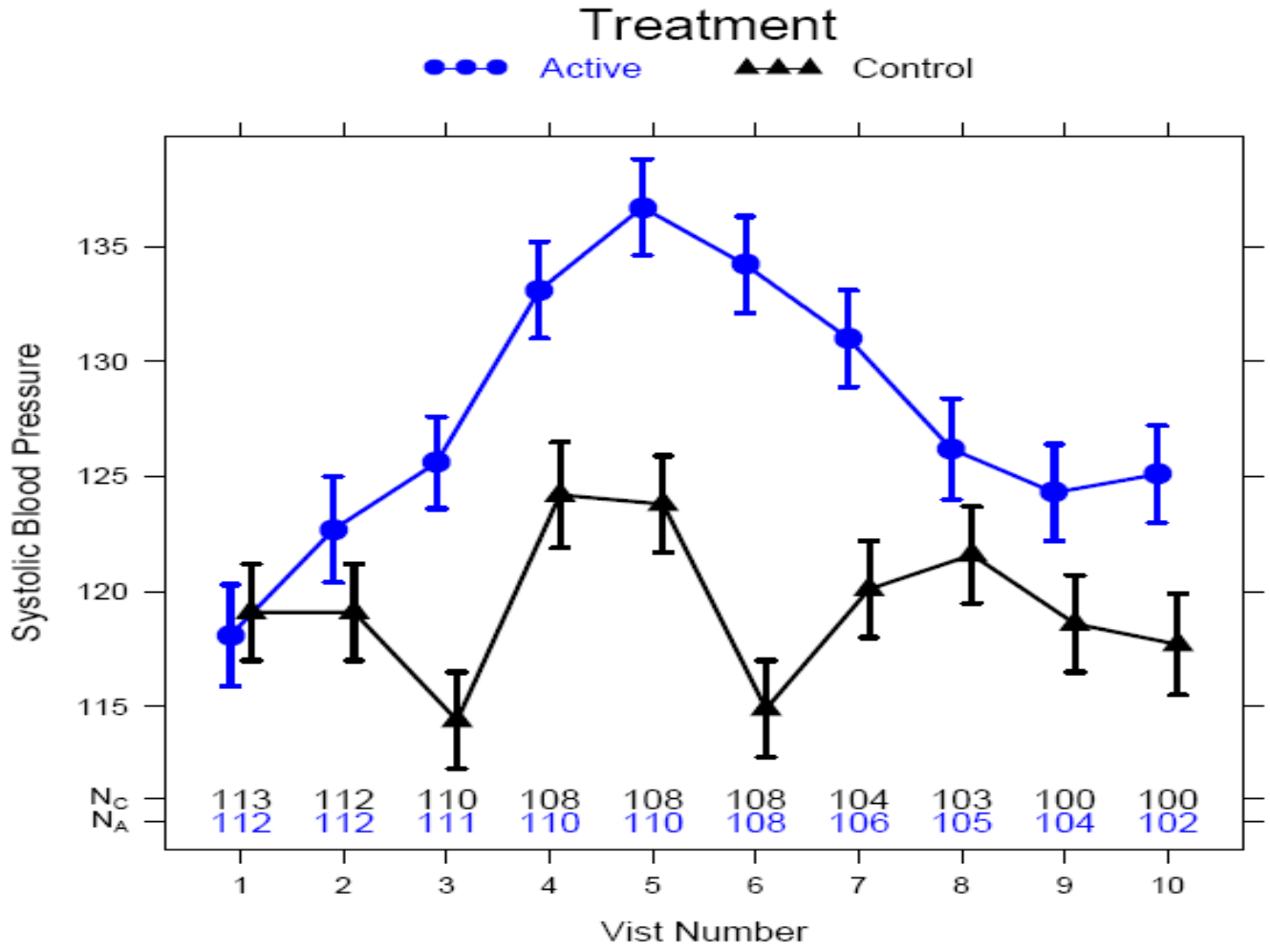
Features of Clinical Safety Data

- Incorporate key features of the data collected *during* clinical trials into the summation and presentation
- Treatment Groups
  - Considering relative safety, how does the investigational product compare to the control?
- Series of Observations
  - Most subjects have multiple observations taken over time. Does a temporal relationship exist?
- Exposure
  - Relationship between product exposure and the timing of the event is often times important.
- Covariates:
  - Do other assessed characteristics influence finding?

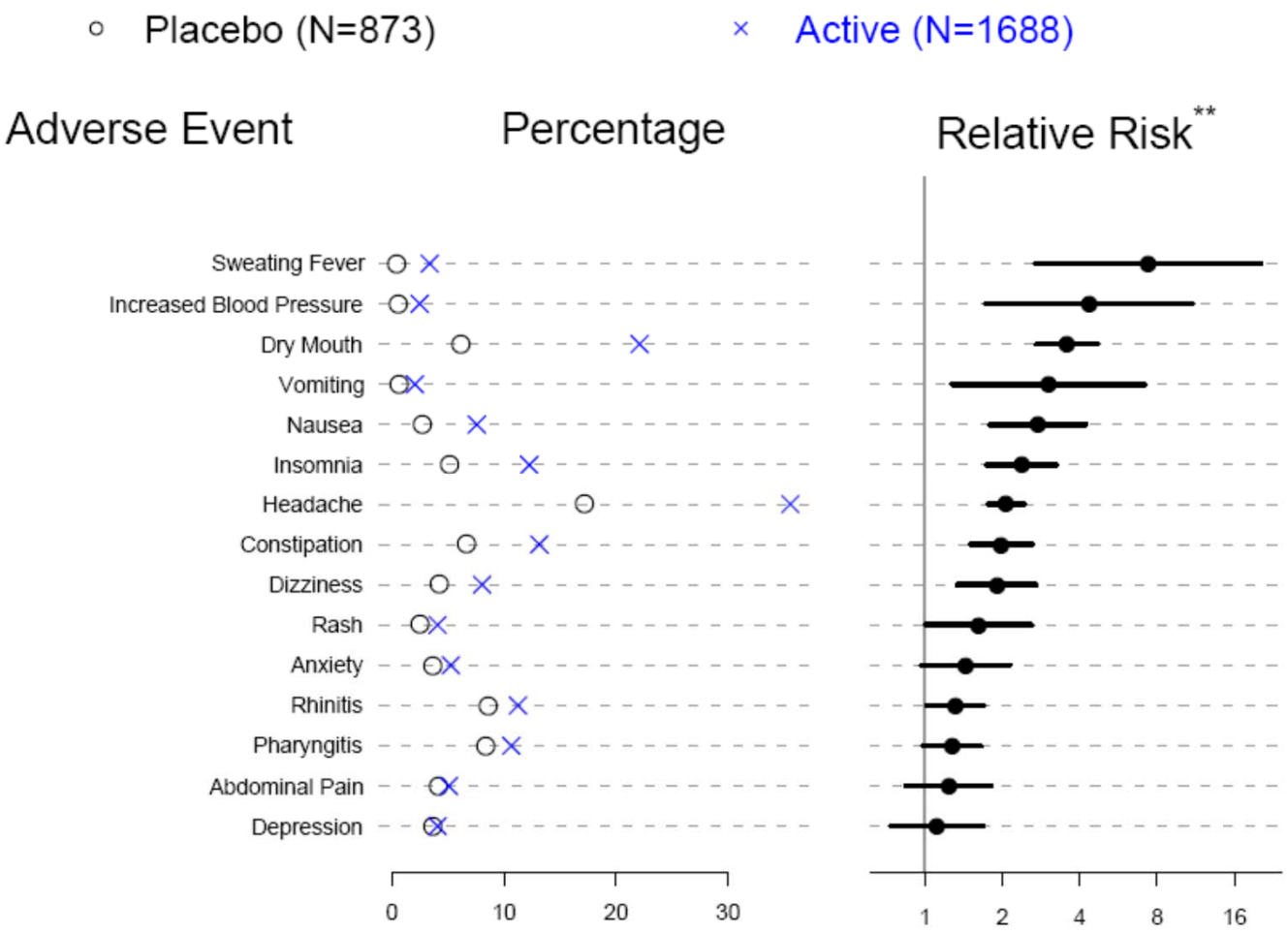
The Good and The Bad

- Whenever Possible
  - Depict subject-level data
  - Depict multivariate structures in the data
  - Use graphical displays in place of or as a supplement to tables
  - Incorporate tabular data values into the graphical display
  - Account/present temporal relationships
- Whenever possible, avoid the following
  - Creating discrete variables from continuous
  - Low data to ink ratio
  - Misuse of scaling
  - Using unneeded dimensions

Understanding Trends



Dotplot w/ Relative Risk



FDA/Industry/Academia Safety Graphics Working Group

- Formed in the Fall of 2009
- Membership Includes
  - Regulatory Agencies: CDER and CBER
  - Pharmaceutical Companies: Pfizer, GSK, Johnson and Johnson, Novartis, Eli Lilly, Merck, Sanofi-Aventis, Roche, Amgen, Actelion, CSL Behring
  - Academia: UC-Davis and Vanderbilt

Graphics WG Project Objectives

- Develop a palette of statistical graphics for reporting on clinical trial safety data.
- Identify areas particularly applicable or useful to regulatory review in which graphics can enhance understanding of safety information.
- Recommend graphics for clinical data based on good scientific principles and best practices.
- Create a publicly-available repository of sample graphics (ensuring appropriate credits are given for contributions), including data sets and code.
- Educate and engage stakeholders through outreach activities.
- Consider publishing with authorship/acknowledgments as is consistent with contributions and policy of the affiliated institution.

Addressing the Barriers

- **Lack of Training**: Developing materials to help scientists select the right graph; outreach through presentations
- **Limited Publications**: Materials will be presented in a public forum
- **Time Restraints**: Standard set of views reduces time to develop graphical approaches, can be planned upfront
- **Software Dependency**: Code to create graphics will be publicly available;
  - Plan to create examples/code from multiple software packages

Safety Graphics Library Public Domain

- Information is publicly available at CTSpedia (www.ctspedia.org)
- CTSpedia is an online collection of best practices, graphics library, tools, educational materials, and other items about biostatistics, ethics, and research design.
- Site is constantly updated/changed to help users.
- CTSpedia Statistical Graphics Home Page
  - https://www.ctspedia.org/do/view/CTSpedia/StatGraphHome
  - Check it out!

Sentinel Initiative

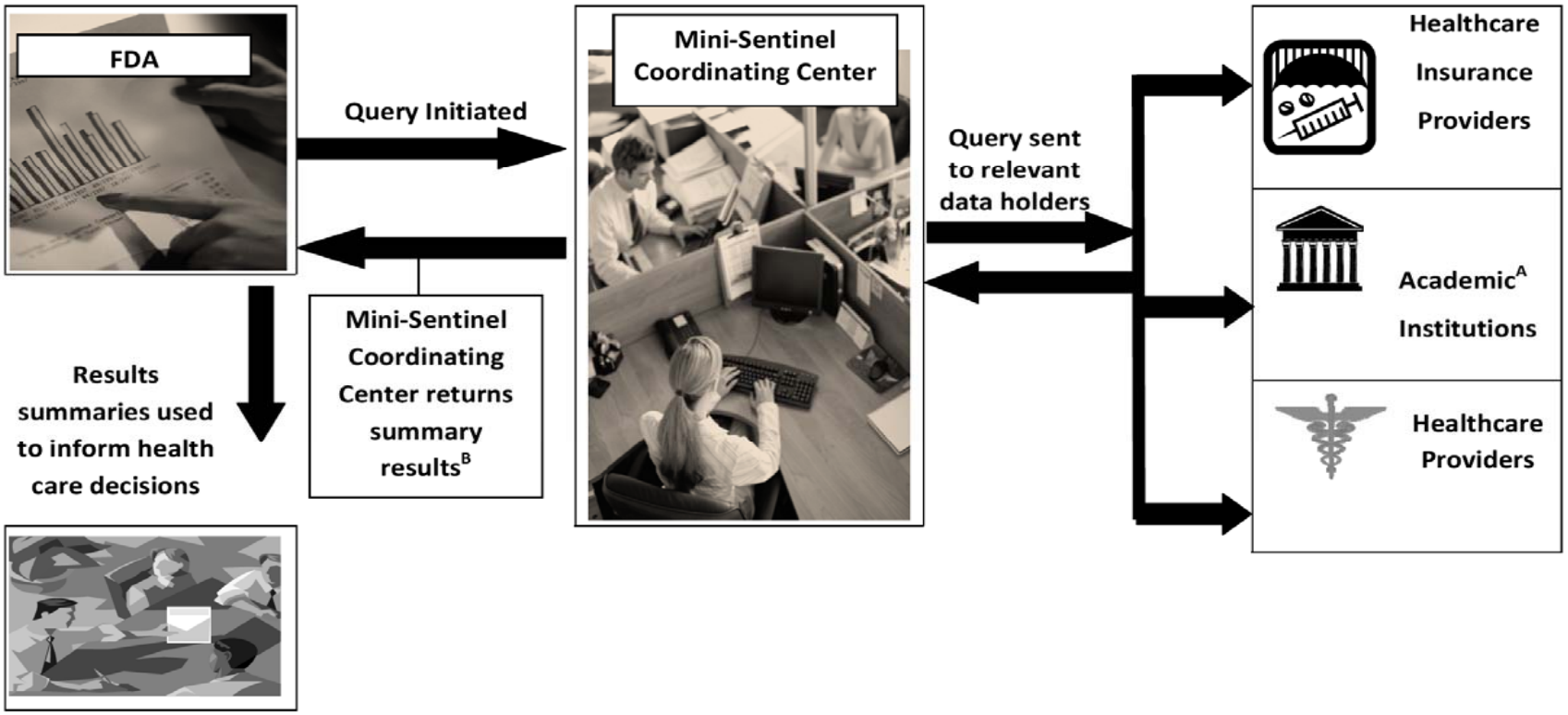
Outline for this section

- Sentinel Initiative Overview
- Components of Sentinel Initiative
- Communications on the Initiative
- Observational Medical Outcomes Partnership (OMOP)
- Summary

Sentinel Overview

- Develop an active electronic safety monitoring system to
  - Strengthen FDA's ability to monitor postmarket performance of medical products
  - Augment, not replace, existing safety monitoring systems
  - Enable FDA to access existing automated healthcare data by partnering with data holders (e.g., insurance companies with large claims databases, owners of electronic health records, others)

Overview of the Mini-Sentinel Query Process



A. Only those academic institutions with automated data will be recipients of queries.

B. No entities will have access to protected health information that they do not already hold. Instead, those whose queries are accepted by the **Mini-Sentinel Coordinating Center** for processing will receive results summaries from analyses conducted by each data holder that receives and agrees to respond to those queries. Results summaries will not include protected health information.

Sentinel Infrastructure - FDA

- Initiative managed by Office of Medical Policy in CDER
  - launched May ’08 with the release of initial report
- Sentinel SMT includes reps from each Center
  - as well as informatics, privacy, and planning staff from OC
- Sentinel Methods working group – Office of Commissioner and the medical product Centers

http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm

Components of Sentinel Initiative

- Mini-Sentinel
- Sentinel Methods Group
- Observational Medical Outcomes Partnership (OMOP)
- Federal Activities
  - Federal Partners Collaboration
  - Federal Partners Working Group
- International activities

Mini-Sentinel

Harvard Pilgrim Healthcare

- Develop the scientific operations needed for the Sentinel Initiative.
- Create a coordinating center with continuous access to automated healthcare data systems, which would have the following capabilities:
  - Provide a "laboratory" for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel Initiative.
  - Offer the Agency the opportunity to evaluate safety issues in existing automated healthcare data system(s) and to learn more about some of the barriers and challenges, both internal and external.

Mini-Sentinel: Distributed approach

- Distributed data model
  - Data partners transform their local data to the Mini-Sentinel common data model
  - Coordinating center distributes analytic code via the distributed querying portal
  - Data partners securely return summary data to the coordinating center via the distributed query portal
  - Coordinating center reviews and analyzes data, provides detailed reports to FDA
- Methods for querying Mini-Sentinel
  - Rapid querying using standardized summary tables
  - Modular programs using the Mini-Sentinel Distributed Database
  - Ad-hoc programs for evaluation protocols using the Mini-Sentinel Distributed Database

Mini-Sentinel: Some activities

Data work

- Data inventory - a prioritized list of data needs; develop and implement Common Data Model
- First version of Mini-Sentinel Distributed Database, encompassing quality checked admin/claims data

Methods development

- Framework for safety surveillance methods &a prioritized list of gaps
- Regression methods applicable for sequential surveillance programs
- Case only methods, e.g., cross-over designs, utilizing time-varying covariates
- Enhance methods for application of high dimensionality propensity score confounder adjustment
- Confounder Adjustment methods
- Re-use of Data

Engaging External Stakeholders:
Convener on Active Medical Product Surveillance
Brookings Institution

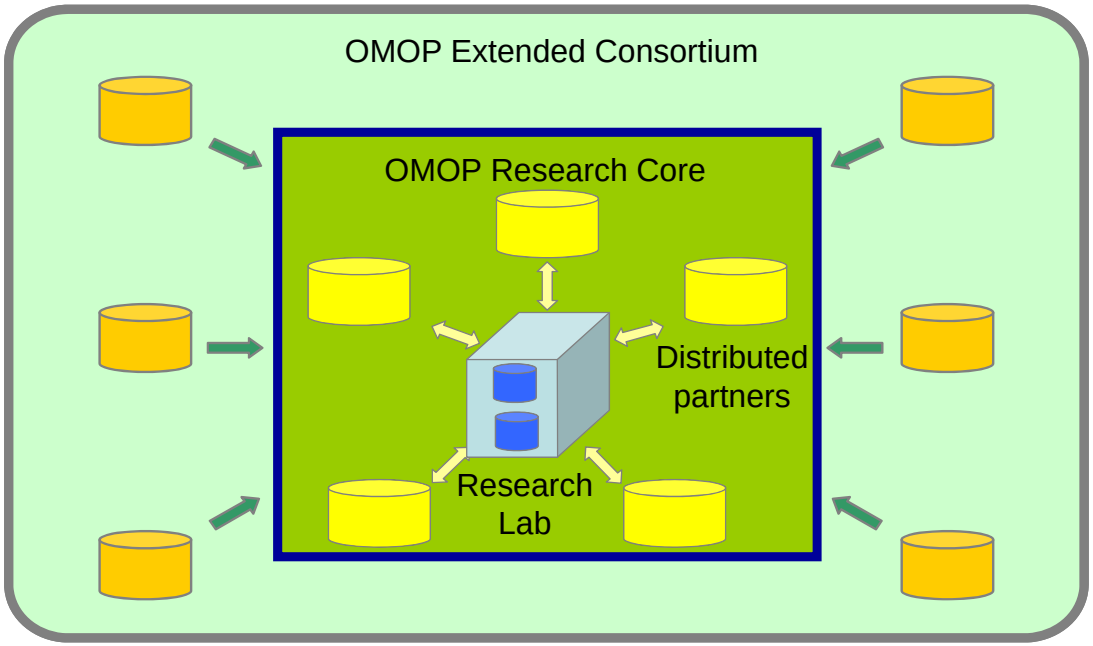
- Expert stakeholder conferences
- Public Workshop each year
- Medical Product Surveillance “Roundtables”
- Active Surveillance Implementation Meetings
- OMOP Symposium

Observational Medical Outcomes Partnership (OMOP)

http://omop.fnih.gov

- Public-Private Partnership with FNIH, FDA, and PhRMA
- Conduct experiments to assess value, feasibility, and utility of observational data
- Test approaches to create infrastructure
  - to access and manage required data
- Two main objectives
  - Monitoring Health Outcomes of Interest (HOI)
  - Identify non-specified conditions

Overview of OMOP Partnership Design



- **OMOP Research Core** is responsible for designing, developing and managing the execution of the approved research proposals.
- **OMOP Research Lab** will be used to manage analysis process across all data sources within the Research Core.
- **Distributed Partners** implement the OMOP Common Data Model and execute protocols within their data environment
- The broader scientific community can voluntarily participate in the **OMOP Extended Consortium**

OMOP Phases

- **Phase 1:** Feasibility of data infrastructure
  Establish a consistent framework to use across disparate observational data sources
  – Establish OMOP Research Community
- **Phase 2:** Feasibility of analyses
  – Develop and test analysis methods within the OMOP Research Lab and other data environments
  – Establish standard data characterization procedures
  – Implement health outcomes of interest definitions
  – OMOP to facilitate comparisons across databases
- **Phase 3:** Performance measurements
  – Evaluate performance of methods+data in identifying drug safety issues
  – OMOP to facilitate comparisons across databases
- **Phase 4:** Utility of analyses & process
  – Assess the effectiveness and usefulness of how the results and comparisons contribute to decision-making

OMOP's methods landscape

Disproportionality analysis

- Proportional reporting ratio
- Multi-item Gamma Poisson Shrinker
- Bayesian confidence propagation neural network
- Temporal pattern discovery

Other novel approaches? OMOP Cup

Exposure-based approaches

- Cohort Screening
- Incident user designs
- High dimensional propensity scoring
- Local control

Sequential methods

- Maximized sequential probability ratio test
- Conditional sequential sampling procedure

Case-based approaches

- Case-control surveillance
- Case-crossover
- Self-controlled case series
- Bayesian logistic regression
- Statistical relational learning

OMOP Methods Library at: http://omop.fnih.org/MethodsLibrary

Federal Activities

- Collaborations with CMS, DoD, and VA
  - SafeRx project with CMS to develop near-real time active surveillance methods using Medicare data
  - Several ongoing projects within medical product Centers to evaluate potential medical product-adverse event signals and develop active surveillance and statistical methodologies
- Federal Partners Working Group
  - Share information and discuss issues related to complementary efforts being carried out by the various Agencies within the Federal government
  - Participants include FDA, ONC, NIH, CDC, CMS, DoD, VA, AHRQ, IHS, HRSA, SAMHSA, OHRP, and CPSC

Federal Partners Collaboration

- An active surveillance initiative via intra-agency agreements with CMS, VA, DoD
- Small distributed system
  - Each Partner has unique data infrastructure
  - No common data model being utilized
- FDA proposes medical product – AE pairs to evaluate
- Develop a shared protocol
- Evaluate active surveillance methodologies
- Assess interpretability of query findings resulting from a decentralized analytic approach

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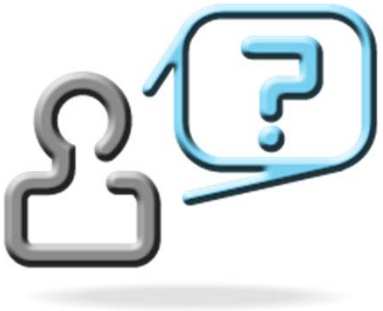
Concluding Remarks

- Since 2009, we have a centralized organizational structure for quantitative safety evaluation
  - Early consultation on focused safety outcome studies are mutually beneficial
- We are looking to a cohesive safety evaluation across the entire lifecycle of a product
  - Pre-specified Safety Analysis Plan
  - Safety Graphics
- Augment the current post-marketing safety evaluation through active surveillance systems
  - Sentinel Initiative

Questions?



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