Drug Safety Surveillance Initiatives

Relevance to PML

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Goals of Drug Safety Surveillance

- To identify previously unknown drug-related adverse events
- To learn more about known drug-related adverse events
- To learn more about how drugs are used in ways that may not promote safe use
- The method you use depends on what you are trying to learn
Components of a Comprehensive Post-marketing Surveillance Program at CDER

- Drug Utilization data:
  - Sales
  - Outpatient
  - Inpatient

- External HealthCare Databases:
  - General population
  - Special population

- Passive surveillance (AERS)

- Active Surveillance

Pharmacoepidemiologic Studies
Passive Surveillance

• Individual case reports
  – Sent to regulator or to company
  – Company sends to regulator
• Based on clinical observations at the point of care
• Concise, accurate clinical details are critical
• Case reports, as a whole, often lack important clinical details
Qualities of a Good Case Report

• What makes a good case report?
  – Description of the event
  – Suspected product(s) and concomitant treatment details
  – Patient characteristics, medical history, treatment history
  – Documentation of the diagnosis
  – Clinical course and outcomes
  – Treatment and lab values at baseline, during therapy, and after therapy
  – Response to dechallenge and rechallenge
  – Any other relevant information

• For PML
  – Not sufficient to say simply that the patient “developed PML”

Drug Utilization Studies

- Quantify drug use in a population
- Can get population-based estimates
- Can quantify prevalent users and incident users
- Can often stratify by age and gender
- Best for outpatient prescriptions
- Difficult to obtain data for over-the-counter medicines and medicines administered in a clinic or physician’s office
  - An issue for many drugs implicated in PML
Pharmacoepidemiologic Studies

• A broad term
  – Case-control studies
  – Cohort studies
  – Registries

• Case-control and cohort studies
  – Hypothesis driven
  – Not useful for extremely rare outcomes

• Registries
  – Can be treatment-based (eg, persons taking drug X)
  – Can be disease-based (ie, persons with cancer)
  – Good for rare exposures and rare diseases
Registries – An Example From Another Field

- Drug Liver Injury Network (DILIN)
Challenges in Studying DILI

- DILI is a rare disease; 10 –15 per 100,000 pt-years
- < 1% of acute liver injury
- By drug, only 1 per $10^4$ to $10^6$ prescriptions
- Clinical diagnosis must exclude competing causes
- Variable latency, lab profile, & histology
- Polypharmacy is common
- Variable quantity and quality of prior reports
- No objective / confirmatory lab test
Approaches to Studying Post-approval DILI

• Reports to regulatory agencies
  – Underreporting ? Data quality/ confirmation

• Retrospective approaches
  – Medical records search ? Evaluation ? History ? Competing causes

• Population based studies

• Prospective multicenter registries
  – Interview, careful phenotyping
  – Expensive, labor intensive ? Referral bias
US DILI Network* (DILIN)

NIDDK U-O1 Cooperative Agreement*

*NIH: J. Hoofnagle, J. Serrano
http://dilin.dcri.duke.edu
FDA Reps: M. Avigan, J. Senior
DILIN Recruitment Methods

- **Local site PIs**
  - Conferences, e-mails, brochures
  - Outreach to MDs, subspecialists, dinner meetings
  - Annual newsletters

- **Network-wide**
  - Journal ads, website
  - DILI symposia at meetings
  - Publications
  - Other research networks
  - FDA, CDC

http://dilin.dcri.duke.edu
Active Surveillance

• Actively looking
• Can be:
  – Disease-based
  – Drug-based
  – Setting-based
• Can use large databases for surveillance
Sentinel Initiative

- FDA initiative
- Use large databases from multiple sources
- Cover a large number of lives
  - 25 million in 2010
  - 100 million in 2012
- Two components:
  - Mini Sentinel
  - Federal Partners Collaboration
Common Data Model Version 1.1
Domain: Administrative and Claims Data

- Enrollment
- Demographics
- Outpatient Pharmacy Dispensing
- Utilization (Encounters, Diagnosis, Procedures)
- Mortality (Death, Cause of Death)
Common Data Model
Enhancement Year 2: Clinical Data

Labs

Vital Signs
### CDM Tables & Data Elements

#### Enrollment
- PatID
- Enc_Start
- Enc_End
- Med_Cov
- Drug_Cov

#### Demographic
- PatID
- Birth_Date
- Sex
- Hispanic
- Race

#### Dispensing
- PatID
- RxDate
- NDC
- RxSup
- RxAmt

#### Encounter
- PatID
- EncounterID
- Adate
- Ddate
- Provider
- Facility_Location
- EncType
- Facility_Code
- Discharge_Disposition
- Discharge_Status
- DRG
- DRG_Type
- Admitting_Source

#### Diagnosis
- PatID
- EncounterID
- Adate
- Provider
- EncType
- Dx
- Dx_Codetype
- OrigDX
- PDX

#### Procedure
- PatID
- EncounterID
- Adate
- Provider
- EncType
- PX
- PX_Codetype
- OrigPX

#### Death
- PatID
- DeathDt
- DtImpute
- Source
- Confidence

#### Cause of Death
- PatID
- COD
- CodeType
- CauseType
- Source
- Confidence
Federal Partners Collaboration

• Intra-agency agreement participants include FDA, CMS, VA, DoD
• Address medical product safety surveillance using a distributed data model where each partner has a unique database structure
• FDA proposes medical product – AE pairs to evaluate
  – Develop a shared protocol
• Small distributed system
  – Each partner has unique data infrastructure
  – No common data model being utilized
  – Decentralized analytic approach
Established to inform the appropriate use of observational healthcare databases for active surveillance by:

• Conducting methodological research to empirically evaluate the performance of alternative methods on their ability to identify true drug safety issues

• Developing tools and capabilities for transforming, characterizing, and analyzing disparate data sources

• Establishing a shared resource so that the broader research community can collaboratively advance the science
OMOP- Analysis problems under study

• **Monitoring of Health Outcomes of Interest (HOIs):**
  – Estimate the strength of the association between drug exposure and specific events (e.g. acute liver failure, bleeding, MI)
  – Modest in number so can customize analytic approach
  – Expert assessment of drug-HOI causal associations based on literature search

• **Identification of non-specified associations (NSA):**
  – More exploratory in nature
  – Same goal: estimate the strength of the association between drug exposure and conditions
  – Necessarily more generic analyses (e.g., adjust for age and sex)
  – Causality assessment relies on the product labels

• **Performance against simulated data**
  – Complement ‘real world’ experiments
Outstanding questions for active surveillance

**Governance**
What are the keys to a successful public-private partnership?

**Data**
Which types of data? administrative claims, electronic health records
Which sources? healthcare providers, insurers, data aggregators

**Performance**
What are appropriate analyses for:
- hypothesis generating?
- hypothesis strengthening?

**Architecture**
What is the appropriate infrastructure:
- hardware?
- software?
- processes?
- policies?

**Methods**
How to maintain collaborations and engage research community?

**Technology**
What are best practices for protecting data?

**Feasibility**
What are viable data access models:
- centralized?
- distributed?
Thank you

Questions?