

Safety Assessment of Pharmaceutical Products



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BASS XIX

Acknowledgement

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- ◆ Some materials came from a presentation by David Jones (Pfizer) on “Timely Safety Surveillance of Clinical Study Safety Data” at a TIBCO-sponsored event earlier this year.
- ◆ Many others whose work is cited on individual slides.

My Question Years Ago

- ◆ **Statistical Safety Analysis: The Stepdaughter or a Future Queen?**



Outline

- ◆ **Safety assessment has come a long way**
- ◆ **Conducting safety review of ongoing trials at Pfizer**
- ◆ **Establishing an Internal Safety Review Committee to meet recent regulations**
- ◆ **Implementing a 3-tier approach for summarizing adverse events in a clinical study report**
- ◆ **Examples of graphic displays**
- ◆ **Program Safety Analysis Plan**
- ◆ **The trial PREDICT-I**
- ◆ **Summary**

Current Environment

- ◆ **Increasing use of pharmaceuticals: Aging population, products for chronic illness and of new mechanism, “feel good” products**
- ◆ **Advancement as well as greater interest in disease modifying products or disease prevention: exposure of healthy population, use of vaccines, potential decades of medication use**
- ◆ **Emerging drug-resistant infectious diseases**
- ◆ **Public expectations of low or no risk from medical interventions**

Source: Modified from Ellenberg (2003). BASS X.

Pfizer Safety SOPs (12)

- ◆ **Suspected Unexpected Serious Adverse Reaction (SUSAR) Reporting**
- ◆ **Risk Management Plan & Risk Evaluation and Mitigation Strategies**
- ◆ **Safety Profile Monitoring of Marketed Products**
- ◆ **Safety Review Plan**
- ◆ **Special Safety Concerns**
- ◆ **Risk Management and Safety Review Committee**
- ◆ **Safety and Advisory Councils**
- ◆ **Medical Governance of Product Benefit-Risk Assessment**

Safety Biostat Groups at Some Companies

At Amgen, the Safety Biostat Group leads efforts on:

- ◆ **Constructing the Program Safety Analysis Plan**
- ◆ **Developing infrastructure and process in support of periodic, aggregate clinical trial safety data review and signal detection**
- ◆ **Planning, execution and analysis of safety studies**
- ◆ **Contributing to rapid responses to regulatory safety queries and issue-driven ad-hoc safety analyses**
- ◆ **Methodology/tool development, consultancy and training relative to safety**

Safety Evaluation Is a Continuum

- ◆ **Discovery and Pre-Clinical: Predict clinical impact**
- ◆ **Clinical Development: Evaluate clinical impact and support initial product label**
- ◆ **Post-marketing and pharmacovigilance**
 - Conduct additional studies; collect additional information through AVERS, VAERS, “sentinel” sites, registries, claims database and electronic health records to enhance product knowledge.
 - Design risk management and risk communication plans

Safety Review of Clinical Trials at Pfizer

Pharmacovigilance DB

- ◆ **Individual SAE review:**
 - A physician in Safety reviews an SAE submitted by an investigator.
 - If enough evidence to suggest the SAE may be a SUSAR, the case will be unblinded. If the subject is on the IMP, the case will be reported to the FDA and investigators.
- ◆ **Cumulative review:**
 - Study Safety Risk Lead (SRL) and clinician(s) review *monthly* incremental and *quarterly* cumulative SAEs.

Clinical DB

- ◆ Study clinicians review patients for targeted medical events (TMEs), designated MEs (DMEs), and non-serious AEs for seriousness, *at least monthly*.
- ◆ Clinicians and SRL review blinded cumulative reports on AEs, labs and discontinuations due to AEs, *quarterly*.
- ◆ Teams describe findings /actions in minutes and document reviews centrally.

Safety First Group at Pfizer

- ◆ **A multi-disciplinary cross-functional team to advance safety review planning and real-time safety assessment of ongoing clinical studies at Pfizer.**
 - Clinical
 - Safety
 - Statistics
 - Development Operations
 - Business Technology
 - QA/QC
 - Project Management
 - Other members as needed



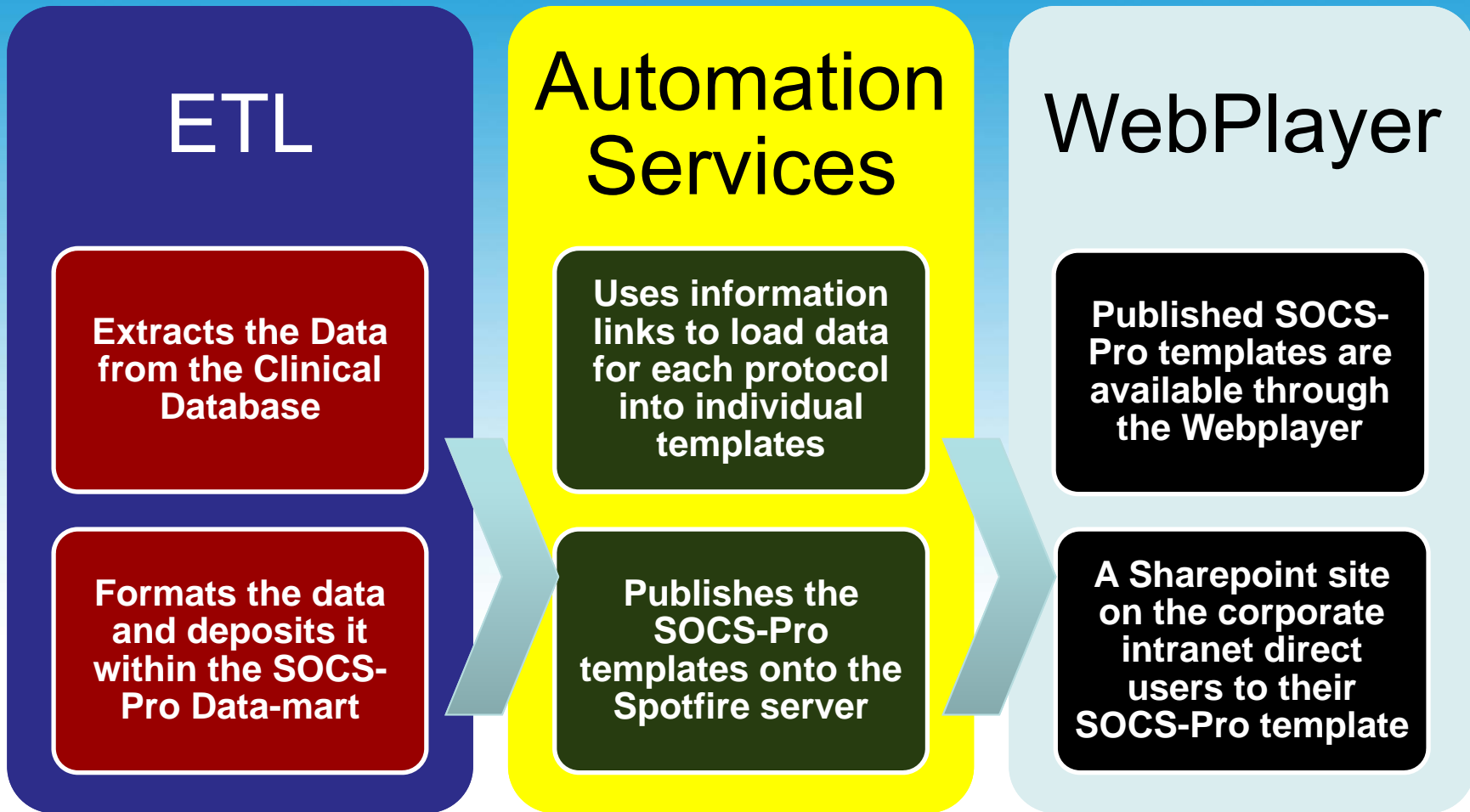
Development of Review Tools

- ◆ **Pfizer Safety First Group was tasked to develop review tools to enable efficient safety reviews.**
- ◆ **Desirable traits of the tools include**
 - **Easy access, self serve and available for all ongoing trials with data in the internal database**
 - **Covering targeted medical events, designated medical events and all AEs, cumulatively and incrementally**
 - **Providing basic statistics, e.g. count, %, AE onset & duration**
 - **Allowing drill down to detailed patient data**
 - **Offering patient profile**

Our Solution: SOCS-Pro

- ◆ **Spotfire for Oracle Clinical Safety – Proactive**
- ◆ **Running on TIBCO Spotfire 3.3.1 using Information links and Automation Services, and published in WebPlayer**
- ◆ **29 templates based on 11 data tables linked by patient identifier; data aggregated over treatment groups**
- ◆ **Data include AEs, demography, labs/ECG, e-diary**
- ◆ **Graphics available for enrollment pattern, AEs, labs/ECG/vitals with % change from baseline, possible drug-induced liver injury (eDISH-like plots)**
- ◆ **Individual patient profile with concomitant data**

Behind the SOCS-Pro Template



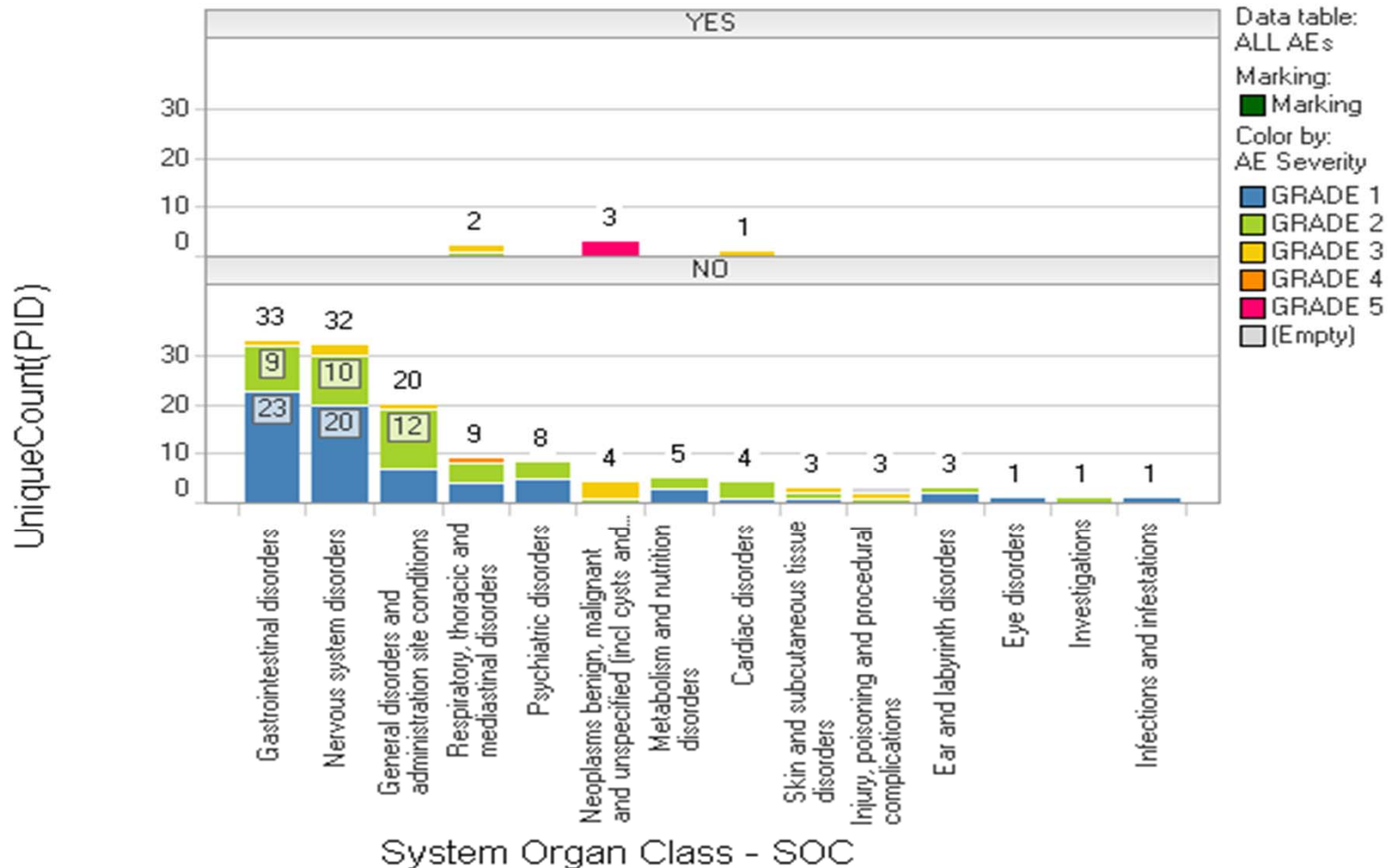
Targeted Medical Events

This Graph shows the count of PIDs in each SOC, split by Serious (Yes/NO) and coloured by Severity.

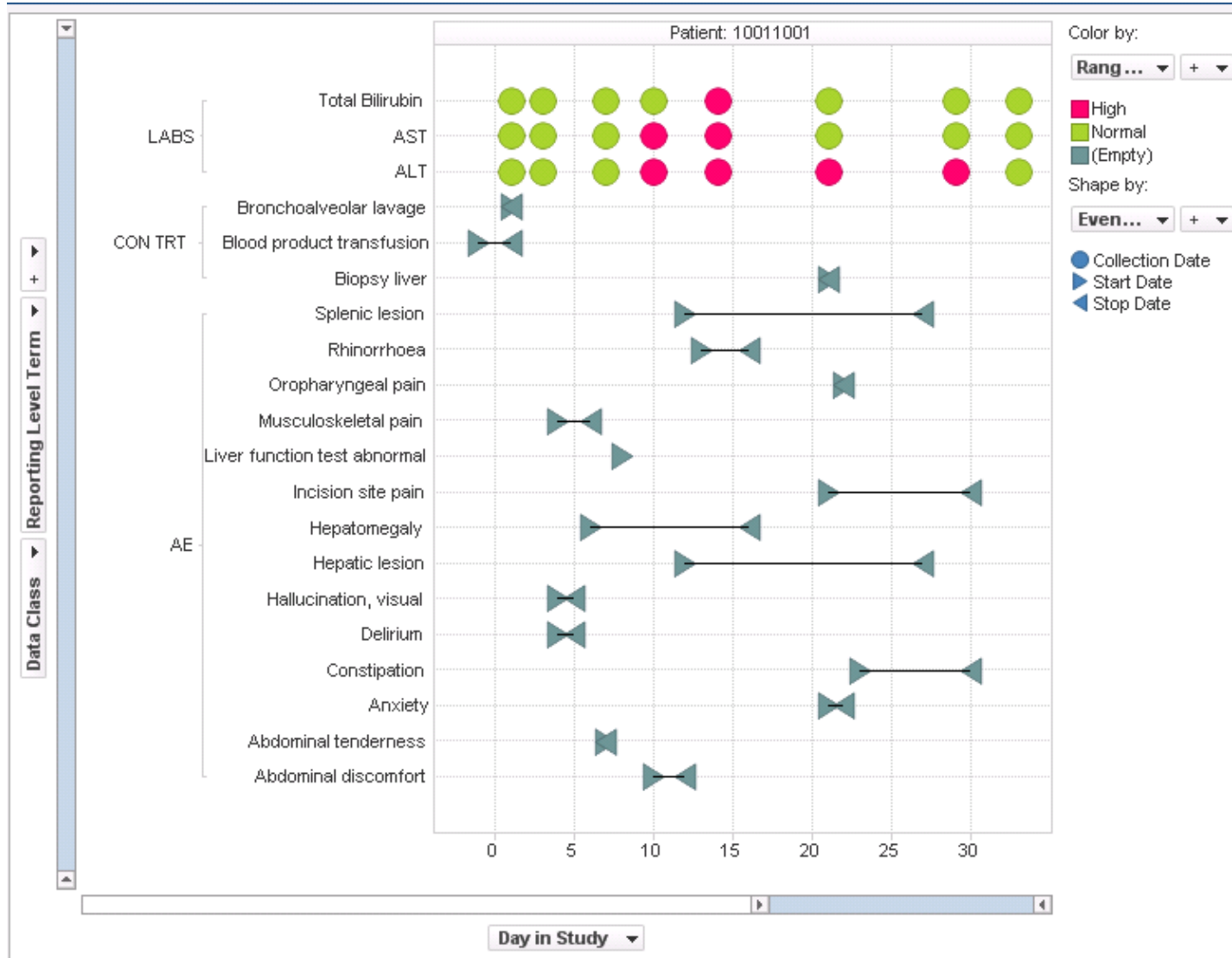
Note this Tab has the TME Filter applied, so only AEs which are flagged as being TMEs will be displayed. The same applies to all Tabs prefixed with TME. The Filters can be changed using the Filter Panel if Required.

[Details of Selected Patients](#)

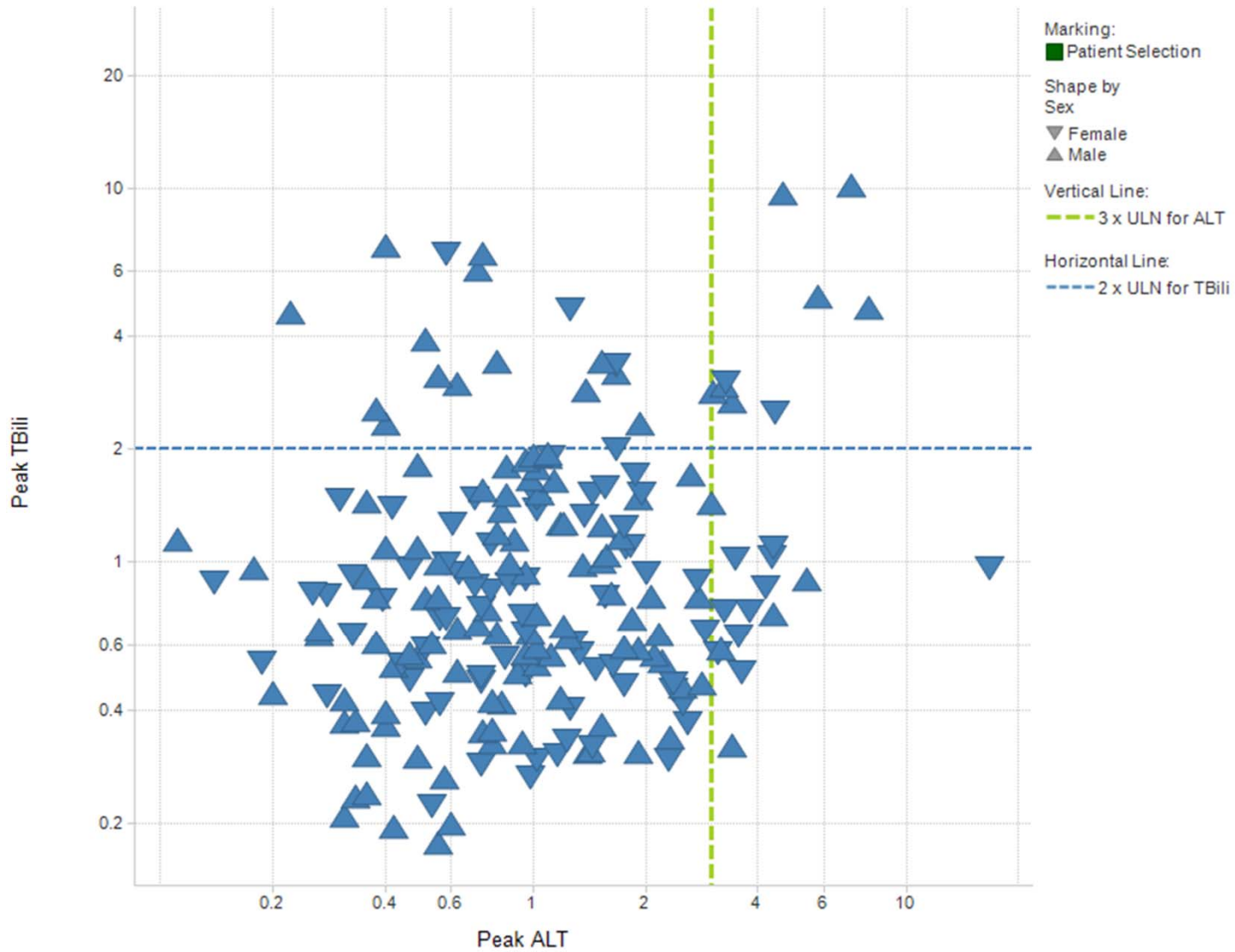
TME SOC Split by Serious



Patient Profile



Standard eDISH Plot



State of SOCS-Pro at Pfizer

- ◆ **SOCS-Pro initiated 2010, designed in collaboration with clinicians for clinicians**
- ◆ **At the beginning of 2012, SOCS-Pro was available to all phase I-IV studies (over 500) in Pfizer OC database.**
- ◆ **Very positive feedback from users - graphics are much easier for conducting safety reviews and better at showing temporal relationship between AEs and medication usage.**
- ◆ **SOCS-Pro Team continues to add enhancements for different disease areas and different phases.**

FDA Final Rule (1)

- ◆ **FDA published IND Reporting Rule (Final Rule) on Sept 29 2010. The rule became effective on March 28 2011 and enforceable on Sept 28 2011.**
- ◆ **The intent of the new rule is to improve the quality of safety reports by minimizing the number of un-interpretable reports that sponsors submit to the FDA and investigators.**



FDA Final Rule (2)

- ◆ FDA is only interested in receiving reports of suspected adverse reactions that are serious and unexpected (SUSAR).
 - “Unexpected” is determined by using a single reference safety document (e.g. IB, Core Data Sheet).
 - FDA defines *suspected adverse reaction* to mean any adverse event for which there is a reasonable possibility that the drug caused the adverse event, and there is evidence to support this determination.
- ◆ The Final Rule requires sponsors to conduct causality assessment. For FDA, a sponsor’s assessment over-rules INV’s assessment in making expedited reporting decision.

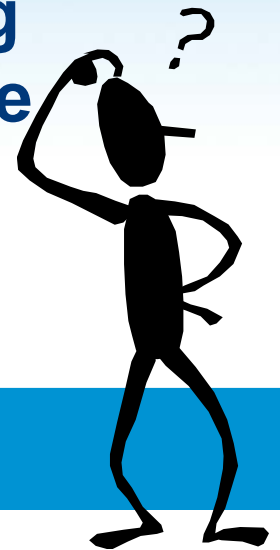
FDA Final Rule on Causality Assessment

FDA describes 3 examples of SUSAR:

- ◆ **A: A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g. hepatic injury, SJS)**
- ◆ **B: One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the study population (e.g. tendon rupture).**
- ◆ **C: An aggregate analysis of specific events (e.g. events related to the disease or events common in the study population) indicates that the events occur more frequently in the drug treatment group than in the concurrent or historical control.**

Challenges with Category C Events

- ◆ How do we determine if a group of specific individual cases should be expedited as a SUSAR to the IND in the U.S. per the Final Rule, while the study is ongoing?
- ◆ To do the above requires unblinding of individual cases (or at least unblinding of case counts by treatment groups) and review of the ensuing results. How do we do this while keeping the study team unblinded?

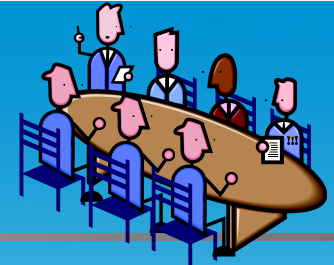


EU Clinical Trial Guidance, CT3, June 2011

- ❖ **Section 3 (paragraph 16) - The sponsor should continuously weigh anticipated benefits and risks of the clinical trial, which includes ongoing safety evaluation of Investigational Medicinal Products**
- ❖ **Section 7 (paragraph 114) - Regarding the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific subject. *The blind should be maintained for persons responsible for the ongoing conduct of the study and those responsible for data analysis and interpretation of results at the conclusion of the study.***

Paragraph 114 is consistent with ICH E9 (*Statistical Principles for Clinical Trials*) for maintaining blind.

Internal Safety Review Committee



- ◆ **FDA Final Rule and EU CT-3 led to the concept of an ad hoc Internal Safety Review Committee (ISRC), effective of Oct 1 2012.**
- ◆ **The primary purpose of an ISRC is to assess a specific group of unexpected adverse events (typically serious) to decide if there is a suspected relatedness of the cases to the product. A “possible relatedness” decision results in expedited reports and possible benefit/risk re-assessment.**
- ◆ **ISRC can review similar events in other ongoing (and completed) trials of the same product for corroborating evidence.**

Additionally...

- ◆ An ISRC can also help decide if the frequency or severity of a previously reported and medically important adverse drug reaction has increased.
- ◆ FDA wants the above to be reported in an expedited fashion if the change in frequency or severity is clinically relevant.



ISRC Function

- ◆ **Complements and supplements existing safety and risk management processes**
- ◆ **Does not replace**
 - **External Data Monitoring Committee (E-DMC)**
 - **Internal Review Committee (IRC)**
 - **Study/program safety data review**
 - **Medical/clinical governance that is responsible for making benefit-risk determination**

Difference between ISRC and E-DMC/IRC

ISRC

- ◆ Ad hoc referral committee that reviews data upon request. ISRC will not review efficacy data.
- ◆ Conduct focused review involving specific events.
- ◆ ISRC looks for “suspected relatedness” of unexpected SAEs to a product.
- ◆ ISRC decides whether there is a special safety concern that may require follow-up actions.

Safety E-DMC/IRC

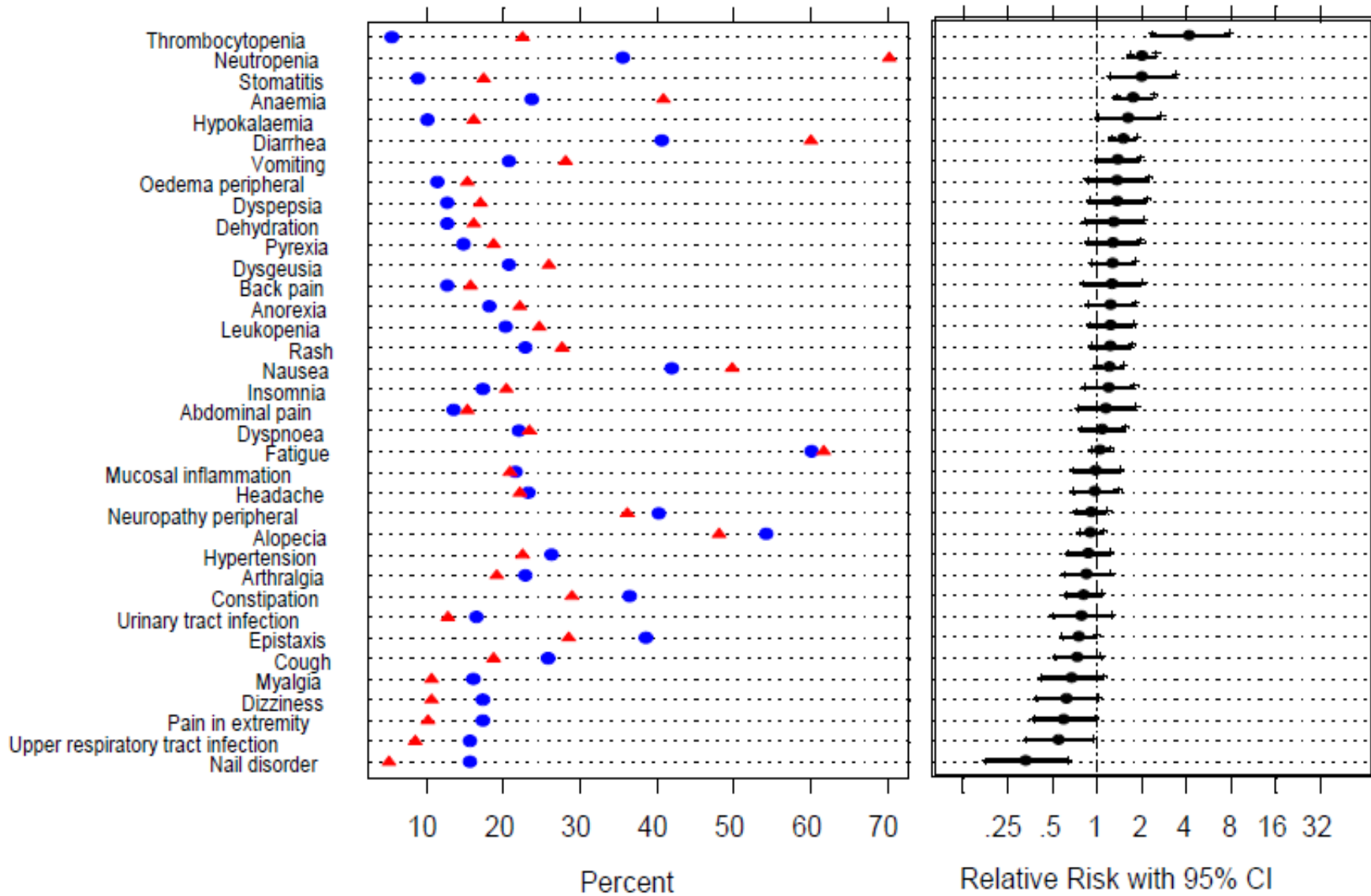
- ◆ A committee that reviews data regularly as agreed in the E-DMC/IRC charter.
- ◆ Review all relevant (pre-specified and additional) safety data.
- ◆ E-DMC/IRC looks for more definitive and substantial relationships that would result in major trial decision.
- ◆ E-DMC/IRC decides if the study can continue, should stop, or requires major change.

Pfizer Implemented 3-Tier Approach for AEs

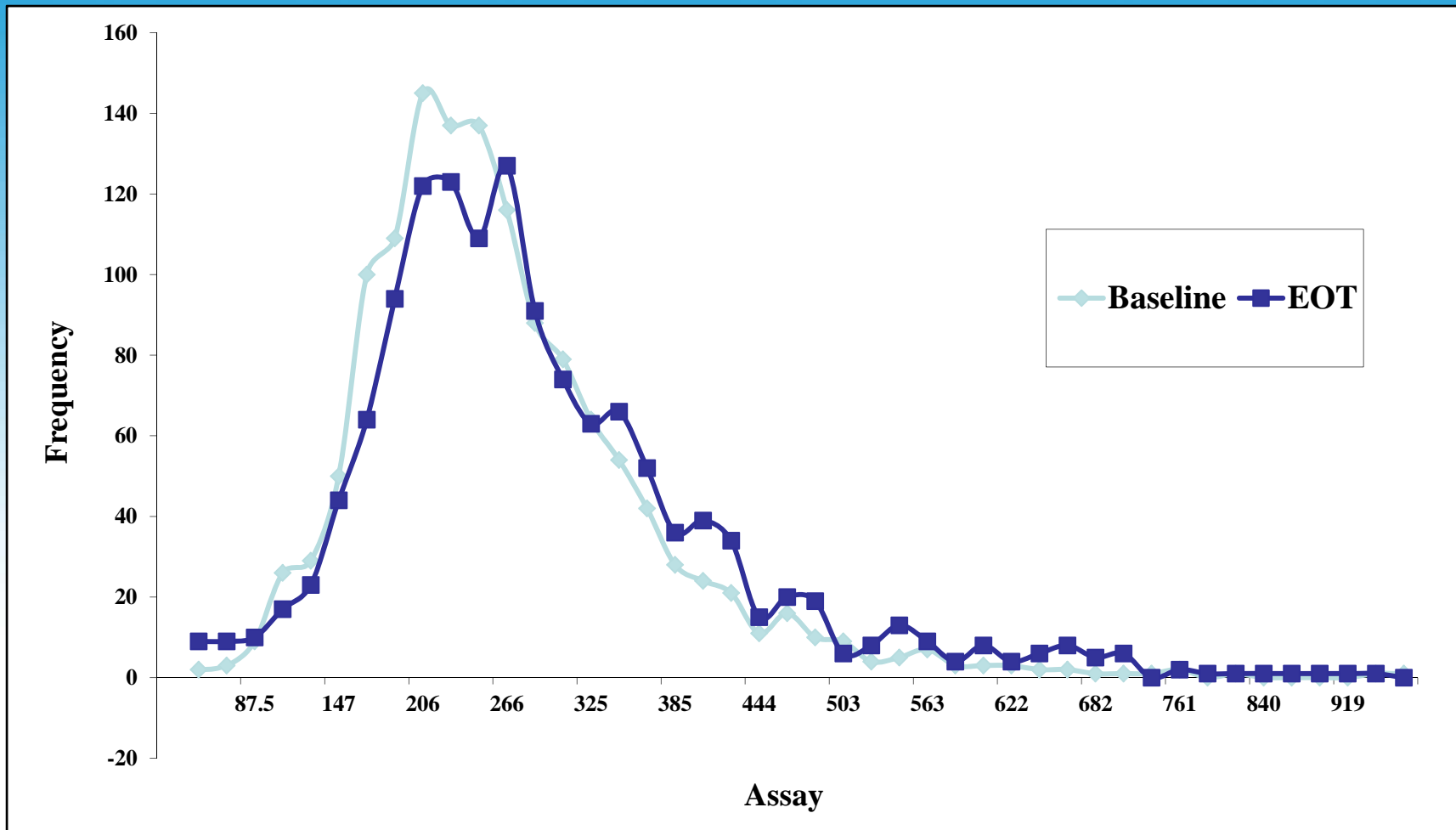
- ◆ Determine the risk measure to compare risk between groups.
- ◆ Classify events into tier-1, tier-2 or tier-3.
- ◆ Tier-1 events are clinically important and pre-specified. P-values and confidence intervals will be presented for the risk measure.
- ◆ Tier-2 events are “common” events, e.g. occurring in $\geq 1\%$ in at least one treatment group. Confidence intervals will be presented.
- ◆ Tier-3 events will be reported with proportion or incidence rate.

Source: Crowe et al. (2009) Clinical Trials , 6(5):430-440.

Tier-2 Events – Blue for Control and Red for New Drug



Baseline and EOT Platelet Plot



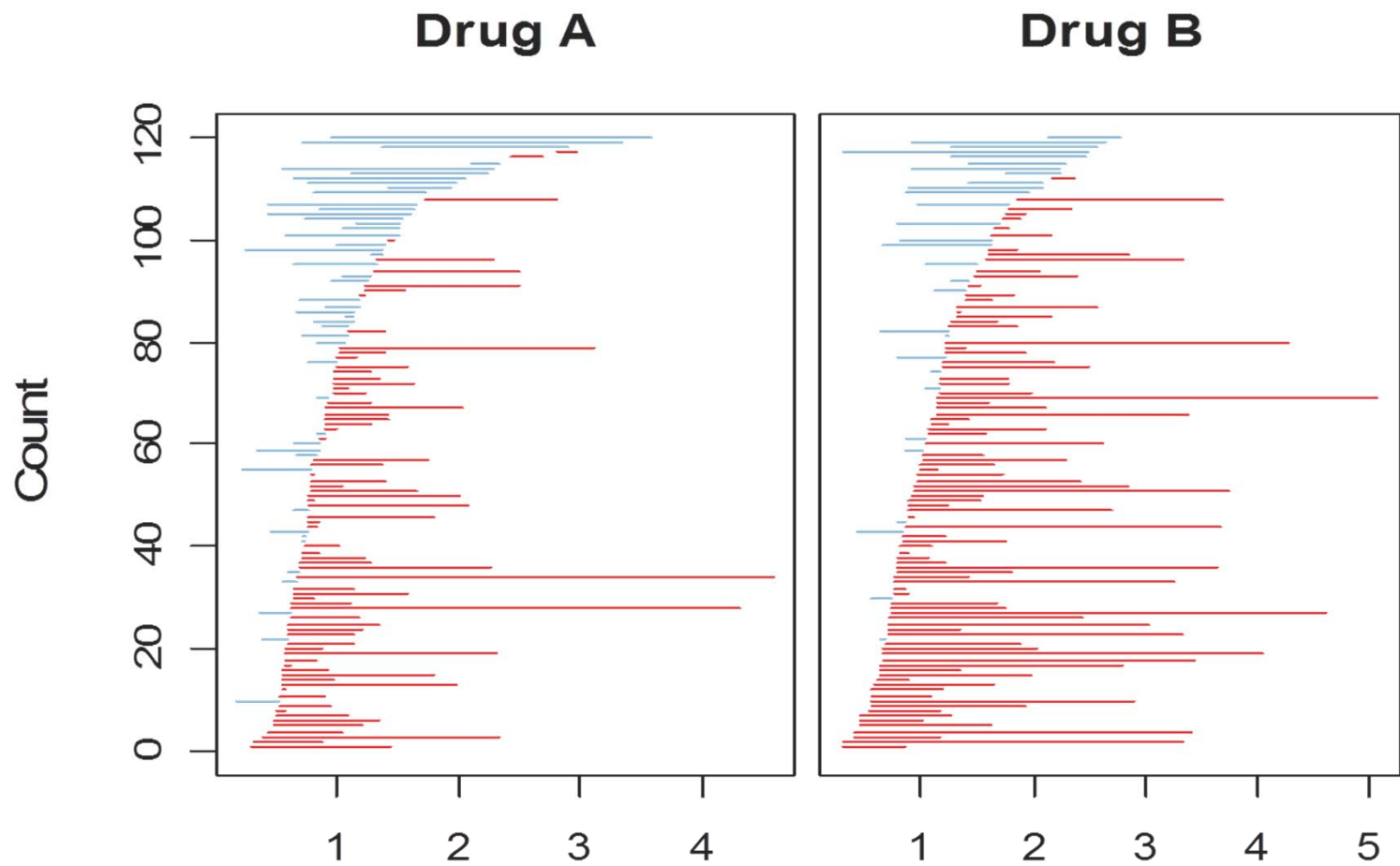


Figure 3. Side-by-side plots of baseline and last follow-up values

Who Is Sitting on the Couch, Girl or Boy?



Program Safety Analysis Plan (PSAP)

- ◆ **A plan for program-associated activities, not for detailed safety analyses for a specific study**
- ◆ **Provides analytical plan for the assessment of prospectively defined safety outcomes as well as identification of safety signals.**
- ◆ **It is a 'living' document, amended as needed and maintained by the multi-disciplinary Safety Management Team**
- ◆ **It is discussed with FDA and other regulatory agencies at milestone meetings (e.g., end-of-phase 2 meetings).**

Source: Xia et al. (2011) Clinical Trials , 8(2):175-182.

Elements of a PSAP Template

◆ Background

- Regulatory agreements
- Definition of safety outcomes

◆ General Plan

- Part I: Prospective AESI
- Part II: Retrospective emerging issues

◆ Data Generation

- Adequacy of safety database
- Size and type of studies (submission or program based analysis)
- Safety populations
- Proper duration of exposure
- Major toxicities
- Data collection methods
- Adjudication procedure
- Safety monitoring algorithms
- Data safety monitoring board

◆ Data Structure and Content

- Data quality and integrity assurance
- CDISC-SDTM, ADaM
- Terminology: WHODrug, MedDRA
- Concordance of AE and laboratory defined abnormalities

◆ Methods for Analysis, Presentation and Reporting

- Major analyses of SAEs and AESIs
- Dropouts, discontinuations and adequacy of follow-up and monitoring
- Biomarker validation
- Drug Interactions: concomitant illness, demographic, geography, substance interactions, medical systems
- Analytical methods for information synthesis for rare/uncommon events
- Tables and Graphs

◆ Problem oriented summary for AESIs

Source: Rochester (2009), FDA/Industry Statistics Workshop, September.

PSAP Implementation at Amgen

- ◆ **Created a PSAP SOP to formalize the PSAP process.**
- ◆ **Created a PSAP template**
 - ◆ **Linked to the above SOP to aid the implementation**

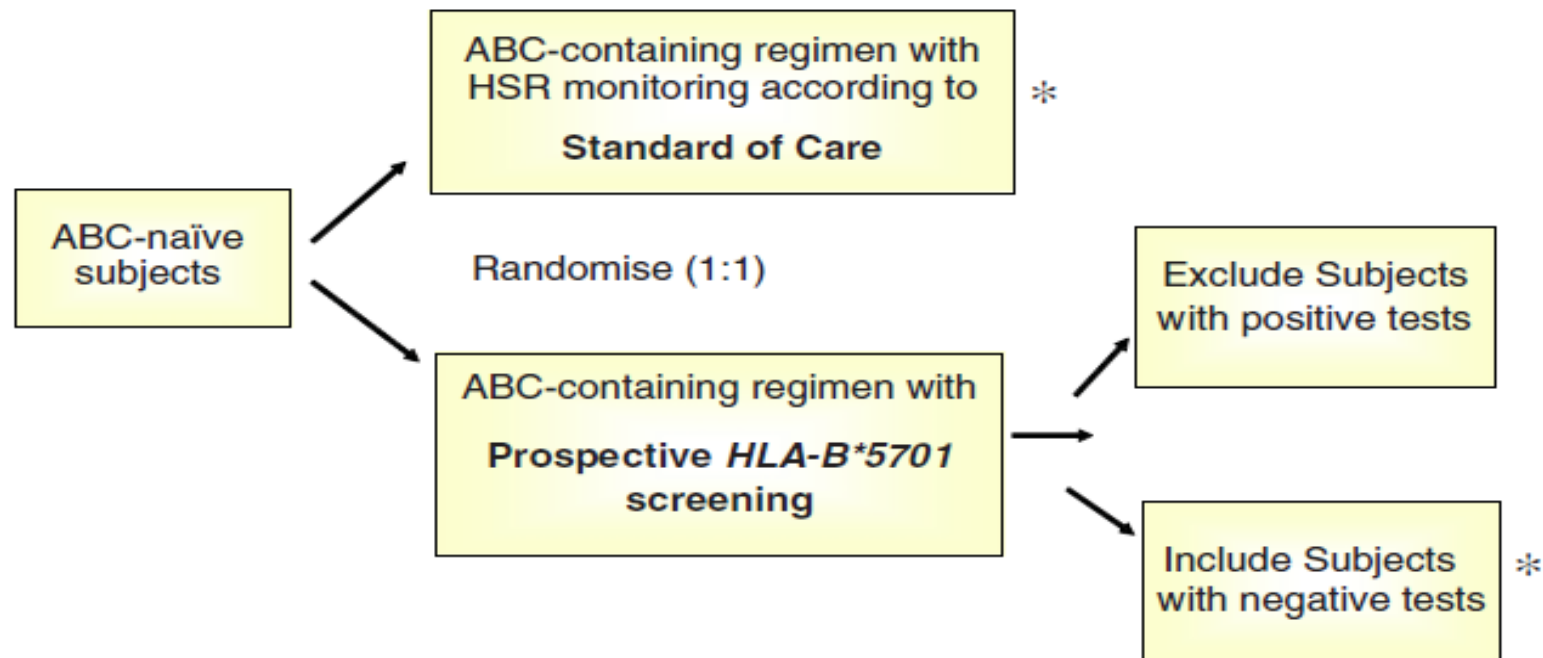


PREDICT-1: Study to Better Manage HSR

- ◆ **First adequately powered, double-blind prospective trial using pharmacogenetic screening to reduce drug adverse event. Recruitment April – Sept 2006.**
- ◆ **Background**
 - Abacavir (ABC) is a nucleoside-analogue reverse-transcriptase inhibitor antiretroviral drug.
 - ABC is associated with hypersensitivity reaction (ABC HSR) in about 5% - 8% patients.
 - Retrospective studies suggest a strong association between ABC HSR and the presence of the major histocompatibility complex HLA-B*5701 in chromosome 6.

Source: Hughes et al (2008). Pharm Stat, 7:121-129.

PREDICT -1 Design



*Clinically suspected HSR confirmed using patch testing
(blinded analysis by independent dermatologist)

Figure 1. Illustration of basic study design.

Source: Hughes et al. (2008). *Pharm Stat*, 7:121-129.

PREDICT- 1 Results

Table 2. Incidence of Hypersensitivity Reaction to Abacavir.*

Hypersensitivity Reaction	Prospective Screening <i>no. of patients/total no. (%)</i>	Control	Odds Ratio (95% CI)*	P Value
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

*: P-values, odds ratios, and 95% confidence intervals were obtained from fitting logistic regression models with several covariates.

Source: Mallal et al. (2008). *NEJM*, 358:568-579.

Warning in Abacavir Package Insert

EPZICOM (abacavir sulfate and lamivudine) Tablets

Initial U.S. Approval: 2004

WARNING: RISK OF HYPERSENSITIVITY REACTIONS, LACTIC ACIDOSIS AND SEVERE HEPATOMEGALY, AND EXACERBATIONS OF HEPATITIS

See full prescribing information for complete boxed warning.

- **Serious and sometimes fatal hypersensitivity reactions have been associated with abacavir-containing products (5.1)**
- **Hypersensitivity to abacavir is a multi-organ clinical syndrome. (5.1)**
- **Patients who carry the HLA-B*5701 allele are at high risk for experiencing a hypersensitivity reaction to abacavir. (5.1)**
- **Discontinue EPZICOM as soon as a hypersensitivity reaction is suspected. Regardless of HLA-B*5701 status, permanently discontinue EPZICOM if hypersensitivity cannot be ruled out, even when other diagnoses are possible. (5.1)**
- **Following a hypersensitivity reaction to abacavir, NEVER restart EPZICOM or any other abacavir-containing product. (5.1)**

Summary

- ◆ **Safety assessment has received much attention over the past 20 years. Some companies have dedicated statistical resource to perform the assessment.**
- ◆ **Safety evaluation is a continuum. It has become better structured and more effective in identifying safety concerns in recent years.**
- ◆ **Risk evaluation, mitigation and communication are essential to maximizing the benefit/risk profile of a pharmaceutical product.**
- ◆ **We can expect even more public scrutiny on product safety in the future.**

The Importance of Clear Communication

