Safety Monitoring in Clinical Development

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Outline

- CIOMS Reports on Safety Monitoring; in particular CIOMS VI (Susan Duke, Abbvie)
- FDA IND Safety Reporting Guidance (Bob Temple, FDA; Stephanie Shapley, FDA)
- Q&A

CIOMS Reports on Safety Monitoring

Susan Duke, Abbvie

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Why talk about CIOMS VI?

In 2011 an FDA "Rule" * went into effect that specifies that

> The sponsor must promptly review **all information relevant to the safety of the drug** . . . including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers . . .

- The CIOMS VI (2005) report was the first comprehensive document to describe how companies could perform such safety reviews

* 21CFR312.32 (b)

CIOMS Working Group on Safety

- Since 1986, CIOMS Working Groups on drug safety have been recognized as "think tanks" for advancing international pharmacovigilance practices.

- The initiatives over the years have resulted in several major published reports.
  - Many of these CIOMS recommendations become part of regulatory guidance by EMA, FDA and ICH etc.

EMA: European Medicines Association; FDA: Food and Drug Association;
ICH: International Conference on Harmonization

CIOMS Working Groups on Safety (cont.)

CIOMS WG	Descriptions	Resulting Regulatory Guidance
I	International Reporting of Adverse Drug Reactions (1990)	ICH E2A
II	International Reporting of Periodic Drug-Safety Update Summaries (1992)	ICH E2C
III	Guidelines for Preparing Core Clinical-Safety Information on Drugs (1999)	
IV	Benefit-Risk Balance for Marketed Drugs: Evaluating Safety Signals (1998)	ICH E2C R2 (PBRER)
V	Current Challenges in Pharmacovigilance: Pragmatic Approaches (2001)	

CIOMS Working Groups on Safety (cont.)

CIOMS WG	Descriptions	Resulting Regulatory Guidance
VI	**Management of Safety Information from Clinical Trials (2005)**	
VII	Development Safety Update Report (DSUR) (2006)	ICH E2F
VIII	CIOMS Working Group on Signal Detection (2006)	
IX	Practical Approaches to Risk Minimisation for Medicinal Products (2010)	
X	Considerations for applying good meta-analysis practices to clinical safety data within the biopharmaceutical regulatory process (In press)	

CIOMS Overview: CIOMS VI

- Introduces proposals for enhancing the collection, analysis, evaluation, reporting and overall management of safety information from all safety data sources (special focus on **clinical trials)**

- A shift from the management of post-marketing safety information (spontaneous reports), to the management of clinical trial information

Key Concept: Sponsor Safety Management Team (SMT)

- Multidisciplinary team
- Primary purpose is to review all safety info (clinical trial, epidemiologic, nonclinical, . . .) for a program on a regular basis so decisions on safety can be made in a timely manner
  - Review frequency depends on the nature of the product, protocol and age of the compound
- (Note how closely this aligns with the “rule”)

CIOMS VI: Key Principles of Systematic Approach to Managing Safety During Clinical Development

1. **Establish a procedure and governance**
   - **Decision-making process, advisory body**
2. Begin early
3. **Establish a Multidisciplinary Safety Management Team (SMT)**
4. **Establish SMT review timeframes, milestones**
5. Establish a project management function
6. Determine background data
7. Ensure accessibility of data
8. **Develop a proactive approach**

These principles are the basis of the Program Safety Analysis Plan (PSAP), recommended by the Safety Planning, Evaluation and Reporting Team (SPERT), Crowe et al. (2009). Recommendations for safety planning, data collection, evaluation and reporting during drug, biologic and vaccine development: a report of the safety planning, evaluation, and reporting team. *Clinical Trials (London, England), 6(5), 430-440.*

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CIOMS VI: Causality Assessment

- Causality judgments (p. 84): "**based on analysis of multiple cases/aggregate data are almost always more meaningful and typically have a greater impact**…"

- This ties into the principle laid out in the FDA IND guidance

CIOMS VI: Statistical Considerations

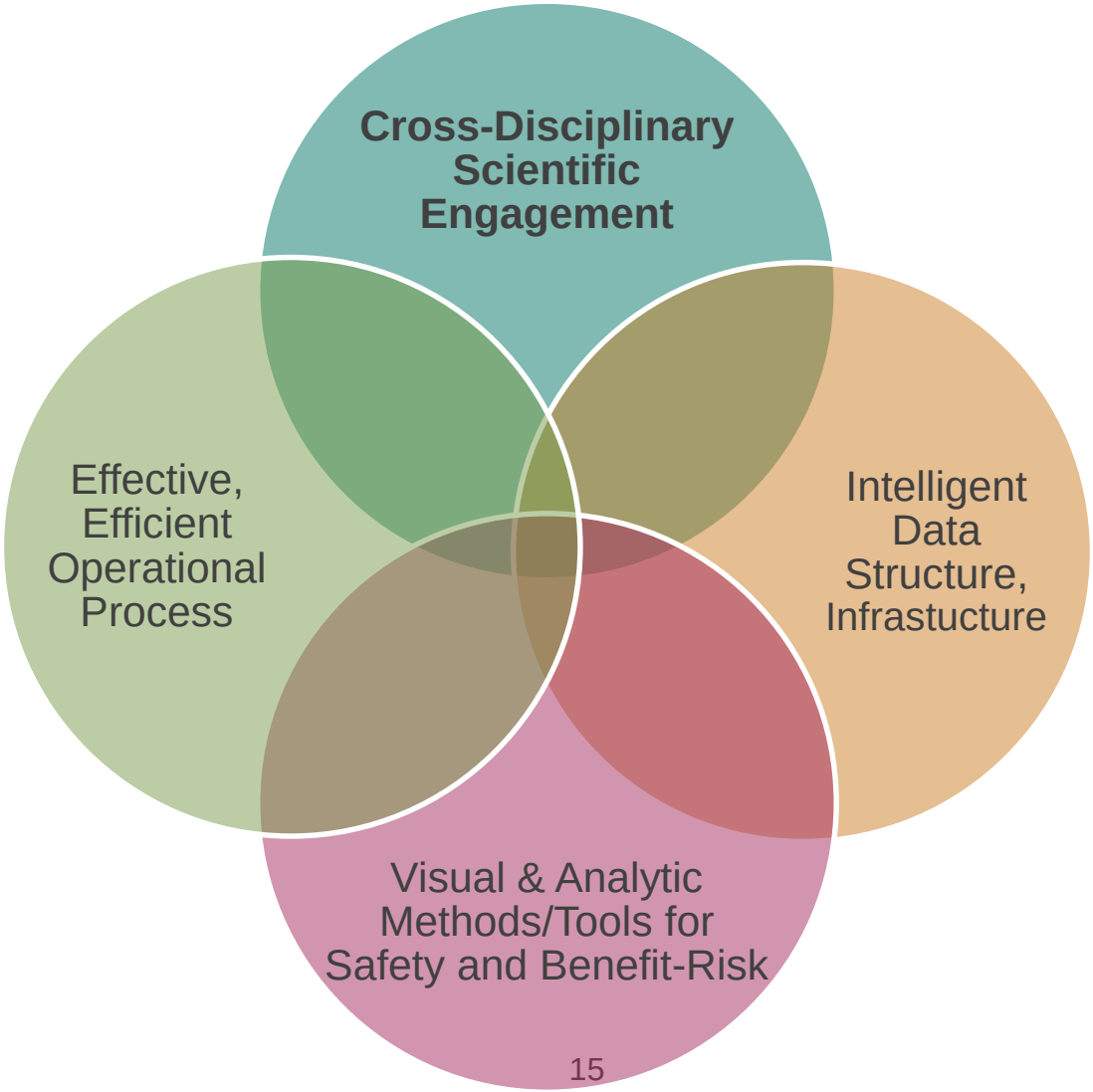
- **Meta-analytic review should be a routine part of the drug development process**
  - Necessary for detection of ADRs, and differences in ADR rates between treatment groups
  - Crude pooling of adverse event numbers across different trials to compare treated and control groups should be avoided where possible
- Clinical judgment based on quantitative assessment is a partnership of both disciplines
- Descriptive methods and well-designed graphics are helpful

Quantitative Enablement and ASA Safety Monitoring Working Group

- In 2015, the ASA biopharmaceutical section established a safety monitoring working group
  - Goal: help the biostat community to better enable quantification of safety monitoring
- Sessions in 2016
  - August: Joint Statistical Meetings, American Statistical Association Biopharm section
  - December: Deming Conference
- What are we learning?

The Four Pillars of Safety Statistics

In the best interest of the patients we serve



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Concluding remarks

- Clinical safety monitoring and IND safety reporting (to be covered by Dr Temple) are important for protecting patient safety
- Systematic approaches have been advocated by CIOMS reports and regulatory guidance
- Biostatistics professionals can and should play an important role. The ASA safety working group is established to help enable this