Analytical Framework : Safety Assessment Committee in Drug Development

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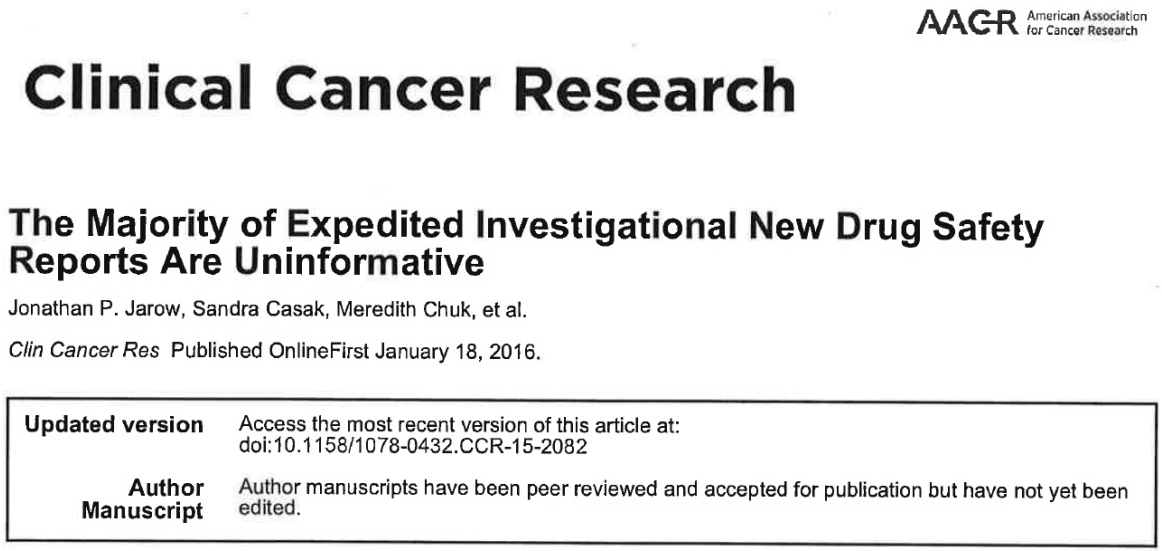
“Reverse” Disclaimer

All Contents and Ideas presented in this presentation reflects the opinion generated by myself and my employer !!!!

Outline

- Scope & Relevance of SAC
- Implementation Stage
- Analytical Framework
- Next Steps

Scope & Relevance of SAC – the "Why"



AACR American Association for Cancer Research

Clinical Cancer Research

The Majority of Expedited Investigational New Drug Safety Reports Are Uninformative

Jonathan P. Jarow, Sandra Casak, Meredith Chuk, et al.

Clin Cancer Res Published OnlineFirst January 18, 2016.

Updated version	Access the most recent version of this article at: doi:10.1158/1078-0432.CCR-15-2082
Author Manuscript	Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

- Office of the Hematology & Oncology Products (OHOP) receives an average of 17,686 expedited safety reports a year. Audit of 160 randomly selected reports in 2015
- About 20% met regulatory definition for reporting

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Evolution of Safety Reporting

September 2010

- 21 CFR 312- final rule for reporting requirements

December 2012

- Safety Reporting Guidance to help sponsors comply

December 2015

- Safety Assessment for IND Draft Guidance to help sponsors develop a systematic approach for IND safety reporting

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Amended 21 CFR 312 Definitions

- Suspected ADR is an AE for which there is a ***reasonable possibility*** that the drug caused the AE
  - **Single occurrence of a known drug related AE**
  - **One or more occurrence of an uncommon event in the population**
  - **Aggregate analysis of specific known events higher in the treatment group than in the underlying population**
- Sponsor is responsible for 'reasonableness' decision
  - **In contrast to ICH E2 which also allows investigator judgement**

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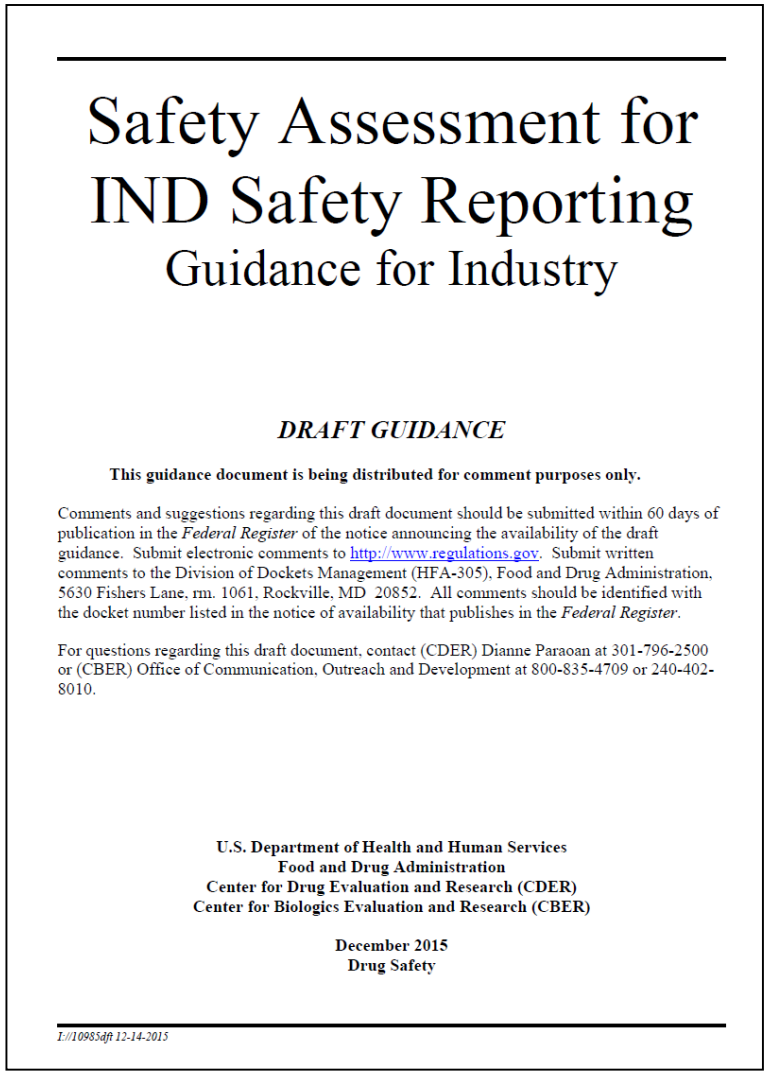
"How" to implement – 2015 DRAFT Guidance (FDA)



Safety Assessment for IND Safety Reporting

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Dianne Paraoan at 301-796-2500 or (CBER) Office of Communication, Outreach and Development at 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2015
Drug Safety

I://10985dft 12-14-2015

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Practical Implications of Rule/Guidance

1. Sponsors should not submit IND safety reports for those serious adverse events that were prospectively identified as anticipated to occur in the study population unless the evidence suggests a causal relationship between the drug and the event (see § 312.32(c)(1)(i)(C))— *which is a matter of judgment*.

2. Determining when the aggregate safety data provide evidence to suggest a causal relationship between the drug and a serious and unexpected adverse event or show a clinically important increase in a previously recognized serious adverse reaction rate is a complex judgment that is, in most cases, not a simple application of a planned statistical analysis.

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"What" to Develop during Drug Development

- Sponsor responsible for managing Safety Reporting in a drug development program to the agency
  - Sponsors create & oversee a Safety Surveillance Plan (SSP)
  - Constitute a Safety Assessment Committee to improve the quality of Safety Reporting to the agency
    - Panel of medical experts and biostatisticians
      - **Independent** of trial/program conduct
      - Meet virtually & periodically as agreed in SAC charter
    - Reviews **unblinded** trial/program data for any safety signals
      - relative to **cumulative** evidence across treatment, disease, other areas
    - Help Sponsor assess if there are AEs considered to be ***suspected unexpected* serious adverse reactions (SUSAR)** that needs reporting

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Analytical Strategy to trigger Safety review by SAC

- Comprehensive analytical strategy to research includes
  - **Systematic Literature Review:** Variety of Information Sources
    - Across Trials/ Registries/ Medical databases/ Epidemiology studies
    - For Treatment Class / Disease States
  - **Identification of Expected Safety Signals:** Find “Unexpected”, eliminating
    - Known events/consequences of disease condition and severity
    - Known safety issues due to treatment class
    - Anticipated events common to population under study

Analytical Strategy to support SAC

- Comprehensive analytical strategy (contd.)
  - **Quantitative Assessment of incidence rate of events**
    - Expected (high incidence) and Unexpected (low incidence) events
    - "Incidence rates per thousand hrs of exposure" accounts for varying duration
    - Credible "Baseline Event Rate" for the population of interest
  - **Develop a "Threshold" for each Serious Adverse Event**
    - Incidence rates above the **"threshold"** is considered **"Unexpected"**
  - **Causal relationship with treatment?**
    - Medical/Clinical input is essential along with quantitative assessments

Statistical Methods to calculate "Threshold" & "Causality"

- Possible Methods may include
  - **Probability of Observing an Adverse Event of Interest (Duke et al 2017)**
    - Difference between Treatment & Placebo using Binomial probability
    - Applicable to single-arm study
    - Risk-based methods
      - Use Incidence Rates (IR) of the trial to calculate 95% CI @ baseline
      - Use of Exact Poisson or Binomial distribution for rare events
  - **Disproportionality Analysis (Data Mining at FDA, Duggirala et al)**
    - Widely applicable in pharmacovigilance, with historical data
    - Applies to a particular AE compared to the incidence rates of other AEs
  - **Tolerance Interval approaches for Incidence Rates**
    - Applicable using historical data and epidemiology data
    - Upper tolerance limit could be considered the "Threshold"
  - **Bayesian analysis to estimate posterior probability of incidence rates**

Challenges for Analytical Considerations

- Predicting SAE rates, and data pooling
- Standard interpretation & Challenges of Meta Analysis – the assumptions and the choice of studies
- Varying rates across subgroups/patient populations, Therapeutic areas, Doses & formulations
- Aggregate analysis when multiple INDs are involved
- Challenges acquiring data from ongoing trials
- Data merges across various platforms and studies – internal, external
- Large Outcome trials may mask rates observed in smaller trials

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Statisticians across the industry are collaborating thru ASA Biopharm section working group in addressing many of these safety related issues & possible solutions/guidance.

The Road Ahead in Unclear

Teamwork is key to success

Thanks

Potential Challenges to overcome in SAC Implementation

- Study Integrity and Patient Confidentiality could potentially be compromised by unblinding
- Uncertainties around urgency of reporting on-time
  - does the clock start at the SAC or the occurrence of events?
- Operational challenges, including resources and expenses, availabilities of appropriate safety experts, especially for small-mid size sponsors & rare diseases
- Potential Overlap of roles with Data Monitoring Committee, or internal Safety Monitoring boards within sponsors
- Lack of Global Harmonization on Safety Monitoring

Factors To Consider For Weighing of Studies in Establishing Baseline Event Rates?

Factors to Evaluate in Past Trials:

- Similarity in clinical indication
- Similarity of subject population in terms of age, race, gender, and other demographic characteristics
- Similarity in disease duration, prior treatments, and use of concomitant medications
- The size of the past trial
- The length of time subjects evaluated in past study
- Similarity in collection and coding of events
- How recent the past studies are
- Choice of Standard of Care or Comparator in studies
- Use of direct/indirect marketplace competitors
- Open label vs. blinded studies
- Study integrity and competence of investigators/sponsor