FDA Draft Guidance on Safety Assessment Committees: How On-Demand Data Facilitates Insightful Assessments
Introductions

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Recent FDA Guidance

- Represents what FDA is currently thinking on IND Safety Reporting

- Although not obligatory, some companies are already doing it – best practices

- DRAFT – subject to comments, revision and even withdrawal

### FIVE MAJOR THEMES

1. Development of a Safety Surveillance Plan
2. Use of a Safety Assessment Committee (SAC)
3. Performance of aggregate analyses to compare AE rates across treatment groups
4. Planned unblinding of safety data
5. Reporting thresholds for IND safety reporting
For IND studies, this plan should include:

- Predicted rates of anticipated SAEs and previously recognized SARs that will be monitored
- Process for routine and timely review of SAEs using aggregate data
- Guidelines to determine when increased observed rate exceeding predicted rate is noteworthy and reportable to FDA
- List of SAEs that will not be reported as 7- or 15-day reports
- Description of the SAC, roles, members & responsibilities plus any other safety committees (e.g. Adjudication or Steering Committees)
- Guiding principles for periodic aggregate safety reviews

Maintained by sponsor or CRO; reviewed by FDA before initiation of phase 2 or 3 studies
Safety Assessment Committees (SACs)

- Analyses should be unblinded
- Multidisciplinary, or cross-functional, team
  - Therapeutic medical expert
  - Epidemiologist
  - Pharmacologist
  - Toxicologist
  - Chemist
  - Biostatistician
- Members sourced internally, externally or both, but should not be directly involved with trials being investigated
- Systematic evaluation of relevant aggregate data required to identify signals that require further action and reporting
- Makes recommendations regarding signals

**Responsible for:**

- Reviewing totality of data for all SAEs, across all completed and ongoing trials
- Detecting relevant safety signals worthy of further assessment to determine if there is a safety risk and if action is required
Rapid and early identification of noteworthy SAEs required for timely implementation of countermeasures

However, it can be challenging to proactively monitor data for one trial, let alone review aggregate data across multiple trials

Given volume of data, identifying important signals and trends is resource-intensive

Often, safety trends are hidden and not obvious by simply looking at tables and listing

Because data quality can significantly affect validity of the signal detection process, safety signals would ideally be detected from data that have undergone periodic quality checks
Integrated Signal Detection Service

- Safety Detection Services (SDS)
  - Integrated service platform, with an SAC, supported by integrated technology platform
  - Reviews aggregate safety data
- dCRO methodology enables on-demand visualizations of all patient safety data as well as ability to detect events of special interest for further signal analysis
- SAC scientifically identifies suspicious or hypothesis-generating activity from the aggregate data stored in TEMPO™
- Conducts impact analyses for potential risk
- Visual summary of analytic results forms basis for decisions by sponsor
## Key Features of the Clinipace Signal Detection Service

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<th>Feature</th>
<th>Description</th>
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| Integrated          | • SAC consists of a cross-functional, experienced team within Clinipace  
                       • All data stored within one platform, facilitating data aggregation  |
| Visual              | • Graphically visualize temporal trends and patterns across the breadth of the platform, including data from other studies  |
| Proactive           | • Real-time access to data that is medically coded  
                       • Benefit-risk decisions can occur much earlier  
                       • Early detection of subtle yet detectable signals  |
| Clean and quality   | • Ongoing quality checks of real-time data within TEMPO™  |
| Efficient           | • Platform enables timely review of data, requiring fewer personnel and less time  |
Study-Level Aggregate Data: No Filters
Study-Level Aggregate Data: SAEs Only
Study-Level Aggregate Data: Unexpected SAEs
Study-Level Aggregate Data: Unexpected Possibly Related SAEs

Top 10 HLGT By CTCAE Grade

Top 10 By SOC / Age Band

- Metabolism and Nutrition Disorders
- Gastrointestinal Disorders
- Blood and Lymphatic System Disorders
- Renal and Urinary Disorders
- Skin and Subcutaneous Tissue Disorders
- General Disorders and Administration Site Conditions
- Investigations

Grade 1 (Mild) - Grade 2 (Moderate) - Grade 3 (Severe)

System Organ Class:
- Blood and Lymphatic System Disorders
- Gastrointestinal Disorders
- General Disorders and Administration Site Conditions
- Metabolism and Nutrition Disorders
- Skin and Subcutaneous Tissue Disorders
- Renal and Urinary Disorders
- Electrolyte and Fluid Balance Conditions
- Body Temperature Conditions
- Anemia
- Neutropenia
- Fever

Preferred Term:
- Anemia
- Blood Creatinine Increase
- Dehydration
- Diarrhea
- Hypotension
- Pyrexia
- Renal Failure Acute
- Swelling Face
- Thrombotic Thrombocytopenic Purpura

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Study-Level Aggregate Data: AEs by Site & Subject
Identifying Safety Issues: Patient-Level Data
Timely knowledge of product effectiveness & safety is extremely important

Ability to access the right data at the right time is necessary

SACs require the right information at the right time to make appropriate decisions regarding patient safety

Clinipace SDS provides:
- Expertise to determine which events require further attention
- Technology to enable proactive & informed decision-making