Statistical assessment and analyses of suicidality data in clinical trials: current challenges

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- Cristiana Gassmann-Mayer is an employee of Johnson & Johnson
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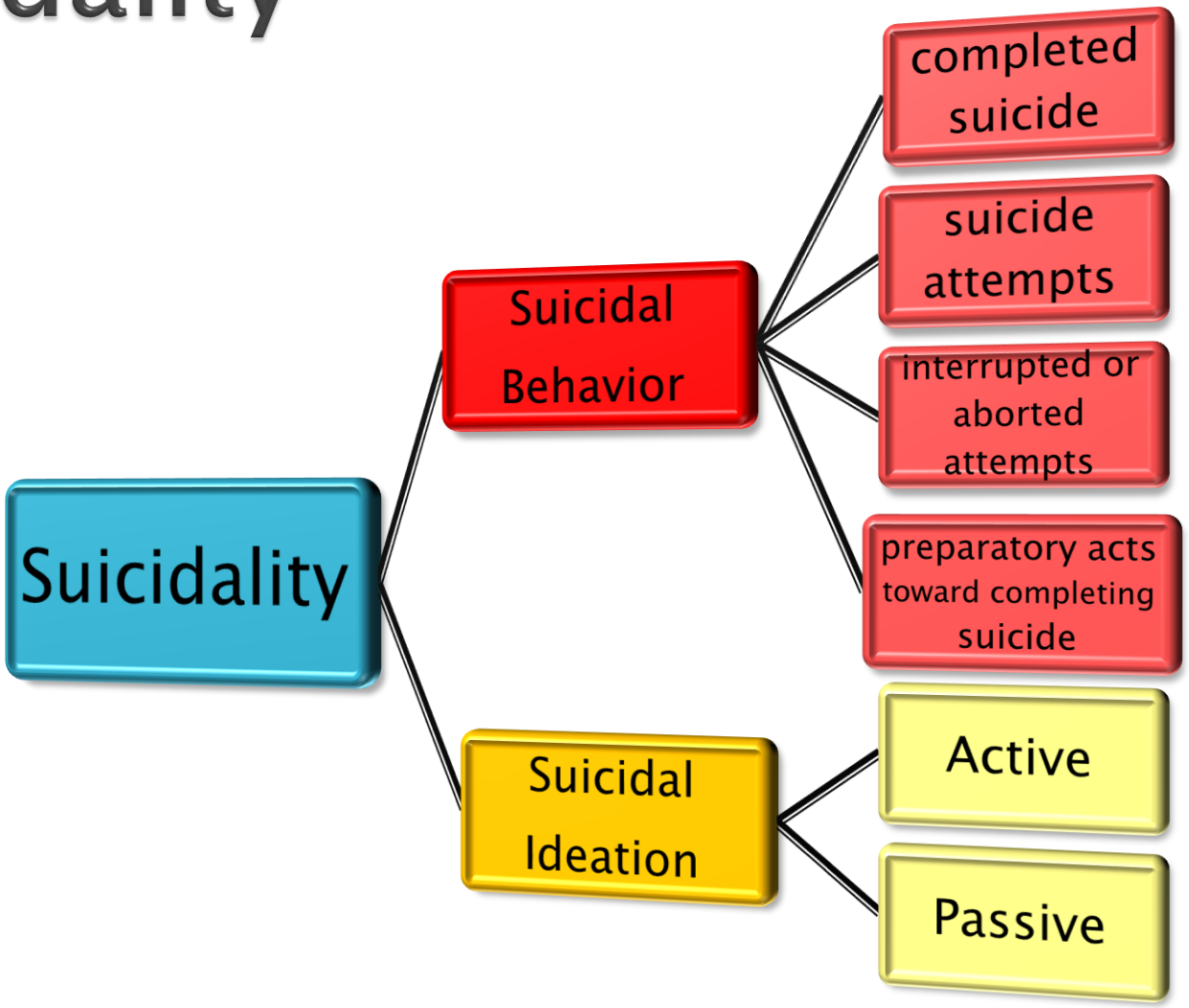
Outline

- What is “suicidality”?
- General background
- Pharmaceutical Research and Manufacturers of America (PhRMA) working group
- Statistical challenges and analyses
- Considerations
- Next Steps
- Conclusions

Suicidality



Increased risk of suicidality ?

General Background

- Issue: Potential association between drugs and increased risk of suicidality
- Media and public attention
- Concerns from regulatory agencies, pharmaceutical industry, investigators, researchers, and patients
- CNS compounds (e.g. for depression, schizophrenia, bipolar disorder, epilepsy, ADHD, etc.) and others (smoking-cessation, obesity, weight loss, alcoholism, etc.)
- Special subgroups: e.g. by age
- Need to collect suicidality data prospectively

Examples of Suicidality Risk Assessment in the U.S.

- 1991 – fluoxetine → no association concluded
- 2004 – SSRIs pediatric data analysis → boxed warning
- 2006/2007 – SSRIs & Adult use of antidepressants* → boxed warning for young adults (<25 years)
- 2007–present: Epidemiologic research on the negative consequences of the "black box warning" in younger patients

* M Stone, et al – *BMJ* 2009;339:b2880

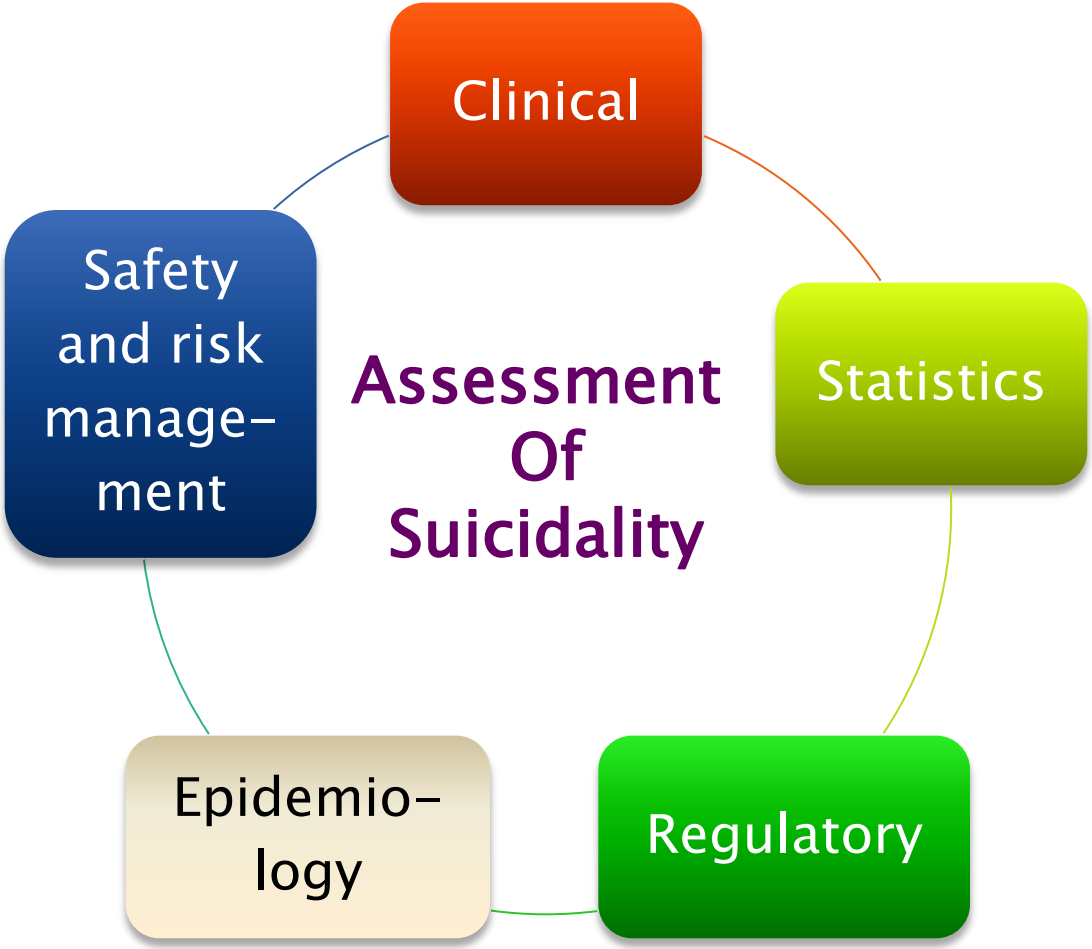
Examples of Suicidality Risk Assessment in the U.S. (cont.)

- 2005 – Atomoxetine (Strattera ADHD) → FDA issued PHA 2005 → Boxed warning in 2008 for increased risk in suicidal thinking for children and adolescents
- 2007 – Acomplia /Rimonabant (weight loss) → increased risks of suicidality (ideation); not approved in the US
- 2008 – Anti-epileptic drugs data review by the FDA in May → public advisory committee meeting in July → public health advisory issued in December

Examples of Suicidality Risk Assessment in the U.S. (cont.)

- 2008 – Chantix (smoking cessation) approved in 2006 → PHA issued in 2008 → boxed warning in 2009
- 2008 – Singulair – Data review by the FDA for detection any signals of association with increased risks of suicidality

PhRMA Suicidality Cross-Functional Working Group



Scope of PhRMA Working Group

- Consensus within PhRMA on the assessment, analysis and reporting of suicidality data
  - Kick off meeting in June 2008
- White paper
  - Finalized and sent to the FDA in December 2008
- Engage in and promote discussion and collaboration
  - PhRMA companies, Regulatory agencies, Academia and Researchers
  - Recent meetings:
    - Columbia U (January 2009) – International suicidality Capstone meeting
    - Institute of Medicine (June 2009) – CNS CT: suicidality and data collection

PhRMA Suicidality Working Group: Statistics

Statistics- (in alphabetical order):

Cristiana Gassmann-Mayer (J&J) – *co-lead*
Paul McSorley (GSK) – *co-lead*

Ramin Arani (BMS)
Suna Barlas (Wyeth)
Sarah DuBrava (Pfizer)
Kaihong Jiang (Sanofi-Aventis)
John Polzer (Eli Lilly)
Shailaja Suryawanshi (Merck)

Joined later: Janice Carlson (Eli Lilly) – MW
Mary Nilsson (Eli Lilly)
David Webb (Eli Lilly) – MW
Lingfeng Yang (Wyeth)

What are the challenges in the statistical assessment and analyses of suicidality data ?

Statistical Challenges

Single trial level:

1. Data collection and classification of events
2. Definition of endpoints
3. Statistical analyses and methods

Compound level:

1. Selection of studies
2. Definition of endpoints
3. Statistical analyses and methods

Data Collection and Classification

- Old Practice:
  - Retrospective search for AE terms and partial strings
  - Classify terms as either suicidal behavior or ideation
  - Tabulate frequency of events

Data Collection and Classification (cont.)

- Ascertainment bias, will subjects be more likely to report a suicidal-related event?
- Classification errors in either direction have serious consequences:
  - Adverse Events that should have been called suicidal may have been missed
  - Adverse Events may have been inappropriately classified as suicidal
- Misclassification may lead to incorrect or inconclusive interpretations of the risk-benefit ratio
- Negative implications for appropriate management of suicidality

→Need a prospective instrument with standardized language, and consistent classification

Data Collection and Classification (cont.)

C-CASA (Columbia Classification Algorithm of Suicide Assessment) [1]

Event Code	Event	
1	Completed suicide	Suicidal
2	Suicide attempt	
3	Preparatory acts towards imminent suicidal behavior	
4	Suicidal ideation	
5	Self-injurious behavior, intent unknown	Indeter-minate
6	Not enough information, fatal	
7	Self-injurious behavior, no suicidal intent	Non-Suicidal
8	Other, accident, psychiatric; medical	
9	Not enough information, non fatal	Indeter-minate

[1] Posner et al. American Journal of Psychiatry. 2007;167:1035-1043

Data Collection and Classification (cont.)

New practice:

- Prospective scale to collect suicidality data
- Example:

C-SSRS: Columbia Suicide Severity Rating Scale:

- the prospective counterpart of the C-CASA classification scheme
- An instrument designed to collect the:
  - **Occurrence**
  - **Severity**
  - **Frequency**

  of both suicidal thoughts and behaviors during the assessment period

Data Collection and Classification (cont.)

Other scales can be used. E.g.:

- Sheehan Suicidality Tracking Scale
- InterSePT Scale for Suicidal Thinking (ISST)
- Scale for Suicide Ideation (SSI)
- Beck Suicide Ideation (BSI)
- Single items of various depression rating scales (e.g. Hamilton Depression Rating Scale, Beck Depression Inventory)

Definition of Endpoints

1. Any suicidality event (behavior or ideation)
2. Suicidal behavior
3. Suicidal ideation

1. Commonly, if multiple events use the most severe one.
2. 3. If the scale allows for collecting ideation separate from behavior

Caution: RARE events !

Selection of Studies

- Prespecify the criteria for data aggregation from multiple studies
- Describe the type of study (e.g. DB, OL, cross- over)
- Distinguish trials with active vs placebo control
- Investigate trials for the same indication vs across indications for the same compound
- Clarify the treatment duration, extent of exposure

Statistical Analyses

- Tabulation, descriptive statistics
- Commonly used odds ratios, incidence rates, exposure adjusted incidence rates
- 95% confidence intervals, forest plots, tests (Fisher exact test, Mantel-Haenszel test, etc.)
- Subgroups: stratification, logistic regression
- Time to event
- Typically no multiplicity adjustment (safety data)
- Assess sensitivity of results to different statistical techniques
- Other methods (Bayesian methods, ZIP model, arcsine difference, etc.)

Considerations

- Importance of prospective instruments, standard terminology and consistent methodology of classification of suicidality events across studies and indications
- Scales to collect suicidality data may be sensitive to: geographical region, investigator, time of conduct of studies
- Sparseness of the events (studies with double zero counts)
- Typically limited power to detect a suicidality safety signal

Considerations (cont.)

- How best to aggregate data, especially in presence of clinical heterogeneity:
  - Study type/duration/design (short/long term, DB/OL, placebo- or active-controlled, cross over, etc)
  - Studies with retrospective and others with prospective suicidality data
  - Within compound: Studies across different indications
  - Within indication: Studies across different compounds (with various mechanisms of action)
- Use inferential statistics with caution
- Interpret results with caution (e.g confounding by indication)

Next Steps for PhRMA WG Statistical Sub-team

- The **PhRMA WG Statistical sub-team** will continue working on:

1. **Publication effort** of the white paper concepts for education purposes targeted to statisticians involved in clinical trial research

2. Development of guidelines on **detailed SAP** for the analysis and presentation of suicidality data

Conclusions

- Data collection: Use a prospective instrument and a standard classification system
- Data analysis: Use different statistical approaches
- Interpretation: Exercise caution in interpreting the results
- Collaboration and more collaboration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Acknowledgments and Thank you !!

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