


Safety Assessment for Investigational New Drug Safety Reporting

Public Workshop

March 8, 2018


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Welcome & Overview

Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

March 8, 2018

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IND Safety Reporting

An Overview

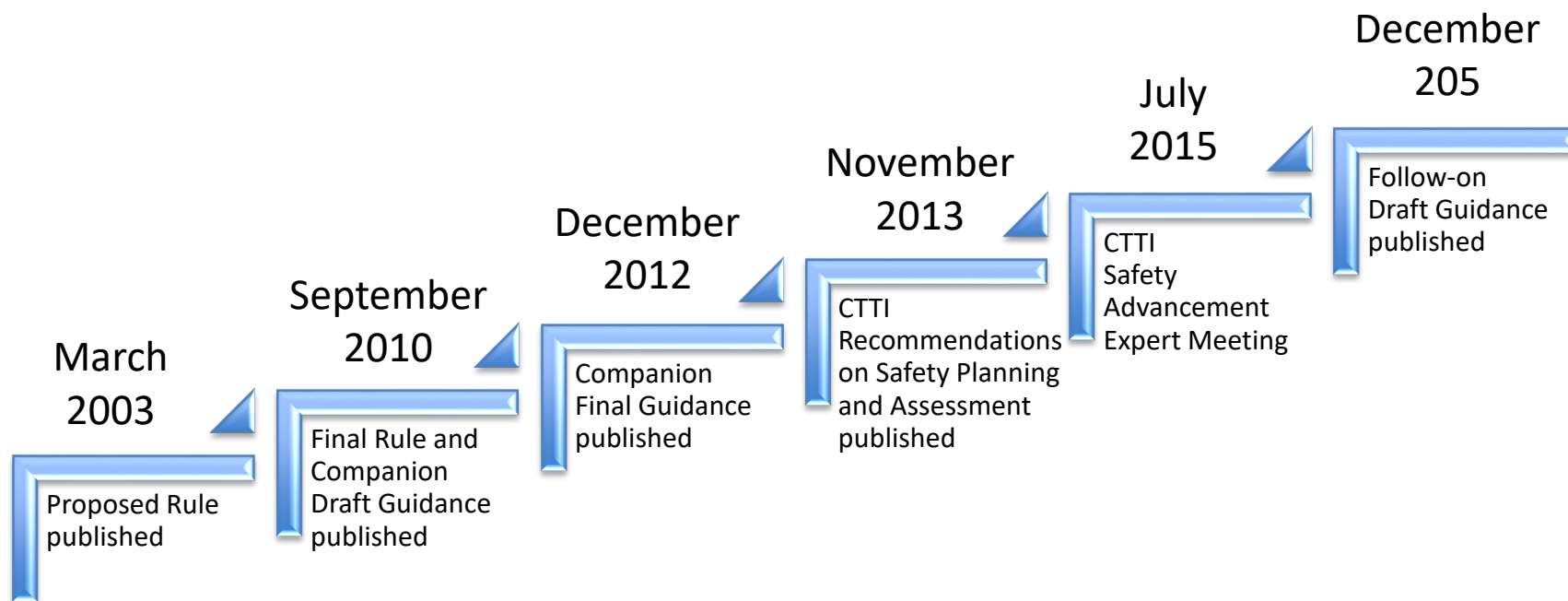
Robert Temple, M.D.

Deputy Center Director for Clinical Science

Center for Drug Evaluation and Research

Food and Drug Administration

Timeline of Policy Development: IND Safety Reporting





IND Safety Reporting

Pre - 2010



- **The reporting rule was intended to find serious and unexpected adverse events associated with the use of the investigational product**
 - “Associated with” defined as a “reasonable possibility”
- **The revision of the long standing IND Safety Reporting Rule was intended to address unnecessary reporting of large number adverse events that were:**
 - Probable manifestations of the underlying disease
 - Adverse events common in the study population independent of drug exposure (e.g., heart attacks or strokes in older people)
 - Study endpoints



IND Safety Reporting

Final Rule 2010



- **2010 Revised IND Safety Rule**: Introduced the term “suspected adverse reaction” and made clear that a “reasonable possibility” means that there is evidence to suggest a causal relationship between the drug and the adverse event
- **Scope** – Required expedited (7 and 15 day) reporting of potential serious risks, including serious and unexpected suspected adverse reactions (no change from previous rules)

Potential Serious Risks that Require IND Safety Reporting



3 easy and 1 hard



Individual Events

- **Uncommon and strongly associated with drug exposure (e.g., Stevens Johnson Syndrome)**
(312.32(c)(1)(i)(A))
- **Not commonly associated with drug exposure but uncommon in population (e.g., tendon rupture)**
(312.32(c)(1)(i)(B))

Aggregate Analyses

Events/findings that:

- **An unexpected adverse event that occurs more frequently in drug treatment group than control** (312.32(c)(1)(i)(C))
- **Suspected adverse events (in the IB) that occur at a clinically important increased rate above that listed in protocol or IB** (312.32(c)(1)(iv))

Review of Accumulating Safety Data – 2012 Guidance



- Periodic review of accumulating safety data and appropriate reporting
- To protect trial integrity, sponsors need a predefined safety monitoring plan with processes and procedures for review of safety data, including the frequency of review
- Guidance addresses the role of unblinding in determining:
 - Whether a single occurrence of an event needs to be reported (Critical to know whether patients received the drug)
 - Whether an event needs to be reported based on an aggregate analysis

Impetus for 2015 Draft Guidance



- **Stakeholders continued to have questions regarding:**
 - reporting thresholds,
 - approaches to unblinding, and
 - aggregate analyses
- **CTTI 2015 Stakeholder Meeting Findings**
 - Rule on IND reporting not effectively implemented by most sponsors
- **FDA experience**
 - Analysis of SAEs submitted on oncology trials found majority were expected events and not informative [Jarow, Casak, Chuk, Ehrlich, Khozin; *Clinical Cancer Research*; 2016]
 - Other experiences suggested that thoughtful discrimination of events likely to be drug-related from those that were severe but anticipated in the study population, was generally not occurring.

2015 Draft Guidance


Guidance to enable sponsors to evaluate unblinded data from ongoing trials (when necessary) to determine if the threshold for IND reporting met, while maintaining trial integrity

- Safety surveillance plan (SSP)
- Safety assessment committee (SAC)
 - Access to unblinded data limited to group of individuals who are firewalled from trial
- Pooled analyses across development program
- Reporting thresholds – factors to consider

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IND Safety Reporting: Addressing Challenges Implementing the 2015 Draft Guidance

Peter Stein, MD
Deputy Director, Office of New Drugs
CDER/FDA

Overview

- **Specific features added in 2015 guidance**
- **What have we heard: issues raised regarding implementation of 2015 guidance**
- **Our goals for the meeting**

2015 guidance: updates to 2012 guidance

- Additional information on content of **Safety Surveillance Plan (SSP)**
- Increased definition of role and responsibilities of **Safety Assessment Committee (SAC)**, membership and data to be reviewed by committee
- Recommendation to perform regular, **unblinded analyses** of aggregated data, **pooled** across program studies for SAC
 - Focused on events only identifiable based upon imbalances between groups
 - Alternate approach of unblinding based upon exceeding threshold levels
- Discussion of **factors to consider** to identify events from aggregate analysis appropriate to report as IND safety updates
- Provides recommendations on **minimizing impact of unblinding** on trial integrity
 - Limit reporting to events deemed suspected – based upon reasonable possibility, i.e., evidence to suggest a causal relationship between the drug and the adverse event – expectation that this will be infrequent

Different “types” of IND safety reports

Goal is earliest possible reporting of serious, unexpected, suspected adverse reactions (21 CFR 312.32)

Identifiable based
upon blinded review

- *Single occurrences of uncommon events typically associated with drug exposure: agranulocytosis, SJS*



- One or more events not commonly associated with drug exposure, but *uncommon in the population*



- Based upon *aggregate analysis*, increased occurrence with drug of events that commonly occur in population



Different “types” of IND safety reports

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What have we heard: challenges raised to implementation of 2015 Guidance

- Trial integrity



Risks of disclosure, and consequent trial impact, with repeated unblinding; impact of unblinded (or blinded) safety reports to sites

- Trial complexity / overlapping responsibilities



Adding new infrastructure, integration of new committee (SAC) with DMC, and internal company safety monitoring group

- Separating signal from noise



Difficulties with *pooling* across a program; *multiplicity issues* with comparison across multiple event types and with multiple looks – sorting out false from true positives – when and what to report, risks to trial of “over-reporting”

- Need for SAC



DMC may be able to carry out objectives of SAC, review of imbalances and flag potentially meaningful signals for reporting

Challenges: trial integrity

- **Repeated unblinding of interim data for SAC and DMC (and potentially to more company personnel) poses challenge to maintaining firewall**
- **Potential impact from IND safety reports (unblinded or blinded) related to imbalances in aggregate reports**
 - Changes in patient follow-up or management: potential for patients to be withdrawn from trial if need for re-consenting

Challenges: trial complexity / overlapping responsibilities



- **SAC is a new committee, requiring additional trial or program infrastructure and resource requirements to support**
- **Challenges of setting up SAC, DMC, and company safety committees for some companies**
- **Complexity of the relationship, and communication, between SAC, DMC, and sponsor: potential for overlapping responsibilities to impede decision-making and action**

Challenges: separating signal from noise

- **Challenges of pooling: trials at different stages of conduct, in different populations, different doses or regimens, designs, randomization ratios (Simpson's paradox)**
- **Determining when an imbalance should be reported**
 - Multiplicity based upon multiple looks, multiple comparisons across AE database: risk of over-reporting of signals
- **For alternate approach: challenges of determining background rate for threshold to trigger unblinding**
 - Limited sources relevant to anticipated frequency of particular event in clinical trial (especially if population not previously well studied)
- **Expertise of SAC – need to fully understand drug's risk profile, patient population – ability to properly identify meaningful potential risks vs “noise”**

Challenges: Need for SAC

- **Adequacy of current approaches and processes: internal company safety group + DMC**
 - Will adding a SAC provide earlier and more accurate signal identification?
- **Can a DMC perform the tasks that are allocated to a SAC in the 2015 guidance?**


Our goals for the meeting

- **To better understand the challenges of implementing the 2015 guidance**
- **To discuss approaches sponsors have used to address 2015 guidance components**
- **To identify issues and approaches that could inform the final guidance**

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TransCelerate Perspective on the FDA's IND Safety Reporting Regulations

Robert Baker, MD

Vice President, Clinical Pharmacology and Global Patient Safety,
and Leader, Clinical Development Design Hub, Eli Lilly and Co.
TransCelerate Initiative Leader, Interpretation of PV Regulations

March 8, 2018

TransCelerate Overview

TransCelerate is a not for profit entity created to drive collaboration

Our vision

To improve the health of people around the world by **accelerating and simplifying** the research and development of innovative new therapies.

Our mission

To collaborate across the global research and development community to identify, prioritize, design and facilitate implementation of solutions designed to drive the efficient, effective and high quality delivery of new medicines.

Founded in 2012 by
10 Members

abbvie

AstraZeneca

Boehringer
Ingelheim

Bristol-Myers Squibb

gsk
GlaxoSmithKline

SANOFI

Lilly

Pfizer

Roche

Johnson & Johnson

TransCelerate's Impact



TransCelerate
Founded

2012

10 Founding Members
5 Active Initiatives

2014

17 Member Companies
12 Active Initiatives
1 Exploratory Initiative

2016



- TransCelerate launched a subsidiary to focus on preclinical
- Currently 6 members
- Conducted Board Strategy Refresh

2017

- 19 Member Companies
- Launch of 2 Pharmacovigilance Initiatives
- Evolving Clinical Portfolio
 - 12 Initiatives Delivering Solutions
 - 7 Initiatives Focused on Facilitating Adoption
- Delivering an R&D Data Sharing Platform
- 25+ Solutions delivered to industry

Growth of Global Impact:

- Country Network of 22 Countries
- Engagement with 14+ Global Regulatory Authorities

TransCelerate and Pharmacovigilance

In 2017, TransCelerate launched the *Interpretation of Pharmacovigilance Regulations* initiative

Initiative Goal

This initiative will share expertise and engage with regulators to more efficiently and effectively meet the intent of ambiguous pharmacovigilance regulations.

Unmet Need

There is an opportunity to assure a universally and systematically consistent understanding and approach to pharmacovigilance regulations

Anticipated Value

- Improved patient safety through the proposal of reasonable interpretations of ambiguous PV regulations
- Reduced compliance risk through better understanding of regulations
- Harmonization across regulators through the proactive sharing of recommendations and best practices

2017 Focus: FDA's IND Safety Reporting Regulations

- 21 CFR Parts 312 & 312, *Investigational New Drug Safety Reporting Requirements for Human Drug and Biological Products and Safety Reporting Requirements for Bioavailability and Bioequivalence Studies in Humans*, was published in 2010
- Guidance for Industry and Investigators, *Safety Reporting Requirements for INDs and BA/BE Studies*, was published in 2012 to help investigators comply with the Final Rule
- Draft Guidance for Industry, *Safety Assessment for IND Safety Reporting*, was released in December 2015 for comment
 - As stated in the draft guidance, when finalized it will represent the current thinking of the Food and Drug Administration on this topic. It does not establish any rights for any person and is not binding on FDA or the public
- FDA has reported comments regarding the 2015 Draft Guidance:
 - Concerns regarding safety assessment organizational structure, unblinding, scope and methodology for aggregate analysis
 - Suggestion to focus on guiding principles and objectives so sponsors have flexibility to implement

TransCelerate sought to assess the current state of how sponsors are addressing the principles of the 2015 Draft Guidance

Our Methods

Evaluate guidance

- The team reviewed the IND safety reporting regulations, and identified areas that may need clarification
- Sections of particular interest included those addressed in the 2015 Draft Guidance:
 - Safety assessment committee
 - Safety surveillance plan
 - Anticipated serious adverse events
 - Aggregate analysis of safety data
 - Aggregate IND safety report submission

Distribute survey

- A survey was designed and distributed that asked how member companies were addressing the principles of the Draft Guidance
- Additional questions were asked pertaining to the impact of implementing the IND rule

Compile results

- Results received were compiled by a third party, blinded, and aggregated
- A summary of results was developed for discussion with regulators

Our Findings

- Member companies have **existing systematic approaches** to reviewing accumulating safety data from clinical trials, including documented plans for review of data and governance committees that review data for the product
- Companies have **variable methodologies** for review of data and unblinding of data
- The anticipated serious adverse events concept has been implemented by some member companies; many are managing it through the **medical review** of IND safety reports through indication, disease confounding, etc.
- Member companies have seen a **decrease** in IND safety report submission due to **reporting rules based on sponsor causality**
- Approaches vary, but **all strive to meet the spirit of the guidance**

Anticipated Serious Adverse Events

FDA's guidance:

"For the purposes of IND safety reporting, anticipated serious adverse events are serious adverse events that the sponsor can foresee occurring with some frequency, independent of investigational drug exposure, in the general patient population under study, in patients with the disease under study, or both."

"...the sponsor should identify...the anticipated serious adverse events that it does not plan to report individually in an IND safety report...together with a plan for monitoring the events..."

(2015 Draft Guidance, Section IV.A, line 327, 367)

Current state:

- Companies who have implemented the identification of anticipated serious adverse events **are documenting them in the Protocol**, with some also including them in the IB and Safety Surveillance Plan
- Companies use **multiple approaches** to determine the background rates for anticipated serious adverse events (placebo data, epidemiology data, published literature, etc.), and analyze them as part of the overall **clinical trial data review**
- Most companies maintain anticipated serious adverse events in both their **clinical database and safety database**
- Most are managing anticipated serious adverse events through **medical review as part of the causality assessment** (disease, indication, population confounding, etc.) to ensure fulsome safety evaluation, and in compliance with IND Rule are not reporting them as IND safety reports to the FDA

Aggregate Analysis of Safety Data

FDA's guidance:

"...requires reporting...including when an aggregate analysis of specific events observed in a clinical trial indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group..."

"The safety assessment committee should regularly perform unblinded comparisons of rates across treatment groups..."

(2015 Draft Guidance, Section IV.B.1, line 285, Section IV.B.1, line 436))

Current state:

- Companies are performing cumulative aggregate analysis of safety data for ongoing and completed trials through **different approaches**, such as:
 - Comparison of rates across treatment arms
 - Pooling across studies as appropriate
 - Comparison of incidence to baseline frequency
- When running blinded studies, most companies perform aggregate analysis on **blinded data** to ensure data integrity of clinical trial; however, **unblinding is done for cause** such as for signal evaluation

Next Steps


- TransCelerate welcomes this dialogue with the FDA and our industry colleagues regarding IND safety reporting
 - Several of TransCelerate's member companies will be presenting their individual company experiences later today
- TransCelerate hopes to engage in further discussions with the FDA regarding our perspective on the 2015 Draft Guidance
- TransCelerate continues to move forward with sharing expertise and engaging with regulators to more efficiently and effectively meet the intent of ambiguous PV regulations
 - CTFG's Reference Safety Information guidance has been our subsequent focus, and we intend to discuss several others before the end of 2018

Thank you

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Statistics•Collaborative

design and analysis for biomedical research

Some Challenges with IND Safety Reporting (and Implementing the 2015 Draft Guideline)

Janet Wittes

8-Mar-2018

The problem with FDA 15-day reports

- Many were sent...
 - And to many people
- Few were read....
- Fewer were interpretable

Goal: Separate wheat from chaff



- The charge
 - Send fewer reports
 - But don't miss signals
- Sponsors need to
 - Assess risk (not vs. benefit)
 - Know what to report
- Ultimate goal: quantify harms

What are we talking about?

- Suspected (there is evidence to suspect relationship)
- Unexpected
 - not known to be associated with the drug, or
 - more severe than known
- Serious (distinguish from severe)
- Adverse (bad)
- Reaction (as distinguished from the more neutral “event”)

Definitions: Expected vs. anticipated

- “Expected” property of the drug
- “Anticipated” property of the population

The FDA's A, B, and C events

A: Single occurrence of event known to be strongly associated with drug exposure (e.g. , Stevens-Johnson syndrome, hepatic injury)

Don't even agonize – just unblind and report.

The FDA's A, B, and C events

B: A few (1? 2? 3?) events not commonly associated with drug exposure but otherwise uncommon in the population exposed to the drug - agonize a bit, but unblind and report – but control also.



Our problem is Type C events

Events that occur more frequently in the treatment group than we would *expect*: no one case a surprise

- May be anticipated events
 - E.g., strokes and MIs in the elderly
 - E.g., Infections in kids
- (If they were truly “unanticipated” they would be Type B)

And what kind of trials...

- Large long-term randomized blinded trials
 - Why large and long term?
 - Because large long-term trials needed to see increase in Type C
 - Why randomized blinded?
 - If open, investigators and sponsors would know what to report

Question of the day: when should these be reported?

- And the answer: when the frequency is higher than in control
- So the 15-day reports should come when the increase is known
- Aye there's the rub...
 - We have to **unblind** to know the answer
 - Part of “evidence” requires knowing if person took the drug
- It is a truth universally acknowledged...
- ~~• ...that a single man in possession of a good fortune must be in want of a wife.~~
- ...that if a person does not take drug x, drug x could not have caused the adverse event experienced.

Who looks at **blinded** data in ongoing clinical trials?

- Participants
 - They have to know to report adverse events
 - They only know about themselves (& others on social media)
- Investigators
 - They only know their participants (and gossip at meetings)
- Sponsors (and their delegates – e.g., CROs)
 - They know the entire development program
 - They don't have access to data from other drugs in the class

Who looks at **unblinded** data from ongoing clinical trials?

Only the DMCs (IDMCs. DSMBs...)

- Culture
 - But they think of risk vs. benefit
 - Are participants safe?
 - (ie, does their likely benefit outweighs their likely risk?)
 - Is the trial still answering an important question?
 - They are very reluctant to report out
- Structural limitation
 - They only know about the trial (or trials) they are looking at

What FDA brings to the table...

- Blinded and unblinded data
- Other drugs in the class
- But not much data from ongoing large trials

How long should participants be followed after they stop study drug?

- Rule of thumb: after 5 half-lives, risk is gone
 - But that ignores cascade of events that might occur
 - That may lead to underestimate of harms
- On the other hand, if people drop off because they are “sick”
 - We can overestimate harms

Who sees what in ongoing trials?

Group	Ongoing trial	Other trials of same drug	Other trials in class
Sponsor	Blind	Full access	No access
DSMB	Unblind	No access	No access
FDA	15 day reports	Depends	Access


Can we (should we) marry these sources in an ongoing way?
Are there cultural, operational, legal (proprietary) roadblocks?
Even if we succeed....

Will we identify harms more quickly and more reliably?
Or, is the guidance's contribution a paper-reduction act?

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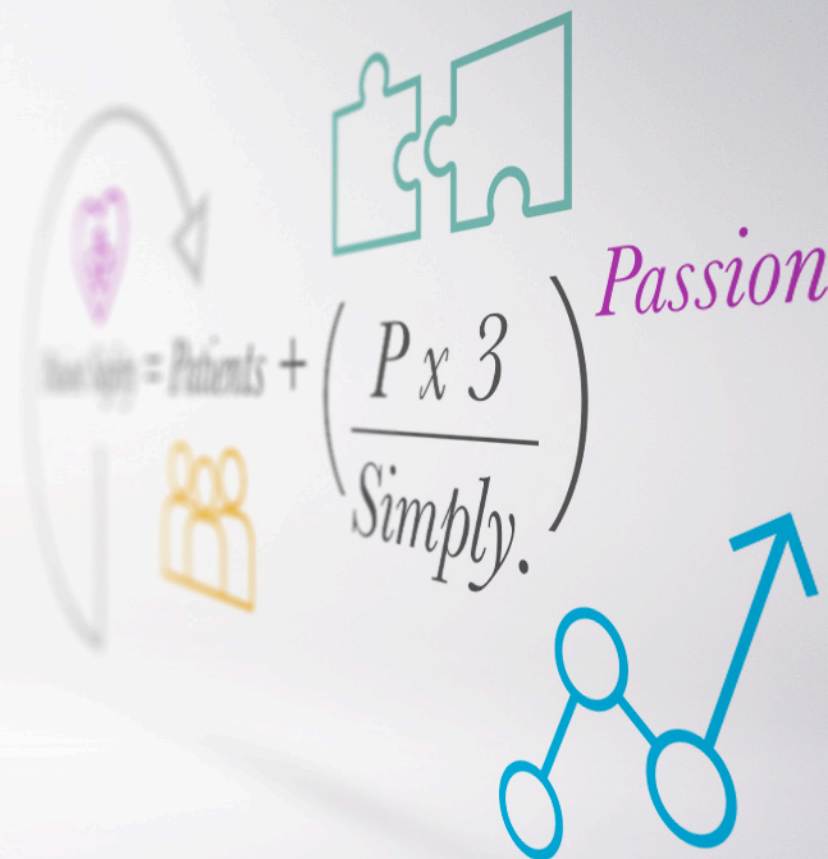
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Identifying Expected Adverse Reactions and Anticipated Events

Barbara Hendrickson, MD

Immunology Therapeutic Area Lead

AbbVie



Disclaimer: This presentation contains opinion and positions that are my own and not that of my company AbbVie.



Anticipated Serious Adverse Events (SAEs)

SAEs that the sponsor can foresee occurring with some frequency, independent of investigational drug.

These events occur in: 1) the general patient population, 2) patients with the disease under study, or 3) both.

These events do not warrant IND safety reporting as individual cases.

Not possible, based on a single case, to conclude that there is a reasonable possibility the investigational drug caused the event.

Safety Assessment for IND Safety Reporting, FDA Guidance for Industry, December 2015



Anticipated Serious Adverse Events (SAEs)

**Known
consequences
of the
underlying
disease or
condition**

**Events common in
a study population
that are unlikely to
be related to the
underlying disease
or condition**

**(e.g. frequent in general
population of similar age)**

**Events known to
occur with drugs
administered as
part of the
background
regimen**

**SAEs that may be
anticipated in a
subset of the
study population**

Safety Assessment for IND Safety Reporting, FDA Guidance for Industry, December 2015



Safety Surveillance Plan (SSP):

Lists anticipated SAEs the sponsor does not plan to report individually to the IND

Outlines a monitoring plan for these events

May include “expected” serious adverse reactions (SARs) per the Investigator Brochure (IB)

Note: individual serious and unexpected suspected adverse reactions interpretable based on single or small numbers of events (e.g. angioedema, hepatic injury, Stevens Johnson Syndrome, agranulocytosis) should be submitted as IND safety reports



Identification of Adverse Reactions

Identification of adverse reactions should proceed per available guidances

(i.e. adverse events for which there is a basis to believe a causal relationship exists between occurrence and use of product)

Serious Adverse Reactions (SARs) - considered expected for the purposes of expedited reporting to global health authorities
-> IB

Expected SARs per IB should be noted in the SSP

- *Monitor for cases different in nature*
- *Monitor ongoing trial rates versus IB reported rate*

e.g. by Product Safety Team, Safety Assessment Committee, or Data Monitoring Committee



Identification of Anticipated Events

Search for types and frequencies of reported SAEs in a similar patient population:

- Comparable clinical studies (ideally same background regimen)
- Registry studies
- Healthcare databases (diagnoses associated with hospitalization)
- Other population based event collection

Potential sources of information:

- Advisory Committee briefing books
- Health authority product approval summaries
- Internal sponsor data sources
- Publications
- TransCelerate Placebo/Standard of Care (PSoC) database
- Regulatory reporting systems (e.g. FAERS)
- Electronic health care records (EHR)/health claims databases
- Prescribing information of background treatment medication

AbbVie Pilot Projects



- Two participating Product Safety Teams (PSTs) initiated pilots
- Created a draft template for the **Safety Surveillance Plan (SSP)** to include:
 - Expected Serious Adverse Reactions (per IB)
 - Disease-Related Events (per protocol)
 - Other Anticipated SAEs



Event of Interest	MedDRA Search (e.g. PT, PT grouping, HLT, SMQ)	Patient-disease population	Reference group	Background incidence rate (E/100 PY)	Supporting References

AbbVie Pilot Projects



- Searched for public information and relevant internal data sources to identify the most frequent SAEs reported in similar patient population studies
- Database created to merge information
- “Heat map” view enhances detection of most frequent SAEs

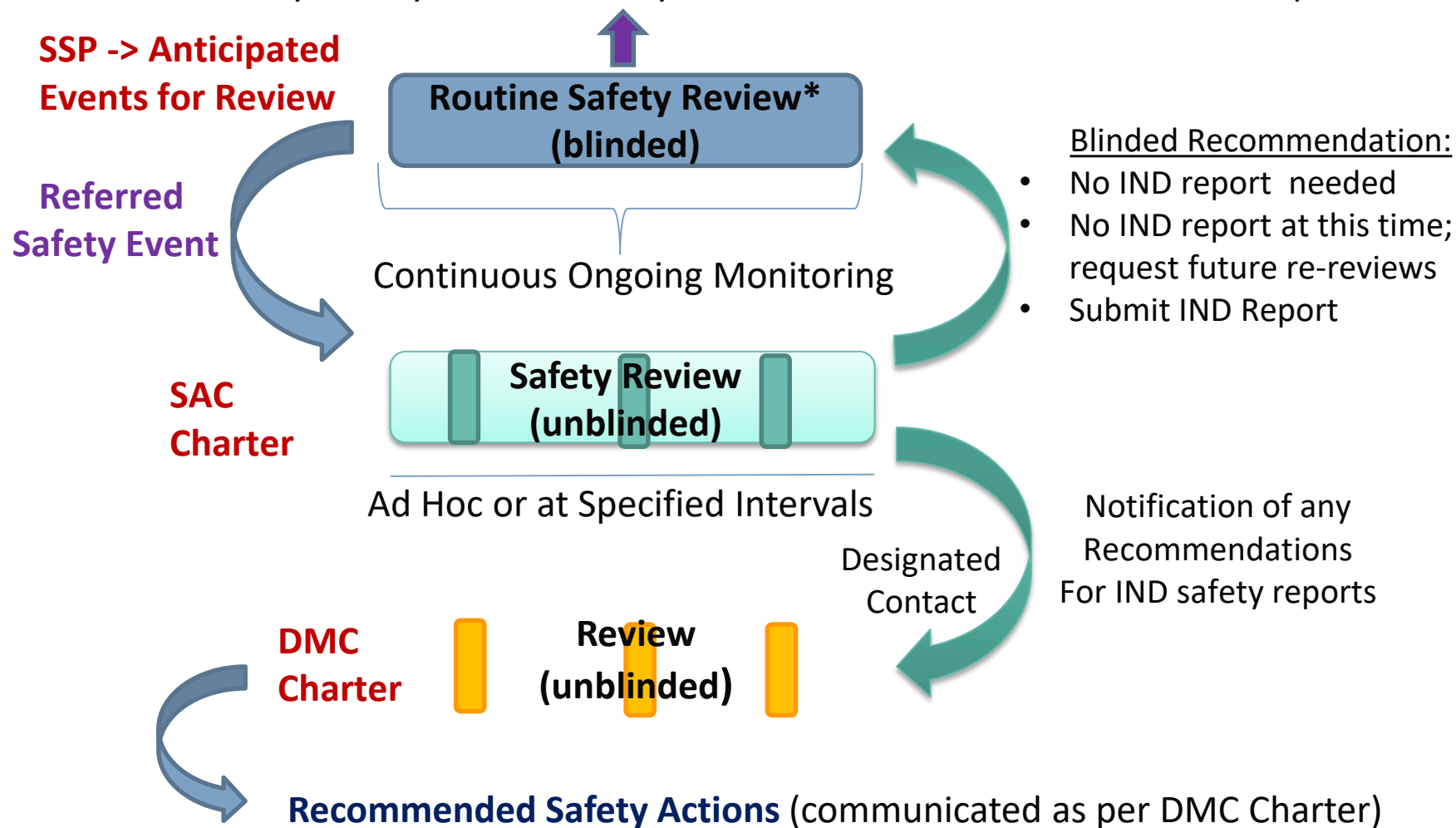
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3	0	6	3	0	4	3	3	0	6	0.03	0	0
3	3	6	6	6	11	3	3	3	7	0.03	0.03	0.03
3	0	0	3	0	19	0	5	0	15	0	0.03	0
3	3	0	6	6	18	0	3	3	17	0	0.03	0.03
3	0	0	6	0	13	0	3	0	20	0	0.03	0
3	0	3	3	0	11	5	3	0	9	0.03	0	0
0	0	6	0	0	9	3	0	0	7	0.03	0	0
0	0	12	0	0	12	6	0	0	16	0.06	0	0
13	0	13	22	0	11	10	14	0	12	0.13	0.16	0
12	0	10	22	0	16	3	14	0	17	0.07	0.13	0
21	9	24	40	19	51	17	25	11	61	0.13	0.26	0.13
10	11	22	12	16	45	14	11	19	28	0.13	0.06	0.2

Safety Assessment Committee – AbbVie Pilot



Execution of IND safety report submission

Day 0= Day Product Safety Team endorses need to submit IND report



*Quantitative assessment of safety data from ongoing studies using historical event rates

Identification of Anticipated Events



Identify search strategy for events, e.g.

Preferred term (PT) or
PT grouping

High level term (HLT)

SMQ



Using estimated background rate, assess which SAEs are likely to be reported in >3 subjects given the planned subject numbers/exposure



Determine which SAEs should be listed as anticipated events in SSP

Considerations: Selection of Anticipated Events



Are the events only anticipated for a subset of subjects?

For known consequences of the disease, how specific is the event's association with the disease?

Is there overlap of the anticipated event with a potential risk of the study product?

What is the capability to assess if the event is occurring at a higher rate than anticipated?



Complexities of multiple product indications

- Need for multiple lists of anticipated SAEs based on the different study populations
- Execution of SSP activities with varying lists of anticipated events for different product studies

Questions about the granularity by which events should be reported as IND safety reports

- Typically individual SAEs are reported at the level of a MedDRA Preferred Term in the MedWatch
- Should anticipated events be listed instead at a “medical concept” level (e.g. PT groupings, HLT, narrow SMQs)



Lack of public information about the rates of anticipated SAEs in the study population

- Full list of SAEs reported in clinical studies rarely available in public documents; level of detail in publications about safety results often small compared to efficacy results
- If rate reported for a “grouped term”, MedDRA PTs included in the grouping may not be provided
- Rates of anticipated SAEs could be influenced by factors that differ among programs (e.g. exclusion/inclusion criteria, investigative site countries)



EHR /Health Claims Databases may present issues for extrapolation to clinical trial databases

- MedDRA coding (clinical trials) versus International Classification of Disease (ICD) coding (EHR/Claims)
- Questions about the matching of patient characteristics in the external database to the clinical study population
- For oncology trials, difficulty identifying similar populations in regards to tumor histology, grade or molecular profile in claims databases
- Approach to recording diagnoses leading to hospitalization may be different for claims databases versus clinical trials
- Events meeting clinical trial seriousness criteria other than hospitalization may be difficult to identify in EHR/Claims

Can be labor intensive depending on approach



Opportunities for...

Identifying Anticipated Events

Consider alignment among relevant stakeholders on elements applicable across multiple product development programs

Known consequences of the underlying disease or condition under investigation

Events common in the study population unlikely to be related to the underlying disease or condition under study

Events known to occur with drugs administered as a background regimen

Event databases could be updated annually with significant new data

Better Estimates for Expected Event Rates

Collaboration to identify potential data sources for anticipated AE background rates earlier in development

Advancing use of EHR systems to offer more granular information compared to availability with claims based analyses


Developing standard of care “synthetic control” arms using similar inclusion / exclusion criteria as the clinical program

Consideration for linking (via a third party) clinical trial patient data and EHR/claims to derive “comparator groups”

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Mounting Challenges of Safety Oversight



- **Innovative/Adaptive design**
- **Sicker patients**
 - Rare diseases
 - Advanced cancer
- **Underlying co-morbidities**



Assessment of Adverse Events

Liver enzyme abnormalities
Cytopenias
Major CV events
Renal injury

Hypothetical Example of Acute Renal Insufficiency



- Study with data on 200 patients with advanced Ca
 - 1:1 randomization (blinded)
- Five SAEs of acute renal failure/insufficiency
 - All with other risk factors (dehydration, diarrhea, previous nephrotoxic chemotherapy)
 - All deemed unrelated by investigators
- Non-clinical evaluation, at high doses: signs of tubular necrosis/atrophy

Safety/PV Considerations



- Cases clearly confounded
- Unrelated per investigators
- Review of literature: renal compromise commonly seen in cancer patients
- Drug effect: vulnerable patients (other risk factors) may present first
- Investigators may not be aware of other cases or specifics of non-clinical findings
- Historical comparisons may have limitations

**Evaluation for INDSR Reporting
Routine Periodic Unblinded (Safety) Data Review
Challenges to Trial Integrity and Other
Considerations**

INDSR Evaluation

Events Requiring Aggregate Review (Category C)

Unexpected serious events

Anticipated events: higher than expected rate

Previously identified suspect events: higher frequency

Events evaluable based on isolated cases or small n's (Categories A and B)

SJS, liver failure

INDSR Evaluation



Events Requiring Aggregate Review

Events evaluable based on isolated cases or small n's

SJS, liver failure

Comparison to contemporaneous or historical controls

Routine unblinded review by oversight committee

Unexpected serious events

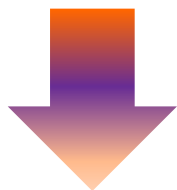
Anticipated events: higher than expected rate

Previously identified suspect events: higher frequency

Challenges to Trial Integrity: Extent of Data Unblinding



**Routine unblinding of all serious events (multiple times)
Across development portfolio**



Large amounts of data will be unblinded

**Many individuals* will generate/review unblinded data
either in aggregate or at a patient level**

***Members of various oversight committees, statisticians, data managers**

Scope of the Unblinding Required



- **Five reports of acute renal failure**
 - Assuming an imbalance (5 vs 0; 4 vs 1)
- **Full assessment may require evaluation of:**
 - **Non-serious Aes**
 - PTs of renal insufficiency, ATN and related terms
 - Proteinuria
 - Creatinine rise
 - **Lab values**
 - Trends (mean and shift from baseline)
 - Creatinine, BUN

- **Unblinding may extend beyond SAEs**

Challenges in decision to unblind supplementary data

May be multiple imbalances

Potentially clinically important SAEs

Small numbers

Incomplete data

SACs: Can we Maintain Appropriate Barriers



- **IDMC model**
 - Members/Statisticians external to sponsor
 - Deliberations (at least partially) closed
- **Independent safety review within sponsor org**
 - Precedent for unblinded parallel data review
 - Number of such committees: small
 - Few colleagues “quarantined”

Constitution of SACs: External vs Internal



- **Completely external**
 - More robust barriers
 - ? Can remit of IDMCs be expanded
- **Rationale to consider internal members**
 - **Scope of the committee is vast and broad**
 - Identify signals from safety data review in context of
 - Population studied/anticipated events
 - Non-clinical data
 - In-depth understanding of all clinical trials
 - Appropriate pooling techniques are employed
 - **Charged to recommend submission of INDSRs**

Challenges to Maintain Trial Integrity: Summary and Considerations



- **Multitude of SACs across portfolio**
- **Large amounts of data will required unblinding**
 - **Many individuals handling the unblinded data**
 - **Unblinding may extend beyond SAEs**

- **Membership: balance between internal members and effective barriers**
- **? Flexibility with regards to need for, and remit of SACs, based on:**
 - **Stage of development**
 - **Population**
 - **Non-clinical evaluation**
 - **Other considerations**

Safety Stewardship: GSK



Governance

CMO/CSO/Global Safety Board

**Advisory
Committees**

**Steering
Committees**

**Safety
Panels**

**Oversight
Committees**

IDMCs

iSRCs

DRCs

**Routine
Safety
Monitoring**

Safety Review Teams

- **Can provide independent (unblinded) review**
 - If required
- **Not mandated across portfolio**
 - IDMCs generally required for pivotal/registration studies
- **If members are close to core team (e.g. reporting line)**
 - Generally noted study is sponsor open
- **Responsibility for INDSRs: core safety team**


- **Formal advisory panels**
 - **Internal (+/- external) experts across various disciplines**
 - **Hepatic**
 - **Cardiac (QT)**
 - **Renal**
 - **Ophthalmology**
 - **Many others**
 - **Assist teams**
 - **Assessment of emerging signals**
 - **Appropriate inclusion/exclusion criteria**
 - **Monitoring of risk**
-

Thank you

Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

March 8, 2018

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Public Workshop: IND Safety Reporting

Timely & Reliable Safety Reporting while Protecting the Integrity of Ongoing Trials

March 8, 2018

Thomas R. Fleming, Ph.D.
University of Washington

- * Ellenberg SS, Fleming TR, and DeMets DL: “*Data Monitoring Committees: A Practical Approach*”, John Wiley & Sons, 2002
- * Wittes J et al. “The FDA’s Final Rule on Expedited Safety Reporting: Statistical Considerations”. *Stat in Biopharmaceutical Res* 2015; 7:3: 174-190
- * Fleming TR et al. “Data monitoring committees: Promoting Best Practices To Address Emerging Challenges”. *Clinical Trials* 2017; 14: 115-123

FDA's Final Rule for Expedited Reporting

- Serious & Unexpected
(*Suspected or Certain*) Adverse Reactions

*...requires evidence to suggest a causal relationship
between the drug and the adverse event...*

FDA's Final Rule for Expedited Reporting

- Categories of Serious Adverse Events:
 - A: Rare events, known strong association w. drug exposure
E.g.: Stevens Johnson Syndrome or PML
 - B: Rare events, not known to be associated with drug exposure
E.g.: M.I. in young female
 - C: Common events in the exposed population
E.g.: MACE in populations with mod/high CV risks
- Evidence required to address drug's causal relationship
 - A: Single cases, occurring in the investigational drug arm
...Potentially assessed by the Medical Monitor
 - B: A few occurrences, occurring on the investigational drug
...Potentially assessed by the Medical Monitor
 - C: Comparison of drug group with proper comparator group
...Assessed by an external Safety Assessment Committee or DMC

(* Wittes et al. *Stat in Biopharmaceutical Research*, 2015)

Safety Assessment (or Review) Committee (SAC)

- Responsibilities
 - Achieve timely identification & reporting of SUSARs
 - Some *important operating procedures* of the SAC
 - **Collectively**, having access to insights from:
 - ✓ both completed and ongoing clinical trials
 - ✓ safety data unblinded by intervention group
- *Overlapping ethical and scientific responsibilities of oversight bodies in ongoing clinical trials*

Oversight Bodies in Ongoing Clinical Trials: Partnership of Responsibilities

- **Sponsors, Investigators, Care Givers**
 - Decision making responsibilities for design, conduct, & analysis of the trial
 - Primary patient care responsibilities
- **Institutional Review Boards & Regulatory Authorities**
 - Approval of ethics/science of the trial design
 - Ongoing monitoring of SUSARs & SAEs
- **Data Monitoring Committees (DMCs)**
 - Sole access during conduct of the clinical trial to:
 - Aggregated efficacy/safety data across the trial
 - Unblinded by treatment group

Mission of the DMC

- To Safeguard the Interests
of the Study Participants
- To Preserve Trial Integrity and Credibility
to enable the clinical trial to provide
timely and reliable insights
to the broader clinical community

Some Fundamental Principles in Achieving the DMC's Mission

To assist the DMC in achieving its Mission,
procedures are needed...

- To reduce pre-judgment of interim data
 - ⇒ *Maintaining confidentiality of interim data*
- To guide the interpretation of interim data
 - ⇒ Group sequential monitoring boundaries
 - ⇒ Unbiased judgment
 - ... *Well-informed*
 - ... *Independent*

... Motivates fundamental principles
for DMC functioning and composition...

Some Fundamental Principles in Achieving the DMC's Mission

- DMC should have *Sole Access* to interim results on relative efficacy & relative safety of interventions
- DMC should have *Multidisciplinary* representation having experience in the DMC process
- DMC should be *Independent* with freedom from apparent significant conflicts of interest ... financial, professional, regulatory

“LIGHT Trial”

Naltrexone SR/Bupropion SR:

“Contrave”

CV risks in Overweight/Obese Subjects
With CV Risk Factors

Key Design Objectives:

At 90 events: **2.0** Margin for CVDeath / Str / MI

At 378 events: **1.4** Margin for CVDeath / Str / MI

...FDA's Part 15 Open Public Hearing, 8/11/2014...

“Confidentiality of Interim Results in Cardiovascular Outcome Safety Trials”

	CVD	<u>Overall Deaths</u>					D
	Stroke	CV		Total	Stroke	MI	Stroke
	MI	Non-CV					MI

“1st Quadrant”: Up to *11/23/2013*

Contrave	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
HR	0.59						0.64

✓ DMC rec: ‘*Release data to FDA per Data Access Plan*’

	CVD Stroke MI	<u>Overall Deaths</u> CV Total Non-CV			Stroke	MI	D Stroke MI
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“2nd Quadrant”: Between 11/23/2013 and 3/3/2015

Contrave	55	12	21	33	15	31	74
Placebo	43	15	14	29	10	23	57
HR	≈1.29						≈1.30

✓ On 3/3/2015, DMC recommended trial continuation...

	CVD Stroke MI	<u>Overall Deaths</u> CV Total Non-CV			Stroke	MI	D Stroke MI
--	---------------------	--	--	--	--------	----	-------------------

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HR	≈1.29						≈1.30

✓ On 3/3/2015, *DMC recommended trial continuation...*
That day, sponsor released “1st Quadrant” in Patent Filing
⇒ Steering Committee recommends trial termination

	CVD Stroke MI	<u>Overall Deaths</u> CV Total Non-CV			Stroke	MI	D Stroke MI
--	---------------------	--	--	--	--------	----	-------------------

“1st Quadrant”: Up to *11/23/2013*

Contrave	35	5	5	10	7	24	40
Placebo	59	19	3	22	11	34	62
HR	0.59						0.64

JAMA 3/8/2016 Final 64%: ‘End of Study’ Results

Contrave	119	26	39	65	31	69	156
Placebo	124	42	29	71	23	71	151
HR	0.95						1.02

Key insights:

- ✓ Potential unreliability of interim data
- ✓ Breaches in confidentiality provide potential for:
 - ⇒ Dissemination of misleading results
 - ⇒ Risks to irreversibly bias subsequent trial conduct

Confidentiality of Interim Data

- DAMOCLES:

- * Grant, Altman, Babiker, et al. *Health Technology Assessment* 2005

- “There is near unanimity
that the interim data and the deliberations of the DMC
should be absolutely confidential...*

- ...Breaches of confidentiality
are to be treated extremely seriously”*

- Formal statements of concordance have been issued by
NIH, WHO, EMA and FDA*

- * Fleming et al. Maintaining confidentiality of interim data to enhance
trial integrity and credibility. *Clinical Trials* 2008; 5: 157–167

Sponsor Access to Interim Safety Data

- Availability of Interim Safety Data on a
“*Need to Know Basis*”

E.g: — Medical Monitors for continuous monitoring of
Category A&B SUSARs & SAEs

- External (or internal?) SACs (for Category C events)
...with aggregate evidence over a clinical program...

(How to handle access to unblinded safety data from ongoing trials?)

- Key principle: The sponsor’s insights from such access
should be shared only with DMCs, regulators and others
also having a “need to know”
in order to address individual & collective ethics

Safety Assessment (or Review) Committee

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 - Those having access to unblinded aggregate data from ongoing clinical trials should be firewalled away from study team (& others in sponsor)...
- motivates limiting wide access of unblinded data from ongoing trials to SRC members external to the sponsor, especially for ‘small’ sponsors

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...Might the DMC be one option for addressing that part of the SAC function regarding Category C events involving access to unblinded data from ongoing clinical trials?

Some Fundamental Principles in Achieving the DMC's Mission

- DMC should have *Sole Access* to interim results on relative efficacy & relative safety of interventions
- DMC should have *Multidisciplinary* representation having experience in the DMC process
- DMC should be *Independent* with freedom from apparent significant conflicts of interest

Motivation for Category C Event Monitoring being conducted by a '*DMC-like independent*' entity

- Reduce pre-judgment and protect trial integrity by
 - ✓ Maintaining confidentiality of interim results on relative efficacy & relative safety of interventions
- Enhance unbiased and informed judgment through
 - ✓ Multidisciplinary & experienced representation
 - ✓ Members free of significant conflicts of interest
- A '*DMC-like*' review process:
 - ✓ “Sees everything” and does not solely depend on investigator relatedness
 - ⇒ ↑ sensitivity and specificity for SUSARs
 - ✓ While Category A,B need continuous monitoring, isn't periodic monitoring adequate for Category C?

Stroke, TIA
M.I., Angina

One Option: The DMC conducts that part of the SAC function regarding Category C events?

- E.g. — A DMC monitoring a single registrational Phase 3 trial
- A single DMC monitoring an overall clinical program that is evaluating a single investigational drug:

Sponsor A: Several trials in Cognitive Function settings

Sponsor B: > 10 trials in Advanced Liver Disease settings

Sponsor C: \approx 20 trials in Psoriasis & IBD settings

Some issues to be addressed:

- ✓ * *Current standards for DMC release of safety information (influenced by Benefit-to-Risk considerations) versus * Establishing thresholds for IND Safety Reporting*
- ✓ *Establishing proper communication between SAC, DMC & FDA*

Safety Assessment (or Review) Committee

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 - Achieve timely identification & reporting of SUSARs
 - Some *important operating procedures* of the SAC
 - **Collectively**, having access to insights from:
 - ✓ both completed and ongoing clinical trials
 - ✓ safety data unblinded by intervention group
 - Those having access to unblinded aggregate data from ongoing clinical trials should be firewalled away from study team (& others in sponsor)...
- motivates limiting wide access of unblinded data from ongoing trials to SAC members external to the sponsor, especially for ‘small’ sponsors
- Activities guided by a Charter addressing procedures for:
 - ✓ the reliable & timely reporting of SUSARs
 - ✓ protecting the integrity of ongoing trials, recognizing the need to maintain confidentiality

Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

March 8, 2018


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Lunch Break

Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

March 8, 2018

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Determining the Threshold for Reporting of Adverse Events

Ann Strauss*, MB BCh (Wits) DA (SA)

Associate Vice President, Clinical
Safety and Risk Management, Merck

*On behalf of the Long Term Quantitative Enablement Team

Safety Assessment for Safety Reporting

FDA Guidance for Industry 2015 (P 406 - 410)

“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 that there has been a clinically important increase in the rate of a previously recognized serious adverse reaction over the rate listed in the protocol or the investigator brochure*

Safety Assessment for Safety Reporting Guidance for Industry - 406 -410

*“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 that there has been a clinically important increase in the rate of a previously recognized serious adverse reaction over the rate listed in the protocol or the investigator brochure **is a complex judgment that is, in most cases, not a simple application of a planned statistical analysis**”.*

Points to Consider

Safety Review Team (SRT)

- Multi-disciplinary experts to review aggregate data on a routine and ad hoc basis.

Aggregate Safety Assessment Plan (AgSAP)

- Strategic, program-level plan
 - Plan and conduct the monitoring and evaluation of aggregated safety information across ongoing and completed trials throughout the product development lifecycle

Key Components of the AgSAP

**Program-
Level
Safety
Topics &
Populations
of Interest**

**Strategic
Consider-
ations for
Blinded-
OASE**

**Strategic
Consider-
ations for
Unblinded-
OASE**

**Preparation
for
Integrated
Safety-
Related
Filing
Documents**

OASE, Ongoing Aggregate Safety Evaluation

Objectives of Blinded-OASE are to Support:

- **Evaluation of the general safety profile** of the product
 - Ongoing characterization of identified and potential risks
- **Detection of emerging safety topics** while studies are ongoing
 - Evaluation of risk elevation for select safety topics of interest
- Evaluation of signals validated by SRT from non-clinical trial sources (such as the literature, individual cases, spontaneous reports)

Key Elements for Blinded-OASE

Key elements in the Blinded-OASE plan:

- Safety topics of interest and other safety endpoints
- Pooling strategy
- Monitoring tools
- Safety data output (tables, listings and figures)
- Statistical considerations
 - Background rates
 - Quantitative frameworks

Key Questions to Answer

- Have more events occurred than were expected? (yes or no)
- What is the magnitude of this relative risk elevation? (how much)

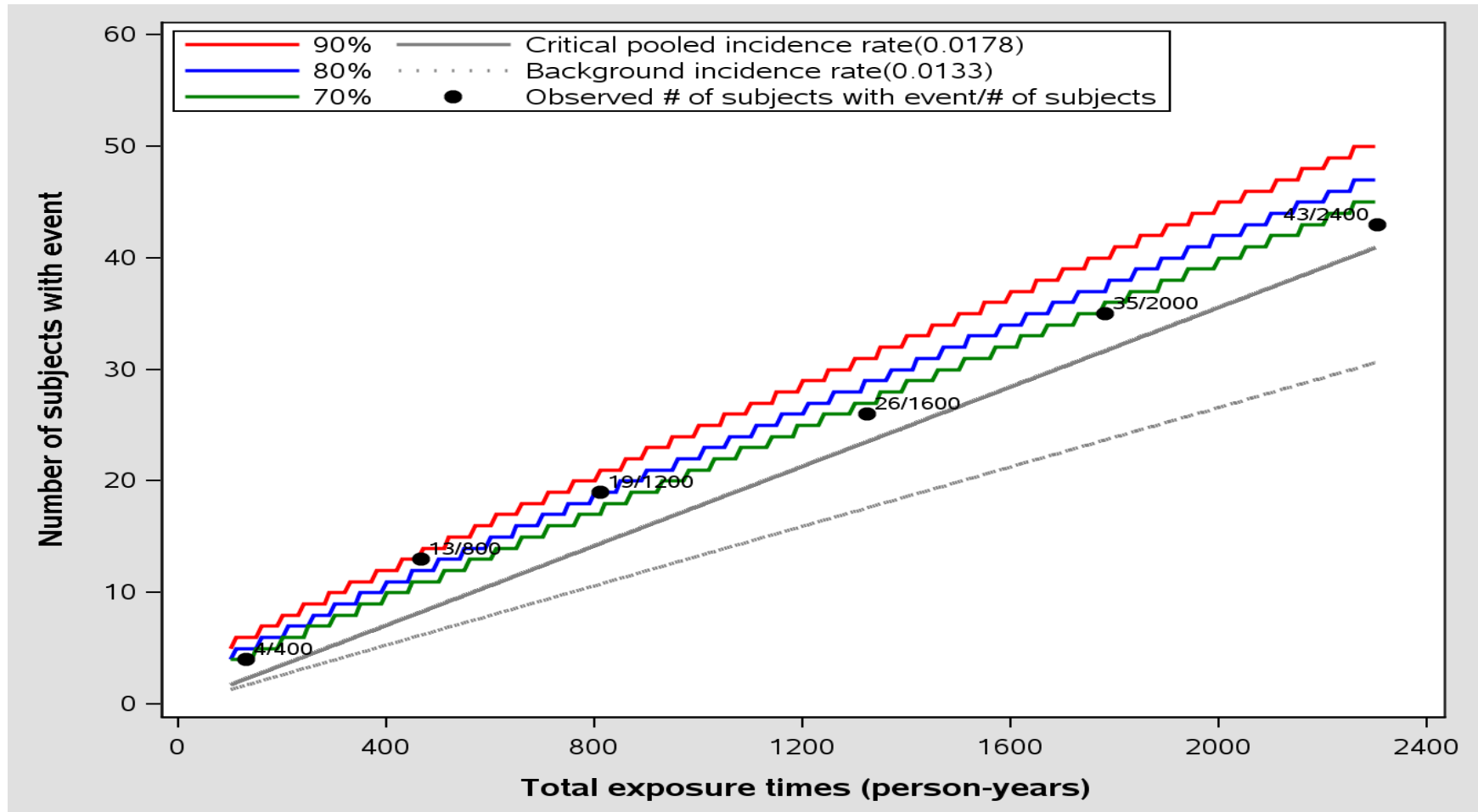
Quantitative framework to stimulate SRT discussions and improve conversations about safety monitoring of accumulating blinded data, these are not a decision rules

Probability threshold boundaries for incidence rates: example

Key inputs: Background Rate 1.33/100 PY

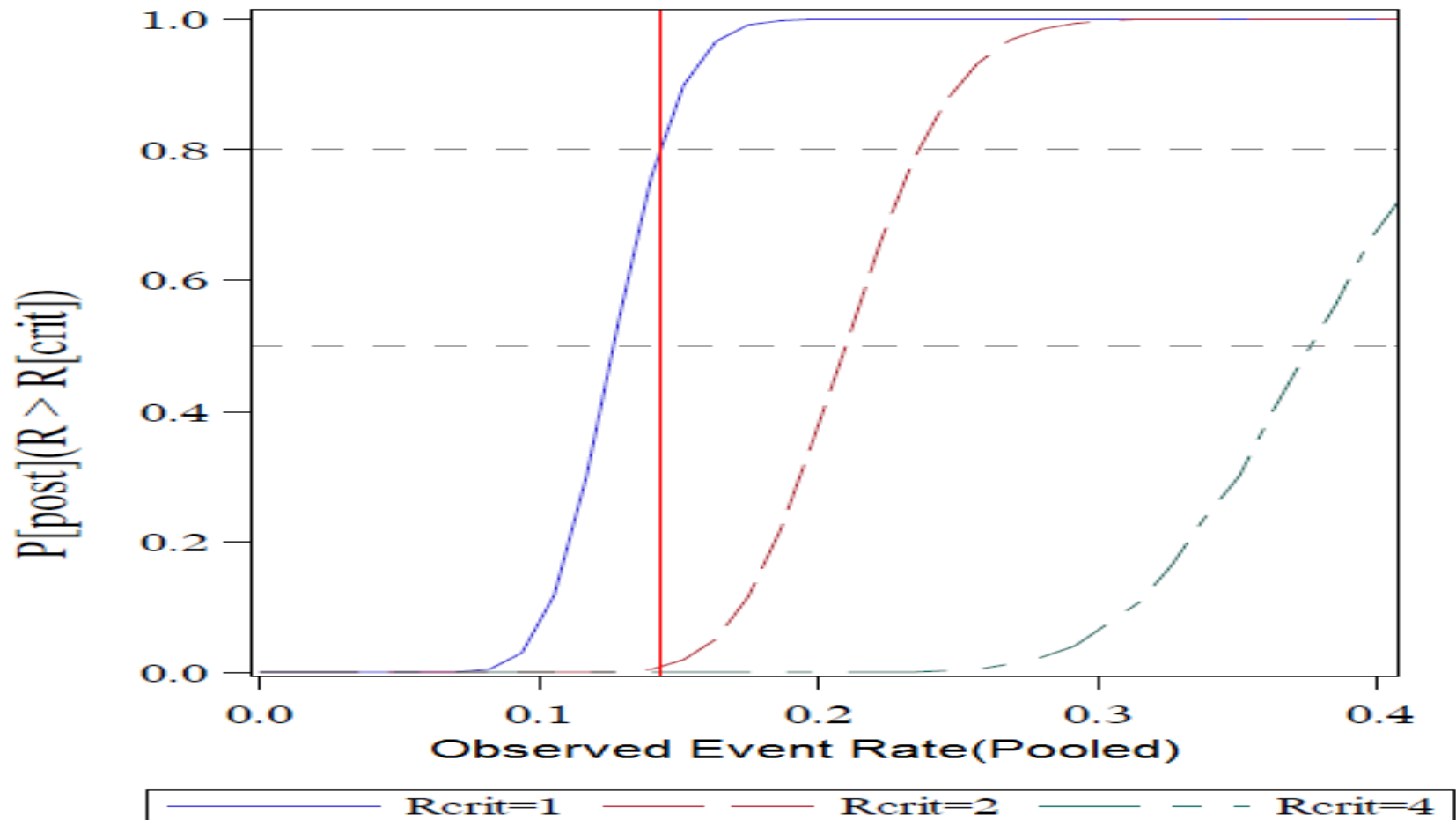
Trigger threshold in treated at RR 1.5 \rightarrow 2.0/100 PY

Translates to 1.78/100 PY in pooled population (diluted for untreated)



What is the magnitude of this relative risk elevation? (how much)?

Evaluation of Relative Risk Elevation



What is an Unblinded-OASE?

Unblinded Ongoing Aggregate Safety Evaluation (U-OASE)

- Is an ongoing, systematic review of safety data combined across clinical trials and/or indications
- Is performed using completed trials with locked databases
- Objectives of Unblinded-OASE are:
 - To support ongoing characterization of the safety profile of the compound
 - To leverage the results for planning and preparation of aggregate safety-related documents in support of a regulatory filing
 - To provide readiness to support preparation of responses to health authority requests received both pre- and post-approval
- Allow for regulatory reporting including Aggregate IND Reports to FDA

The FDA's Final Rule on Expedited Safety Reporting: Statistical Considerations

Janet WITTES, Brenda CROWE, Christy CHUANG-STEIN, Achim GUETTNER, David HALL, Qi JIANG, Daniel ODENHEIMER, H. Amy XIA, and Judith KRAMER, for the Biostatistics Working Group of the CTTI-IND Safety Reporting Team

Published with license by Taylor & Francis
Statistics in Biopharmaceutical Research
August 2015, Vol. 7, No. 3
DOI: 10.1080/19466315.2015.1043395

Analysis of a Single Type of Class C Outcome Based on Observing Increased Frequency Relative to Control

Table 3. Sample decision tree for expedited reporting of type C events

Analysis of Category C events Based on observing increased frequency relative to control

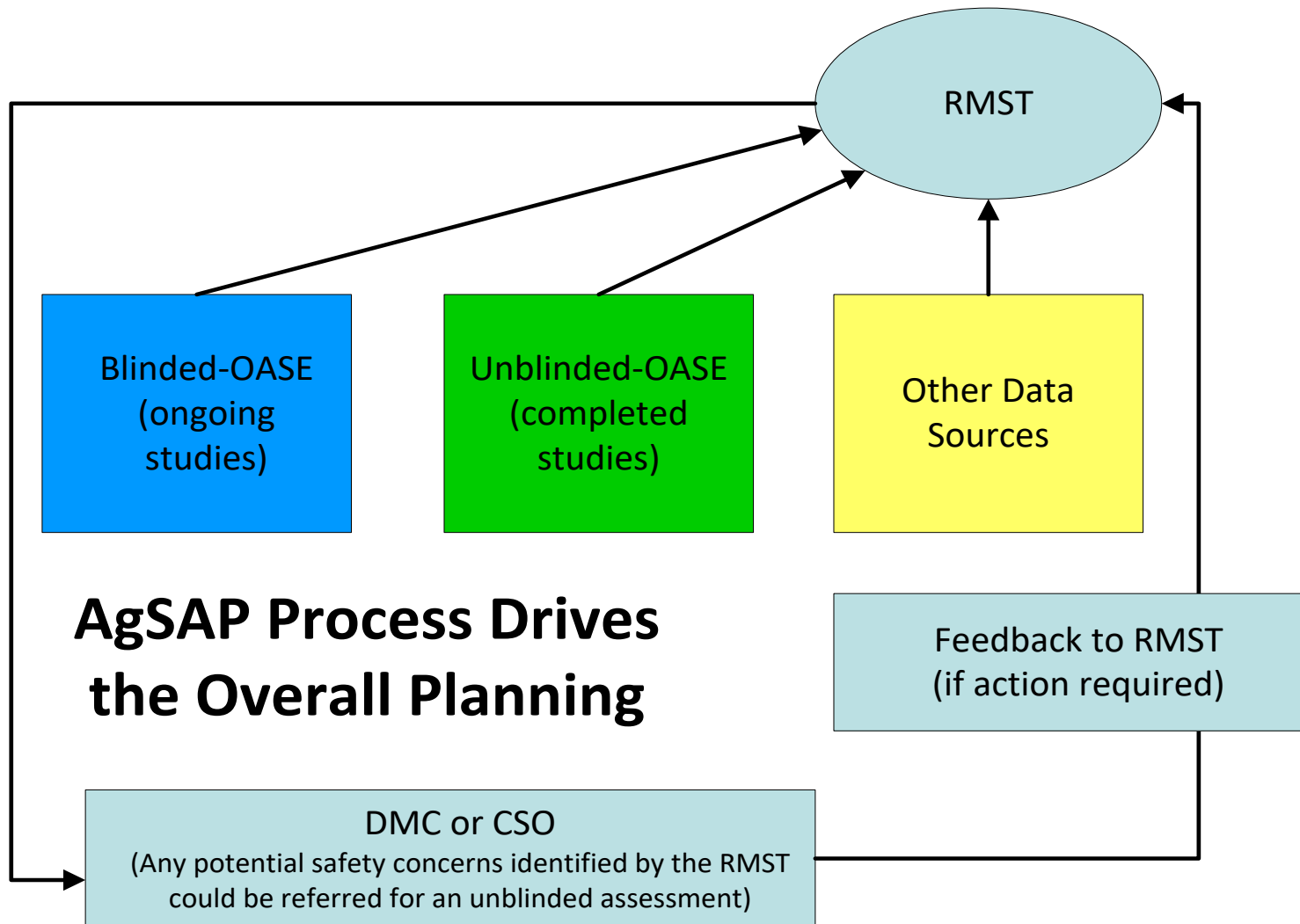
Is imbalance clear?

- Does a one-sided 80% confidence interval of the difference between observed and control (perhaps using meta-analysis of all related completed and ongoing studies) include 0? (or does the 80% confidence interval for a relative metric include 1?)
- Is the relative risk compared to control less than 2? (For studies without controls, the risk is relative to expectation in a relevant historical population; for studies with controls, the risk is relative to the controls or to the historical population, or both.)
- Does lumping similar events make the signal disappear?

If the answers to all three are “yes,” the data do not show sufficient evidence of imbalance to file a 15-day report. If the answers to all three are “no,” the evidence of causality is clear enough to file a 15-day report. Otherwise, the increase is unclear.

Wittes et al, The FDA's Final Rule on Expedited Safety Reporting: Statistical Considerations. SBR 2017, 7:3, 174-190

Central Role of the SRT in Safety-Related Decision-Making



DMC: Data Monitoring Committee; CSO: Chief Safety Officer
RMST: Risk Management Safety Team

Conclusions

- Appropriate Expertise
 - Safety
 - Disease area and populations
 - Epidemiology
 - Statistics
- Proactive Strategic Planning
 - Customized according to program and phase of development
- Ongoing Safety Review
- Quantitative Framework


Acknowledgements

- Janet Wittes
- Merck Long Term Quantitative Enablement Team

Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

March 8, 2018

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Developing Best Practices for Data Pooling

Mary Nilsson

Safety Analytics, Global Statistical Sciences

Eli Lilly and Company

Safety Assessment for IND Reporting Workshop; 08 March 2018



Overview

- ◆ Where data pooling fits in the IND safety reporting process
- ◆ Potential pitfalls of data pooling
- ◆ Best practices
- ◆ How Lilly incorporates best practices in the IND safety reporting process



IND Safety Reporting Rule

- ◆ Reasonable possibility of causality rests on positive evidence of an association and may require unblinding. The following must be reported to FDA and investigators quickly
 - A. Single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
 - B. One or more occurrences of an event that is not commonly associated with drug exposure but is otherwise uncommon in the population exposed to the drug (e.g., tendon rupture)
 - C. An **aggregate analysis** of specific events observed in a clinical trial (such as known consequences of the underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a **concurrent** or historical **control group**



Challenge

- ◆ How should aggregate analyses be conducted in the IND safety reporting process?
 - How can we right-size the effort while avoiding common pitfalls that could lead to misleading results?

Pitfall #1

- ◆ Aggregate summary where study and treatment (or treatment arm) are confounded
 - In an attempt to create a very simple summary, it's easy to become susceptible to this pitfall



Pitfall #1 – Example 1

Study	New Drug	Placebo	Active	Risk Ratio	Risk Ratio
1	2/60	2/60		1.0	
2	9/400	5/400		1.8	
3	10/500	5/500		2.0	
4	13/500	7/500		1.9	
5	5/1000		2/1000		2.5
6	6/1000		3/1000		2.0
Pooled	1.3%	1.3%	0.25%	1.0	5.2

Data from: Lièvre M, Cucherat M, Leizorovicz A. Pooling, meta-analysis, and the evaluation of drug safety. *Current Controlled Trials in Cardiovascular Medicine*, 3(1), 3-6 (2002).



Pitfall #1 – Example 2

Study	Placebo	Low Dose	Middle Dose	High Dose
1	10/100 (10%)	10/100 (10%)	10/100 (10%)	
2	20/100 (20%)		20/100 (20%)	20/100 (20%)
Pooled	30/200 (15%)	10/100 (10%)	30/200 (15%)	20/100 (20%)



Pitfall #1 – Example 3

Study	Placebo	Low Dose	Middle Dose	High Dose
1	10/100 (10%)	10/100 (10%)	20/100 (20%)	20/100 (20%)
2	20/100 (20%)		30/100 (30%)	
Pooled	30/200 (15%)	10/100 (10%)	50/200 (25%)	20/100 (20%)

Pitfall #2

- ◆ Aggregate summary without accounting for potential study differences (ie, not “adjusting” for study)
 - Even if the studies all have the same treatment arms, if randomization ratios are not consistent across the studies, there’s a potential for misleading results



Pitfall #2 – Example

Study	New Drug	Placebo
1	30/300 (10%)	10/100 (10%)
2	133/700 (19%)	67/350 (19%)
3	200/500 (40%)	200/500 (40%)
Pooled	363/1500 (24%)	277/950 (29%)



Best Practices

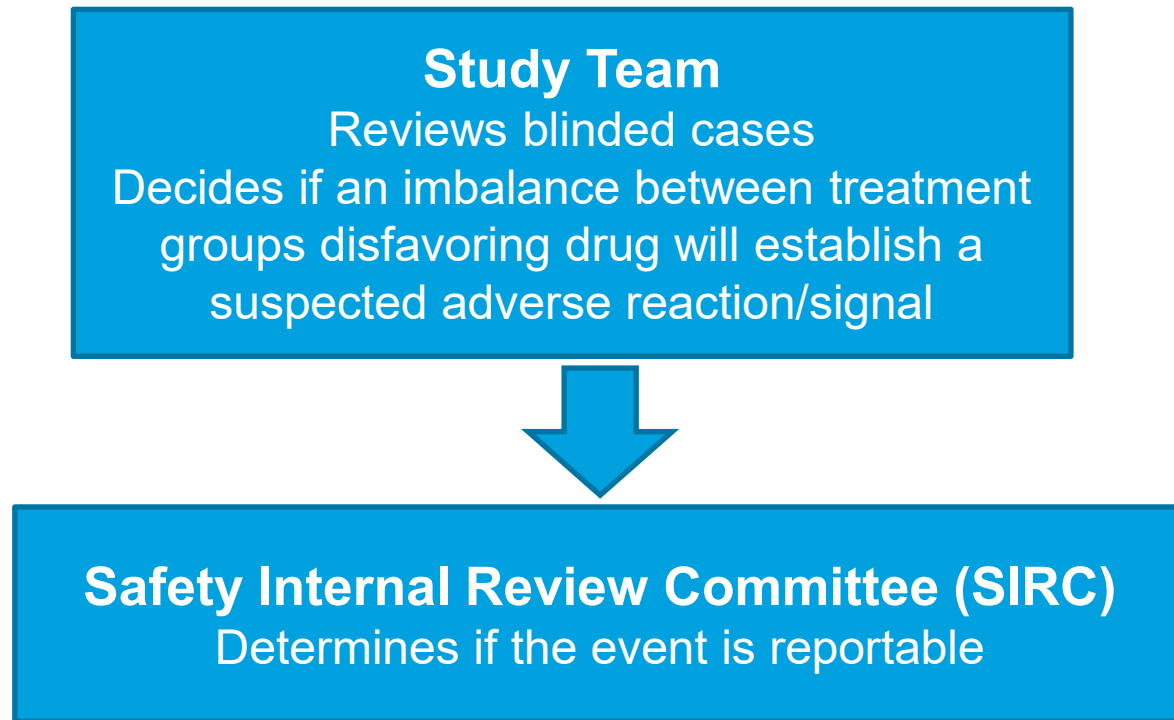
- ◆ Aggregate analyses for comparing treatment arms
 - Avoid confounding
 - Adjust for study, or at least look for potential study differences
 - Study-size adjusted percentage, Mantel-Haenszel odds ratio, forest plot
 - There could be situations where more advanced methods are warranted (e.g., Bayesian indirect comparison methodology)
- ◆ Less common events
 - Create a table/display showing where each case occurs
 - Create an exposure-adjusted incidence rate to compare with literature; off-drug time should not be included
 - Individual case reviews important



Pitfall #2 – Example Revisited

	New drug n/N (%)	Placebo n/N (%)	Total n patients in study
Study 1	30/300 (10%)	10/100 (10%)	400
Study 2	133/700 (19%)	67/350 (19%)	1050
Study 3	200/500 (40%)	200/500 (40%)	1000
Overall	363/1500 (24%)	277/950 (29%)	2450
Study-size adjusted incidence	$\frac{400}{2450} \times \frac{30}{300} + \frac{1050}{2450} \times \frac{133}{700} + \frac{1000}{2450} \times \frac{200}{500}$ = 26%	$\frac{400}{2450} \times \frac{10}{100} + \frac{1050}{2450} \times \frac{67}{350} + \frac{1000}{2450} \times \frac{200}{500}$ = 26%	

Lilly's Process





Lilly's Process

- ◆ Data provided from the study team to SIRC
 - List of cases
 - Exposure table by study
 - For blinded studies, treatment group n's are estimated
- ◆ Data provided from case management to SIRC
 - Treatment assignments for the cases
- ◆ SIRC looks for imbalance
 - Statistician prepares “proper” summary stats
 - By study results
 - In some situations, study-size adjusted percentages, Mantel-Haenszel odds ratio stratified by study



Concluding Remarks

- ◆ Proper statistical thinking is important
- ◆ There's an educational gap in proper data pooling
 - The potential pitfalls are not well known
 - People/groups are trying to address the educational gap, but it has been a challenge
- ◆ There's a need for more innovation for displaying data from multiple studies
 - New ideas or existing ideas, that account for potential study differences, need to be brought to predominant practice

References

- ◆ Making a case for the study-size adjusted percentage to become part of predominant practice:
 - Crowe B, Chuang-Stein C, Lettis S, Brueckner A. Reporting adverse drug reactions in product labels. *Therapeutic Innovation & Regulatory Science*, 2016, 50(4): 455-463.
 - [PhUSE Computational Science Deliverables Catalog](https://www.phuse.eu/documents/working-groups/cs-whitepaper-adverseevents-v10-4442.pdf). Analysis and Displays Associated with Adverse Events: Focus on Adverse Events in Phase 2-4 Clinical Trials and Integrated Summary Document. 2017. <https://www.phuse.eu/documents/working-groups/cs-whitepaper-adverseevents-v10-4442.pdf>
 - [PhUSE Computational Science Deliverables Catalog](https://youtu.be/GGU6-Pmhq-g). Crowe B. Study-size adjusted percentages: why, when & what? <https://youtu.be/GGU6-Pmhq-g>
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Safety Assessment for Investigational New Drug Safety Reporting

Margolis.IND@duke.edu

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Closing Remarks

Adjournment