CTTI Information Request Regarding IND Safety Assessment and Communication Practices

IND Safety Assessment and Communication Practices

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Processing and Evaluation of Individual Serious Adverse Events (SAEs) in Clinical Trials Conducted under IND

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Describe the key aspects of your processing and evaluation of individual SAEs relative to single case signal detection.

Page 1 - Question 1

What specific criteria, if any, are used to determine that a single case may constitute a reportable safety event?

Page 1 - Question 2

Who reviews individual SAEs for an IND and determines whether a given event constitutes a reportable event (i.e., a dedicated reviewer, an individual member of a safety team, the entire safety team)?

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Please describe how your safety databases are organized.

Description

Page 1 - Question 3

Do you maintain a dedicated safety database, separate from the clinical trial database? If so, is there a separate safety database for each trial, indication, or product, or does the database include your entire portfolio?

Page 1 - Question 4

Is the safety data also entered in a clinical trial database? If so, is there a separate clinical database for each individual trial, indication, or product, or does the clinical database include your entire portfolio?

Page 1 - Question 5 - Open Ended

If safety data is entered in more than one database, how are these data sources reconciled?

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Aggregate IND Safety Data Review and Assessment (Part 1)

Describe your practices for aggregate analysis of IND safety data, considering the following:

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Organization

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Roles and responsibilities for routine review of aggregate safety data by the sponsor:

Page 2 - Question 6

Who within the sponsor organization compiles aggregate safety data for review?

Page 2 - Question 7

Who leads the review of aggregate safety data?

Page 2 - Question 8

Is there a dedicated in-house safety team for such reviews? What is the composition of this team and who leads it (e.g. clinical trial physician/scientists, safety physicians/scientists, people from parts of the company not involved with the particular drug, biostatisticians, epidemiologists)?

Page 2 - Question 9

Is there regular inclusion of outside expertise?

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Protocol vs Program-level:

Page 2 - Question 10

Previous FDA guidance has suggested a possible kind of internal safety team that would monitor early studies and look over the whole data base on a product, not just single studies. A similar approach has been advocated in CIOMS VI and by the Safety Planning Evaluation and Reporting Team (SPERT). Are you using this approach? Please describe your approach in this scenario. If you have such an internal safety team, is this group also involved in single case processing and assessment? How many such safety teams exist in your organization? One for each drug? One for each indication? One for each therapeutic area? Do the teams ever have overlapping responsibilities?

Page 2 - Question 11

Are the roles and responsibilities for review of aggregate safety data organized identically across therapeutic areas and/or products? Or does your organizational approach to aggregate safety data vary (e.g., safety management in some instances operates at the level of individual studies, whereas in other instances safety management operates at a program or product level)?

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External Consultation:

Page 2 - Question 12

If this safety evaluation group is internal, under what circumstances would external expertise be sought?

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Analysis of Blinded Studies:

Page 2 - Question 13

Are the safety cases, individually or in aggregate, generally looked at unblinded by the safety team?

- If yes, how is the blinding of the rest of the study maintained?
- If not, how are blinded aggregate reviews performed (e.g. data presented Treatment Group A vs B)?

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Escalations:

Page 2 - Question 14

Who is involved in the final review of the determination of a safety signal by the safety group or DMC? (e.g. Does it go through a Chief Medical Officer, a "Head of Safety" or "Head of Clinical Development"?)

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Aggregate IND Safety Data Review and Assessment (Part 2)

Describe your practices for aggregate analysis of IND safety data, considering the following:

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Routine Review of Aggregate Safety Data

(We recognize that exceptional situations may require special approaches, but ask that you provide only an overview of your standard processes in responding to the questions below)

Page 3 - Heading

Data Sources:

Page 3 - Question 15

What type of safety data are reviewed (e.g., only SAEs or are AEs and/or laboratory or other supporting data reviewed)?

Page 3 - Question 16

If so, at what frequency, if different from SAEs?

Page 3 - Question 17

Please describe your use of databases as sources of aggregate data (e.g., which database(s) are sources of aggregate safety data - safety database only or are data also derived from the clinical database for these reviews; Are safety and clinical databases interrogated jointly to identify potential safety signals? If so, please describe how; Are clinical databases interrogated independently to further evaluate potential signals under consideration?)

Page 3 - Question 18

Are data reviewed specific to a study, indication, IND or aggregated across all studies or INDs for the product?

Page 3 - Question 19

Do you maintain a program-level safety database (i.e., one that includes all studies in all indications)? If so, how are data from dissimilar studies integrated into a program-level safety database?

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Data presentation:

Page 3 - Question 20

What is the format of the outputs reviewed - line listings vs raw data? or other looks?

Page 3 - Question 21

Are specific reports produced from the safety database for SAE review?

Page 3 - Question 22

Is the primary review of data blinded or unblinded?

- ○ Blinded
- ○ Unblinded

Page 3 - Question 23

Any stratification into treatment arms (e.g. A vs B)?

Page 3 - Question 24

Do secondary safety committees review data blinded or unblinded?

Page 3 - Question 25

Beyond individual serious and unexpected suspected adverse reactions, are any data unblinded prior to study completion?

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Aggregate IND Safety Data Review and Assessment (Part 3)

Describe your practices for aggregate analysis of IND safety data, considering the following:

Page 4 - Heading

Tools / Assessment

Page 4 - Heading

Routine Assessments:

Page 4 - Question 26

How frequently is safety data aggregated? How frequently does this safety team meet to review data? (e.g., Does it depend on the phase of development or the known safety profile of the product?)

Page 4 - Question 27

Are assessments of the data largely qualitative using clinical judgment or quantitative using specific statistical algorithms?

Page 4 - Question 28

Are processes for the routine review and confirmation of safety signals documented in SOPs or other controlled documents?

Page 4 - Question 29

If quantitative assessments are performed, are thresholds pre-defined and consistently applied or dependent on product/indication/nature of the event?

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Additional Analytic Approaches:

Page 4 - Question 30

Are analyses of data sources (e.g., published literature, existing registries, CMS data, previous related experiences) from outside of the trial databases ever incorporated into an evaluation of a potential safety signal to assist in assessing background rates or potential class effects?

Page 4 - Question 31

Please describe the range of sources used.

Page 4 - Question 32

What types of statistical analyses or tools are employed to leverage these data sources?

Page 4 - Question 33

What weight do you give to such additional analyses when the results conflict with the data from the clinical trial(s) under IND in deciding whether to send an expedited IND safety report based on aggregate data?

Page 4 - Question 34

Please describe the range of disciplines (biostatistics, epidemiology, etc) involved in these additional analyses. Please also describe the organizational relationship of these experts to the safety team (e.g., are they dedicated members, internal consultants, external experts)?

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Aggregate IND Safety Data Review and Assessment (Part 4)

Describe your practices for aggregate analysis of IND safety data, considering the following:

Page 5 - Heading

Confirmation and Regulatory Reporting Practices

Page 5 - Heading

Escalation of potential safety signals:

Page 5 - Question 35

How are decisions made in terms of confirming safety signals?

Page 5 - Question 36

Is this done at a single product or therapeutic area-specific level, or is there a standardized escalation process for notification of potential signals across all products/therapeutic areas?

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Threshold:

Page 5 - Question 37

Please describe internal processes, if any, for determining that a potential safety signal has crossed a threshold and requires specific management.

Page 5 - Question 38

Are there specific processes currently in place to determine that a threshold for reporting to FDA has been reached for a given potential safety signal? If you do not have processes in place, are you contemplating any for possible future implementation?

Page 5 - Question 39

Are these processes based on a statistical analysis, clinical judgment, or both?

Page 5 - Question 40

How is this different from the confirmation of a safety signal resulting in an update to the IB? (e.g. would only an update to an IB trigger an IND safety report based on aggregate data, or would IND reports be sent for signals that are still under evaluation)?

Page 5 - Question 41

Approximately what percentage of signals reviewed (e.g. by a safety team) result in IND safety reports and what percentage result in an update to the IB or other similar action? If you have not begun submitted IND safety reports based on aggregate analysis, you may limit your answer to the second half of the question.

Page 5 - Question 42

Are there processes for seeking outside input?

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Reporting:

Page 5 - Question 43

Please describe any impact that the new US regulatory requirements related to IND safety reporting have had on the content and format of IND Safety Reports. Please describe any changes to the content and format of these reports currently under consideration.

Page 5 - Question 44

How do you prepare or intend to prepare IND safety reports of aggregate analysis of a safety signal? When do you provide narratives of each individual event versus only a summary narrative of the aggregate events? Do you provide both? If you do not intend to use one consistent approach, how will you decide which approach to use?

Page 5 - Question 4

Please describe any processes currently in place or under consideration for determining when the sponsor defines clock-start date for IND safety reports based on aggregate data review?

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Aggregate IND Safety Data Review and Assessment (Part 5)

Describe your practices for aggregate analysis of IND safety data, considering the following:

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Data Monitoring Committees (DMCs):

Page 6 - Heading

Integration:

If you use or have used external, independent DMCs for one or more clinical trials in an IND phase development program, please comment on the following:

Page 6 - Question 46

How does the DMC, which is usually monitoring a single trial, interact with the internal safety team with regard to the oversight of the emerging trial safety data and to the detection of new safety signals?

Page 6 - Question 47

Do current external DMCs regularly (e.g., monthly) evaluate the emerging unblinded trial safety data for imbalances that might suggest a new safety signal within that trial?

Page 6 - Question 48

If they do, is there a general threshold and/or statistical approach for the DMC to notify the internal safety team of such an imbalance or is the threshold left to the best judgment of the specific DMC members?

Page 6 - Question 49

If such notifications of emerging safety imbalances based on aggregate unblinded DMC analyses have occurred in the past, have they led to regulatory notification? If so, what has been the format and process for such notifications to FDA?

Page 6 - Question 50

Based on the past and current practice of DMCs that oversee individual trials for your company, would the new FDA final rule/draft guidance on premarket IND safety reporting require changes in their remit and current practices? If so, which of these changes are already implemented or planned for implementation and which ones remain challenging and require additional FDA guidance?

Page 6 - Question 51

How have the DMC aggregate unblinded analyses complemented internal aggregate blinded analyses in reaching decisions requiring revision of reference safety documents (IB, ICF, DCSI, etc) and regulatory notification? Has regulatory notification followed a process analogous to expedited IND ICSRs or a different process?

Page 6 - Question 52

When you use an external DMC for a clinical trial or trials, are they the only group evaluating the emerging trial safety data in an unblinded fashion during the blinded randomized portion of the trial or is there an internal safety team (or individual safety staff) also reviewing the unblinded data in parallel with the DMC?

Page 6 - Question 53

If you use external, independent DMCs, do you always rely on different DMCs for individual trials in a program or do you sometimes create a DMC responsible for 2 or more (or all) trials in a development program? Can you describe your experience with either or both approaches and how they may differ with regard to interaction with the internal safety team and with respect to the approach to safety signal detection?

Page 6 - Question 54

The FDA rule and DMC guidance suggests an internal safety team with responsibility for monitoring the overall safety database (see also 2.1.2). Larger studies will generally have an existing, dedicated DMC. If you have used this type of internal safety teams, describe how the internal program-level safety team interacts with an individual study DMC.

Page 6 - Question 55 - Name and Address (U.S)

Enter your organization below:

- Organization