FOLLOW UP OF CARDIOVASCULAR EVENTS

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Disclaimer

- I am a full time employee of GlaxoSmithKline
- The information presented represents my personal opinion and does not necessarily reflect the opinion or policy of any companies or organizations

Challenges in Assessing CV Signals in Non-CV Outcomes Studies

- While imbalances in the frequency of CV events often occur in non-CV outcomes trials
  - May take review of several trials or of a program at time of submission to recognize that there is an imbalance
  - At which point, obtaining sufficient information from years earlier can be nearly impossible
- Investigators and medical monitors are often not cardiologists
  - May not be focused on CV events
  - May not take history with pertinent positives and negatives
- Lack of adequate information collected at time of event prevents proper evaluation and definitive adjudication
  - May result in an unrecognized patient safety issue
  - May also result in a CV effect being attributed to compound unnecessarily

Cardiovascular Safety Signals in Non-CV Trials

- CSRC has developed a set of targeted follow-up questions for use in non-CV outcomes trials to collect information as temporally close to the occurrence of an event as possible
- Purpose: To ensure that information is available in case a CV signal is detected at a later point in time

Cardiovascular & Death CRFs

- Although comprehensive information and source documentation regarding any adverse event should be sought, this is not necessarily always possible or pragmatic in all settings
- The goal was to balance the need to have sufficient information to adjudicate without being overly detailed or overwhelming
  - Not meant to be definitive, proscriptive or overly comprehensive
- Important to note that no one is suggesting that all CV events require adjudication, but rather, that if needed, the key information is available for post-hoc evaluation

Cardiovascular & Death CRFs

- Arrhythmias
- Cerebrovascular Events (Stroke & TIA)
- Heart Failure
- Death
- Deep Venous Thrombosis/Pulmonary Embolism
- Myocardial Infarction
- Peripheral Arterial Thromboembolism
- Pulmonary Hypertension
- Valvulopathy

Cardiovascular & Death CRFs

- Use of the forms is optional
- No regulatory requirement to use the forms
- Sponsors may adjust the forms to suit their needs and method of database collection
  - Some may want to modify for certain populations being studied
  - More questions on diagnostic tests, more questions on H+P, simplify forms, etc
  - These can be implemented for all studies/programs or they can be targeted for ones with preclinical signals, class effects, etc

Means to Trigger Forms

- Sponsors will need to determine how they want to implement the forms and in particular how they want to trigger them
- In general, one way would be to use MedDRA event codes or the occurrence of death as a trigger

How would data collection with MedDRA terms or occurrence of death work?

- For CV events, trigger would be MedDRA terms used to report event
  - Upwards of ~2,000 cardiovascular-related terms map to the events of interest as listed earlier
- For death, trigger would be
  - Outcome of death for an SAE, or
  - Status question in a survival study, or
  - Question on a conclusion form in a non-survival study

Cardiovascular & Death CRFs

- From a larger standpoint, if sponsors utilize the forms, it is anticipated that the overall CV characterization of drugs under development will be markedly improved
  - Which is in keeping with CSRC's public safety goals
- Important to know that CSRC realizes these forms may require modifications and updates
  - They have not been through a "validation" process
  - Work will be ongoing to incorporate feedback and adjust accordingly

Summary

- The CSRC will be posting these forms to the website for public use www.cardiac-safety.org (note: these forms have not been validated)
- One size will not fit all – forms may need modifications for individual sponsor needs and taking sponsor's current data collection questions into consideration
- Ultimately, goal is to proactively collect CV event information when there is the best chance of characterizing the event so that sufficient information is available in case a signal is detected at a later point in time