CV ADJUDICATION IN SMALL AND LARGE DATABASES

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Small Databases

- This could represent a database from a small single study or combination of studies (phase I or phase II)
- Or a database from an entire development program in which there are small numbers of patient exposures e.g., oncology/rare diseases.
- Ultimately, what is the purpose of the adjudication in these types of databases?
  - Are there just a handful of "concerning" events that sponsor is trying to better understand?
  - Is there really a true (non-statistically significant) imbalance of CV events?

Small Databases

- Small single study or group of small studies
  - In these situations, a formal external independent adjudication may not be necessary; rather, consider having internal/external experts look at case and evaluate as part of a comprehensive safety evaluation.
  - Go beyond adjudication and consider whether or not it is *drug related* (temporal factors, rechallenge, etc). This represents process for typical developmental "safety" evaluation with an early understanding of cardiac events/signal.
  - This could lead to more intensive monitoring, or as previously described, enhanced CV event follow-up.

Small Databases

- When evaluating an entire development program with small exposures:
  - The relatively frequency of events in treatment vs. control groups may determine if cardiac event is potentially related to drug
  - This can have implications on labeling, risk management, approvability.
  - In these situations, there may be a **regulatory** or other need to consider external, independent adjudication of events. It would be difficult to predefine what level of imbalance would trigger this type of external adjudication review but consider factors such as:
    - Mechanism of Action, Class effects, CV events seen in earlier studies
    - Grouping of related SAEs and AEs to see if there is a consistent story; e.g, if the signal is MI, look at all types of ischemic events, arterial thrombosis, chest pain episodes, etc. and see if all of these events go in the same direction or are just scattered randomly between treatment and control groups.
- The external adjudication will assist in deciding which cases really comprise the "safety signal" and what may represent noise.

Large Databases

Scenario

- Global trial(s) evaluating drug X for treatment of disease Z, a chronic, but not life-threatening, non CV condition
- > 2500 subjects; duration of clinical development program = 10 years; population being studied not at high risk for CV events
- Numeric imbalance in # of CV events noted in interim analysis; overall small # of CV events
- No known class effects

Large Databases: Key Questions

1. Should these events be adjudicated?
2. What type of adjudication?
3. What issues are likely to arise when adjudication is not preplanned?
4. Has the value of adjudication in large non CV trials been demonstrated?

Large Databases: Considerations

Should these events be adjudicated?

Scientific perspective

- Global trial- different standards for diagnosis
- Expertise of Investigators (non CV trial)
- Long duration-standards for diagnosis change over time

Large Databases: Considerations

Should these events be adjudicated?

Regulatory perspective

- Expectation of regulatory agencies
- Necessary for approval?

Large Databases: Considerations

What type of adjudication?

- External vs. internal
- CEC membership
- Case ascertainment-wide net vs. PI reported AEs?
- SAEs vs. all AEs?
- Beyond AEs?

Large Databases: Considerations

What issues are likely to arise when adjudication is not preplanned in a non CV trial?

- CV events are not prespecified endpoints
- Limited or no access to source documents
- CV endpoint definitions may be challenging to meet
- Large number of cases with insufficient information to adjudicate

Large Databases: Considerations

Has the value of adjudication in large non CV trials been demonstrated?

- Does adjudication in this scenario, especially in a low risk population, impact the trial results or conclusions?
- In which trials is it worth the cost and time?