General Comments for the CV/Death Case Report Forms for Non-Cardiovascular Studies

Goal: To collect the minimal amount of information necessary to adjudicate CV events and death post-hoc in the event a signal is detected, potentially even years later. By focusing on the minimal amount of information necessary, it is hoped that the forms will not be burdensome to investigators and will allow streamlined data collection from a data management perspective.

Key Points:

- Involve Data Management early as options will be dependent on available means to database clinical trial information.
- Keep in mind the need to balance "need to know" (basic form) vs. "nice to know" (supplemental form).
- The suggested and supplemental forms are only suggested and not required by any regulatory authority.
- Concomitant meds are often desired. Ideally these should be obtained from the usually already existing concomitant medication eCRF.
- Revascularization usually is a procedure and not an AE, it will likely be used in association with other CRFs and not as a separate one.
- Some companies may want to only have a checklist of source documents are requested in real time.
- Some companies may want to add on all of the forms if the patient was seen/treated by a specialist (cardiologist, or neurologist)

QUESTIONS & COMMENTS

- Some of the forms are designed to very well characterize 'real' CV events. However, because of limited information collected, do not allow evaluation of alternative diagnosis or evaluation of other potential causes for the AE. Why?
    - A balance between burden to non-cardiologist investigators and information needed to adjudicate properly.
    - Does FDA have enough information to make a regulatory decision?
- Some forms have a note referring to the SAE report. Most of these events will be reported as SAEs. Should the same note be included in all these CRFs?
    - Some companies report a 50:50 ratio of how CV events are reported (50% AE & 50% SAE).

- May want to include standard language on each form re: where some information may be filled in. May want to say if it has been filled in elsewhere, it is not necessary to re-fill. Some data managers discourage this type of wording.

- Couldn't the SAE reporting process be tweaked so as to not need these forms?
  - If the information requested has already been included in the SAE report, it could be considered sufficient to cross reference the SAE form (in this case the tool is only a reminder of key data to include in the SAE report). This is not recommended by some data managers.

    or

  - Collect some targeted data PLUS the standard information available on a SAE form (which is what the current forms up for discussion do).

- Death is usually the outcome of an event. Shouldn't only "death cause unknown" should be reported as an AE?
  - "Death cause unknown" may be databased differently depending on the company. Most important is that it is done consistently across any single company.
  - Death reported as an event (not often), but have seen it if there is no additional information available (usually spontaneous, but sometimes occurs in clinical trials when a subject has died and the clinical team cannot get any further information).
  - In cancer survival studies, subjects may be reported to have died from underlying disease and death would not then be reported as an SAE.

- Suggest having a reminder to add in the AE form a clear description of the clinical course and outcome of the event (ideally in the first page).
  - Company dependent. Some company AE forms allow for narrative portions, whereas others allow only tick boxes.
    - Could consider: These could be included as categories (i.e. resolved with or without sequelae, treatment needed or not, medical or surgical treatment and death as an outcome.

- Some forms have little to no information to understand alternative causes. Including past medical history of CV risk factors, co-medications, drugs of abuse, past CV disease, vascular malformations (angiomas/aneurism), hematological disorders (thrombocytosis, polycythemia, sickle cell, coagulopathy, etc.), vascular disorders (vasculitis), migraine, etc.

- Suggest that companies consider collecting cardiovascular risk factors as either a separate eCRF or as part of their key past medical history page (waiting till there is a signal to ask these questions is problematic and asking these questions on all nine CV forms is very redundant if they have more than one event). Would be best to collect as some part of the PMH or direct cardiac risk factor questions.

- How will MedDRA PTs trigger each CRF. Are we recommending SMQs (narrow vs. wide)? Or tailored per program?
  - Will be company dependent as to how their IT staff can accommodate this. May use up to 2,000 MedDRA terms to trigger the forms. Specifics will vary company to company, in particular whether company is small and "asleep" overnight or whether running any large terms of interest will interfere with someone's work somewhere because the company is always "awake."
  - Tailoring towards program is always a consideration; however, it becomes more labor intensive when trying to implement across a large portion of R&D studies.
- Should "not known" be added to all of the forms?
  - Depends on the implications. Would help with metrics regarding completion of forms; however, needs to be balanced with offering investigator an easy way out to answering the question.
- What is the recommended scope?
  - Will be company dependent. Obviously the more studies that can include it, improves ability to detect signal.
    - Some areas where inclusion of forms may not be as helpful, would include:
      - Normal healthy volunteer studies
      - Compassionate use studies
      - Paper-based studies
- How will the data captured on the CV CRFs be displayed in a clinical study report and submission?
  - Would be up to each company. Some may want to have fields automatically dump into a pre-populated order to tell a "story" or narrative.