Sampling Model for Adjudication

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Selection of terms for adjudication

✦ Program Details

 ➢ **CV Safety Study**

 ➢ **Non-CV patients and non-CV investigators**

 ➢ **Enrollment > 8000, Multi-year, Multi site**

✦ Patient Characteristics

 ➢ **Low risk of 'true' CV endpoints**

 ➢ **High risk of multiple and repeat cardiac symptoms**

✦ Challenge

 ➢ **How to do cost-effective but rigorous endpoint adjudication**

Ensure high sensitivity of detection

- ✦ To enable the coverage so that all potentially positive events get sent for adjudication – various strategies
    1. Send cases with pre-identified set of terms to adjudication
        - e.g. Broad and extended definition by SMQ and preferred term
        - May still have concerns about coding, coverage and sensitivity of detection
    2. Send all cases for adjudication
        - Not efficient use of resource

Events that would be adjudicated as 'positive' events
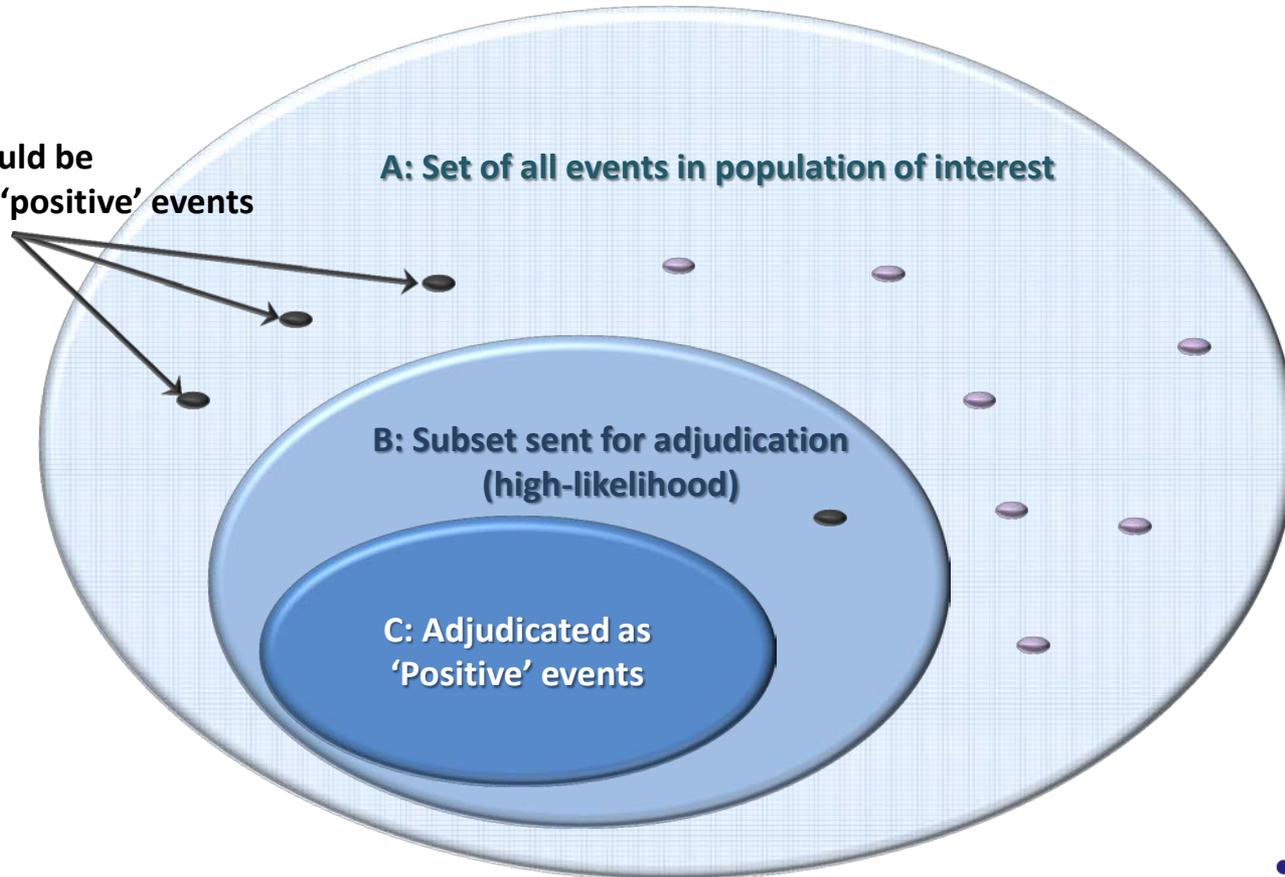
A: Set of all events in population of interest

B: Subset sent for adjudication (high-likelihood)

C: Adjudicated as 'Positive' events

Address concern that all positive events have been sent for adjudication

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Adaptive approach

- ✦ Driven by the terms that occur

- ✦ High likelihood group

  - ➢ **Pre-defined high likelihood group of terms - events matching these terms always sent for adjudication (could be defined by SMQs – defined set of preferred terms)**

  - ➢ **Possibly defined from a pilot period for events where positively adjudicated terms (adjudicated as a clinical event) added to high likelihood group**

  - ➢ **This group of terms grows as the adjudication process continues**

- ✦ All other events (not in high likelihood group)

  - ➢ **Sampled at defined rate for adjudication**

  - ➢ **Any adjudicated as positive added to the high likelihood group**

Adaptive process

- Step 1: Define high likelihood group initially
  - Pre defined preferred terms defined high risk group and are always adjudicated

  And/Or

  - From a pilot period where positively adjudicated terms contribute to this list
  - Associated preferred terms for cases positively adjudicated will be placed on the high likelihood list

Adaptive process

- **Step 2: Continue adjudication in batches**
  - All cases with high likelihood terms are sent for adjudication
  - Remaining cases are sampled
    - The terms for any of the positively adjudicated cases in the sampled set are added to the high likelihood group of terms
    - Cases with multiple trigger events and the CEAC members made the final decision based on the combination of trigger events then the combination of events will be placed on the high likelihood list
    - All previous unadjudicated cases are searched for the newly added high likelihood terms – any of those with matching terms are sent for adjudication

Sensitivity estimates

✦ **Sensitivity of detection process**

➢ At the conclusion of the adjudication process, a certain number of positively adjudicated events will have been identified and the sensitivity of their detection can be calculated as:

$$\frac{\text{Positively adjudicated events}}{(\text{Positively adjudicated events} + \text{Positive events remaining})}$$

➢ An upper bound of the 95% confidence limit for the rate of positive events among the remaining events can be estimated as by $3/n_{low}$,

➢ n_{low} is the number of sampled trigger events in the low likelihood group.

➢ Best case number of total clinical events in the low likelihood group is calculated as $3/n_{low}*N_{low}$, if no positive events identified from sampling process

➢ N_{low} is the size of the population of trigger events not matching terms in the high likelihood list at the conclusion of the project.

✦ Sample calculation, for project with 15,000 trigger events

➢ 600 with high likelihood terms, 14,400 with other terms, 3,000 terms sampled

➢ Total of 300 positively adjudicated events

➢ A minimum sensitivity is $300/(300 + (3/3,000)*14,400)$ or 95.5%

Implementation

- Adaptive approach in use in prospective adjudication project
  - **Pilot period generate initial set of terms**
  - **Helped determine**
    - Event rate
    - Positive event rate
    - Sampling rate
  - **Process monitored to ensure effective sampling rate and achieve levels of sensitivity of detection**