Building a Generalized Framework for Signal Refinement

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Signal refinement: evaluating magnitude and clinical significance of suspected product-event association*

- Magnitude: how important is the signal and how will this adverse event impact the population based on the use and benefit of the product in the population
- Clinical Significance: does product-event make clinical sense and is it important
  - Sentinel should factor in what we know from other data sources as part of triaging potential signals to determine which signals to further evaluate or take action on

* Used definition provided without questioning whether I agree or disagree with the terminology or the processes

What are the goals of signal refinement, and how do we know when they have been met?

- Goal: Efficiently and accurately determine which potential “signals" need to go to Evaluation Phase
- Enhance product monitoring beyond spontaneous AEs through appropriate analyses of systematic information from more reliable data sources, such as:
  - Randomized trials, mechanistic studies and well-designed pharmacoepidemiology studies
- Provide information on subgroups at increased risk or for whom little data is available from clinical trials and understand risk factors for "signal“
- Monitor success: evaluate proportion of signals "strengthened or refined" and subsequently "confirmed or replicated" through evaluation

Standardize steps in signal refinement?

- Identify specific medical product-adverse event pairs prior to product launch based on drug class or product (Risk Management Plan)

- Develop standard definitions and code lists for events:
  - Literature, medical expertise review, data on validation of event definition
  - Event definitions may vary based on type of database and ability to validate endpoints - if not able to validate endpoint with chart review may require greater event specificity:
    - E.g. MI diagnostic code versus MI diagnostic + results of laboratory tests or EKG or minimum hospital length of stay

- Previous validation may not be sufficient if differential detection or misclassification of diagnoses between treatments due to detection or notoriety bias:
  - e.g. intussusception may be more likely incorrectly diagnosed in a claims database for a new rotavirus vaccine than for DTaP vaccine due to previous signal from older rotavirus vaccine

Standardize steps in signal refinement?

- Create criteria for choosing electronic databases; understand advantages and limitations of each
- Develop framework in which multiple databases can be analyzed (common data model)
- Establish procedures to "split samples" from databases for both signal refinement and signal evaluation
- Define and test analytical methods and understand advantages and limitations of each method
- Develop cohorts of patients with specified diseases in databases to make future anticipated analyses more efficient
- Pre-define primary exposure and comparator group(s), events of interest, potential confounders, statistical methods including sensitivity analysis
- Develop best practices for interpretation and reporting of findings

Issues and challenges to create the capacity for signal refinement in Sentinel?

- Define “best” method applied consistently with good reliability to confirm known drug/event associations and non-associations
- “Acceptable Threshold” to define need for further evaluation - trade off between too many FP signals and possibility of missing FN signals
  - May vary based on benefit risk profile of product, disease, type of safety issue, population at risk
- Sequential Probability Testing – speed vs. greater specificity:
  - Near “Real Time” interpretation when events may not be validated
  - Lack of control for confounding
- Potential to use multiple methods and databases simultaneously to confirm that signal with one method is replicated with another method and database
- Role of multiplicity: multiple looks, comparing multiple exposures for multiple endpoints

Role for ongoing/existing registries and prospective trials in signal refinement?

- Meta-analyses of ALL relevant trial data may be useful
- Completed RCTs and interim results from ongoing RCTs:
  - Often event is not pre-specified endpoint and therefore may lack validation (diagnostic certainty will depend on type of event)
  - May not have adequate information on baseline disease state
  - Need to consider adequacy of sample size for frequency of events of interest (problem of small number) and adequacy of follow-up time for events that take longer to develop
- Ongoing or Completed Product registries
  - May not provide comparison group within registry
  - Same method issues as databases due to lack of randomization
    - Issues related to differences in use of products (channeling), time trends, difficulty to define a comparable population

Signal Refinement: remove seed coverings, stems and leaves to get to the wheat

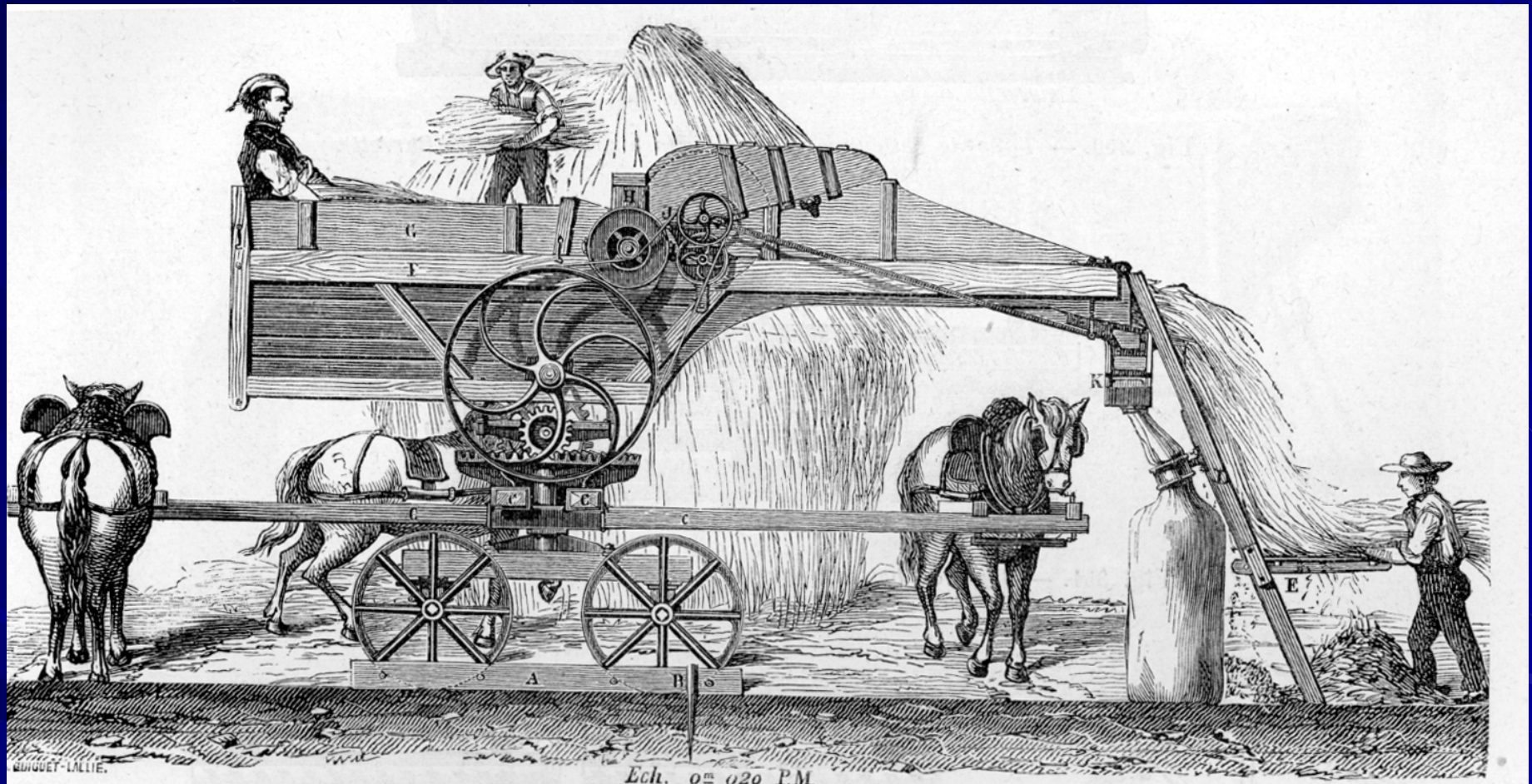

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Fig. 349. — *Batteuse Damey à manège direct placé sous la batteuse.*