Advances in safety data analysis – the journey

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Evolution of safety as a fundamental part of regulations
The story of evolution

Science
Process
Impact

Outcome
The evolution

• Pre-modern/ traditional times
  – Simple trials
  – Minimum transparency/ patient protection
  – Minimum trial regulations
  – Maximum faith in medicine

• Modern times
  – Increasing trial complexity
  – Increasing transparency/ checks for patient safety
  – Stringent regulations
  – Somewhat reduced faith in the system

  – Time is money
    • Business decisions
    • Regulatory decisions
    • Patient centric/ ethical/ safety decisions
Focus on efficacy and safety in clinical trials & thereafter
Determinants

• Acquisition of safety data
  – Multiple site, multinational trials
• Data collation and processing
  – Increasing number of users... sponsor, CROs, trial site, regulators
• Data evaluation
  – Business decisions
  – Regulatory decisions
  – Patient centric/ ethical/ safety decisions
Evolution of methodology

- Microdosing
- Adaptive designs
- DSMBs for RCTs
- Real time monitoring
- Remote Data monitoring
- Data elements (biomarkers)
Issues with safety data evaluation

• The premarketing clinical trials required for approval of a drug primarily guard against type 1 error.
• RCTs are usually statistically underpowered to detect the specific harm either by recruitment of a low-risk population or low intensity of ascertainment of events.
• The lack of statistical significance should not be used as proof of clinical safety in an underpowered clinical trial.
Issues with safety data evaluation

• Inconsistencies in adverse effects reported in clinical trials can create challenges

• Adverse events are recorded as secondary outcomes in trials and are usually not prespecified

• Misclassification of adverse events is possible, particularly where the outcomes are collected through spontaneous reports from trial participants rather than systematic monitoring

Example: use of inhaled corticosteroids in patients with chronic obstructive pulmonary disease or thiazolidinediones among patients with type 2 diabetes may increase the risk of pneumonia. Radiographic or microbiologic confirmation of pneumonia was not available. Pneumonia was not prespecified as an outcome of interest, but ascertained as adverse events or serious adverse events in these trials. Whether the risk of pneumonia seen in clinical trials of inhaled corticosteroids represents a potential misclassification of a subset of COPD exacerbations is unknown.
Issues with safety data evaluation

• Limited generalizability - study participants are often carefully selected, and the trial may have been designed to evaluate only one particular dose, so there is no information on dose-responsiveness - difficult to extrapolate to wider populations who may be taking different doses or formulations
# Challenges in safety data assessment

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Key Features</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Spontaneous or voluntary reporting systems, including journal-published case reports | Captures very wide range of events  
Particularly useful for detecting signals of rare (low background incidence in treated population) and/or unexpected events (e.g., new unrecognized pathology)  
Sophisticated statistical techniques have been developed for signal detection | No denominator or control group, difficult to quantify risk  
Format and type of information differs substantially among regulators and journals  
Clinical details may be incomplete, causality uncertain  
Selective reporting or under-reporting of cases |
## Challenges in safety data assessment

<table>
<thead>
<tr>
<th>Study Design</th>
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<th>Limitations</th>
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</thead>
<tbody>
<tr>
<td>Randomized clinical trials</td>
<td>Randomization reduces possibility of confounding at baseline</td>
<td>Rigid recruitment criteria may lead to exclusion of patients who are at risk of adverse effects</td>
</tr>
<tr>
<td></td>
<td>Certain adverse effects can be prospectively specified for detailed monitoring</td>
<td>Powered for detection of significant difference between groups for beneficial effect, estimates for adverse effects may lack precisions</td>
</tr>
<tr>
<td></td>
<td>Intervention is typically well defined</td>
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# Challenges in safety data assessment

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<tr>
<td>Non-randomized studies</td>
<td>‘Real-world’ use with more generalizable data and longer follow-up</td>
<td>Monitoring for rare or unexpected events may be less rigorous, and the trials may not be of sufficient duration to detect long-term problems</td>
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<tr>
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<td>Potentially able to specify and assess rare events as primary outcomes in case control designs</td>
<td>Non-randomized nature is susceptible to confounding</td>
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<td>May be able to explore relationship to dose, duration and patient susceptibility factors</td>
<td>Drug exposures are often based on computerized records rather than dispensing or actual use</td>
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# Challenges in safety data assessment

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<td>Meta-analysis of controlled observational studies and/or trials</td>
<td>Pooled analysis has greater power to detect significant differences, even with rare events</td>
<td>Reliant on quality of primary data</td>
</tr>
<tr>
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<td>Aims to summarize complete data set</td>
<td>Missing or unreported data on adverse events is a major problem, as are the statistical techniques of pooling sparse Data</td>
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<td>Susceptible to selective outcome reporting of primary studies and can evaluate consistency of findings among studies</td>
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<td>Heterogeneity within the pooled analysis</td>
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Post marketing Phase
No. of patients required with no background incidence of adverse reactions to unveil a Signal

<table>
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<tr>
<th>Expected incidence of ADR</th>
<th>Required number of Adverse Reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>1 in 100</td>
<td>300</td>
</tr>
<tr>
<td>1 in 200</td>
<td>600</td>
</tr>
<tr>
<td>1 in 1000</td>
<td>3000</td>
</tr>
<tr>
<td>1 in 2000</td>
<td>6000</td>
</tr>
<tr>
<td>1 in 10000</td>
<td>30000</td>
</tr>
</tbody>
</table>

Can you spot the ‘signal’?
This indeed is the real aim of Pharmacovigilance!
Issues in Post-marketing Safety data

• Chronic under-reporting
• Occasional publicity-driven and litigation-driven episodes of over-reporting and misreporting, incomplete and missing information, and inconsistencies and changes over time in reporting and naming/coding practices
• Uncertainty regarding the quality and completeness of the information contained in each data field
Possible resolutions despite the limitations

• Trials are usually powered to detect benefit and seldom designed with adverse events as primary outcome. It is not possible to design trials to evaluate unexpected or unknown adverse effects that have yet to be linked to the intervention.

• Clinical trials should include explicit pre-specified monitoring of pharmacologically predictable adverse events and ensure adequate follow-up of withdrawn participants.

• Recent regulatory guidance from the FDA has limited the reporting of adverse events in clinical trials from sponsors to those that are unexpected and considered related to the drug.
Possible solutions despite the limitations

• Empirical work is needed to evaluate whether novel approaches such as mechanism-based drug toxicity prediction can complement safety data from clinical trials and improve an assessment of drug safety.

• Multi-criteria decision analytical techniques that accurately capture quantitative inputs and qualitative values from various stakeholders for risk-benefit tradeoffs and allow for quantitative analysis and modeling uncertainty on a range of outcomes can improve complex regulatory decisions about drug safety.
Possible solutions despite the limitations

• Conducting **health outcome trials** prior to approval increases the evidence base on safety

• **Post-marketing safety studies** of adequate design become mandatory in circumstances when surrogate endpoints are used to approve a drug
The increasing pressure by the public to make all clinical trial results available and heightened public awareness about emerging drug safety issues ensure that analyses of safety data from clinical trials will remain central to the discussion around drug safety in the foreseeable future.
The Interoperable Clinical Research and Pharmacovigilance Network (ICRPN)
Benefits of a Standard-based combined PV system

- Early drug safety detections
- Clinical collaborations among clinical partners or different functional groups
- Assisting in safety decision making
- Data mining results interpretation
Thank you