Signal detection in a global database

Monica Plöen 16th of April 2018

Head of Pharmacovigilance Collaborations
Disclaimer

The opinions expressed in this presentation are the presenter’s and are not the opinion of either Uppsala Monitoring Centre or the World Health Organization.
Outline

• WHO Programme for International Drug Monitoring
• VigiBase – WHO global database of individual case safety reports
• Use of MedDRA in signal process and analysis
WHO Programme for International Drug Monitoring

- Thalidomide 1961
- In 1968 WHO creates the Programme for International Drug Monitoring (PIDM)
- In 1978 Swedish Government and WHO creates UMC and Collaborating Centre
Established as a foundation in 1978

Provider of scientific leadership and operational support to the WHO PIDM

Custodian and manager of VigiBase

Maintenance organization for WHODrug

Self funding
Identifying sources of potential harm to patients is the highest priority. Detecting and communicating signals of such harm lies at the heart of pharmacovigilance.
WHO Programme for International Drug Monitoring
1968 – founding members

- Australia
- Canada
- Czechoslovakia
- Ireland
- Netherlands
- Germany
- New Zealand
- Sweden
- United Kingdom
- United States
WHO Programme for International Drug Monitoring
COUNTRY DISTRIBUTION SINCE 1968

- United States of America: 48%
- Republic of Korea: 6%
- United Kingdom: 5%
- China: 5%
- France: 4%
- Germany: 4%
- Canada: 4%
- Italy: 2%
- Thailand: 2%
- Australia: 2%
- Other Countries in VigiBase: 18%
Our signals aim to be an aid and a complement to the National Centres’ own signal detection

But what is a ‘signal’...?
A signal is essentially a hypothesis of a risk with a medicine with data and arguments that support it, derived from data from one or more of many possible sources. The evidence in a signal is not conclusive (is, in the technical sense, uncertain), and is only an early indication (preliminary), as it may change substantially over time as more data accumulates. Sometimes a signal may provide additional or new information about adverse or beneficial effects of an intervention, or information about an already-known association of a medicine with an adverse drug effect, for example: on the range of severity of the effect or its outcome; postulating a mechanism; indicating an at-risk group; suggesting a dose range which might be more risky/perilous, a pharmaceutical group-effect or a lack of effect by a particular medicine.
What is a signal?

• A signal is an evaluated combination which is considered important to investigate further

• A signal is an early hypothesis together with data and arguments.

• A signal is not only uncertain but also preliminary in nature.

• The situation may change substantially over time one way or another until more data is gathered.
Signal detection

Small database
• Identification of potential signals on an as-you-go / case-by-case basis
• Causality assessment of ICSRs and case series

Large database
• Automated search for disproportionalities (ADR-drug combinations reported more often than expected)
• Causality assessment of ICSRs and case series
UMC Signal detection process

National PV centres → VigiBase → First-pass statistical screening → Initial manual assessment → In-depth manual assessment → Signal
First-pass statistical screening

vigiRank
- Disproportionate reporting
- Report quality & content

Basic criteria
- Inclusion/exclusion criteria

Focus area
- Paediatric
- Vaccine
- Regional
- Drug-drug interactions

Prioritization of drug-ADR combinations for manual review
What are the challenges?

Statistical screening

• Substance and preferred term
• WHO-ART
• Different reporting
The result of the first pass screening is a list of prioritized drug-ADR combinations, ranked according to strength of evidence.

<table>
<thead>
<tr>
<th>vigiRank</th>
<th>DrugText</th>
<th>Preferred term</th>
<th>Observed</th>
<th>IC025</th>
<th>SeriousProportion</th>
<th>IME</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.33</td>
<td>Heparin</td>
<td>Gastric ulcer</td>
<td>25</td>
<td>2.24</td>
<td>98%</td>
<td>1</td>
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<tr>
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<tr>
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<tr>
<td>0.07</td>
<td>Tetanus antitoxin</td>
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UMC Signal detection process

National PV centres → VigiBase → First-pass statistical screening → Initial manual assessment → In-depth manual assessment → Signal
UMC Signal detection process

- Each drug – ADR combinations go through the following steps
- Substance and preferred term
  - *Initial manual assessment*
  - *Decision on whether or not the combination should be further assessed in-depth*
  - *Documentation*
UMC Signal detection process

1. National PV centres
2. VigiBase
3. First-pass statistical screening
4. Initial manual assessment
5. In-depth manual assessment
6. Signal
In-depth assessment – after sprint

• Potential signals go through in-depth review to decide if signal is to be communicated
• Signal review panel consulted
• Review includes
  – Clinical assessment of individual case reports
  – Literature review
  – Consider expanding review to similar drugs/ADRs
  – Consider requesting original reports
• Outcome: Signal, Not signal, KUR, Publication
The result of the first pass screening is a list of prioritized drug-ADR combinations, ranked according to strength of evidence.

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MedDRA use in signal detection process

HLGT

HLT

Hepatitis (PT)

Hepatomegaly (PT)

Other (PTs)

LLTs

LLTs
MedDRA use in signal detection process

Investigational (SOC) → HLGT → Liver function analysis (HLT)

HLGT

Liver function analysis (HLT) → HLGT → HLT → Hepatic function abnormal (PT)

Aspartate aminotransferase increased/decreased/abnormal (PT)

Gamma-glutamyltransferase increased/decreased/abnormal (PT)

Hepatic function abnormal (PT)
MedDRA use in signal detection process

SMQ?
UMC Signal detection process

1. National PV centres
2. VigiBase
3. First-pass statistical screening
4. Initial manual assessment
5. In-depth manual assessment
6. Signal
Signal communication

Signal document restricted to National Centres

Identified patent holders invited to preview and comment

All recipients encouraged to comment on topics

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Thank you for listening

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