

Principles of Signal Detection in a Spontaneous Reporting System

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MURIA 2019



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Outline

What is a signal?

Signal sources

Triggers

Assessment of potential risk

Signal evaluation

Outcome



What is a signal?

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Usually more than one report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

WHO

<http://www.who-umc.org/DynPage.aspx?tid=115092&mn1=7347&mn2=7252&mn3=7613&mn4=7614>



or

A safety signal is information on a new or known adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature.

EMA

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/06/WC500129138.pdf



UMC website

A signal is a hypothesis 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 (...), and is only an early indication (preliminary), as it may change substantially over time as more data accumulates.....



Signal sources

Individual Case Safety Reports
Clinical studies
Literature
WHO Programme-UMC
Scientific conferences
Drug Regulatory Authorities
Media



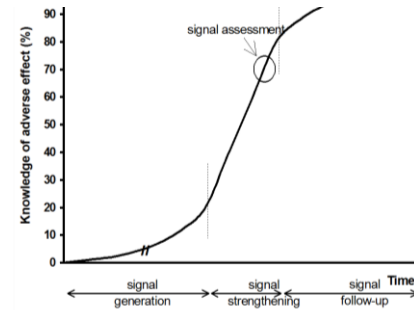
DRA websites



Media



Meyboom RH et al, Drug Safety 1997; 17(6): 374-89



Signal bells

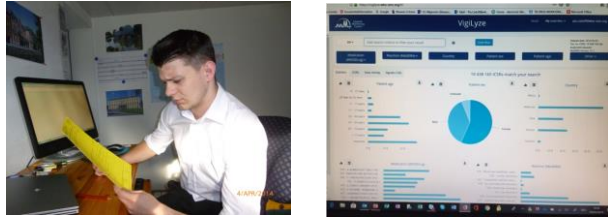


.... when should they
start ringing?

Triggers

- ADR reported is unexpected
- Unusual aspects of expected ADRs
- Fatal outcome or life threatening course
- Specific ADRs
 - SJS, TEN
 - Agranulocytosis
- Cluster

Hypothesis driven signal detection



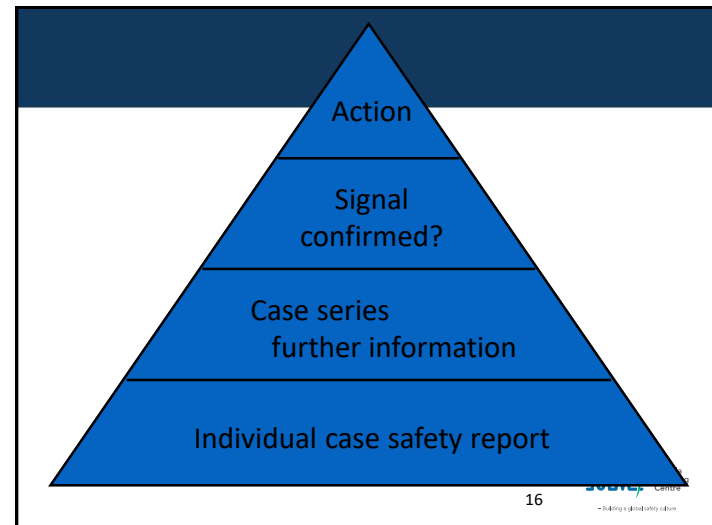
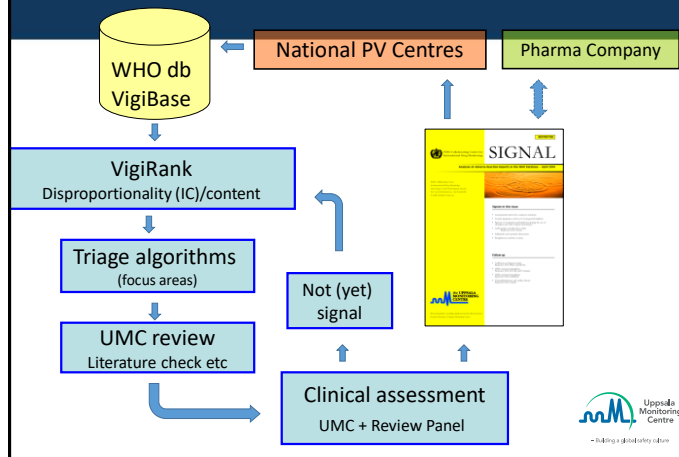
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Data mining – data driven signal detection

Automatic analysis of large dataset with the aim of discovering ADR-drug combinations that stand out statistically

→ ADR-drug combinations reported more often than expected

UMC signalling process



How many reports make a signal?

More than one

Confirmed signals usually have

- A few index cases
 - Completely documented
 - No or only minimal confounders
 - Positive de-/rechallenge

Lancet 1990 Jul 21;336(8708):156-8

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"Further information"?

What do we know about the drug itself?

What do we know about the way it is used?

What do we know about similar drugs (class effects)?

Is there a reasonable causal relationship between drug and reaction in our case reports?

Signal assessment => causality assessment



Signal assessment

Case series in databases?

- Local database
- International databases

Labelling

- national and international

Literature

Evidence from pre/postapproval studies (incl preclinical studies)

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Identification and assessment of potential signals

Small database

- Identification mostly hypothesis driven
- Clinical assessment

Large database

- Identification mostly data driven
- Clinical assessment



Single case assessment

Demographic data
Medical history
Chronology
Risk factors
Differential diagnosis
De-/Rechallenge
Concomitant medication
Other confounders/bias

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Signal assessment is about pattern recognition – who is at risk?

Are there patient specific risk factors?

- Demographics
- Medical history
- Genetic factors
- Recreational habits
- Indication for treatment

Are there drug specific risk factors?

- Dosage and interval
- Formulation
- Concomitant therapy

Is there a geographical pattern?

- Across borders
- Within the country

Does the ADR follow a pattern?

- Time to onset
- Clinical features
- Development over time
- Outcome

Signal assessment

There is no magic button...



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Signal assessment is...

...hard and patient intellectual work



www.mobile9.com

...and

Decision making



Dilemma

A signal should be identified as soon as possible to allow early warning

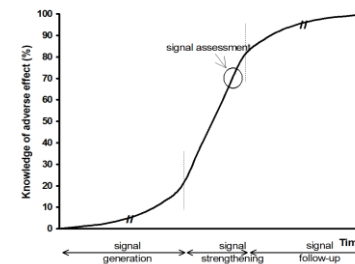
but

should be documented as well as possible (credibility)

→ When is there ENOUGH evidence?

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Meyboom RH et al, Drug Safety 1997; 17(6): 374-89



Signal detection hands on

It is your turn now



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