

Principles of Signal Detection

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Outline

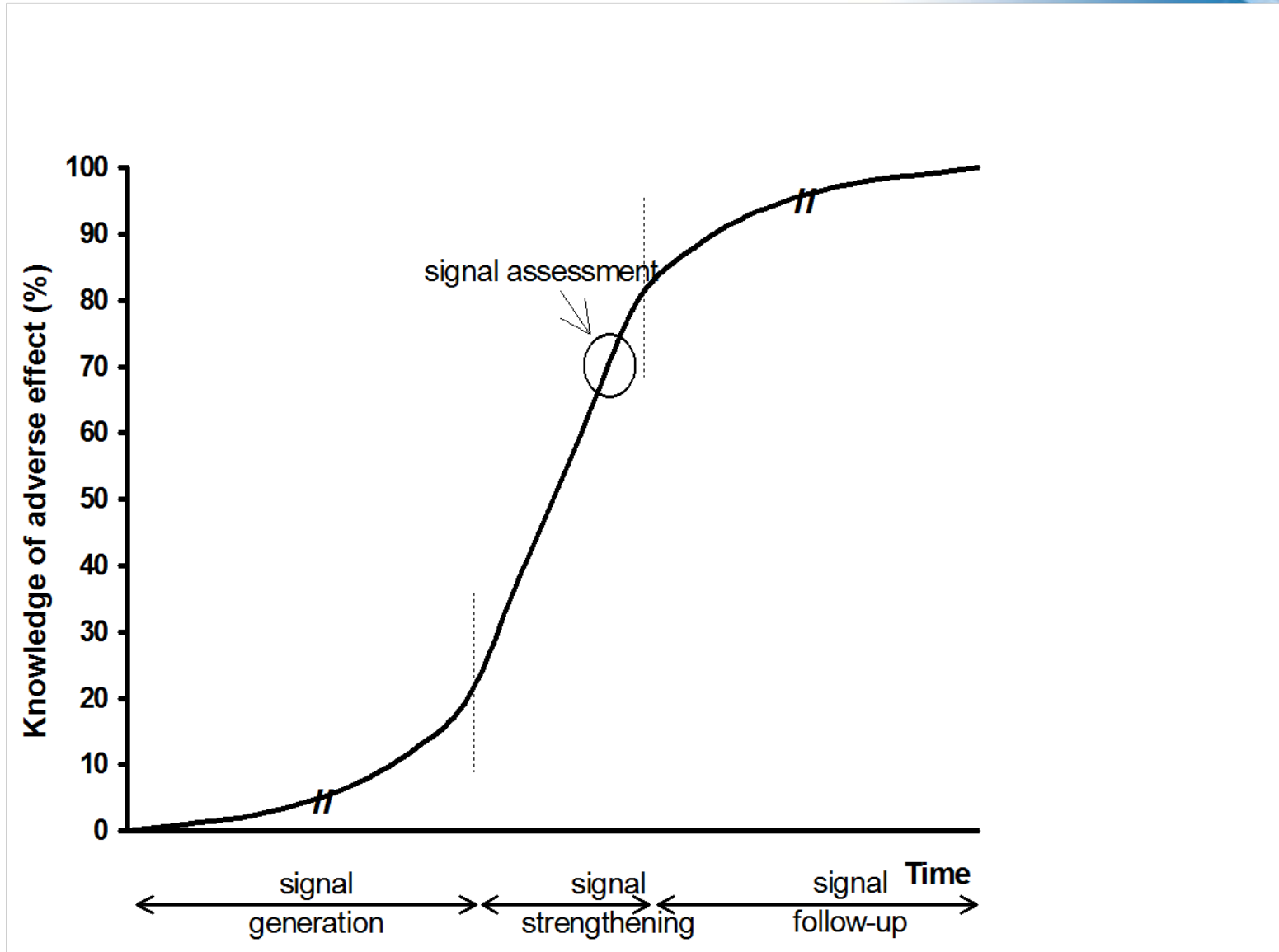
- What is a signal?
- Signal sources
- Triggers
- Assessment of potential risk
- Signal evaluation
- Outcome

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 a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. The publication of a signal usually implies the need for some kind of review or action.

Signal sources

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



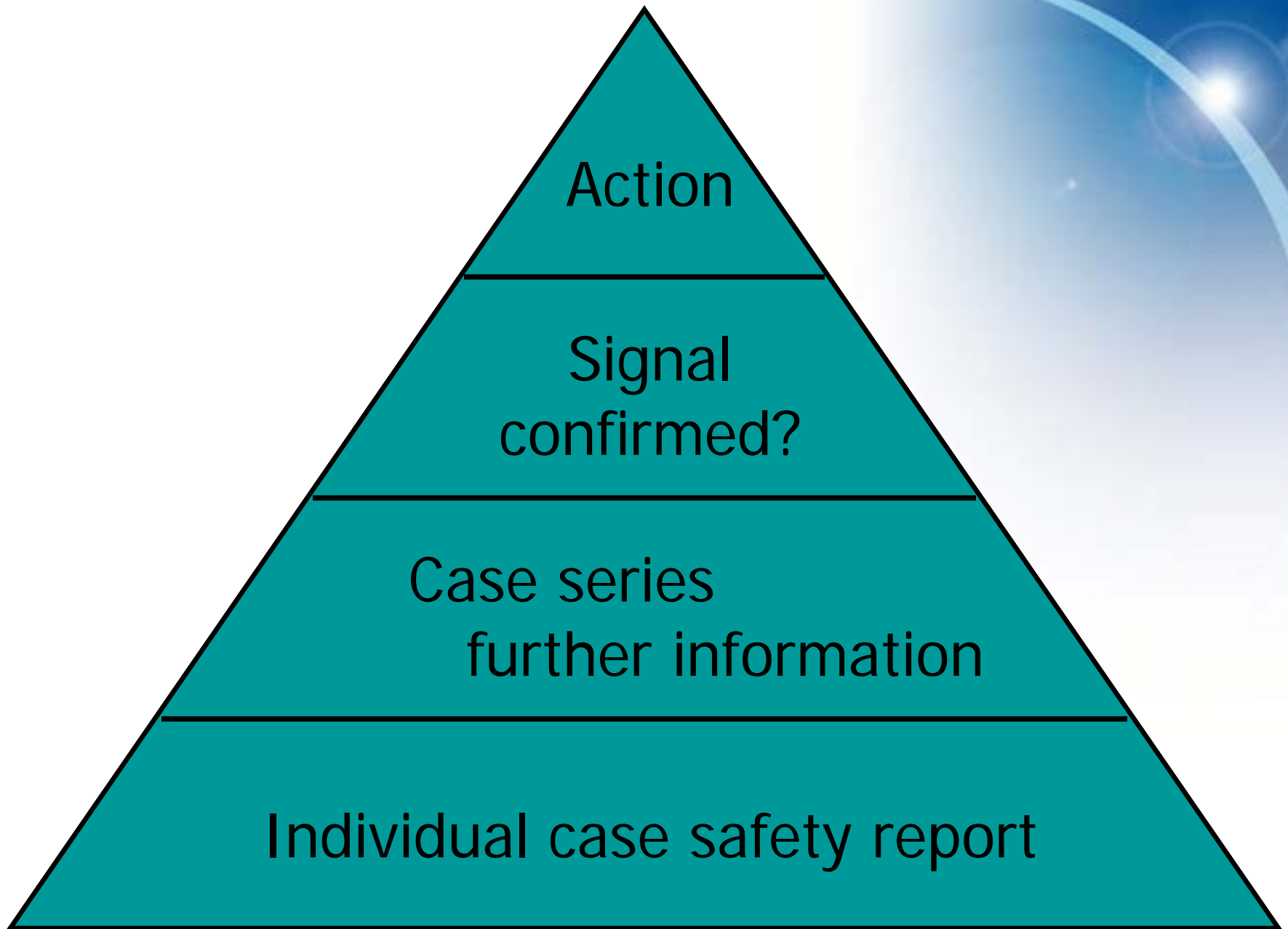


Signal bells...

.... when should they start ringing?

Triggers

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



How many reports make a signal?

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

"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??

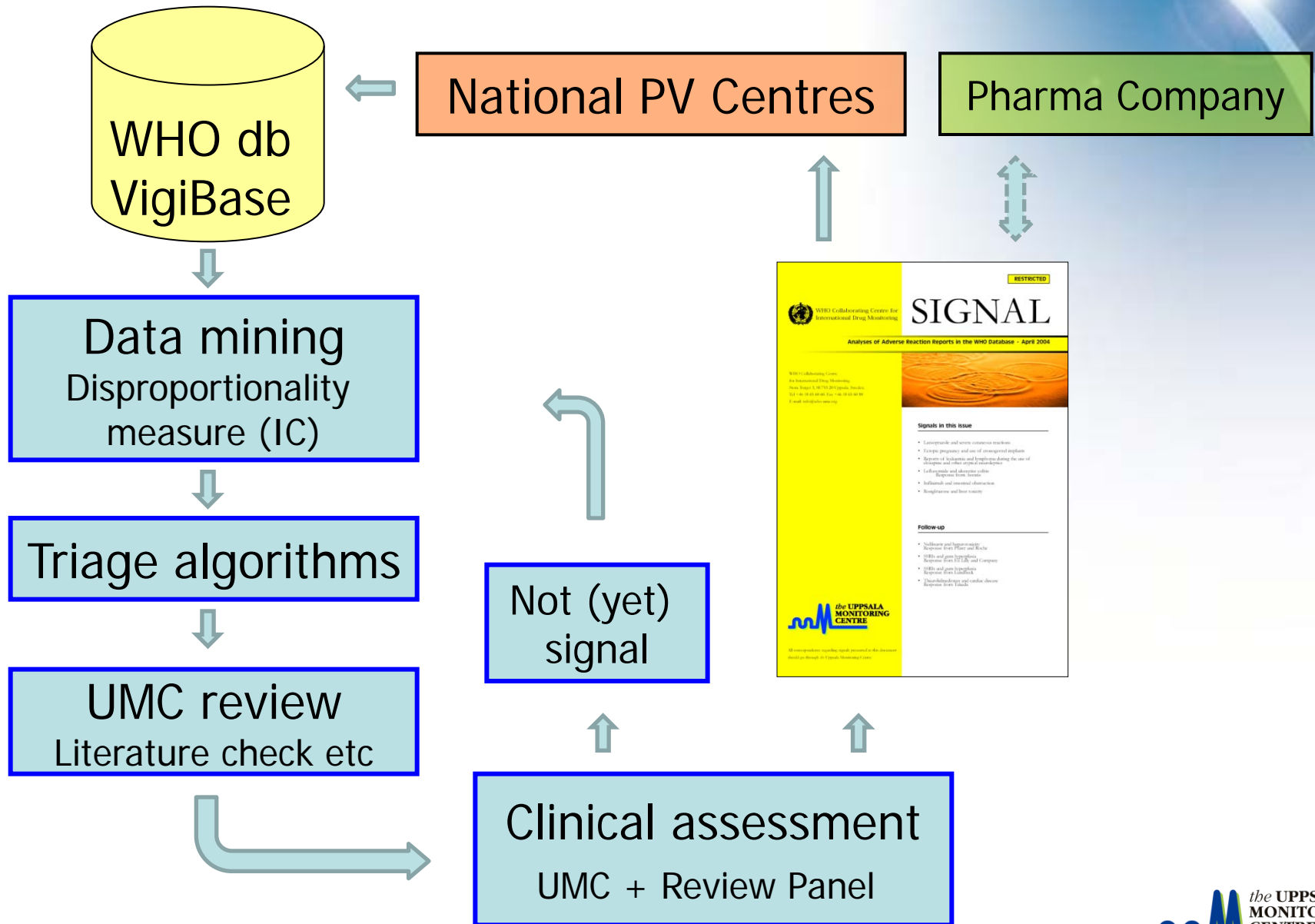
Signal assessment

- Labelling
 - national and international
- Case series in databases?
 - National database
 - VigiBase/VigiLyze
- Literature

Signal assessment

- "Small" database
 - Mostly case series and assessment of ICSRs
- Large database
 - Automated search for disproportionalities
 - Case series

UMC signalling process



Data analysis – single case

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

Signal assessment is about patterns

- Who is at risk?
- Are there patient specific risk factors?
- Are there drug specific risk factors?
- Is there a geographical pattern?
- Does the ADR follow a pattern?

Signal assessment

- There is no magic button...



Signal assessment is about...

- Hard and patient intellectual work



...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?**

Risk minimization

- Action taken (mostly) by Regulatory Authorities with the aim of keeping a positive benefit risk balance

Potential risk

- Exposed population (size, sensitive populations)
- Essential medicinal product
- Seriousness and severity of ADR
- Avoidable ADR?
- Rapid increase of number of reports
- Public impact and perception

The risk potential defines the next move



- If the risk is assessed as very high, risk minimizing actions might be justified even if the signal is not (yet) confirmed

More on this....

- ...on Monday May 27th @ 8.30 am



Take home messages

- A signal is a work hypothesis that needs to be confirmed or refuted
- Signal assessment is a dynamic process
- Signal detection is a lifelong process for every medicinal product
- Well documented ICSRs (index cases) are one of the most precious elements in signal detection and assessment
- Signal assessment is intellectual work

Questions?





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