Data Assessment in Pharmacovigilance

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Definition of pharmacovigilance (WHO, 2002)

- ✓ **The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem**

- ✓ **Pharmacovigilance is the same as ‘drug monitoring’**

Why pharmacovigilance?

- **Limited value of animal experiments in predicting human safety**
- **Clinical trials are limited in time and number of patients; are ‘artificial’. Patients are selected (adults, no other drugs, no other diseases). Not representative of real-life use.**
- **Rare or delayed serious reactions are likely to remain unnoticed**

Functions of pharmacovigilance (WHO Guidelines, 2000)

- **Detection and study of adverse reactions**
- **Measurement of risk**
- **Measurement of effectiveness**
- **Benefit & harm evaluation**
- **Dissemination of information, education**

⇒***Early warning***

⇒***Rational and safe use of medicines***

Methods in Pharmacovigilance

- **Spontaneous Reporting**
- **Prescription Event Monitoring**
- **Case Control Surveillance**
- **Record Linkage (automated population databases; ‘data mining’)**

Formal Studies

- Defined aim, hypothesis testing (problem solving)
- Established methods (clinical trial, case control, cohort study)
- Limited as regards drugs, parameters, population (disease, number, region) and duration

Vigilance

- Open question, search-ing for the unexpected (‘problem raising’)
- Exploratory, controversial (SR, PEM, CCS)
- Ongoing, unrestricted (‘all’ drugs, ‘all’ patients, including subgroups)

Spontaneous Reporting

- ✓ **Country-wide, structured system for the reporting of suspected adverse reactions to drug**

Spontaneous Reporting

- ✓ **A ‘case report’ is a notification from a practitioner regarding a patient with a disorder that is *suspected* to be drug-related**
- ✓ **Medical secrecy, privacy**
- ✓ **Suspicions, voluntary, confidential**

Spontaneous Reporting

- ✓ **When different doctors independently report the same unknown and unexpected adverse experiences with a drug, this *can* be an important signal**

What should be reported?

- Unknown, unexpected
- New drugs
- Serious (also when known)
  - Fatal, life-threatening
  - Hospitalisation
  - Persistent incapacity or disability
  - Dependence
  - Malformations
- Unexpected beneficial effects
- Unexpected ineffectiveness

Data assessment in Pharmacovigilance

1. Individual case report assessment
2. Aggregated assessment and interpretation
    - Signal detection
    - Interactions and risk factors
    - Serial (clinicopathological) study
    - Frequency estimation

Individual case report assessment

- Relevance of observation
- Coding
- Quality of documentation
- Case follow-up
- Case causality assessment

Components of a case report

- **Patient**
- **Adverse event**
- **Drug exposure (suspected and other)**
- **Source**

Patient

- Age
- Sex
- Medical history
- Case identification (confidential)

Adverse event

- **Description: aspect, place, severity, diagnosis**
- **Outcome, course, time relationship (‘challenge, dechallenge, rechallenge’)**
- **Laboratory data**

Suspected drug

- **Name (product, generic, ingredients, batch no.)**
- **Dose, route, dates (interval, duration)**
- **Indication**

Coding of adverse events

- Drug
  - WHO Drug Dictionary
- Adverse event
  - WHOART
  - MedDRA
  - Snomed?

Coding of adverse events

‘Reporting adverse drug reactions. Definitions of terms and criteria for their use.’

Council for International Organizations of Medical Sciences CIOMS. C/o World Health Organization, Avenue Appia, 1211 Geneva 27, 1999.

Case follow-up

- Missing data
- Laboratory data, pathology
- Outcome data (if not yet recovered)
- Underlying disease
- Verification of findings

Standardised causality assessment

- **WHO system**
- **French system**

Relevance of observation

- **Unknown, unexpected, unlabeled**
- **Serious**
- **New or important drug**
- **Regulatory**
- **Scientific**
- **Educational**

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WHO-UMC definition of 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.**

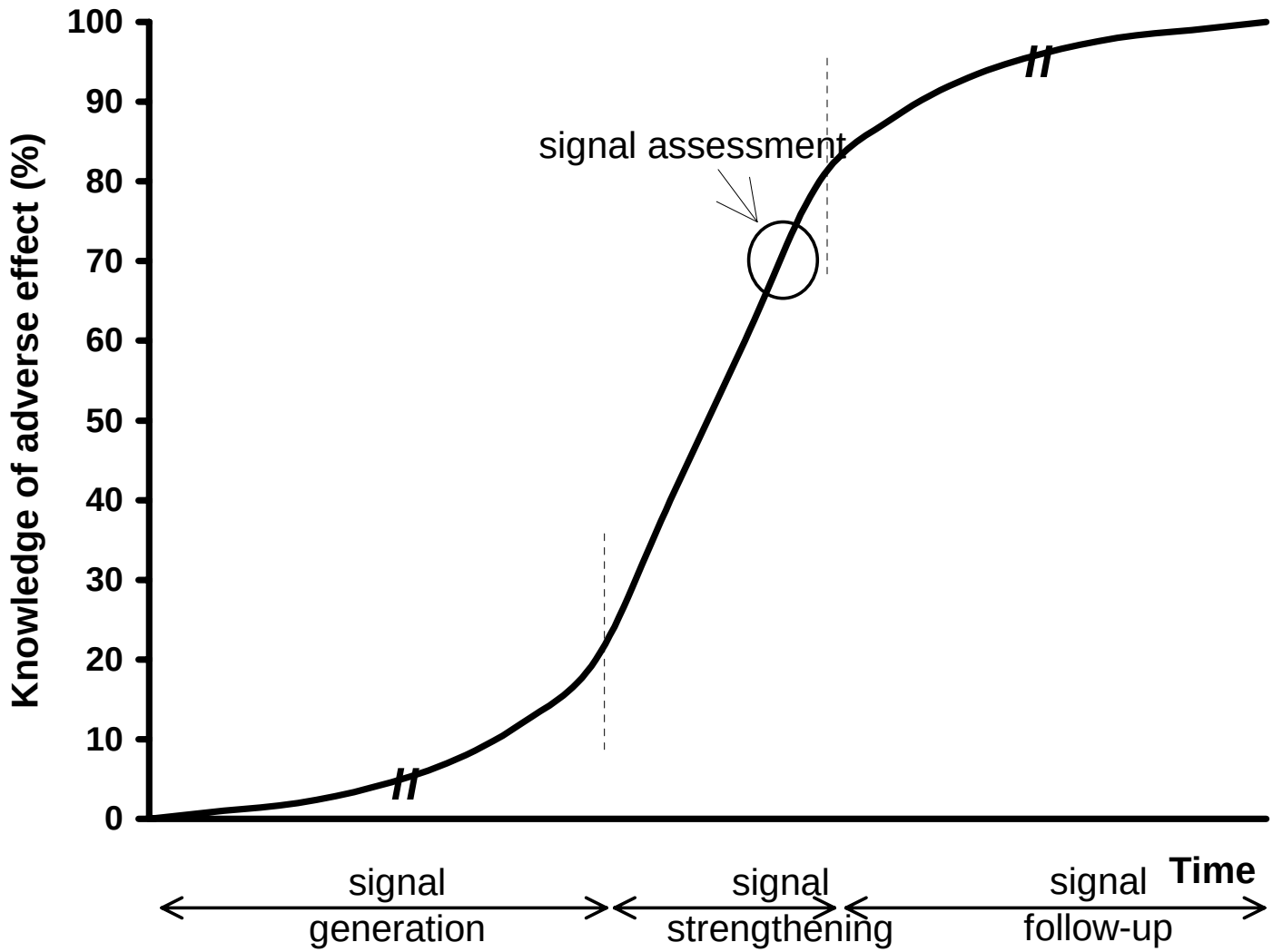
Edwards IR, Biriell C. Drug Safety 1994;10:93-102

A signal consists of

- **Hypothesis**
- **Data**
- **Arguments, in favor or against**

Data of a signal

- **Qualitative (clinical)**
- **Quantitative (epidemiological)**
- **‘Experimental’**
- **Develops over time**


Knowledge of adverse effect (%)
100
90
80
70
60
50
40
30
20
10
0
signal assessment
Time
signal generation
signal strengthening
signal follow-up

1. **Signal detection**
   - **Selection of a possibly relevant association (hypothesis generation)**
   - **Preliminary assessment of the available evidence (signal strengthening)**
2. **Signal follow-up**

Criteria for selecting a signal

+	-
• Unknown adverse reaction	• Known (and labelled)
• Unexpected	
• Expected but ‘unlabelled’	
• Strong statistical connection	• Weak statistical connection
• Low background frequency	• High background frequency
• Specific, characteristic	• Unspecific, trivial event
• Objective (definitive) event	• Subjective event
• Typically drug-related event or Critical Term	• Common disorder, e.g. infectious or ‘endogenous’
• Serious	• Not serious
• High potential relevance	• Low relevance

When is a signal likely to be relevant?

- ***Early Warning***
  - **New adverse reaction; new drug**
- ***Public health perspective***
  - **Important drug (serious indication; widely used)**
  - **Serious reaction**
  - **Large number of cases; rapid increase in reporting**
  - **Regulatory intervention (prevention)**
- **Change in benefit/risk**
- **Scientific or educational value**

Retrospective analysis of 107 published pharmacovigilance topics in The Netherlands

Meyboom RHB et al. Clin Drug Invest 1996;4:207-19

• Anaphylactic reactions	10%
• Hepatitis	13%
• Blood dyscrasias	10%
• Nervous system	16%
• Interactions	13%
	62%

Signal follow-up (same database)

- Drug exposure
- Development over time of the quantitative data and the consistency of the pattern
- Signal strengthening
  - individual case report assessment
  - reporting distribution
  - ‘best case-worst case’ scenario
  - targeted comparisons
  - nested case control studies

Signal follow-up (other sources)

- Similar connection in other countries
- WHO-UMC international database,
- Additional observations (e.g. literature, registration file, other databases)
- Experimental data (e.g. pharmacological, immunological)

The balance of evidence in a signal

- Quantitative strength of the association
  - number of case reports
  - statistical disproportionality
  - drug exposure
- Consistency of the data (pattern)
- Exposure-response relationship
  - site, timing, dose, reversibility
- Biological plausibility of hypothesis
  - pharmacological, pathological
- Experimental findings
  - e.g. dechallenge, rechallenge, blood levels, metabolites, drugdependent antibodies
- Analogies
- Nature and quality of the data
  - objectivity, documentation, causality assessment

From signal to action

- **Internal communication (national centres, UMC, company, academia)**
- **Initiation of further study (signal testing)**
- **Regulatory action (e.g. data sheet change)**
- **Extermal communication (drug information centres, national drug bulletin, publications)**

Advantages of Spontaneous Reporting

- **Effective!**
- **Wide coverage (‘all patients, all drugs, all adverse reactions’)**
- **Continuous**
- **Rapid**
- **Cheap**

Limitations of Spontaneous Reporting

- **Suspicions**
- **Underreporting and bias**
- **Insensitive to type C adverse effects**
- **Drug consumption data available? (denominator)**
- **No quantitative assessment**
- **Comparison of drugs difficult**
- **No proof of causality**

➢ ***Often further study needed (hypothesis testing, evaluation)***

Signal detection

- Searching for the unexpected; ongoing
- A signal should be early and credible at the same time
- Signals may consist of only a few cases. An important signal may not be statistically prominent
- Signal testing and explanation require further study
- Many signals remain unconfirmed
  - scientific limitations
  - no funding

Standardised Case Causality Assessment

Meyboom RHB, Hekster YA, Egberts ACG, Gribnau FWJ, Edwards IR. Drug Safety 1997;17:374-89

Three key questions relating to uncertainty:

- **Can the drug cause the adverse reaction?**
- **Has the drug caused the adverse reaction?**
- **Will the drug cause the adverse reaction?**

- F Karch, L Lasagna. Clin Pharm Ther 1977;21:247-54
- MS Kramer, JM Leventhal, TA Hutchinson, et al. JAMA 1979;242:623-31
- A Emanueli, G Sacchetti. Agents Actions 1980;7:318-22
- C Naranjo, U Busto, EM Sellers, et al. Clin Pharm Ther 1981;30:239-45
- Bégaud B, Evreux JC, Jouglard J, Lagier G. Thérapie 1985;40:111-8
- J Venulet, AG Ciucci, GC Bernecker. Int J Clin Pharmacol 1986;24:559-68

General design of systems:

- Questions
  - Sub-questions
  - Scores
- Overall score
- Causality category,

  e.g. possible, probable, etc

Four assessment criteria

- The association in time (and place) between drug administration and event
- Pharmacology (features, previous knowledge of side effects)
- Medical plausibility (characteristic signs and symptoms, laboratory tests, patho-logical findings)
- Likelihood or exclusion of other causes

The importance of criteria may differ for different types of reactions

- Application site reactions
- Immediate reactions
- Pharmacological effects
- Immunological reactions
- Congenital malformations
- Cancer

None of the available systems has been validated, i.e. that they consistently and reproducibly give a reasonable approximation of the truth

- **Validation = ‘proving that a procedure actually leads to the expected results’**
- **Causality category definitions**
- **No gold standard**

- **What causality assessment can do**
  - **Decrease disagree-ment between assessors**
  - **Classify relationship likelihood (semi-quantitative)**
  - **Mark individual case reports**
  - **Education / improve-ment of scientific assessment**

- **What causality assessment cannot do**
  - **Exact quantitative measurement of relationship likelihood**
  - **Distinguish valid from invalid cases**
  - **Prove the connection between drug and event**
  - **Quantify the contribution of a drug to the development of an adverse event**
  - **Change uncertainty into certainty**

WHO Causality Categories

(All points should be reasonably complied with)

Certain

- **Event or laboratory test abnormality with plausible time relationship to drug intake**
- **Cannot be explained by disease or other drugs**
- **Response to withdrawal plausible (pharmacologically, pathologically)**
- **Event definitive pharmacologically or phenomenologically *(An objective and specific medical disorder or recognised pharmacological phenomenon)***
- **Rechallenge (if necessary)**

Drug Safety 1994;10:93-102

Probable

- Event or laboratory test abnormality with reasonable time relationship to drug intake
- Unlikely to be attributed to disease or other drugs
- Response to withdrawal clinically reasonable
- Rechallenge not necessary

Possible

- Event or laboratory test abnormality with reasonable time relationship to drug intake
- Could also be explained by disease or other drugs
- Information on drug withdrawal lacking or unclear

Unlikely

- Event or laboratory test abnormality with a time relationship to drug intake that makes a connection improbable (but not impossible)
- Diseases or other drugs provide plausible explanations

Conditional / Unclassified

- Event or laboratory test abnormality
- More data for proper assessment needed
- Or additional data under examination

Specific etiologic-diagnostic systems

- **Disease definition (including other forms)**
- **Clinical appearance and pathology**
- **Signs of severity**
- **Aetiology (various possible causes) and diagnosis**
- **Evidence implicating a drug**
- **Chronological criteria**
- **Management**

Bénichou C. Adverse Drug Reactions. John Wiley, 1996

Questions for the future

- **Causality assessment as a routine of all reports, or only in selected cases?**
- **One general system, or special systems adapted to specific adverse reactions?**

Signal management (1)

- Selection of the relevant data (case reports) and delineation of the signal (hypothesis)
- Literature search
- Survey of available data and identification of missing data and unanswered questions
- Gathering of missing data (follow-up of cases; structured enquiry)
- Consultation with the WHO Uppsala Monitoring Centre
- Contact between National Centre and company; study of the data in the registration file

Signal management (2)

- **(Re)assessment of all available data**
- **Writing a report, containing:**
  - **summary of the signal**
  - **presentation of original data**
  - **presentation of additional information**
  - **discussion, with reference to positive and negative arguments**
  - **hypothesis (preliminary conclusion)**
  - **suggestions for further study**

This report may serve as a basis for decision-making by the regulator and the pharmaceutical company, for communication between national centres, and for the preparation of information for practitioners and in the published literature

Pharmacovigilance can only be effective through the active participation of practitioners!!