PHARMACOVIGILANCE PASSIVE SURVEILLANCE

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University of Namibia, Windhoek, ISPE & ISPE African Chapter

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Pharmacovigilance Methods

- Passive Surveillance
- Stimulating Reporting Systems
- Active Surveillance
- Comparative Observational Studies
- Targeted Clinical Investigations
- Descriptive Studies

ICH Harmonised Tripartite Guideline. Pharmacovigilance Planning E2E, 2004

Passive Surveillance

- Spontaneous Reports
  - Systematic Methods for the Evaluation of Spontaneous Reports (Data Mining)
- Case Series

ICH Harmonised Tripartite Guideline. Pharmacovigilance Planning E2E, 2004

Spontaneous Reports

- Passive and voluntary reports
- Definition: **Unsolicited communication** from an individual (e.g., health care professional, consumer) to a company or regulatory authority or other organization (e.g. WHO, Regional Centres, Poison Control Centre) that describes **one or more adverse events in a patient** who was given **one or more medicinal products** and that does not derive from a study or any organized data collection scheme.
- They have a major role in the identification of safety signals once a drug is marketed.

ICH Harmonised Tripartite Guideline. Pharmacovigilance Planning E2E, 2004; FDA 2018

Who should report an adverse effect?

- Every person who experiences or know someone who experience a side effect should report the event to their local health authority and/or manufacturer.
- There is an initiative from the UMC to encourage the reporting of a side effect: take and tell

https://www.youtube.com/watch?v=dkvaYzaZ_Uk

https://www.youtube.com/watch?v=7x0T7hBnReI

https://www.youtube.com/watch?v=x7LJkW3vHk0

https://www.who-umc.org/safer-use-of-medicines/taketell/

Case Report

- 49-year old female patient
- Diagnosis: Bipolar Disorder
- Treatment: Antipsychotic medication started one year before the reported adverse events
- After stopping therapy, she developed “dizziness, can hardly walk and feet are going numb”
- Concomitant therapy: not provided
- Outcome: unknown

Principles of Case Evaluation

- Temporal relationship
- Causality assessment-World Health Organization, the Uppsala Monitoring Centre (WHO-UMC):
  - Certain
  - Probable/Likely
  - Possible
  - Unlikely
  - Conditional/Unclassified
- Key factors in causality assessment including, but not limited to
  - Dechallenge/rechallenge
  - Comorbidities
  - Concomitant medications
  - Consistent with pharmacological effects (biologic plausibility)

Table 1. The causality assessment checklist

I. Is there strong evidence for other cause?	Y	N	UK	NA	Remarks
Does a clinical examination, or laboratory tests on the patient, confirm another cause?	□	□	□	□	
II. Is there a known causal association with the vaccine or vaccination?					
Vaccine product(s)					
Is there evidence in the literature that this vaccine(s) may cause the reported event even if administered correctly?	□	□	□	□	
Did a specific test demonstrate the causal role of the vaccine or any of the ingredients?	□	□	□	□	
Immunization error					
Was there an error in prescribing or non-adherence to recommendations for use of the vaccine (e.g. use beyond the expiry date, wrong recipient etc.)?	□	□	□	□	
Was the vaccine (or any of its ingredients) administered unsterile?	□	□	□	□	
Was the vaccine's physical condition (e.g. colour, turbidity, presence of foreign substances etc.) abnormal at the time of administration?	□	□	□	□	
Was there an error in vaccine constitution/preparation by the vaccinator (e.g. wrong product, wrong diluent, improper mixing, improper syringe filling etc.)?	□	□	□	□	
Was there an error in vaccine handling (e.g. a break in the cold chain during transport, storage and/or immunization session etc.)?	□	□	□	□	
Was the vaccine administered incorrectly (e.g. wrong dose, site or route of administration; wrong needle size etc.)?	□	□	□	□	
Immunization anxiety					
Could the event have been caused by anxiety about the immunization (e.g. vasovagal, hyperventilation or stress-related disorder)?	□	□	□	□	
If (limn). If "yes" to any question in II, was the event within the time window of increased risk?					
Did the event occur within an appropriate time window after vaccine administration?	□	□	□	□	
III. Is there strong evidence against a causal association?					
Is there strong evidence against a causal association?	□	□	□	□	
IV. Other unifying factors for classification					
Could the event occur independently of vaccination (background rate)?	□	□	□	□	
Could the event be a manifestation of another health condition?	□	□	□	□	
Did a comparable event occur after a previous dose of a similar vaccine?	□	□	□	□	
Was there exposure to a potential risk factor or toxin prior to the event?	□	□	□	□	
Was there acute illness prior to the event?	□	□	□	□	
Did the event occur in the past independently of vaccination?	□	□	□	□	
Was the patient taking any medication prior to vaccination?	□	□	□	□	
Is there a biological plausibility that the vaccine could cause the event?	□	□	□	□	

Note: Y: Yes; N: No; UK: Unknown; NA: Not applicable.

Drug-Event Causality Assessment

Exercise

Provide a comment to each case included in the table:
1) Establish the criteria to be used, 2) Do the assessment, 3) Propose next step

Cases	Assessment
Spontaneous report from a physician concerning an 88-year-old male who experienced tongue oedema, acute respiratory failure and respiratory acidosis after his 3rd dose of amiodarone. Patient was also on insulin, naproxen and gentamicin. All events were reported as life threatening.	Med History? Time to event? Concomitant Medications – characteristics Treatment? Dechallenge? Outcome?
Spontaneous report from a pharmacist related to an 89-year-old male patient who experienced gastric haemorrhage in the last 24 h. He has a medical history of cardiac failure, hypertension, hyperlipidaemia, hyperuricaemia, chronic subdural haematoma. He has been on warfarin for three weeks. Concomitant medications included digoxin, allopurinol, atorvastatin, serotonin and candesartan.	Concomitant Medications – characteristics Treatment? Dechallenge? Outcome?
Spontaneous report of erythema, disseminated red-bean-sized papules and erythema on chest, abdomen, back and both legs as well as blistering on neck and low back; pyrexia of 38ºC, lack of appetite, malaise, chills, arthralgia; conjunctivitis, stomatitis and swelling of lips in a 58-year-old male patient after 4 days on cephalosporin, metformin and "Bepridil" (calcium channel blocker). Patient has an ongoing history of alcohol use, paroxysmal atrial fibrillation and inguinal hernia.	Time to event? Concomitant Medications – detailed information Treatment? Dechallenge? Outcome?

Case Series

- Group case reports that can provide evidence of an association between a drug and an adverse event
- They are generally more useful for generating hypotheses than for verifying an association between drug exposure and outcome.
- Some adverse events are known to be associated more frequently with drug therapy: anaphylaxis, aplastic anemia, toxic epidermal necrolysis and Stevens-Johnson Syndrome

ICH Harmonised Tripartite Guideline. Pharmacovigilance Planning E2E, 2004

Case Series

No reference group; To quantify the incidence of an event/ disease in exposed patients

Exercise

- You receive a case series, analyze the table carefully and decide if the reported event(s) represents a potential safety signal or if you need additional information

Case/ Gender/ Age (yrs)	Major malformations	Minor anomalies	Normal variants	Positional defects	Abnormally small body size	Functional anomalies	Ophthalmology	Gestational age (weeks)	Birth weight (g)	Birth length (cm)	Perinatal data
1M/16	Retentio testis						Astigmatism	40	3750	53	
2M/4			Pes planus valgus, hydrocele testis					38	3110	50	
3ºF/18	Pulmonary atresia, ASD							31	1325	No info	Twin, preterm
4ºM/9	Retentio testis		Inguinal hernia, hydrocele testis				VA 0.7/0.4, myopia	39	2925	48	
5ºM/7							VA 0.4/0.5, astigmatism	39	3010	49	
6/F/12		Asymmetry of the thoraco-lumbar back, preauricular fistula	Pes planus valgus				Hyperopia, astigmatism	42–43	3990	54	
7/F/8				Hip luxation				40	3580		
8/M/7						Autism	VA 0.5 binocular	41	4578	55.5	
9/F/1								28	1140	39	Preterm
10ºM/1/6								36	2440	47	Preterm
11ºF/10					Growth delay			40	2530	45	SGA
12ºF/6								38	2490	45	SGA
13/F/A0			Pes calcaneus valgus				VA 0.6/0.9, emitropia	40	3220	50	
14ºF	Died within 24 hr post delivery							31	900	No info	Twin, preterm

ºASD, atrial septal defect; preterm, gestational age ≤37 weeks; VA, visual acuity.
ºSiblings, born to same TE mother.
ºSiblings, born to same TE mother.
ºSiblings, born to same TE father.
ºDied.

Teratology 66:115–121, 2002.

What information is this table providing to you?

Case/Gender/Age (yrs)	Gender of parents with TE	Anomalies in parents with TE	Pregnancy history	Mode of delivery
1/M/16	Mo	Thumb hypoplasia	Infection of urinary tract (ab)	Vaginal
2/M/4	Fa	Thumb hypoplasia, Duane	Spontaneous abortion	Vaginal
3*/F/18	Mo	Anotia, absence of ear canal, preauricular tag	Cervical insufficiency	ECS
4*/M/9	Mo	Anotia, ear hypoplasia, 6th (Duane), 7th cranial nerve palsy	Maternal tachycardia (antiarrythmica class II)	Vaginal
5*/M/7	Mo	Anotia, ear hypoplasia, 6th (Duane), 7th cranial nerve palsy	Maternal tachycardia (antiarrythmica class II)	Vaginal
6/F/12	Fa	Thumb aplasia, hearing loss, Duane	Pneumonia (ab)	ECS
7/F/8	Mo	No info		Vaginal
8/M/7	Mo	Anotia, 6th (Duane), 7th cranial nerve palsy, hearing loss, VSD, LVH	Spontaneous abortion	Vaginal
9/F/7	Mo	Uterus septum defect, hearing loss	Two spontaneous abortions	ECS
10*/M/16	Fa	No info		Vaginal
11*/F/10	Fa	No info		Vaginal
12*/F/8	Fa	No info		Vaginal
13/F/10	Fa	Thumb hypoplasia, upper limb malformations	Infection of urinary tract (ab)	Vaginal
14*†/F	Mo	Anotia, absence of ear canal, preauricular tag	Cervical insufficiency	ECS

*ab, Antibiotics; Duane, Duane syndrome (sixth cranial nerve palsy characterized by a marked limitation or absence of abduction, restriction of adduction, retraction of the globe and narrowing of the palpebral fissure on adduction); ECS, emergency caesarian section; Fa, father; LVH, Left ventricular hypertrophy; Mo, mother; No info, no information; VSD, Ventricular septal defect; TE, Thalidomide embryopathy.
*Siblings, born to same TE mother.
†Siblings, born to same TE mother.
‡Siblings, born to same TE father.
§Died.

Teratology 66:115–121, 2002.

Example

- Literature report of 72 yrs. old female
- History of type 2 diabetes mellitus and hypercholesterolemia treated with 850 mg metformin once daily, 12.5 mg hydrochlorothiazide once daily and 0.2 mg cerivastatin once daily.
- Lab showed normal creatinine and hyperlipidemia, prescriber added 600 mg gemfibrozil.
- After 3 days she was admitted because of chest pain, severe muscle pain. Lab showed increased of serum potassium, serum creatinine and creatine kinase, prolonged PQ-time, severe widening of QRS segment. Patient was treated with glucose, insulin and hemodialysis. Patient improved, potassium decreased and ECG abnormalities disappeared. Patient continued on hemodialysis for 7 weeks until her creatinine clearance reached normal levels.

Nephrol Dial Transplant 2001;16:2418-2419

Case Series of Rhabdomyolysis

Table 1. Patient Demographics

Age (yrs)/ Gender	Height (in.)	Weight (kg)	Body Mass Index (kg/m^2)
74/F	60.5	53.8	22.2
74/M	71.0	107.9	33.2
72/M	59.5	97.3	31.2
65/F	62.0	76.9	31.0
63/M	70.5	106.4	33.2
75/F	57.5	49.3	23.1
59/M	67.0	78.0	26.9
68/M	66.0	54.0	19.2
55/F	63.0	61.0	23.8
59/M	68.0	97.0	32.5
75/F	59.0	53.0	23.6

Cerivastatin-Induced Rhabdomyolysis: 11 Case Reports, Ravnan SL, Locke C, Yee WP, Haase K, Pharmacotherapy 2002;22(4):533–537)

Table 2. Concomitant Medical Conditions That Could Increase Risk of Rhabdomyolysis

History of Diabetes Mellitus	History of Hepatic Impairment	History of Renal Impairment	Surgery or Trauma < 30 Days Earlier
No	No	No	No
No	No	No	No
Yes	No	No	No
No	No	No	No
No	No	No	No
No	No	No	No
Yes	No	Yes	No
Yes	No	Yes	No
No	No	Yes	No
Yes	No	No	No
Yes	No	No	No

Information obtained from patients' medical records.

Cerivastatin-Induced Rhabdomyolysis: 11 Case Reports, Ravnan SL, Locke C, Yee WP, Haase K, Pharmacotherapy 2002;22(4):533–537)

Table 4. Drug History, Concurrent Therapy, and Scores on Naranjo Adverse Drug Reaction Probability Scale[27]

Lipid Management History (before hospital admission)	Concurrent Therapy	Naranjo Score*
Cerivastatin 0.4 mg x 30 days	Captopril, aspirin, felodipine, atenolol chlorthalidone	7
Niacin 1 g/day (long term), cerivastatin 0.8 mg h.s x 28 days	Naproxen, atenolol	7
→ Gemfibrozil 600 mg b.i.d (long term), cerivastatin 0.4 mg h.s. x 1 wk	Enalapril, hydrochlorothiazide-triamterene	4
→ Atorvastatin x 3 years, gemfibrozil 600 mg b.i.d. x 1 year, cholestyramine x 33 days, atorvastatin changed to cerivastatin 0.8 mg h.s. x 33 days	Naproxen, propoxyphene, hydrocodone-acetaminophen	4
→ Simvastatin x 2 years, changed to cerivastatin 0.4 mg h.s. x 2 mo, gemfibrozil 600 mg b.i.d. x 21 days	Fosinopril, aspirin, amiodarone, furosemide	4
Pravastatin x 4 mo, changed to cerivastatin 0.4 mg h.s. x 14 mo	Etodolac, aspirin, levothyroxine	7
→ Fluvastatin 40 mg h.s., changed to cerivastatin x 24 days, gemfibrozil 600 mg b.i.d. x 28 days	Felodipine, verapamil, aspirin, insulin	7
Cerivastatin 0.4 mg h.s. x 29 days	Benazepril, clopidogrel, atenolol, aspirin	7
Fluvastatin (long term), changed to cerivastatin 0.4 mg h.s. x 9 mo	Benazepril, amitriptyline, nitroglycerin, hydrochlorothiazide-triamterene, clopidogrel	7
→ Cerivastatin 0.8 mg h.s. + gemfibrozil 600 mg b.i.d	Amlodipine, glyburide, cyclobenzaprine, tramadol	4
→ Cerivastatin 0.4 mg h.s. x 30 days, gemfibrozil 600 mg b.i.d. x 14 days	Nifedipine, atenolol, aspirin, glipizide	4

*Adverse events are defined as ≥ 9 = definite, 5–8 = probable, 1–4 = possible, and ≤ 0 = doubtful.

Cerivastatin-Induced Rhabdomyolysis: 11 Case Reports, Ravnan SL, Locke C, Yee WP, Haase K, Pharmacotherapy 2002;22(4):533–537)

Spontaneous Reports

- Safety reviewers can be alerted to rare adverse events that were not detected in earlier clinical trials or other pre-marketing studies.
- Spontaneous reports can provide important information on at-risk groups, risk factors, and clinical features of known serious adverse drug reactions.
- Issues: Underreporting, incomplete data, selective reporting. It could be impacted by PV-related regulatory activities, media attention, indication of the product, incidence rates can not be generated accurately but reporting rates can be estimated

ICH Harmonised Tripartite Guideline. Pharmacovigilance Planning E2E, 2004; FDA 2018

Postmarketing Safety Reporting Requirements in the USA

- Under 21 CFR 314.80 postmarketing safety reports must be submitted to the agency for the following:
  - 15-day Alert reports: Serious and unexpected adverse experience from all sources (domestic and foreign)
  - Periodic Adverse Experience Reports: Domestic spontaneous adverse events that are:
    - Serious and expected
    - Non-serious and unexpected
    - Non-serious and expected
    - Quarterly for the first 3 years then annually

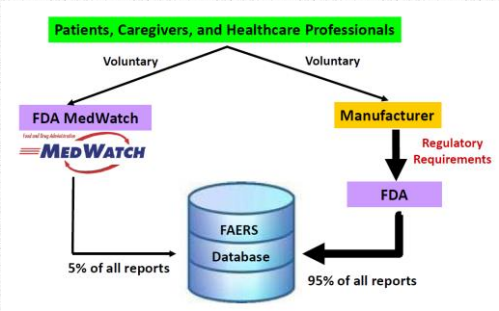
FDA, 2018

FDA Adverse Event Reporting System

- Fully automated computerized database
- Spontaneous reports
- Contains human drug and therapeutic biologic reports
- ~14 million reports since 1969
- Over 1.81 million new reports in 2017

FDA, 2018

Postmarketing Reports Sent to FDA



FDA, 2018

FAERS Strengths

- Can report even if causality is uncertain
- Less restrictive than clinical trials
  - Reports can be submitted for any drug, old and new
  - Entire US population is "eligible"
- Reports emerge from usual healthcare settings
  - Patient and prescriber population more heterogeneous
  - All stages of treated disease
  - Longer duration of use
  - Captures "off-label" use, including diagnosis and dose
  - Co-morbidities, concomitant products and procedures

FDA, 2018

FAERS Example of Output

	Generic_Name	SOC	HLT	PT_plus_Narrow_Alg_SMQ	N	EB05	PRR	Prior Assessments
1	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Embolic stroke	31	50.47	115.309	
2	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Cerebral infarction	84	28.633	39.106	
3	Warfarin	Renal	Urinary abnormalities	Haematuria	46	11.225	14.259	
4	Warfarin	Gastr	Non-site specific gastrointestinal haemorrhages	Melaena	30	10.839	13.11	
5	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Ischaemic stroke	29	9.856	24.551	
6	Warfarin	Skin	Skin and subcutaneous tissue disorders	Gangrene of skin	3	2.1	2.0	
7	Warfarin	Skin	Skin and subcutaneous tissue disorders	Rash	300	7.824	8.912	
8	Warfarin	Skin	Skin and subcutaneous tissue disorders	Pruritus	300	7.8	8.857	

FAERS Output for warfarin, PTs, N, EB05/PRR among elderly patients with atrial fibrillation

FAERS Example of Output

	Generic_Name	SOC	HLT	PT_plus_Narrow_Alg_SMQ	N	EB05	PRR	Prior Assessments
1	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Embolic stroke	31	50.47	115.309	Common in the Population
2	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Cerebral infarction	84	28.633	39.106	Common in the Population
3	Warfarin	Renal	Urinary abnormalities	Haematuria	46	11.225	14.259	Listed/Expected
4	Warfarin	Gastr	Non-site specific gastrointestinal haemorrhages	Melaena	30	10.839	13.11	Listed/Expected
5	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Ischaemic stroke	29	9.856	24.551	Common in the Population
6	Warfarin	Skin	Skin and subcutaneous tissue disorders	Gangrene of skin	3	2.1	2.0	Potential signal
7	Warfarin	Skin	Skin and subcutaneous tissue disorders	Rash	300	7.824	8.912	Listed/Expected
8	Warfarin	Skin	Skin and subcutaneous tissue disorders	Pruritus	300	7.8	8.857	Listed/Expected

FAERS Output for warfarin, PTs, N, EB05/PRR among elderly patients with atrial fibrillation

FAERS Limitations

- Passive, voluntary surveillance
- Underreporting occurs and is variable from drug to drug and over time
  - Some literature cites 1-10%
  - Actual is unknown so FDA does not assume extent
- Reporting bias exists
- Quality of the reports is variable and often incomplete
- Duplicate reporting of the same case occurs
- Not population-based data source
  - Can not reliably estimate incidence or prevalence
  - Numerator uncertain, denominator can only be projected from drug utilization data

FDA, 2018

FAERS is less useful for:

- Events with high background rates
- Worsening of pre-existing disease
- Issue is beyond the name of the drug
- Comparative incidence rates
- Comparing drugs in the same class
- Adverse events that could also be manifestations of the disease for which the drug is indicated
- Reporting biases

Factors Affecting Reporting

- Media attention
- Litigation (class action lawsuits)
- Nature of the adverse event
- Type of drug product and indication
- Length of time on market
- Extent and quality of manufacturer's surveillance system
- Prescription or over-the counter (OTC) product status
- Reporting regulations

FDA, 2018

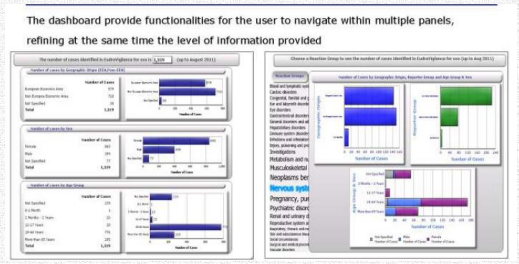
EudraVigilance

- It was launched in Dec 2001
- Electronic reporting of individual case safety reports (ICSRs) are mandatory since 2005
- Electronic exchange of suspected adverse reaction reports (Individual Case Safety Reports, ICSRs) between the Agency, NCAs, MAHs, and sponsors of clinical trials in EEA
- Early detection of possible safety signals associated with medicinal products for Human Use
- Continuous monitoring and evaluation of potential safety issues in relation to reported adverse reactions

EMA, 2017

EudraVigilance

- 15.7 million transactions during 2013
- >450,000 product presentations in EVMPD
- over 1 million adverse reaction reports received and processed in 2013
- 52% increase in patient reporting (EEA)
- In total >7 million reports (approx 4.6 million cases)
- EudraVigilance among 3 largest databases of ADRs in the world
- Signal detection, best evidence/decision making, transparency



WHO Programme for International Drug Monitoring

- Includes >150 countries whose aims are the safer use of medicines for patients everywhere and building a global culture of patient safety.
- They work nationally and collaborate internationally to monitor and identify the harm caused by medicines, to reduce the risks to patients and to establish worldwide pharmacovigilance standards and systems.
- The WHO Program was created in 1968.
- The Uppsala Monitoring Center is responsible for the technical and operational aspects of the program since 1978.

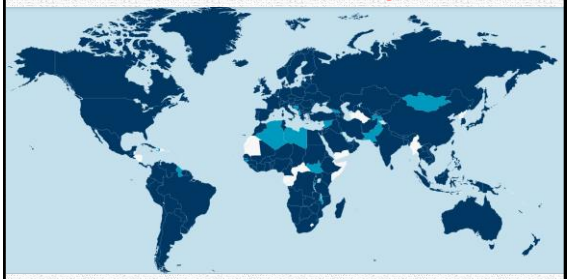
https://www.who-umc.org/global-pharmacovigilance/who-programme/

Vigibase

- WHO global database of individual case safety reports (ICSRs).
- It is the largest database of its kind in the world, with over **16 million** reports of suspected adverse effects of medicines submitted since 1968 by member countries of the WHO Programme for International Drug Monitoring.
- The vigiflow is a web-based Individual Case Safety Report (ICSR) management system

https://www.who-umc.org/vigibase/vigibase/

Members of the WHO Programme



On May 2018, 131 countries are members of the WHO Programme for International Drug Monitoring, and 29 associate member countries

Dark blue: Full member Light blue: Associate member White: Non-member. https://www.who-umc.org/global-pharmacovigilance/members/. Accessed on May 2018

https://www.who-umc.org/global-pharmacovigilance/members/who-programme-members/

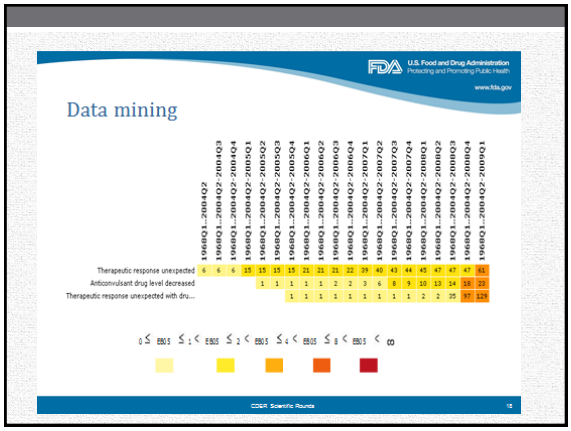
https://www.who-umc.org/media/3036/1475-2875-10-57.pdf

Systematic Methods for the Evaluation of Spontaneous Reports

- Data Mining
  - Calculation of the proportional reporting ratio, as well as the use of Bayesian and other techniques for signal detection
  - Used to examine drug-drug interactions
  - They should always be used in conjunction with, and not in place of, analyses of single case reports.
  - Facilitate the evaluation of spontaneous reports by using statistical methods to detect potential signals for further evaluation.

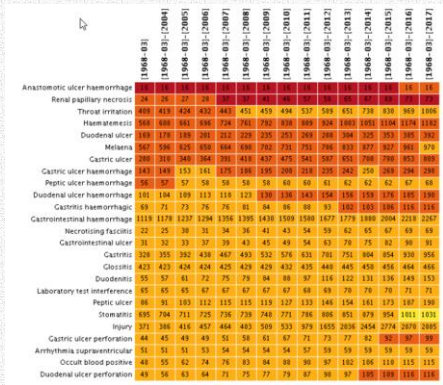
Use of Data Mining

- Mathematical tool identifies higher-than-expected frequency of product-event combinations
- Tool for hypothesis generation
- Supplements FAERS data review
- Does not replace expert clinical case review



Example of Quantitative Signal Detection

Generic_Name	ATC4	ATC3	ATC2	ATC1	PT_plus_Narrow_Alg_SMQ	HLT	HLGT	SOC	N	EBGM	EB05 ▼	EB95	PRR	RR	X	PRR_CHISQ	P_
Rofecoxib	Coxibs	Antiinflammatory And Antirheumatic Products, Non-Steroids	Antiinflammatory And Antirheumatic Products	Musc	Myocardial infarction	Ischaemic coronary artery disorders	Coronary artery disorders	Card	17970	7.33	7.24	7.42	22.1	7.33	2451.5	318134.689	
Valdecoxib	Coxibs	Antiinflammatory And Antirheumatic Products, Non-Steroids	Antiinflammatory And Antirheumatic Products	Musc	Myocardial infarction	Ischaemic coronary artery disorders	Coronary artery disorders	Card	3564	7.15	6.96	7.35	17.3	7.17	497.2	54144.36	
Celecoxib	Coxibs	Antiinflammatory And Antirheumatic Products, Non-Steroids	Antiinflammatory And Antirheumatic Products	Musc	Myocardial infarction	Ischaemic coronary artery disorders	Coronary artery disorders	Card	6494	3.62	3.55	3.70	5.32	3.62	1791.7	21943.663	
Etoricoxib	Coxibs	Antiinflammatory And Antirheumatic Products, Non-Steroids	Antiinflammatory And Antirheumatic Products	Musc	Myocardial infarction	Ischaemic coronary artery disorders	Coronary artery disorders	Card	32	0.693	0.517	0.913	0.825	0.686	46.7	1.03	
Parecoxib	Coxibs	Antiinflammatory And Antirheumatic Products, Non-Steroids	Antiinflammatory And Antirheumatic Products	Musc	Myocardial infarction	Ischaemic coronary artery disorders	Coronary artery disorders	Card	2	0.901	0.388	1.85	1.13	0.891	3.37	0.009	



Exercise

- Review the output obtained from a data mining analysis, identify potential safety signals and establish the next steps

	Generic_Name	SOC	HLT	PT_plus_Narrow_Alg_SMQ	N	EB05	PRR	Prior Assessments
1	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Embolic stroke	31	50.47	115.309	Common in the Population
2	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Cerebral infarction	84	28.633	39.106	Common in the Population
3	Warfarin	Renal	Urinary abnormalities	Haematuria	46	11.225	14.259	Listed/Expected
4	Warfarin	Gastr	Non-site specific gastrointestinal haemorrhages	Melaena	30	10.839	13.11	Listed/Expected
5	Warfarin	Nerv	Central nervous system haemorrhages and cerebrovascular accidents	Ischaemic stroke	29	9.856	24.551	
6	Warfarin			Ischaemic central nervous system vascular conditions (SMQ) [narrow]	243	9.043	9.805	Common in the Population
7	Warfarin			Central nervous system haemorrhages and cerebrovascular conditions (SMQ) [narrow]	300	7.824	8.912	Listed/Expected
8	Warfarin			Central nervous system vascular disorders (SMQ) [narrow]	300	7.8	8.857	

PHARMACOVIGILANCE STIMULATING REPORTING

Stimulating Reporting

- Methods to encourage and facilitate reporting by health professionals in specific situations (e.g., in-hospital settings) for new products or for limited time periods
- Includes:
  - On-line reporting of adverse events
  - Systematic stimulation of reporting of adverse events based on a pre-designed method.
- Issues similar to spontaneous reports (selective reporting and incomplete information)
- Stimulated adverse event reporting in the early post-marketing phase can lead companies to notify healthcare professionals of new therapies and provide safety information early in use by the general population (e.g., Early Post-marketing Phase Vigilance, EPPV in Japan)
- Data obtained from stimulated reporting cannot be used to generate accurate incidence rates, but reporting rates can be estimated

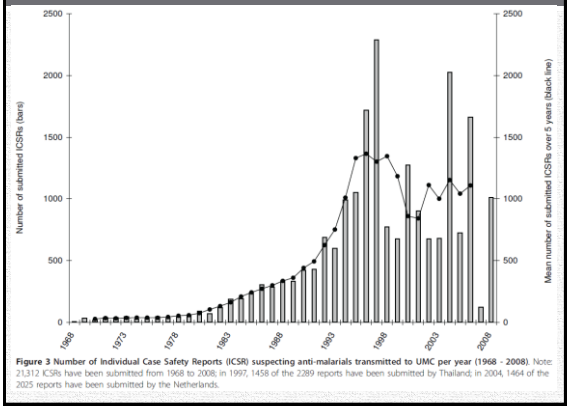


Figure 3 Number of Individual Case Safety Reports (ICSR) suspecting anti-malarials transmitted to UMC per year (1968 - 2008). Note: 21,312 ICSRs have been submitted from 1968 to 2008; in 1997, 1458 of the 2289 reports have been submitted by Thailand; in 2004, 1464 of the 2025 reports have been submitted by the Netherlands.

In Conclusion….