Pharmacovigilance Methods

The Spectrum of PV

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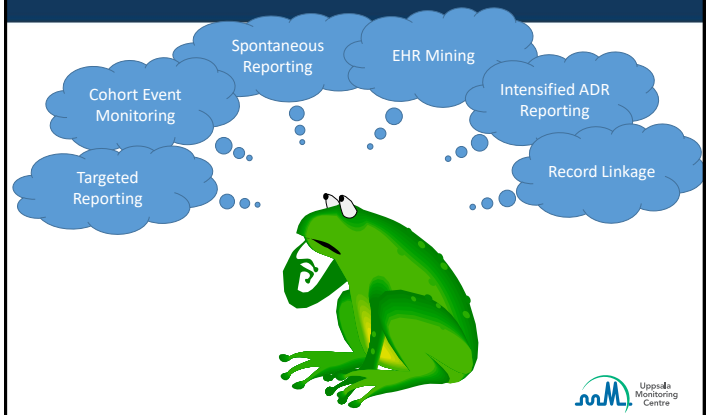
MURIA 2019

Dr Geraldine Hill

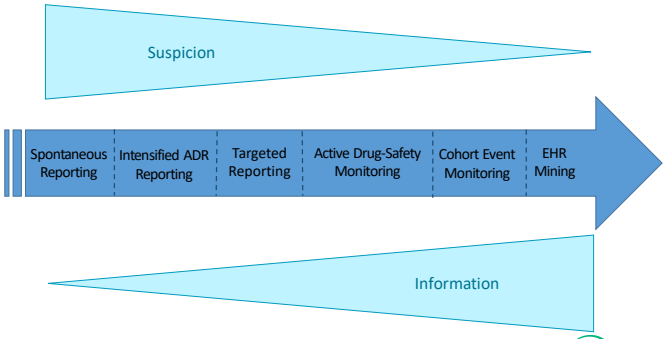
PV Methods: which one?



What is your objective?

- To establish a functional reporting system to monitor the safety of all medicines
- To learn more about the safety profile of new medicines in the early post-marketing phase
- To learn more about the ADR profile of a specific medicine(s) in your population
- To estimate the incidence of a known ADR to a specific medicine in your population
- To make use of existing electronic health records and registries to support pharmacovigilance activities

PV Methods Spectrum



Spontaneous Reporting

Objective: a functional ADR reporting system to monitor the safety of all medicines

Voluntary submission of ICSRs by health professionals, pharmaceutical manufacturers, and patients to the national pharmacovigilance centre

Requires two initial steps by primary reporter:

1. Suspect that an undesirable medical event may have been caused by exposure to a medicine
2. Report their suspicion to the national pharmacovigilance centre

Spontaneous Reporting: what to report?

Developing Pharmacovigilance System

All suspected ADRs

- Encourage a culture of ADR reporting
- Build PV capacity
- Develop a profile of ADRs experienced with locally used medicines

If in doubt, report!

Spontaneous Reporting: what to report?

Established Pharmacovigilance System

May wish to restrict what is reported

For example

- All suspected ADRs for new medicines
- All suspected ADRs occurring in children, even if a medicine has been used off-label
- All serious* suspected ADRs for established vaccines and medicines, including unlicensed medicines, herbal remedies and medicines used off-label.

* fatal, life-threatening, causing permanent disability, prolonging hospitalisation or medically significant

If in doubt, report!

Spontaneous Reporting

Pros	Cons
Covers the whole population	Inherent under-reporting
Includes all medicines	Captures only suspected ADRs
Continual monitoring throughout life-cycle of a medicine	Reporting bias e.g. Seriousness, severity New medicine Advertising of product Publicity of specific ADR
Detects signals of new, rare or serious ADRs	Denominator unknown
Most commonly used method	Difficult to detect – delayed ADRs & – ADRs with high background incidence
Easiest method to establish	
Relatively inexpensive	
Least labour intensive	

Intensified ADR Reporting

Objective: to enhance ADR reporting of specific medicines in early post-marketing phase

Black Triangle Scheme

▼ This medicinal product is subject to additional monitoring.

Extension of Spontaneous Reporting Programme

System in place in UK for many years; introduced in EU in 2013.

List of medicines 'under additional reporting' reviewed monthly

http://www.mhra.gov.uk

http://www.ema.europa.eu

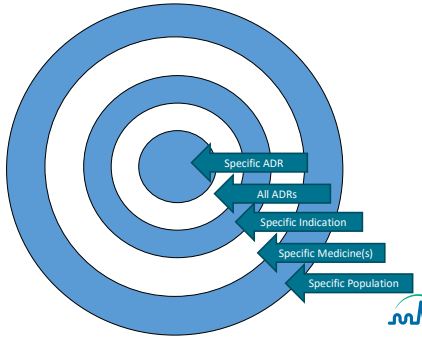
Intensified ADR Reporting

Medicines 'under additional monitoring' include:

- Medicines containing a new active substance
- Biological medicines
- Medicines given conditional approval or approved under exceptional circumstances
- Medicines that require additional studies (e.g. more data on long term use or on a rare side effect seen in clinical trials)

Targeted Reporting

Objective: To learn more about the ADR profile of a specific medicine(s) in your population



Targeted Spontaneous Reporting

Example

Renal toxicity associated with tenofovir-based ART regimens in Uganda

- **Specific drug (tenofovir)**
- **Specific ADR (renal toxicity)**
- **Specific population (2 public health facilities in Uganda)**

Ndagije, H., et al., *Targeted Spontaneous Reporting of Suspected Renal Toxicity in Patients Undergoing Highly Active Anti-Retroviral Therapy in Two Public Health Facilities in Uganda.* Drug Safety, 2015. 38(4): p. 395-408.

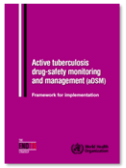
Active Drug-Safety Monitoring (aDSM)

Objective: To gather more information on the safety profile of new TB medicines to assess safety and inform future policy on the use of these medicines.

Developed by WHO specifically for monitoring new and repurposed TB medicines and regimens within Programmatic Management of Drug-Resistant TB (PMTB)

World Health Organization, *Active tuberculosis drug-safety monitoring and management (aDSM): Framework for implementation.* 2015, World Health Organization: Geneva.

http://www.who.int/tb/publications/aDSM/en/



aDSM

Involves three essential activities

- Active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs
- Management of AEs in timely manner
- Systematic collection of standardised data for any SAEs.

Three levels of monitoring described

- All Serious AEs (core package)
- SAEs and AEs of special interest (intermediate package)
- All AEs of clinical significance (advanced package)

Cohort Event Monitoring (CEM)

Objective: To gather more information on the safety profile of a new chemical entity in early post-marketing phase

Suitable for:

New class of medicine

Medicine related to class of medicine that has previously caused problems

Potentially significant adverse event observed during pre- or post-marketing surveillance (SR)

Decision to monitor influenced by:

A need for more safety data (in general or in relation to a particular clinical use)

Expected long-term use

Expected widespread use

Where increase in risk/benefit ratio would be unacceptable (e.g. 'life-style drugs')

One of several treatment options for a disease, where other treatment options are considered safe and effective.

Cohort Event Monitoring (CEM)

A prospective, longitudinal, observational, cohort study of adverse events associated with one or more monitored medicines

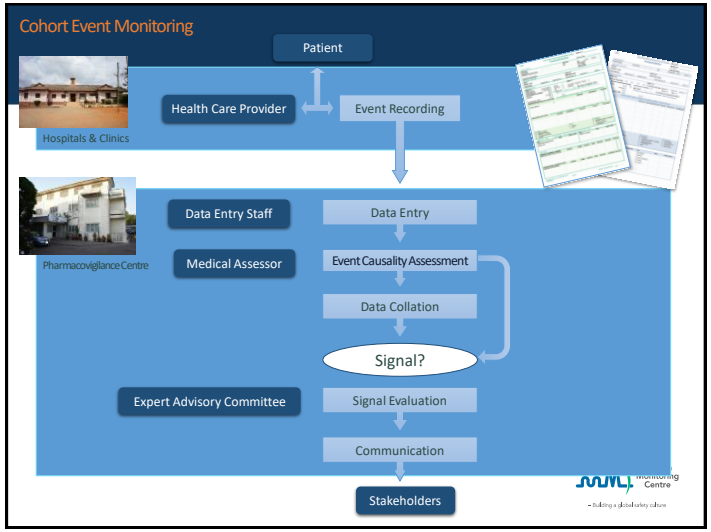
Cohort Event Monitoring

Prospective	'Real-time' monitoring
Longitudinal	Over a period of time
(Inceptional)	From start of treatment
Observational	Does not interfere with patient management
Cohort	Defined group of patients
Adverse events	*'Any new clinical experience (favourable or unfavourable) that is worthy of a record in the patient's file, regardless of its severity and without judgement on its causality'*
Monitored medicine	Specific medicine(s)

Cohort Event Monitoring

Records ALL CLINICAL EVENTS not just suspected adverse reactions

A time-limited programme to complement other PV activities; not intended to replace spontaneous reporting



CEM enables us to:

- Characterise known reactions
- Detect signals of unrecognised reactions
- Identify interactions with other medicines
- Detect lack of effect
- Assess safety in pregnancy & lactation
- Quantify risk - including comparative risk
- Identify risk factors for ADRs

CEM Programmes (examples)

HIV	Belarus	RCETH	CEM for ARV medicines in Republic of Belarus
	Tanzania	TFDA	CEM of ARVs in Tanzania
Malaria	Ghana	FDA (Ghana)	CEM Malaria (WHO)
			CEM Malaria (AMFm)
	Kenya	PPB	CEM-AL Kenya
	Nigeria	NAFDAC	CEM for Malaria (Pilot)
			CEM for Malaria (Scale-up)
	Tanzania	TFDA	TANCEM (ALu)
			TANCEM – DHA/PPQ
	Zimbabwe	Medicines Control Authority of Zimbabwe	ZimCemFlow ACT

Monitored Antimalarial Medicines

Ghana	CEM Malaria (WHO)	All antimalarials
	CEM Malaria (AMFm)	AL, AsAq
Kenya	CEM-AL Kenya	AL
Nigeria	CEM for Malaria (Pilot)	AL, AsAq
	CEM for Malaria (Scale-up)	AL, AsAq
Tanzania	TANCEM (ALu)	AL
	TANCEM –DHA/PPQ	DP
Zimbabwe	ZimCemFlow ACT	AL

AL artemether+lumefantrin
AsAq artesunate+amodiaquine **DP** dihydroartemisinin+piperaquine

Cohort Event Monitoring

Pros	Cons
Early detection of signals of unsuspected ADRs	More labour intensive than SR or TSR
Denominator information allows incidence rates of ADRs to be calculated	More costly
Near complete profile of AEs/ADRs for medicine of interest	Much data collected most of which represents 'background noise'
Assessment of risk; identification of risk factors; between drug comparisons	New to health professionals and PV Centres
Pregnancy outcomes	Training required
Deaths recorded	LTFU may be substantial and needs to be actively managed

Workload considerations

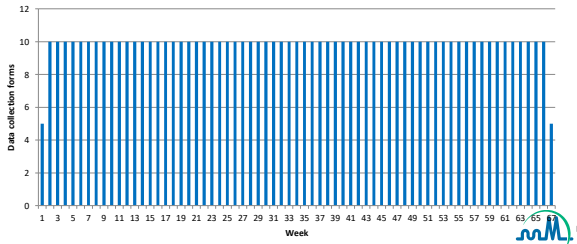
Example: Antimalarial Monitoring

Target size of cohort: 3000 patients (3300 patients to allow for 10% LTFU); 10 sites (330 patients per site)

5 patients per week, 2 visits over 1 week

660 data collection forms (DCFs) from 1 monitoring site

6600 DCFs in total



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Workload considerations

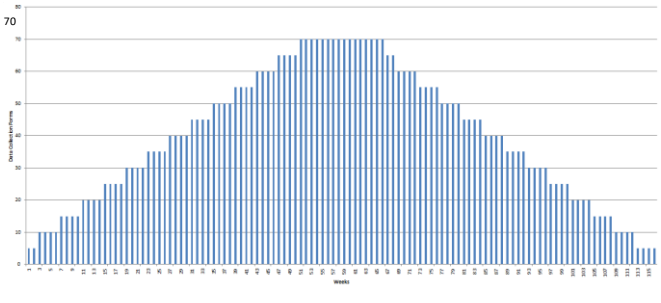
Example: ARV Monitoring

Target size of cohort: 3000 patients (3300 patients to allow for 10% LTFU); 10 sites (330 patients per site)

5 patients per week, 14 visits over 12 months (wk 0, 2, 6, 10... (monthly)...50)

4620 reports from 1 monitoring site

46200 reports in total



Electronic Health Record Mining

Objective: make use of existing health records to supplement pharmacovigilance activities

Electronic Health Records - a potentially rich source of ADR data

Caveat:

- Broad use of compatible EHR is most common in countries with a centralized health care system that determines which drugs are to be used mostly based on financial criteria -> limited dataset on new medicines

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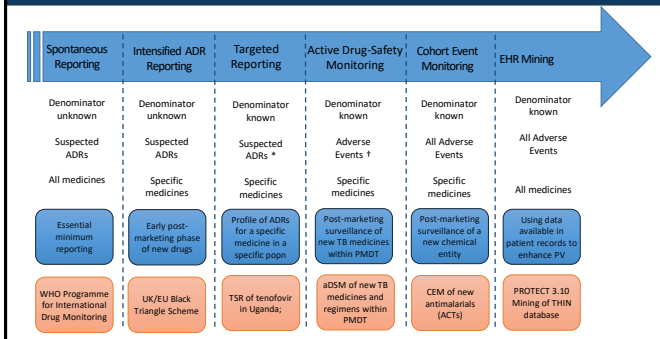
PV Methods Spectrum



* Could be limited to serious ADRs or specific ADR(s) of interest

† Specified as:
- Serious AEs
- Serious AEs + AEs of special interest
- All AEs

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Comparing the methods

Method	Medicines	Population	Reports
Spontaneous Reporting	All medicines, life-cycle of product	All exposed individuals but denominator unknown	Suspected ADRs
Intensified ADR Reporting	Specific medicines	All exposed individuals but denominator unknown	Suspected ADRs
Targeted Reporting	Specific medicines	Defined cohort	Suspected ADRs
Active Drug-Safety Monitoring	Specific medicines	Defined cohort	Adverse Events (SAEs, ± Special Interest or All AEs as defined by programme)
Cohort Event Monitoring	Specific medicines	Defined cohort	All Adverse Events
EHR Mining	All medicines	Defined cohort	All Adverse Events

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A WHO Collaborating Centre

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WHO Collaborating Centre for International Drug Monitoring

One goal
In our role as a WHO Collaborating Centre, we adhere to WHO policies and work in close liaison with WHO headquarters. We provide scientific leadership and operational support to the WHO Programme for International Drug Monitoring. We share the WHO's goal of better health for all, but are organisationally and professionally distinct from the WHO itself.

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