Pharmacovigilance Methods

The Spectrum of PV

the UPPSALA MONITORING CENTRE

PV Methods: which one?

Spontaneous Reporting

EHR Mining

Cohort Event Monitoring

Intensified ADR Reporting

Targeted Reporting

Record Linkage

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 gather more information on the safety profile of a new chemical entity in early post-marketing phase
- To make use of existing electronic health records and registries to support pharmacovigilance activitites

PV Methods Spectrum

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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:

  A patient or health professional

  1. suspects that an undesirable medical event may have been caused by exposure to a medicine
  2. reports the 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

  e.g. MHRA and EMA countries limit reporting to:

  – 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

- Extension of Spontaneous Reporting Programme

Black Triangle Scheme

▼ This medicinal product is subject to additional monitoring

- System in place in UK for many years; to be introduced in EU from Autumn 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 Spontaneous Reporting

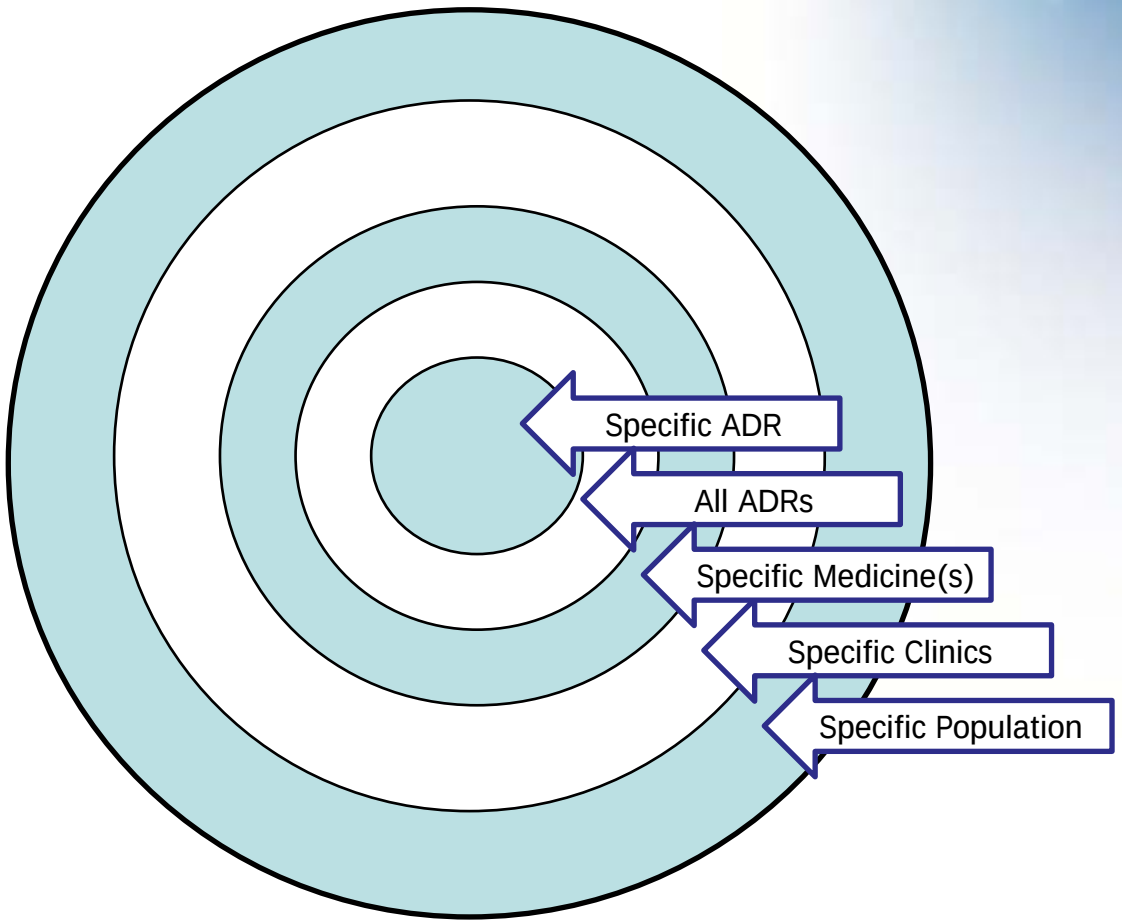
Objective:

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

or

- To estimate the incidence of a known ADR to a specific medicine in your population

Targeted Reporting



Targeted Reporting

TSR of suspected ADRs to ARVs, AMPATH, Eldoret, Kenya

- AMPATH (Academic Model Providing Access to Healthcare)
  - Partnership between Moi University School of Medicine, Moi Teaching and Referral Hospital and a consortium of US medical schools led by Indiana University.
  - Treats over 125,000 HIV-positive patients at 53 sites in and around Eldoret, Western Kenya.
- Focusing on treatment-threatening ADRs (change or discontinuation of treatment)
- Investigating different methods of collecting ADR data, including:
  - Spontaneous reporting of suspected ADR by clinician
  - Spontaneous reporting of suspected ADR by pharmacist
  - Interview by pharmacist of random sample of patients
  - Interview by peer of random sample of patients
  - Pharmacy dispensing data (to assess under-reporting)

Targeted Reporting

TSR pilot project in Uganda:

- Monitoring Medicines Project
- Collaboration between National Pharmacovigilance Centre and AIDS Control Programme
- Objectives include:
  - To monitor renal toxicities related to use of Tenofovir (TDF)-based regimens in adults
  - To monitor ADRs related to use of Zidovudine (AZT) for PMTCT
  - To enhance pharmacovigilance in AIDS control programme
- Screening for renal toxicity follows routine practice
- ADRs are reported ‘spontaneously’ if observed

Cohort Event Monitoring (CEM)

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

- 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

Cohort Event Monitoring

Patient

Health Care Provider

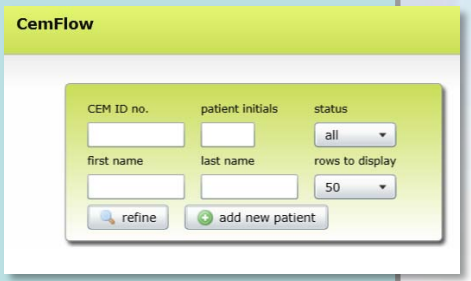
Event Recording

Hospitals & Clinics

Pharmacovigilance Centre

Data Entry Staff

Data Entry



Medical Assessor

Event Causality Assessment

Data Collation

Signal?

Expert Advisory Committee

Signal Evaluation

Communication

Uppsala Monitoring Centre

Stakeholders

CEM enables us to:

- Characterise known reactions
- Detect signals of unrecognised reactions
- Identify interactions with other medicines and TCAMs
- Detect inefficacy of medicine
- Assess safety in pregnancy & lactation
- Measure risk (including comparative risk)
- Identify risk factors for ADRs

CEM Programmes (CemFlow)

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

Monitored Antimarlarial Medicines

Ghana	CEM Malaria (WHO)	All antimalarials
	CEM Malaria (AMFm)	AL, AsAq
	INESS International CEM Ghana	AqAr
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
	INESS International CEM Tanzania	AL
Zimbabwe	ZimCemFlow ACT	AL

AL artemether+lumefantrin
AsAq artesunate+amodiaquine
AqAm amodiaquine+artemether
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

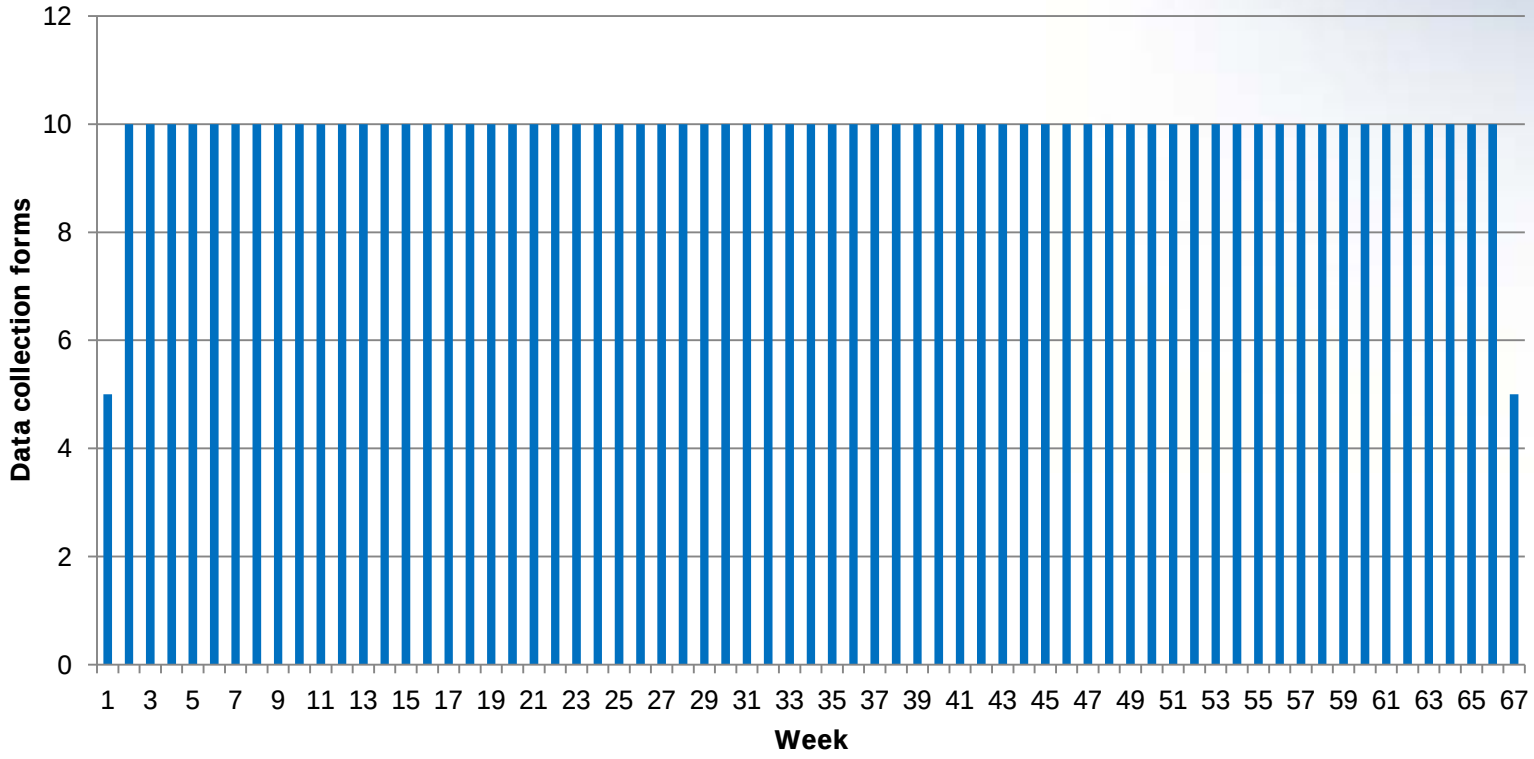
Example: Antimalarial Monitoring

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

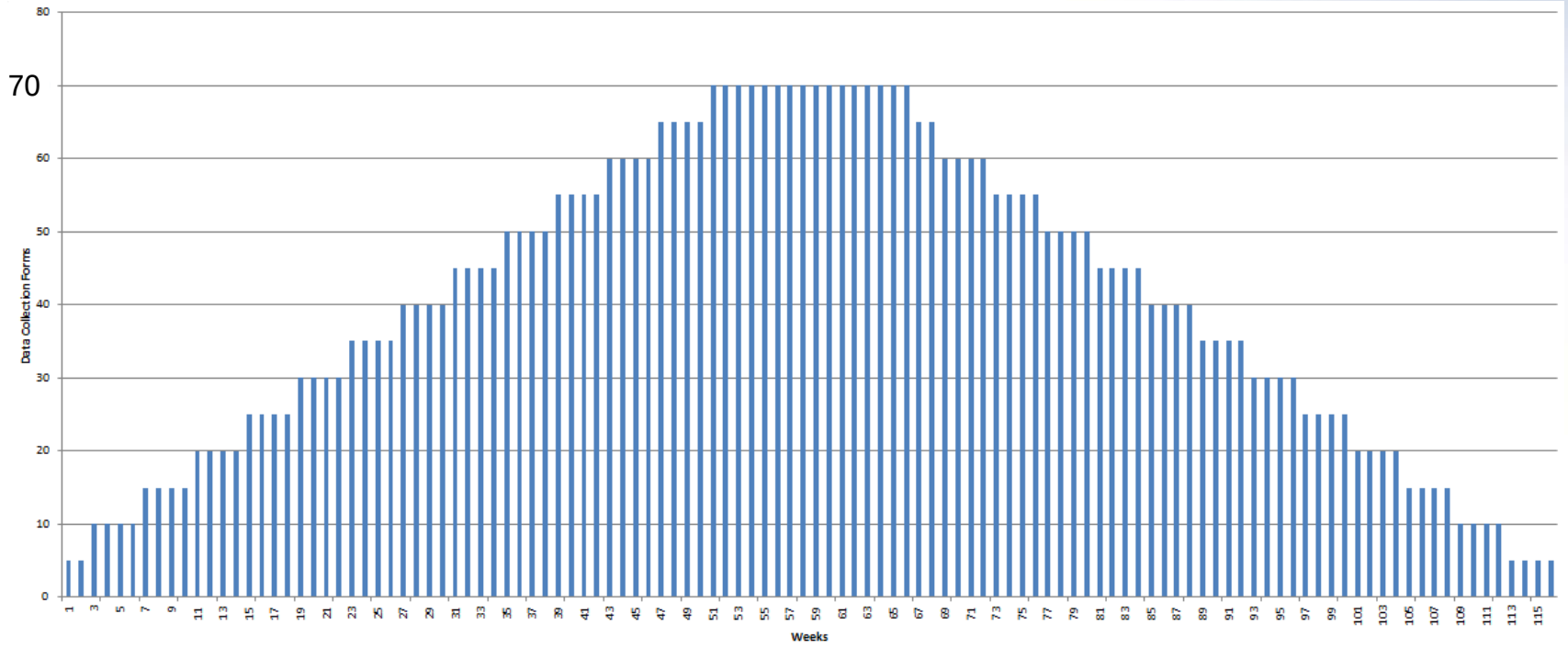
Example: ARV Monitoring

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



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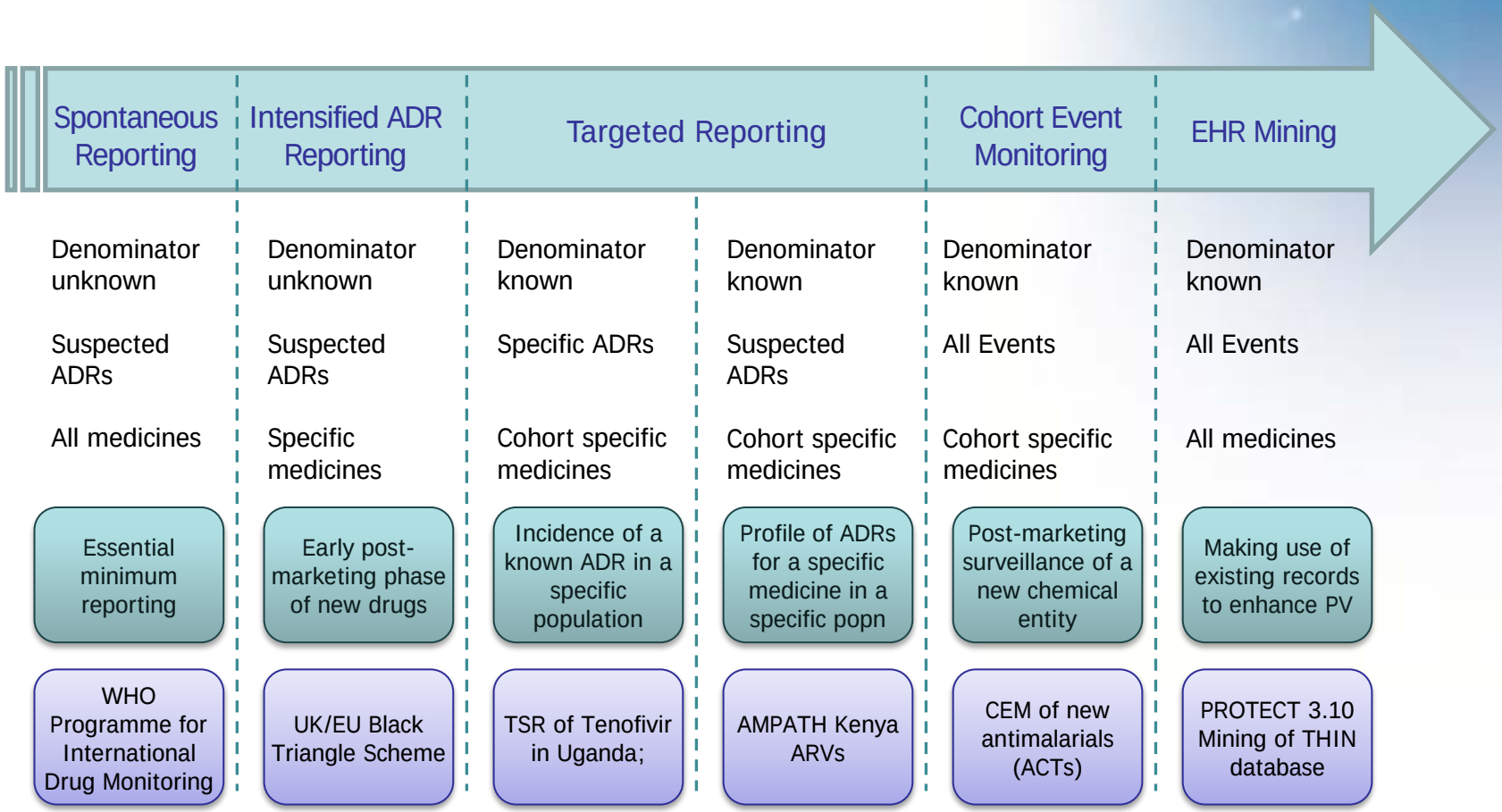
Electronic Health Record Mining

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

- Electronic Health Records - a potentially rich source of ADR data
- Mining of the THIN data-base is currently being evaluated
- More to come on this later…!

PV Methods Spectrum



Comparing the methods

Method	Medicines	Population	Reports
Spontaneous Reporting	All medicines, life-cycle of product	All exposed individuals but denominator unknown	All ADRs
Intensified ADR Reporting	Specific medicines	All exposed individuals but denominator unknown	All ADRs
Targeted Reporting	Specific medicines	Defined cohort	Specific ADRs
			All ADRs
Cohort Event Monitoring	Specific medicines	Defined cohort	All Events
EHR Mining	All medicines	Defined cohort	All Events

Tack så mycket

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