Pharmacovigilance Methods

The Spectrum of PV
PV Methods: which one?

- Spontaneous Reporting
- EHR Mining
- Intensified ADR Reporting
- Record Linkage
- Cohort Event Monitoring
- Targeted Reporting
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 activities
PV Methods Spectrum

- Spontaneous Reporting
- Intensified ADR Reporting
- Targeted Reporting
- Cohort Event Monitoring
- EHR Mining
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

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

Specific ADR
All ADRs
Specific Medicine(s)
Specific Clinics
Specific Population
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

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prospective</td>
<td>‘Real-time’ monitoring</td>
</tr>
<tr>
<td>Longitudinal</td>
<td>Over a period of time</td>
</tr>
<tr>
<td>(Inceptional)</td>
<td>From start of treatment</td>
</tr>
<tr>
<td>Observational</td>
<td>Does not interfere with patient management</td>
</tr>
<tr>
<td>Cohort</td>
<td>Defined group of patients</td>
</tr>
<tr>
<td>Adverse events</td>
<td>‘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’</td>
</tr>
<tr>
<td>Monitored medicine</td>
<td>Specific medicine(s)</td>
</tr>
</tbody>
</table>
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 and TCAMs
- Detect inefficacy of medicine
- Assess safety in pregnancy & lactation
- Measure risk (including comparative risk)
- Identify risk factors for ADRs
# CEM Programmes (CemFlow)

<table>
<thead>
<tr>
<th>Country</th>
<th>Agency</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIV</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Belarus</td>
<td>RCETH</td>
<td>CEM for ARV medicines in Republic of Belarus</td>
</tr>
<tr>
<td><strong>Malaria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ghana</td>
<td>FDA (Ghana)</td>
<td>CEM Malaria (WHO)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEM Malaria (AMFm)</td>
</tr>
<tr>
<td></td>
<td>INESS</td>
<td>INESS International CEM Ghana</td>
</tr>
<tr>
<td>Kenya</td>
<td>PPB</td>
<td>CEM-AL Kenya</td>
</tr>
<tr>
<td>Nigeria</td>
<td>NAFDAC</td>
<td>CEM for Malaria (Pilot)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CEM for Malaria (Scale-up)</td>
</tr>
<tr>
<td>Tanzania</td>
<td>TFDA</td>
<td>TANCEM (ALu)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TANCEM – DHA/PPQ</td>
</tr>
<tr>
<td></td>
<td>INESS</td>
<td>INESS International CEM Tanzania</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>Medicines Control Authority of Zimbabwe</td>
<td>ZimCemFlow ACT</td>
</tr>
</tbody>
</table>
## Monitored Antimalarial Medicines

<table>
<thead>
<tr>
<th>Country</th>
<th>Programme</th>
<th>Antimalarials</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ghana</td>
<td>CEM Malaria (WHO)</td>
<td>All antimalarials</td>
</tr>
<tr>
<td></td>
<td>CEM Malaria (AMFm)</td>
<td>AL, AsAq</td>
</tr>
<tr>
<td></td>
<td>INESS International CEM Ghana</td>
<td>AqAr</td>
</tr>
<tr>
<td>Kenya</td>
<td>CEM-AL Kenya</td>
<td>AL</td>
</tr>
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<td>AL</td>
</tr>
<tr>
<td></td>
<td>TANCEM – DHA/PPQ</td>
<td>DP</td>
</tr>
<tr>
<td></td>
<td>INESS International CEM Tanzania</td>
<td>AL</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>ZimCemFlow ACT</td>
<td>AL</td>
</tr>
</tbody>
</table>

**AL**  artemether+lumefantrin  
**AsAq**  artesunate+amodiaquine  
**AqAm**  amodiaquine+artemether  
**DP**  dihydroartemisinin+piperaquine
### Cohort Event Monitoring

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

• Mining of the THIN data-base is currently being evaluated

• More to come on this later…!
PV Methods Spectrum

- **Spontaneous Reporting**
  - Denominator unknown
  - Suspected ADRs
  - All medicines
  - Essential minimum reporting
  - WHO Programme for International Drug Monitoring

- **Intensified ADR Reporting**
  - Denominator unknown
  - Suspected ADRs
  - Specific medicines
  - Early post-marketing phase of new drugs
  - UK/EU Black Triangle Scheme

- **Targeted Reporting**
  - Denominator known
  - Specific ADRs
  - Cohort specific medicines
  - Incidence of a known ADR in a specific population
  - TSR of Tenofivir in Uganda; AMPATH Kenya ARVs

- **Cohort Event Monitoring**
  - Denominator known
  - Suspected ADRs
  - Cohort specific medicines
  - Profile of ADRs for a specific medicine in a specific population
  - CEM of new antimalarials (ACTs)

- **EHR Mining**
  - Denominator known
  - All Events
  - All medicines
  - Post-marketing surveillance of a new chemical entity
  - Making use of existing records to enhance PV
  - PROTECT 3.10 Mining of THIN database
## Comparing the methods

<table>
<thead>
<tr>
<th>Method</th>
<th>Medicines</th>
<th>Population</th>
<th>Reports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Reporting</td>
<td>All medicines, life-cycle of product</td>
<td>All exposed individuals but denominator unknown</td>
<td>All ADRs</td>
</tr>
<tr>
<td>Intensified ADR Reporting</td>
<td>Specific medicines</td>
<td>All exposed individuals but denominator unknown</td>
<td>All ADRs</td>
</tr>
<tr>
<td>Targeted Reporting</td>
<td>Specific medicines</td>
<td>Defined cohort</td>
<td>Specific ADRs</td>
</tr>
<tr>
<td>Cohort Event Monitoring</td>
<td>Specific medicines</td>
<td>Defined cohort</td>
<td>All Events</td>
</tr>
<tr>
<td>EHR Mining</td>
<td>All medicines</td>
<td>Defined cohort</td>
<td>All Events</td>
</tr>
</tbody>
</table>
Tack så mycket

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