Kia Ora!
Cohort Event Monitoring
Prescription event monitoring (PEM)

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Intensive Medicines Monitoring Programme)
CEM worldwide

- NZ Intensive Medicines Monitoring Programme (IMMP), NZ, 1977
- Drug Safety Research Unit (PEM), Southampton, UK, 1980
- Tanzania
  - CEM of anti-malarials
- Nigeria
Plan of presentation

- Objectives
- What results can you get? *Examples and methods from the NZ Intensive Medicines Monitoring Programme (IMMP)*
- How do we get them?
- Observations & comments
The objectives of CEM

1. Characterise known reactions
   - Mean age
   - Gender
   - Mean dose
   - Treatment duration
   - Time to onset
   - Seriousness profile
   - Incidence
   - Outcomes
   - Effect on treatment (% withdrawals)
   - Part of syndrome?
The objectives of CEM

2. Detect signals of unrecognised reactions

3. Interactions with
   - Other medicines
   - Complementary and alternative medicines
   - Foods

4. Identify risk factors so that they can be avoided
   - Age
   - Duration of therapy
   - Gender
   - Concomitant disease
   - Dose
   - Concomittant therapy
The objectives of CEM

5. Assess safety in pregnancy & lactation

6. Estimate risk (including comparative)

7. Provide evidence for effective risk management
   - Safer prescribing
   - Benefit / harm assessment
   - Regulatory changes
The objectives of CEM

8. Detect inefficacy, which might be due to

- Faulty administration
- Poor storage conditions
- Out of date
- Poor quality product
- Counterfeit
- Interactions
The objectives of CEM

9. Hypothesis generation

10. Cohorts for study
The objectives

Achieve maximum benefit, least harm for patients
What results can you get?
COX-2 inhibitors
celecoxib, rofecoxib

Preliminary monitoring data
The following will be summarised

- Cohort description & drug utilisation
- Preliminary events data
- Preliminary review of deaths
IMMP Process

- Prescription
- Follow-up questionnaires
- Event information
- Patient and Prescription details

Cohort data

Relationship assessment

NZHIS
<table>
<thead>
<tr>
<th></th>
<th>Prescriptions</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celecoxib</td>
<td>98,975</td>
<td>32,630</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>52,874</td>
<td>26,666</td>
</tr>
</tbody>
</table>
Profile of Ages at First Prescription

![Bar chart showing the distribution of ages at first prescription for Celecoxib and Rofecoxib.](image)
## MMP example – COX-2

<table>
<thead>
<tr>
<th>Age</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>63</td>
<td>58</td>
</tr>
<tr>
<td>Mode</td>
<td>59</td>
<td>53</td>
</tr>
<tr>
<td>&lt;40 years</td>
<td>6.9%</td>
<td>12.6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highly significant</td>
</tr>
<tr>
<td>70+ years</td>
<td>32.7%</td>
<td>25.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Highly significant</td>
</tr>
</tbody>
</table>
### Gender and term

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>61.6%</td>
<td>60.5%</td>
</tr>
<tr>
<td>Short term</td>
<td>6879 (21%)</td>
<td>9843 (37%)</td>
</tr>
<tr>
<td>mg/day</td>
<td>No.</td>
<td>%</td>
</tr>
<tr>
<td>--------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>12.5</td>
<td>11,695</td>
<td>28.3</td>
</tr>
<tr>
<td>25</td>
<td>26,027</td>
<td>63.0</td>
</tr>
<tr>
<td>37.5</td>
<td>36</td>
<td>0.1</td>
</tr>
<tr>
<td>50</td>
<td>3,546</td>
<td>8.6</td>
</tr>
<tr>
<td>Celecoxib dose mg/no./%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 6,622 8.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>200 65,591 80.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 274 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>400 8,927 11.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>600 46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>800 30</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
IMMP Process

- Prescription
- Follow-up questionnaires
- Event information
- Patient and Prescription details
- Cohort data
- Relationship assessment
- NZHIS
## Indications for use

(Or type/seriousness of malaria)

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
<th>Difference Chi-square</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients</strong></td>
<td>6,200</td>
<td>4,536</td>
<td></td>
</tr>
<tr>
<td><strong>Inflammatory</strong></td>
<td>211 (3.4)</td>
<td>129 (2.8)</td>
<td>P&gt;0.05</td>
</tr>
<tr>
<td><strong>Osteoarthritis</strong></td>
<td>1805 (29)</td>
<td>775 (17)</td>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td><strong>Musculoskel</strong></td>
<td>1668 (27)</td>
<td>1105 (24)</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td><strong>Other pain</strong></td>
<td>2479 (40)</td>
<td>2495 (55)</td>
<td>P&lt;0.0001</td>
</tr>
</tbody>
</table>
Baseline information 1

Questions

1. Current Acid Related Disorder
2. Past ARD
3. NSAID exposure
   - Past GI problems
   - Direct switch to COX-2
   - Concurrent aspirin
4. Past cardiovascular disease
   - Hypertension / Heart failure
   - MI / Angina
   - Dysrhythmia / Stroke - TIA
Baseline information 2

Questionnaire response rate

- **Celecoxib**: number sent 4635
  - No. returned with information 3985 (91%)

- **Rofecoxib**: number sent 3050
  - No. returned with information 2725 (89%)
Baseline information 3
No. & % of positive responses to question

<table>
<thead>
<tr>
<th></th>
<th>CEL</th>
<th>ROF</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ARD</td>
<td>2281 (68%)</td>
<td>1341 (60%)</td>
<td>1.4 (1.27-1.58)</td>
</tr>
<tr>
<td>NSAID/ARD</td>
<td>2136 (62%)</td>
<td>1199 (54%)</td>
<td>1.4 (1.28-1.59)</td>
</tr>
<tr>
<td>Switch</td>
<td>1345 (36%)</td>
<td>824 (34%)</td>
<td>1.9 (0.98-1.21)</td>
</tr>
<tr>
<td>Aspirin</td>
<td>352 (9.3%)</td>
<td>173 (6.9%)</td>
<td>1.4 (1.15-1.69)</td>
</tr>
<tr>
<td>Cardiovasc</td>
<td>1361 (36%)</td>
<td>797 (31%)</td>
<td>1.2 (1.11-1.38)</td>
</tr>
</tbody>
</table>
### Baseline information 4

**Cardiovascular disease**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>843 (22%)</td>
<td>498 (19%)</td>
<td>1.1 (1.04-1.26)</td>
</tr>
<tr>
<td><strong>MI/angina</strong></td>
<td>547 (14%)</td>
<td>298 (12%)</td>
<td>1.2 (1.09-1.42)</td>
</tr>
<tr>
<td><strong>HF</strong></td>
<td>206 (5.4%)</td>
<td>115 (4.5%)</td>
<td>1.2 (0.97-1.51)</td>
</tr>
<tr>
<td><strong>Dysrhythmia</strong></td>
<td>141 (3.7%)</td>
<td>86 (3.3%)</td>
<td>1.1 (0.85-1.44)</td>
</tr>
<tr>
<td><strong>Stroke/TIA</strong></td>
<td>40 (1.0%)</td>
<td>17 (0.7%)</td>
<td>1.6 (0.90-2.80)</td>
</tr>
</tbody>
</table>
The events
Profile of Events - Celecoxib and Rofecoxib

n=1714    n=982

Accidents 13  273
Alimentary 33  273
Autonomic  17  181
Circulatory 22  301
Died  17  198
Endocrine/Metabolit  32  293
ENT  17  179
Eyes  22  3
Haematological  3  51
Hepatobiliary 12  44
Immunological  13  28
Infections  9  19
Musculoskeletal  1  32
Neoplasms  12  21
Neurological  12  35
Psychiatric  39  78
Respiratory  51  156
Skin  50  64
Urogenital  40  64

Percentage of Total Events

Celecoxib  Rofecoxib

System Organ Class
## Most common events 1

rates /1000 patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Rate</td>
<td>No.</td>
</tr>
<tr>
<td>ARD</td>
<td>129</td>
<td>3.4</td>
<td>89</td>
</tr>
<tr>
<td>Rash</td>
<td>86</td>
<td>2.6</td>
<td>30</td>
</tr>
<tr>
<td>HF</td>
<td>74</td>
<td>2.3</td>
<td>55</td>
</tr>
<tr>
<td>IHD</td>
<td>57</td>
<td>1.8</td>
<td>38</td>
</tr>
<tr>
<td>Event</td>
<td>Celecoxib</td>
<td>Rofecoxib</td>
<td>RR</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td>-----------</td>
<td>--------</td>
</tr>
<tr>
<td>LRTI</td>
<td>56</td>
<td>29</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>1.7</td>
<td>1.1</td>
<td>(1.0-2.5)</td>
</tr>
<tr>
<td>Dysrhythmias</td>
<td>49</td>
<td>19</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.7</td>
<td>(1.2-3.6)</td>
</tr>
<tr>
<td>Angioedema</td>
<td>48</td>
<td>14</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>0.5</td>
<td>(1.6-5.1)</td>
</tr>
<tr>
<td>Stroke</td>
<td>37</td>
<td>18</td>
<td>NS</td>
</tr>
</tbody>
</table>
## Most common events 3

<table>
<thead>
<tr>
<th>Event</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No</td>
<td>Rate</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>36</td>
<td>1.1</td>
</tr>
<tr>
<td>Asthma</td>
<td>34</td>
<td>1.0</td>
</tr>
<tr>
<td>RF</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>33</td>
<td>1.0</td>
</tr>
<tr>
<td>HT</td>
<td>13</td>
<td>0.3</td>
</tr>
</tbody>
</table>
Signals identified 1

- Coughing
- Visual field defect / temp blindness
- Acute psychiatric events
- Pancreatitis
- Hepatotoxicity
- Psoriasis
- Acute urinary retention
Signals 2

- Mouth ulceration
- Lower bowel effects
- Cardiac dysrhythmias
- Cardiac arrest
- Myocardial infarction / stroke
- Anaphylaxis
- Serious skin infection
- Acute labyrinthitis
Signals 3

Interactions

- Tricyclics causing arrhythmias
- Warfarin causing increased INR (rofecoxib)
# Deaths

**Causes by SOC (% of total deaths)**

<table>
<thead>
<tr>
<th></th>
<th>Celecoxib No. (%)</th>
<th>Rofecoxib No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All deaths</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>116 (40)</td>
<td>68 (38)</td>
</tr>
<tr>
<td><strong>Circulatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>34 (11.6)</td>
<td>23 (12.9)</td>
</tr>
<tr>
<td><strong>Malignancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>115 (39)</td>
<td>92 (51)</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>59 (20)</td>
<td>24 (13)</td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>23 (8)</td>
<td>8 (5)</td>
</tr>
<tr>
<td><strong>Infection</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>13 (4)</td>
<td>11 (6)</td>
</tr>
<tr>
<td><strong>Alimentary</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Causal</td>
<td>10 (3)</td>
<td>8 (5)</td>
</tr>
</tbody>
</table>
Risk factors 1

by multiple logistic regression

- Renal failure
  - Age
  - Inflammatory arthritis

- Heart failure
  - Age
  - P/H heart failure
  - Inflammatory arthritis
Risk factors 2

- Ischaemic heart disease
  - Age
  - P/H of any type of heart disease
  - Inflammatory arthritis (celecoxib)

- Cardiac dysrhythmias
  - Age
  - Past history of heart failure
  - Inflammatory arthritis (celecoxib)
Risk factors 3

Stroke / TIA

- Age
- Hypertension
- Inflammatory arthritis
Did we reach the objectives?
Study demonstrates

- High compliance
- Demographics of cohorts
- Background data
  - Indication
  - Relevant past/current history
- Prescribing practices
- Early signal identification
- Significant events
- Comparative rates
- Risk factors
Concerns raised

- High volume of prescribing
- High doses of rofecoxib
- Substantial prescribing to patients at high risk
  - very elderly
  - history of cardiovascular disease
  - history of ARD
- Apparent high death rate
Concerns

- High rate of cardiovascular events
  - Heart failure
  - Dysrhythmias
  - Prothrombotic effects
    - Myocardial infarction
    - Stroke
    - Renal infarction

- High rate of alimentary events
How do we get results like this?

The principles
Cohort event monitoring

How is it done?

**Two Principles**

- **Identifying patients exposed (cohort)**
  - the denominator
    - as complete as possible

- **Systematically soliciting adverse EVENTS**
  - the numerator
    - as complete as possible
1. Identifying the patients

How can this be done?

The cohort of patients is established using the best source of usage data available

- Dispensings (pharmacies or central records)
- Patient records
  - Doctors
  - Clinics
  - Hospitals
  - Other
- Programme records

Adequate cohort (10,000 patients)
IMMP Process

Prescription

Follow-up questionnaires

Event information

Patient and Prescription details

Cohort data

Relationship assessment

NZHIS

Other Rx Sources
**Cohort size**

- General aim 10,000 (IMMP 11,000)
- Greater numbers required to detect differences
  - if events naturally common
  - for sub-group analyses
- Smaller numbers still produce good data
  - fluoxetine <7000
- Signals can be identified / confirmed with much smaller numbers (<1000)
  - eg nifedipine & eye pain
2. Soliciting the events

How can this be done?

- **Actively** asking for the events
- **Systematically** asking for the events
Soliciting the events

How is it done?

The events are collected using the best source(s) available

- Survey prescribers (questionnaires or other)
- Survey patients (questionnaires or other)
- **Real-time recording***
- Telephone, or visit***
- Record searches (manual, electronic)
- Registers of death or morbidity
- Record linkage with registers or hospital records
- Intensified spontaneous reporting
- Other
- Several
IMMP Process

Cohort data

Event information

Follow-up questionnaires

Prescription

Patient and Prescription details

Other Rx Sources

Relationship assessment

NZHIS

Other Sources
Actively & systematically asking

- Ask after every treatment

- Patients in cohort checked to see that follow-up information received

- Repeat request for missed patients

- Make strenuous efforts to avoid missing anyone
Adverse event (experience)

Definition (WHO)

Untoward medical occurrence temporally associated with the use of a medicinal product, but not necessarily causally related
It is EVENT monitoring

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.
Events = reactions + incidents

**Reactions**
1. Definite
2. Probable
3. Possible

**Incidents (background noise)**
4. Unlikely
5. Unclassified (conditional)
6. Unassessable
Incidents

(Making music from the noise)

- Should represent background morbidity

- May contain unrecognised signals
  - unexpected profiles

- Useful for assessing reporting bias
  - as within-drug controls
  - as between-drug controls

- Unmasking
Why adverse events?
To identify signals of new reactions

- If only known or expected adverse reactions are reported, unexpected adverse reactions will not be identified.

- It is important to identify signals, validate them, determine the incidence, understand their significance and identify the risk factors as soon as possible.

- It is not logical to specify the types of events to be recorded. Unexpected reactions cannot be identified by recording only the known or expected.
Reporting requirements

- All new events even if common & minor
- Change in a pre-existing condition
- Abnormal changes in laboratory tests
- Accidents
- All deaths with date & cause
- Possible interactions
  - NB alcohol, OCs, CAMs
Reasons for stopping

- Poor compliance (adherence)
- No longer necessary
- Change of diagnosis
- Inadequate response
- Suspected ADR
- Death
- Lost to follow-up
Pregnancy

- Routine questions about pregnancy and lactation for all women of child bearing age – computer generated

- Pregnancy register established

- Time / period of exposure identified

- Routine follow-up of all pregnancies after expected delivery date
Non-serious events

- May indicate serious problem
- May affect compliance
  - nausea
  - Rash / pruritus
  - Diarrhoea
- May be more important than serious reactions
- Recording all events is easier than being selective
CEM in the IMMP

Prospective observational cohort studies on new drugs in normal clinical practice

- Cohorts established from prescription data from pharmacies
- Events data mainly from questionnaires sent to prescribers
Compliance

- Voluntary / unpaid
- Doctors 80%
  - Limiting factor is workload
- Patients higher
- Pharmacists 93%
- Good feedback essential
- Value appreciated
‘Controls’

- Controls create an artificial situation

- The aim is a non-interventional study in normal clinical practice

- Comparators are desirable
  - not always possible
  - possibility of confounding

- A good study of a single drug
  - provides valuable data
  - has benchmark value
Record linkage

- Linking databases using unique ID
- IMMP - routine link with
  - NZHIS – identify deaths
  - Register of deaths for certified cause(s)
- IMMP – special studies
  - Suicide & antidepressants
  - Reactions of long latency – cancer registers / hospital discharge diagnoses
  - Conditions of interest eg MI
Cohort investigations

- Patient questionnaires
  - Eye pain and nifedipine / taste disturbance and captopril

- Doctor questionnaires
  - Angina and bezafibrate
    (confounding by indication)

- Reactions of long latency
  - Omeprazole

- Case control studies (nested)
  - Genetic studies
Don’t ask for too much

- The more you ask for, the less you get
- A delicate balance
- Concomitant therapy
- Information can be requested if needed
- Unnecessary data increases workload
Be open minded

- Unexpected reactions will occur
- Predictions of safety unreliable
- Experience based only on spontaneous reporting unreliable
  - 2.1 million patient exposures with olanzapine
    'no significant safety concerns'
- No dominant pre-conceived ideas
- All data should be collected & analysed in a totally objective manner
Cohort event monitoring

- Is an early warning system
- New drugs (post-marketing surveillance)
- Can be used to validate signals
- Can be used to characterize reactions
- Normal clinical practice, real life situations
Cohort event monitoring

- Exposure in pregnancy / lactation
- Death rates
- Reasons for stopping therapy
- Inefficacy
- Limited study period
- Reactions of long latency
- Events examined clinically and epidemiologically
The epidemiology

- observational cohort studies
- prospective
- longitudinal
- non-interventional
- inceptional
- dynamic
- descriptive
Analysis

- Collation and signal identification

- Rates and profiles
  - Comparisons by drug, age group, etc
  - By system organ class
  - Within system organ class
  - Individual events

- Life table or survival analysis

- Multiple logistic regression
  - esp. for risk factors
Advantages of CEM

- Provides comprehensive information
- Provides near complete information
  - On the target population
  - Drug utilisation
  - Effectiveness
  - Risks and how to prevent them
- Provides the information needed to
  - Handle drug scares
  - Minimise harm
  - Ensure treatment success
Advantages of CEM

- Stimulates interest in drug safety
- Improves spontaneous reporting
- Can concentrate resources on drugs of particular importance to a country or programme
- Can be applied regionally
- Adaptable
The essentials

- Identify the cohort
- Identify the events

With this information, you can find all you need to know (almost) concerning safety
Mann & Andrews *Pharmacovigilance*

**Title:** Pharmacovigilance (2nd Edition) 2007

**Publisher:** John Wiley & Sons, Ltd.

**Author:** Mann, Ronald D.; Andrews, Elizabeth B.

**Includes chapters on:**
- PEM in the UK
- PEM in NZ
Thank-you