Working together for improved safety of medicines

Marie Lindquist

Uppsala Monitoring Centre

The WHO Drug Monitoring Programme

- Started in 1968 to prevent drug disasters
  - by pooling data from 10 countries with existing spontaneous reporting systems
- Scientific and technical operations moved to Uppsala, Sweden in 1978
  - The WHO Collaborating Centre for International Drug Monitoring (Uppsala Monitoring Centre, UMC) was set up specifically for this purpose
- VigiBase is the data repository
  - Holds adverse drug reaction data from 1968 to date
  - Is managed by the UMC
  - Database now contains >5 million case reports

UMC strategies

To achieve our vision we will:

- lead the research and development of tools and methodologies for pharmacovigilance and patient safety
- lead and support pharmacovigilance activities and develop structures globally
- apply best practises in communication and networking with relevant stakeholders
- build an effective organisation for the future that promotes and stimulates creativity and engagement based on a solid competence

Provisions to WHO Programme

- Access to an international network
- Early information about potential safety signals
- Access to VigiBase
- Terminologies and software
- Support, resources, training
- Publications, guidelines

Provisions to other clients

- WHO Drug Dictionaries
  - Subscription product
- (Limited) access to VigiBase
  - Caveat document applies
- Terminologies
  - WHO-ART medical terminology
  - List of medicinal herbals, w. classification
- Publications

WHO Programme today

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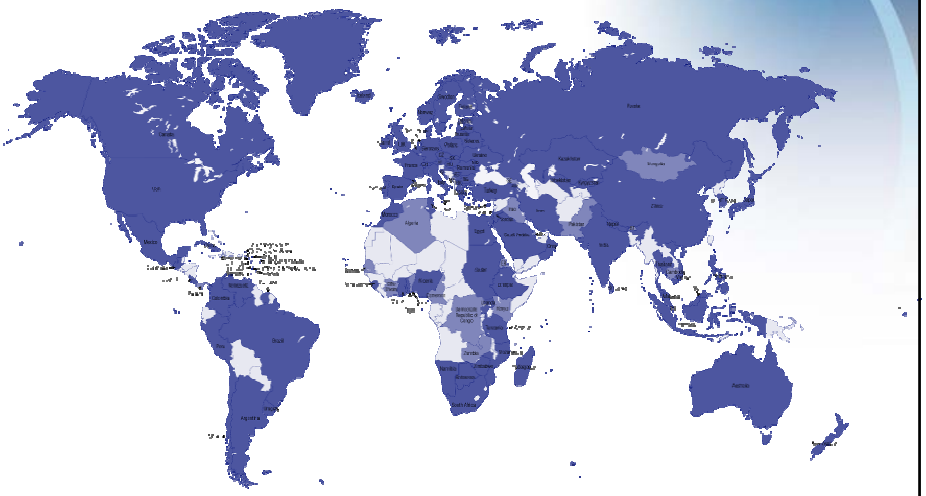
WHO drug monitoring programme
Participating countries 2009



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The role of the WHO Programme

- Developing systems and science for identification and communication of international safety information
- Pursuing active collaboration and communication with all stakeholders
- Pursuing the goal of a single, global database for drug safety data
- Promoting global pharmacovigilance through education and training

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Pharmacovigilance
WHO definition

The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem

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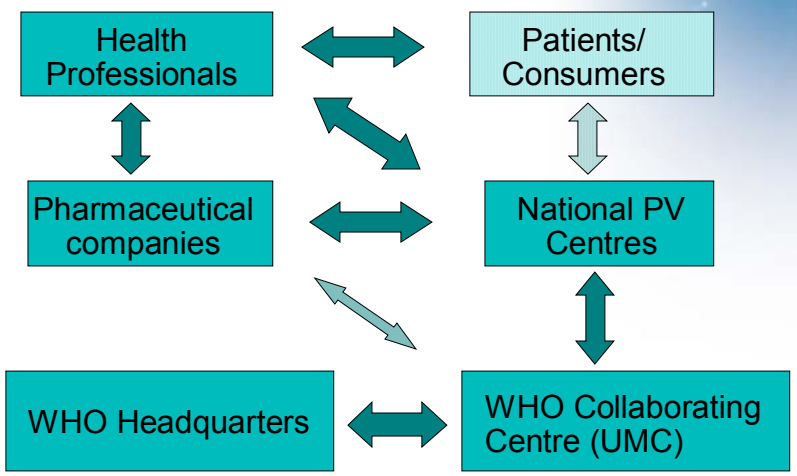
World-wide network of knowledge and competence

- National pharmacovigilance centres in >100 countries
- WHO HQ
  - QSM – Quality and Safety of Medicines
  - Public Health Programmes
- Working relations with ISOP, CIOMS, ISPE, IPCS, HAI, IMS, DIA, ISO, ICH, University of Utrecht and other organisations
- Network of consultants/experts

Acronyms explained

- **ISOP – International Society of Pharmacovigilance**
- **CIOMS – Council for International Organizations of Medical Sciences**
- **ISPE – International Society of Pharmacoepidemiology**
- **IPCS – International Programme of Chemical Safety (WHO)**
- **HAI – Health Action International**
- **IMS – IMS Health (world wide medical statistics)**
- **DIA – Drug Information Association**
- **ISO – International Standards Organization**
- **ICH – International Conference on Harmonisation**

Flow of information

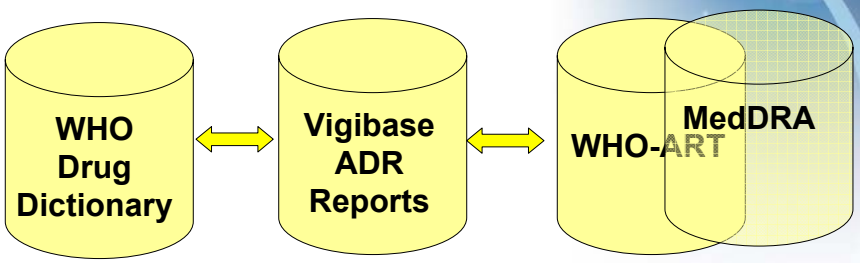


UMC work areas

- Collection and processing of international medicines safety data
- Signal detection and analysis
- Training, education and support
- Tools
  - terminologies, classifications, reporting, search and analysis tools
- Research
- Harmonisation and standards development
- Communication

Collection and processing of international medicines safety data

Vigibase main databases



- Anatomical-Chemical-Therapeutic (ATC) classification (4 levels)
- Generic level (ingredient(s))
- Pharmaceutical product level (ingredient(s)/form/strength)
- Medicinal product level (the named product marketed and sold in a particular country).

- System-Organ Class
- High level term
- Preferred term
- Included term
- Mapped to MedDRA
- Incoming MedDRA terms mapped to WHO-ART and vice versa

From 2008, Vigibase runs WHO-ART and MedDRA in parallel

How are reports sent to UMC?

- Data in ICH E2B format
  - XML files
- Direct data entry through web based interface (VigiFlow)
  - developed and maintained by the UMC
  - available to all National Centres
  - currently used by >30 countries in resource limited settings

Signal detection and analysis

What should be achieved?

- Signals should not be missed
- Signals should be found early
- 'False' signals should be kept to a minimum

How do we find signals?

Manual investigations + clinical judgement

- Clinical review
  - all cases at data entry, and 'flag' relevant associations
- Search for and review
  - accumulated data based on hypotheses generated from other sources e.g. literature
- Look at total number
  - of reports of a combination, or changes in number of reports

As reports are piling up…

..data printouts become unmanageable

A more powerful signal process is needed

Requirements

- An automated procedure with a power to consider all combinations
  - drug – ADR
  - drug - indication - age - ADR
- Objective initial assessment of all drug - ADR combinations
- Strong associations highlighted for clinical assessment
- To be part of an integrated process for signal detection and analysis

Quantitative signal detection

Different approaches

- Aim to detect what is more frequently reported than expected
  - relative to a background of other reports
- Use statistical approach and measure of 'disproportionality'
  - observed/expected ratio
- Can be more or less automated
- Works for screening of large amounts of case reports
  - depending on implementation method

BCPNN method

Used since 1998 by the UMC on VigiBase

Bayesian statistics

+

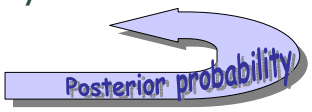
- A neural network implementation

↓

Bayesian Confidence Propagation Neural Network (BCPNN)

Bayesian methods

- An alternative statistical approach
- Derived from Bayes' Law
- Uses 'probability' to express subjective 'degree of belief' in a specific outcome
- Current probability based on
  - prior probability
  - new data
    - *constantly updated on addition of new data*



Bayesian statistics

Applied to ADR data

- Prior probability
  - Drug-ADR combination (weakly) assumed unrelated
- Data: Reporting to the ADR database
- Posterior probability
  - Drug-ADR combination related?
    - Given Prior, and Reporting to the database

Without including prior knowledge we are over-sensitive to data
⇒ 'false' signals

BCPNN method

What is a neural network?

- A matrix of inter-connected nodes; each node is connected to all others
- The network is used to count
  - All reports in the database (C)
  - All occurrences of variable x (e.g. ADR - c_x)
  - All occurrences of variable y (e.g. Drug - c_y)
  - All occurrences of x and y together - c_{xy}

BCPNN method

What is a Bayesian neural network?

- Uses the principles of Bayes' law to calculate
  - Prior and posterior probabilities
  - Dependence between variables
  - Confidence intervals allow to examine
    - Point estimate of unexpectedness (Information Component)
    - The level of certainty associated with it

BCPNN method

What is the Information Component (IC)?

- The measure of disproportionality
  - IC = log2 (posterior/prior probability)
  - Is zero (0) when variables are independent
  - Is > 0 when a combination occurs more often than expected
- Use within BCPNN allows us to have useful dampening property
  - When there are few reports

Information Component (IC)

Frequentist estimate

	ADR Y	Other ADRs
Drug X	A	B
Other drugs	C	D

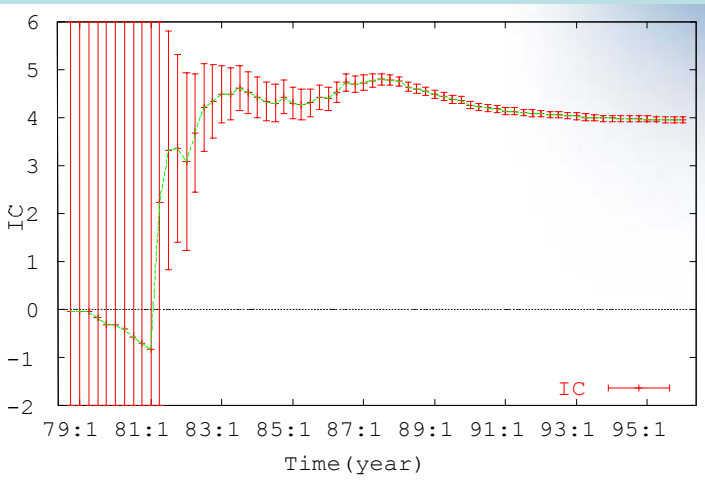
$IC = \log_2 (\text{Observed} \div \text{Expected})$

$IC = \log_2 (A \quad \div (A+B)(A+C)/(A+B+C+D)]$

*(logarithmic form of **Empiric Bayes Geometric Mean** (EBGM) used by the US FDA)*

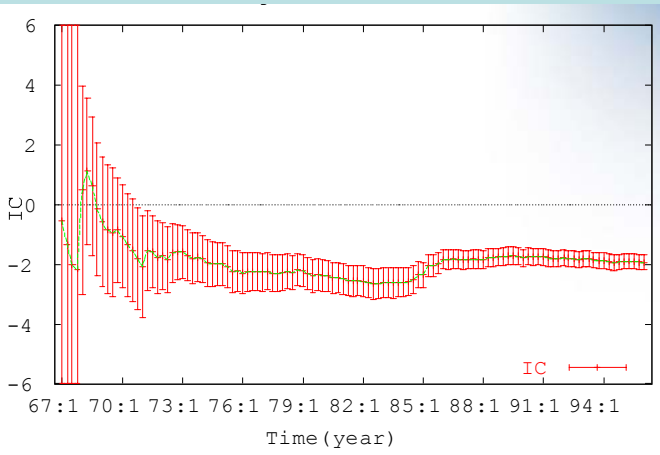
IC development over time

Example captopril - coughing



IC development over time

Example digoxin - rash



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BCPNN method

Advantages

- Transparent - easy to see what has been calculated
- Robust - valid results can be produced in spite of missing data
- Reproducible results - making validation and checking easy
- Time efficient - network only needs one pass across data

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BCPNN method

More advantages

- Readily applicable even with
  - repeated measurements (implicit!)
  - zero counters (use prior beliefs)
  - low counter values (more reliance on priors)
    - dampening when data is sparse
- Can incorporate prior knowledge explicitly in the analysis
- Intuitive relationship between IC and its credibility interval
  - IC is a distribution

An automated UMC signalling process

The start

- 1995 - Pilot study using a data mining approach
  - Developments together with Royal Institute of Technology, Stockholm
- Implemented as a Bayesian Confidence Propagation Neural Network (BCPNN)
- 1996 - Validation and testing
- 1998 - Routine quarterly production

BCPNN validation

Retrospective predictive value test

	Signal	Non-signal	Total
+ Associations	42	53	95
- Associations	2	11	13

Signal: Not listed in Martindale (MD) '93 but listed in MD- or PDR '00

Non-signal: Listed in MD '93 or not listed in MD-or PDR '00

WHO database

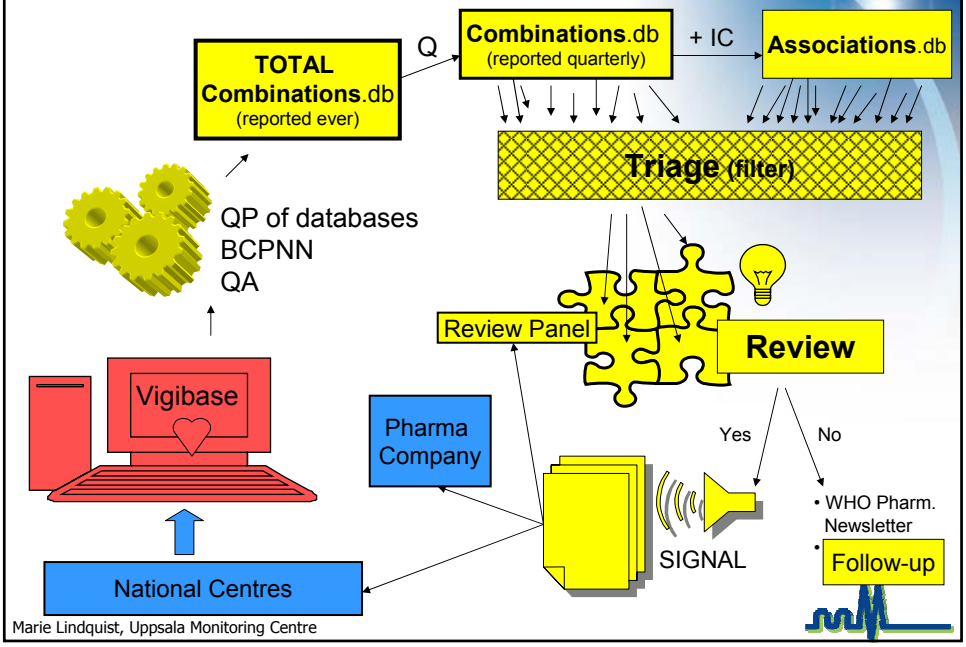
- Strengths
  - Database size (>5 million cases, 200+ fields)
  - Number of new reports (about 60,000 quarterly)
  - International coverage since 1968
    - Reporting of all marketed drugs from 100 countries
- Weaknesses
  - Missing data
  - Under-reporting
  - No denominator
  - 'Noise'
  - Duplication of reports
  - Delayed reporting

WHO database

- BUT few alternatives to spontaneous reporting for the detection of:
  - Rare unpredictable ADRs
  - Interactions
  - High risk patient groups

  (Although not yet especially effective for the latter…
- Other large data sets have similar strengths and weaknesses

UMC Signal Detection Process



Triage

Different selection criteria is used to filter out combinations of **greatest interest**

(predefined algorithms)

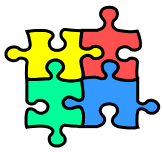
- Triage on **associations** (positive IC):
  - "Serious New"
  - "Delta IC more than 2"
- Triage on special **terms of interest** (independent of IC):
  - Agranulocytosis
  - Stevens Johnson syndrome
  - Rhabdomyolysis

Triage = from the french word trier, *to sort*

"The screening and classification of casualties to make optimal use of treatment resources and to maximize the survival and welfare of patients"

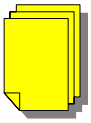
Literature Reference Check

- Always check the **drug reference literature** (Martindale, Physician Desk Reference) and at least one European **Summary Product Characteristics (SPC)** (Swedish, UK or EPAR).
- Should this combination be sent for review? Final assessment by UMC medical director
  - Is the association known?
  - How many cases?
  - IC value increased?
  - Fatal?
- "Potential signals"



Review Panel

- 35 expert reviewers in 21 countries
- Evaluation divided by System Organ Classes, ATC groups and special interest
- Evaluation
  - Clinical assessment
  - Pharmacological assessment
  - Case evaluation
  - Experience, scientific literature
- Summary of findings presented in SIGNAL



The SIGNAL Document

Definition of a signal:

"Reported information on a **possible causal relationship** between an adverse event and a drug, the relationship being unknown or incompletely documented previously."

- Document is produced ~3-4 times/year
- Sent to National Centres
- Individualized section available to MAH
- All recipients are encouraged to comment on topics presented in SIGNAL

Follow-Up

- ✓ ”Not a signal yet”
  - → Follow-up
  - → WHO Pharmaceuticals Newsletter
- ✓ Table contains drug-ADRs of current interest selected for follow-up

  (includes ”Not a signal yet”, External and Programme Requests)
- ✓ Possible to signal following new information
- ✓ Finals (after two years) are checked internally

Training, education and support

Education and technical support

- Training
  - Training course in Uppsala
  - Internet based training
  - Regional and local training activities
- Technical support
  - web-based reporting tool (VigiFlow)
  - web-based search tool (VigiSearch)
  - terminologies

Tools

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Terminologies & classifications produced by UMC

- Medical terminology
  - WHO Adverse Reaction Terminology (WHO-ART)
- Drug classification
  - WHO Drug Dictionary (WHO-DD)
  - Herbals Drug Dictionary (HDD)
  - Herbals ATC (HATC)

Terminologies & classifications – collaboration with WHO

- Medical terminologies
  - ICD Classification *)
  - Links with WHO Family of International Classifications
- Drug classification & nomenclature
  - Anatomical-Therapeutic-Chemical Classification (ATC **)
  - International Nonproprietary Names (INN**)

*) included in the WHO ADR database (to code indication for drug use
**) included in the WHO Drug Dictionary

Terminologies & classifications – collaboration with other organisations

- Medical terminologies
  - Bridge WHO-ART - MedDRA; with MSSO/MedDRA Management Board/IFPMA
- Medicinal product classification
  - WHO Drug Dictionary adheres to concepts defined by European Standard CEN ENV 12610 Medicinal Product Identification
  - Working with ISO on development of standards for medicinal product information
    - Links with ICH M5 (Data elements and standards for Drug Dictionaries)

Search and analysis tools

- VigiSearch
  - Web based search and statistics
  - Browsers for medical terminologies and drug classification
- Data mining
  - Regular screenings of VigiBase
  - Pattern recognition capability
  - Duplication detection

Research

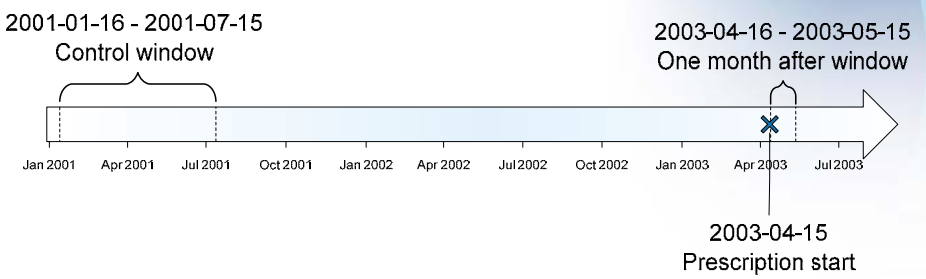
Research

- Development of data mining methods to analyse VigiBase data
  - New interactions
  - New syndromes
  - Clusters of adverse reactions – risk groups
  - Identification of duplicate reports
- New methods to analyse other data sets
  - Patient records/longitudinal health care databases
  - Cohort event data
    - Collaboration with WHO public health programmes (malaria/HIV/tuberculosis)
- In depth analyses of safety problems
  - Clinical analysis + novel methods/tools

Analysis of patient records

- UMC works together with THIN, UK
  - THIN has the data
    - Currently ~2 million UK patient records
  - UMC develops the analysis tool
    - Built on Bayesian data mining methodology

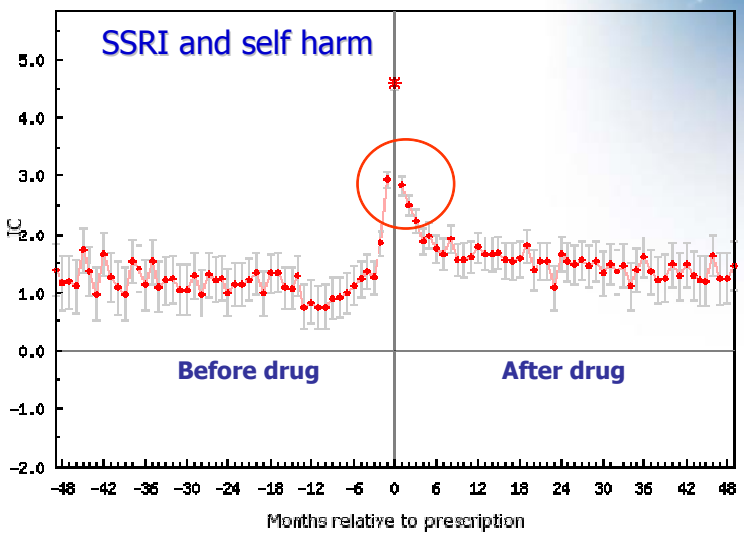
Events before and after prescription can be compared



Issues in choice of control window:

- seasonal variation
- pregnancy

Analysing signals identified by traditional signal detection methods



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Harmonisation and standards

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Harmonisation and standards

- Definitions in pharmacovigilance
  - Adverse reaction
  - Adverse event
  - Side effect
  - Signal
  - Serious reaction
  - Causality
- Terminologies and classifications
- Guidelines

Guidelines & publications

Standards development

- UMC represents WHO in ICH
  - M5 (Data elements and standards for Drug Dictionaries)
  - E2B (Data elements for transmission of Individual Case Safety Reports)
- Both the above now accepted as new work items for ISO (International Standards Organization)
  - The result will be globally accepted standards
- UMC has offered to become the international maintenance organisation for two of the ISO deliverables:
  - controlled vocabularies for ingredients and pharmaceutical products identifiers

UMC safety information and communication

UMC safety information and communication

- VigiBase data
  - available on-line (VigiSearch)
  - searches by UMC staff
  - quarterly output documents
- Signal document
  - distributed to all national PV centres
- VigiMed e-mail discussion group
  - open to all national PV centres

UMC safety information and communication

- Scientific publications
  - Contributions to WHO Pharmaceuticals Newsletter
  - VigiBase data included in Reactions Weekly
  - Ad hoc publications in scientific journals
- Uppsala Reports
  - newsletter sent to a wider audience (~3000)
- Internet web site

Priorities for the coming years

- Support WHO in safety activities
  - incl. malaria, TB, HIV/AIDS public health programmes
  - extending the PV tool kit and outreach to countries/regions
- Increase quality and quantity of ICSRs
  - Frequently submitted reports from all EU countries and US
  - Reports from large emerging countries (China, India, Brazil)
  - UMC's web based reporting tool (VigiFlow) available to all NCs
- Patient safety instead of drug safety
  - Addressing medication error, substandard/counterfeit drugs
- Signal detection and analysis using new data sets
  - Healthcare records, insurance data, Cohort Event Monitoring

ICSR= Individual Case Safety Report

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Global Surveillance of Antiretroviral Drug Safety

Washington June 11, 2010

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Uppsala Monitoring Centre

WHO Collaborating Centre for International Drug Monitoring

Pharmacovigilance – What's changed

- Globalisation
  - Also in pharmacovigilance
    - e.g. counterfeiting no longer a problem only for developing countries
- Multiple players showing interest in PV
  - More stakeholder involvement
    - Patients demand a stronger role
  - Links to other professional groups/areas
  - Emerging countries

→ Fragmentation

What is needed

- Sustainable pharmacovigilance systems
- Monitoring of all products
  - But use different tools
- Life cycle management
- Collaboration between all stakeholders
  - Learning from each other
  - Identifying and filling the gaps
  - Avoid overlaps and re-inventing the wheel!

UMC provisions to WHO Programme

- Access to an international network
- Early information about potential safety signals
- Access to the WHO Global Individual Case Safety Report database - VigiBase
- Terminologies and software
- Support, resources, training
- Publications, guidelines
- Research – new and better methods for safety and benefit – risk assessment

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What we can offer

- A global database for adverse event reports
  - Standardised, structured information
  - Allows for comparable information across countries/regions
  - Analytical tools and routing screening using data mining methods
- Reporting/management tool
  - Used by >30 countries in resource limited settings
- Data mining methods for analysing patient records
- A tool for cohort event monitoring (CEM) data collection and analysis

CemFlow main features

- Collection of CEM data
  - on central level as well as primary reporter level
  - supports paper based data collection
- Analysis of CEM data
  - structured data entry with controlled vocabularies allows for comparable information across countries/regions
- Supports export/import of data from other systems/cohorts
- Language independent software interface
- Supports non-latin character sets
- Can incorporate/link to treatment/management support systems

Cohort Event Monitoring and CemFlow

Magnus Wallberg
& Marie Lindquist
Uppsala Monitoring Centre

Presentation outline

- Where does Cohort Event Monitoring fit
  - Walk through other pharmacovigilance methods
    - Adverse reaction reporting schemes
    - Analysis of longitudinal data (patient records)
    - Comparison, including CEM
  - Cohort Event Monitoring
  - CemFlow

Pharmacovigilance methods

Adverse reaction reporting schemes

- The most common way of performing pharmacovigilance today
  - often referred to as 'spontaneous reporting'
- Reports (ICSRs) are "spontaneously" arriving from different sources like physicians or companies
- Describes a possible Adverse Drug Reaction (ADR) suspected to be caused by a drug
- Report data stored in local databases but also collected in the global WHO database - VigiBase

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Analysis of patient records

- Extending pharmacovigilance 'tool kit' to analysis of longitudinal health care data
- Data mining methods and prototype analysis tools already available in the UMC research and signal departments
- Based on patient record data
  - Method developed to work on different datasets (but with similar content)
  - Can be adapted for more generalized datasets

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Cohort Event Monitoring

- The main differences from adverse reaction reporting schemes:
  - Selected medicine or group of medicines is monitored
    - (not any medicine)
  - The data is collected in a systematic way
    - (not 'spontaneously')
  - All events are recorded
    - (not necessarily ADRs)
  - Data for all patients in the cohort is collected
    - (not only patients that experience an event/ADR)

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Different focus (simplified)

- Adverse reaction reporting schemes
  - Focus on ADRs
  - Tools developed by UMC for use on WHO database, VigiBase
    - VigiSearch/VigiMine (retrieval/analysis)
    - VigiFlow (reporting/data management for national PV centres)
- Patient records
  - Focus on patients
  - Tools under development by UMC for use on various existing databases, e.g. IMS, THIN
- Cohort Event Monitoring
  - Focus on drugs
  - Tool developed by UMC
    - CemFlow

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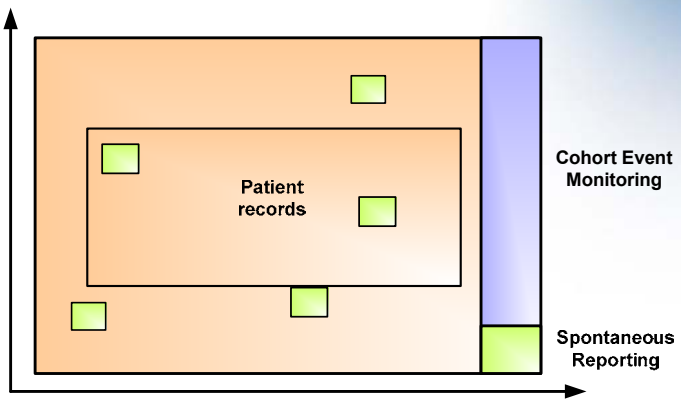
Different perspectives



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Overall objective

- Achieve maximum benefit, least harm, for patients

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How?

- **Monitor** a specific medicine, substance or group of medicines by
  - Collecting:
    - All data
      - **Events**, patient details, concomitant medications, outcomes…
    - For "all" patients
      - In the **Cohort**
  - Analyze
    - To get risk profiles and other statistical data
  - Produce recommendations

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What is Cohort Event Monitoring - CEM

- In Cohort Event Monitoring (CEM) a group (cohort) of patients are monitored while treated with a specific medicine (or group of medicines).
- **All events** in a control period **before** and **during** treatment shall be recorded.

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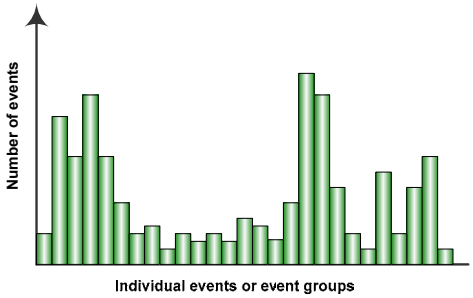
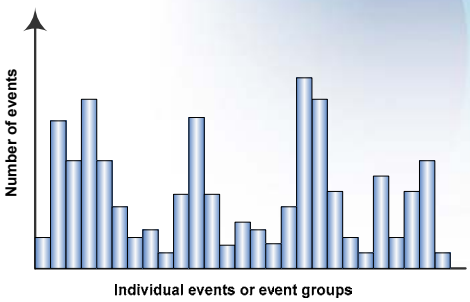
Why collect events before and after



Events in the control period (before treatment)



Events after treatment

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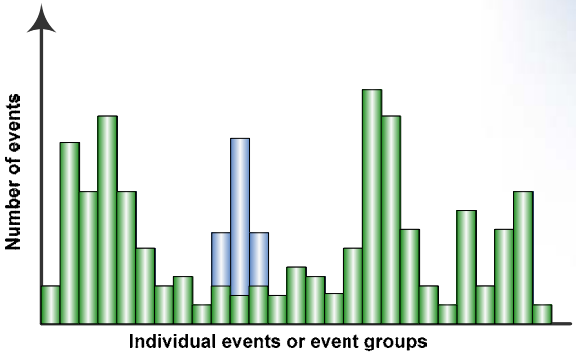
Why collect events before and after



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Objectives

- Characterise known reactions
- Measure risk
- Detect signals of unrecognised reactions
- Detect interactions
- Identify risk factors like age, gender, dose…
- Assess safety in pregnancy & lactation
- Detect inefficacy
- Provide a scientific base for prescription and patien management support systems

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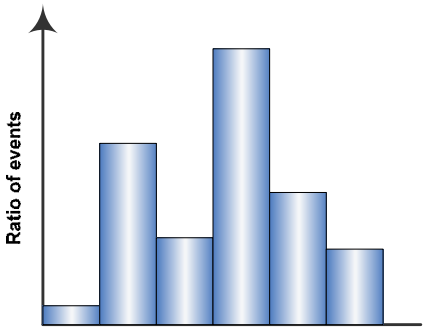
Stratification possibilities



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Selection of cohort

- The cohort should be picked without biases among "all" patients being treated.
  - For example, all patients visiting the clinic on Tuesdays and Wednesdays that have been prescribed the monitored drug
- All patients, falling into the rules of the cohort setup, must be enrolled *(to avoid biases)*
- Continue the enrolment until the predefined size of the Cohort is reached

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What to record

- All new **Events** even if common & minor
- Change in a pre-existing condition
- Abnormal changes in laboratory tests
- Accidents
- All deaths with date & cause
- Concomitant medications
- Concomitant diseases
- Lost to follow up!!

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Events = reactions + incidents

- **Reactions**
  - definite
  - probable
  - possible
- **Incidents (background noise)**
  - unlikely
  - Unclassified (conditional)

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A tool for CEM – CemFlow

CemFlow features

- CemFlow is a tool for:
  - Collection of CEM data
    - on central level as well as primary reporter level
    - supports paper based data collection
    - supports export/import of data from other systems/cohorts
  - Analysis of CEM data
    - structured data entry with controlled vocabularies allows for comparable information across countries/regions
  - Management of:
    - users
    - reporters
    - reporter organizations
    - CEM programs
    - CEM event dictionary

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CenFlow features cont.

- Supports export/import of data from other systems/cohorts
- Language independent software interface
- Supports non-latin character sets
- Can incorporate/link to treatment/management support systems

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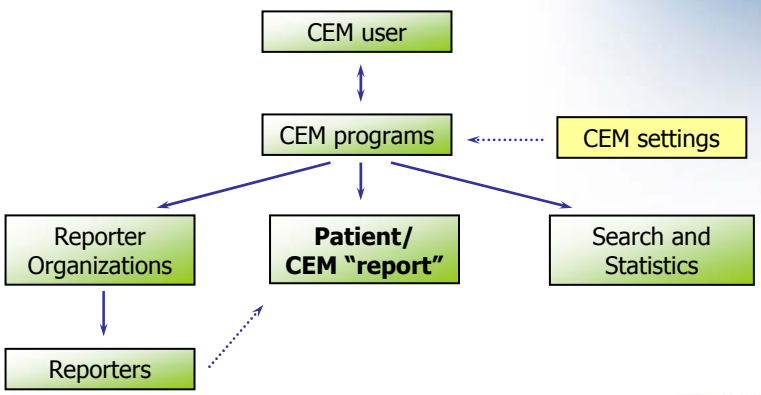
CemFlow 1.0 structure



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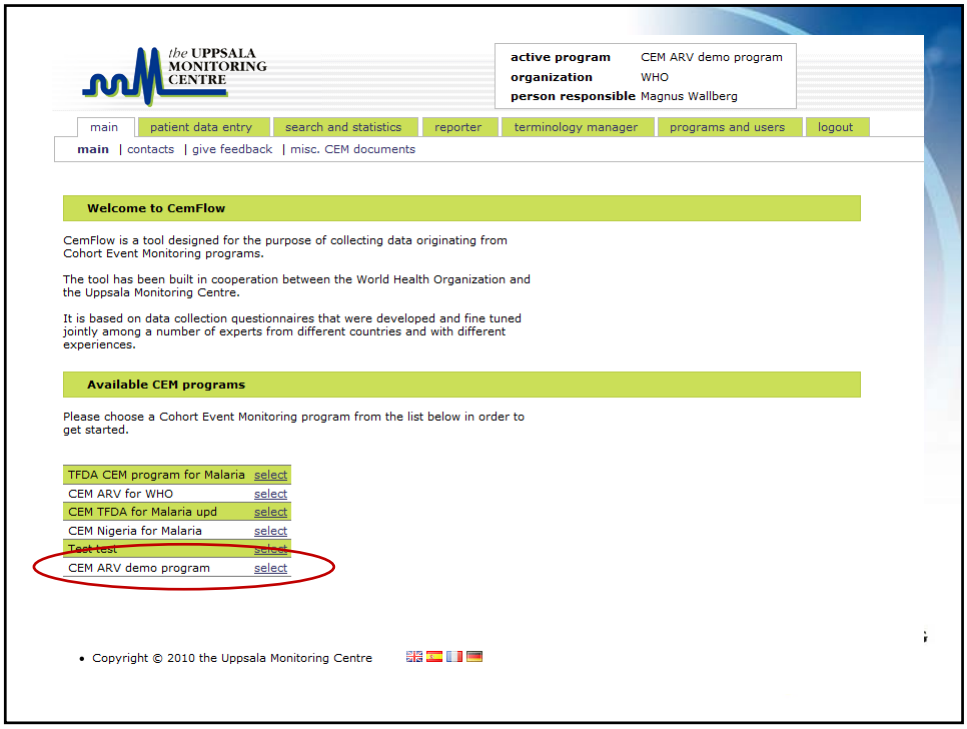

CEM program

- A CEM program is the main "entity" of the CemFlow tool.
  - CemFlow supports many CEM programs in parallel
  - All "reports" and reporters belong to a specific program
  - Search and Statistics are made on reports for a specific program
    - However, reports from other programs may be used as comparator/baseline data

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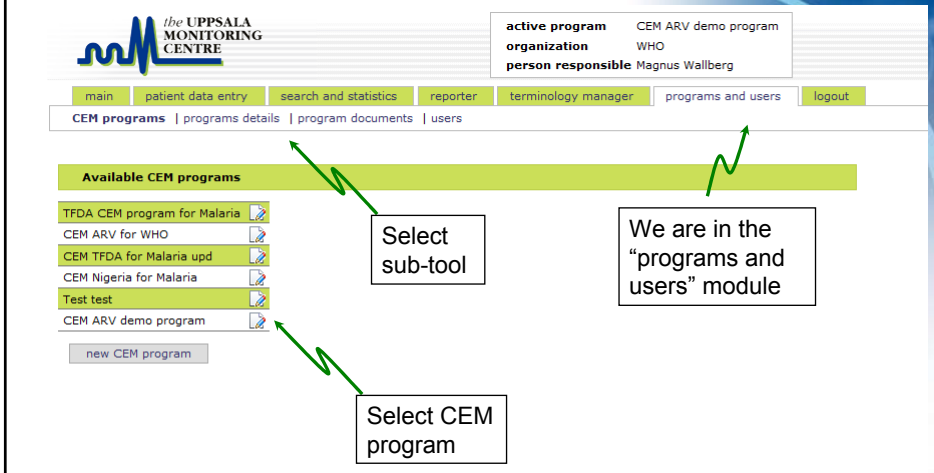
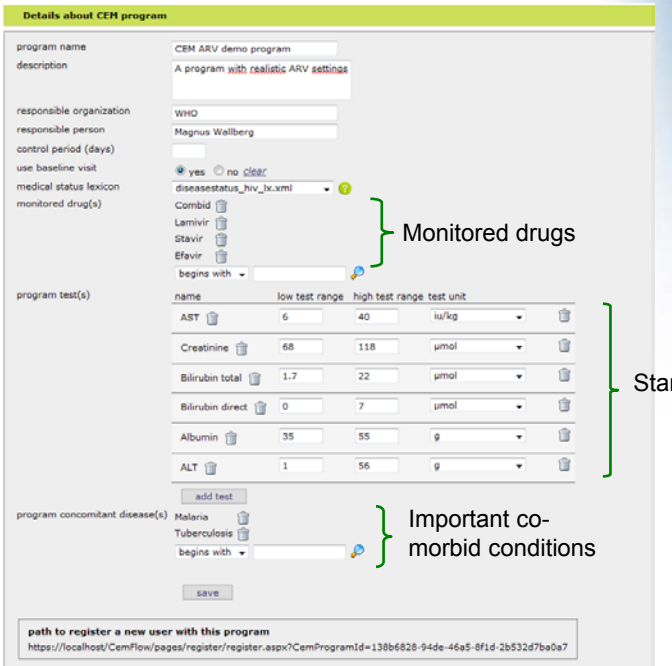
CEM program settings

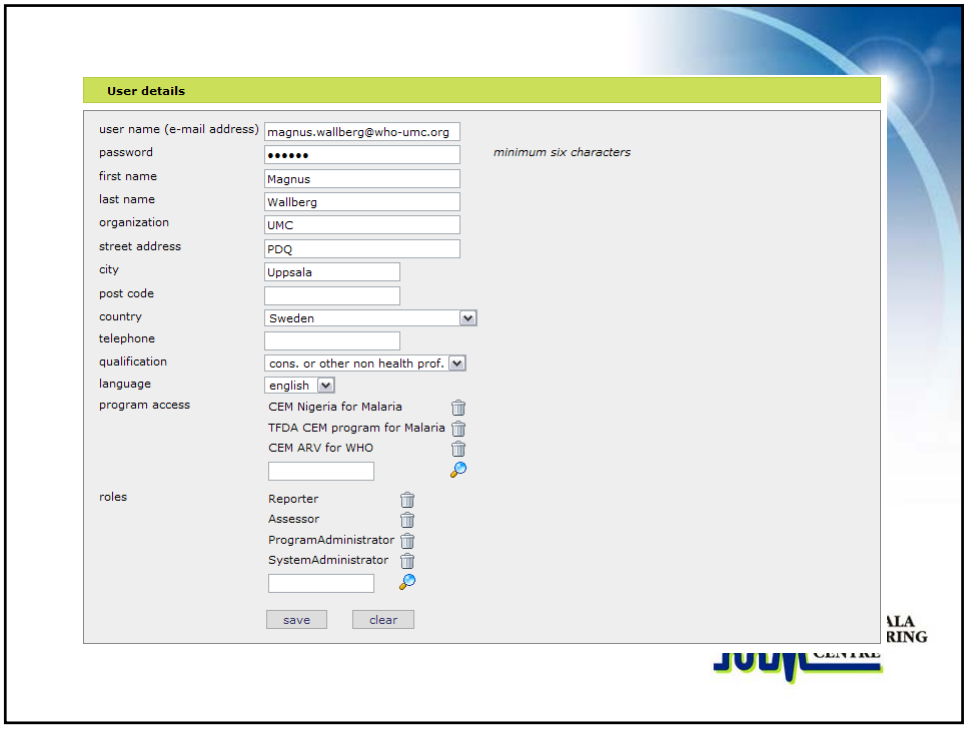
- A CEM program has:
  - *Organization ("owner" and contact person)*
  - Description
  - *Documents (like SOPs, Questionnaires and manuals)*
  - Settings
    - Program drug(s)
    - Definition of control period
    - Predefined laboratory tests
    - Set up of visits
      - use of base line visit
      - multiple follow ups
    - …

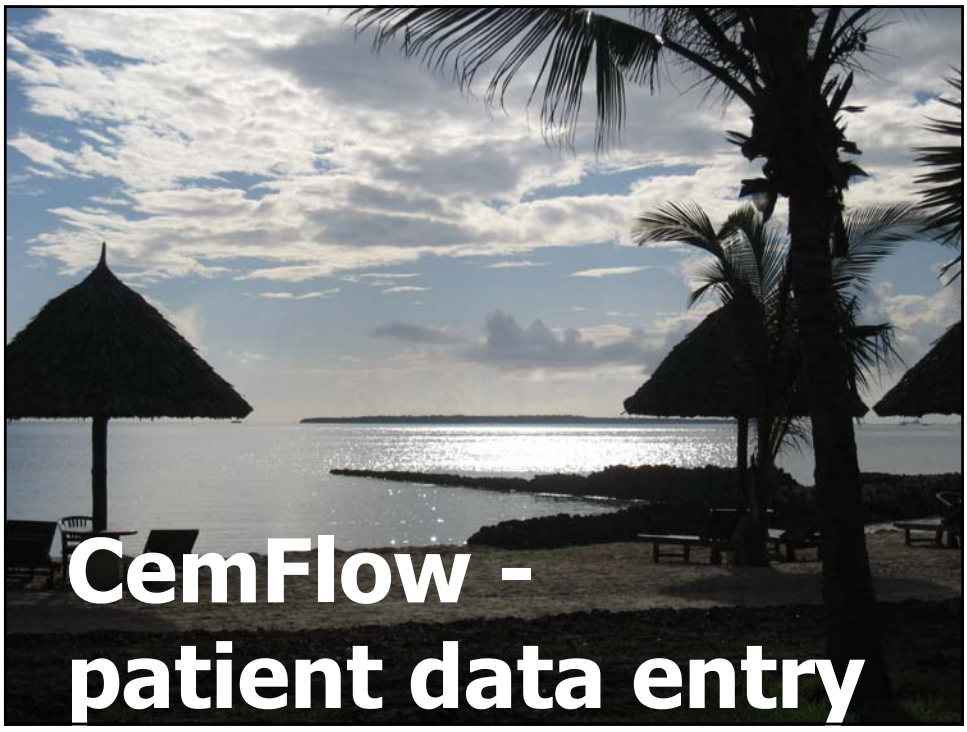




User

- The "users" of the CemFlow system register themselves and are assigned the access to a CEM program by an administrator.
- The users can be:
  - Assessors at the head organization
  - Data entry staff
  - Reporters at regional sites
- A user can have access to any number of CEM programs





CemFlow - patient data entry

CEM "report" - patient

- A CEM "report" is the CemFlow equivalent to the CEM questionnaires but it can also be seen as the "patient"
  - All questionnaires collected in **one** CEM report
    - *Baseline*, Pre, Post, Pregnancy and Pregnancy outcome questionnaires
    - The equivalent to an individual questionnaire is entered as a "visit" with the events as the most important information items *(except for baseline visits)*
- CEM reports are managed through the Patient Data Entry module of CemFlow

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List of patients/CEM reports

- To be able to access old patients/reports a patient list with a filter is the first view in the patient data entry area
- There are several reasons to open "old patients"
  - Adding additional information (about for example a follow up visit)
  - Doing an assessment
  - Viewing a specific report
  - …

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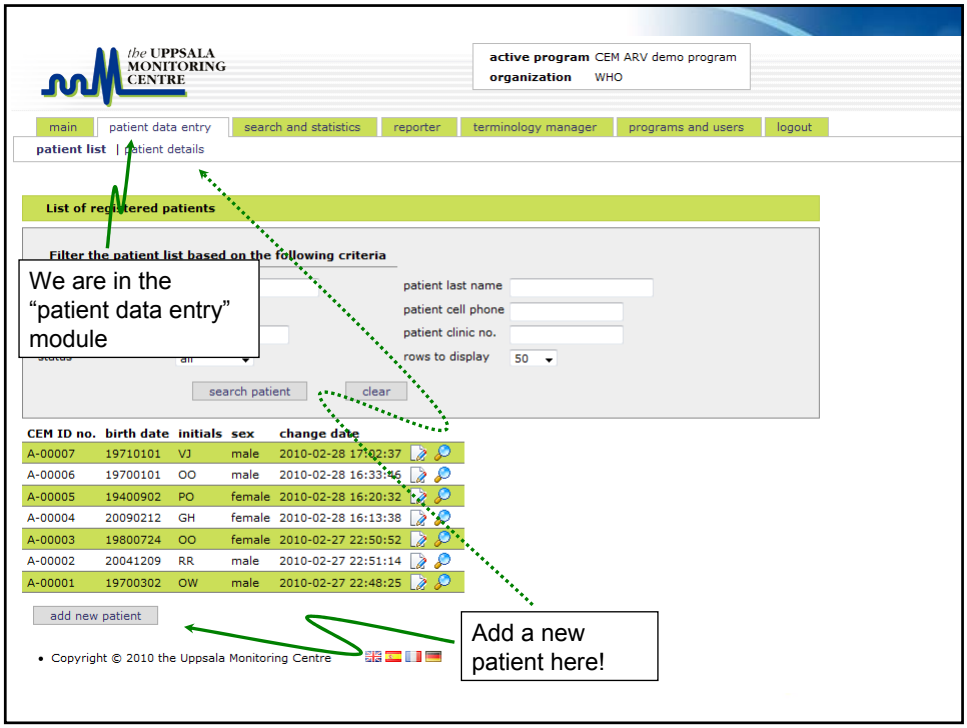
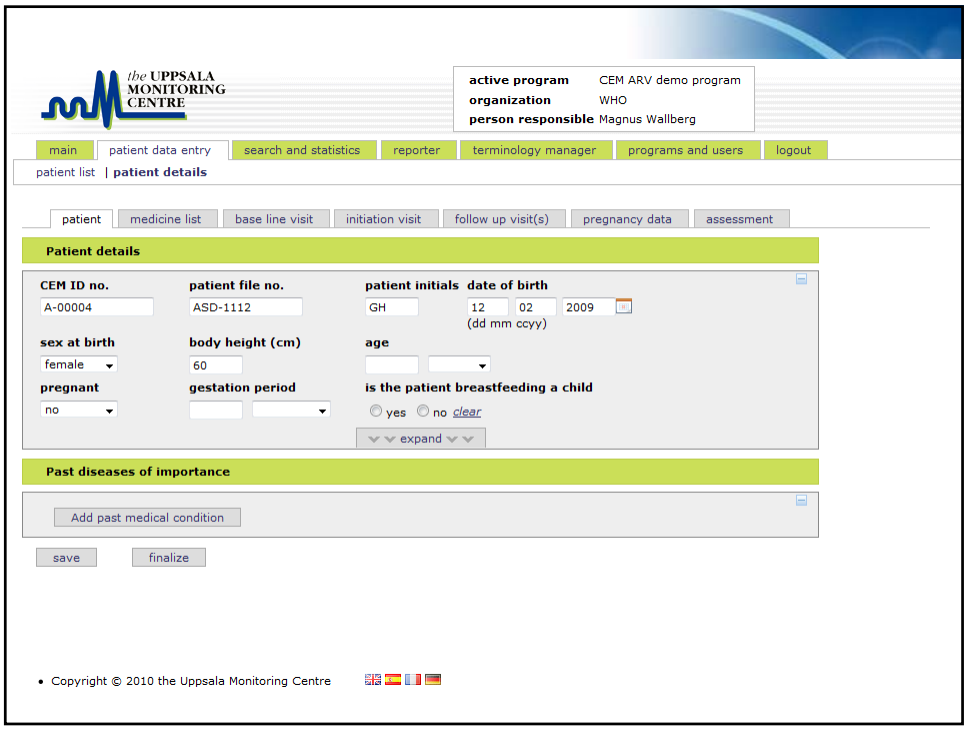

the UPPSALA MONITORING CENTRE
active program CEM ARV demo program
organization WHO
main
patient data entry
search and statistics
reporter
terminology manager
programs and users
logout
patient list | patient details
List of registered patients
Filter the patient list based on the following criteria
patient last name
patient cell phone
patient clinic no.
rows to display
50
search patient
clear
CEM ID no. birth date initials sex change date
A-00007 19710101 VJ male 2010-02-28 17:02:37
A-00006 19700101 OO male 2010-02-28 16:33:46
A-00005 19400902 PO female 2010-02-28 16:20:32
A-00004 20090212 GH female 2010-02-28 16:13:38
A-00003 19800724 OO female 2010-02-27 22:50:52
A-00002 20041209 RR male 2010-02-27 22:51:14
A-00001 19700302 OW male 2010-02-27 22:48:25
add new patient
Copyright © 2010 the Uppsala Monitoring Centre
We are in the "patient data entry" module
Add a new patient here!


the UPPSALA MONITORING CENTRE
active program CEM ARV demo program
organization WHO
person responsible Magnus Wallberg
main
patient data entry
search and statistics
reporter
terminology manager
programs and users
logout
patient list | patient details
patient
medicine list
base line visit
initiation visit
follow up visit(s)
pregnancy data
assessment
Patient details
CEM ID no.
A-00004
patient file no.
ASD-1112
patient initials
GH
date of birth
12 02 2009
(dd mm ccyy)
sex at birth
female
body height (cm)
60
age
pregnant
no
gestation period
is the patient breastfeeding a child
yes no clear
expand
Past diseases of importance
Add past medical condition
save
finalize
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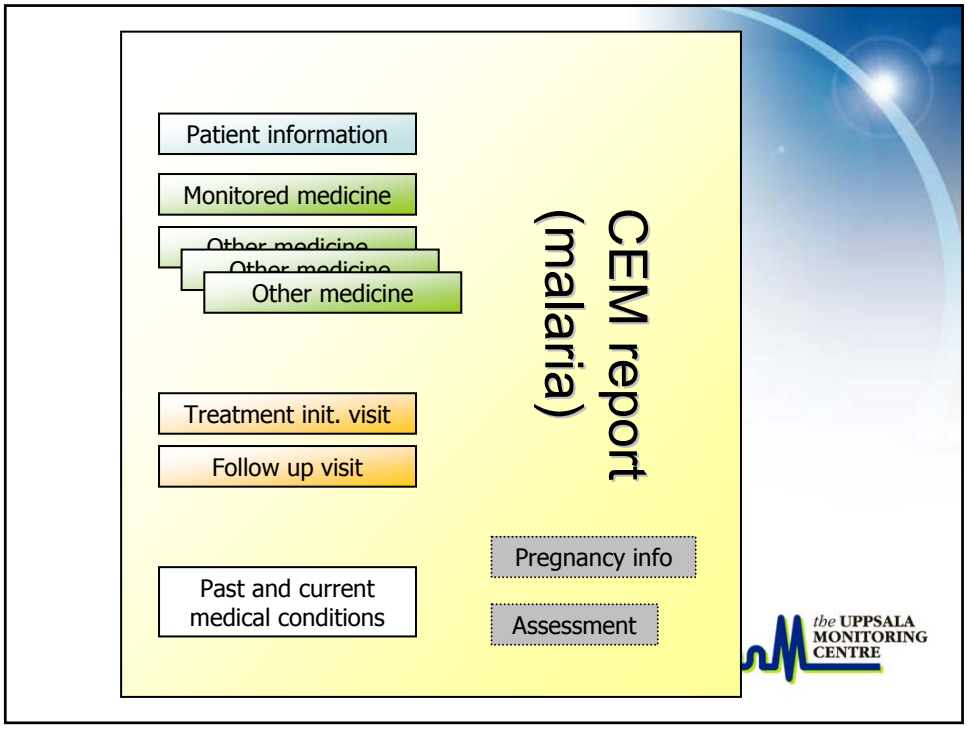
CEM report (malaria)
Patient information
Monitored medicine
Other medicine
Other medicine
Other medicine
Treatment init. visit
Follow up visit
Past and current medical conditions
Pregnancy info
Assessment
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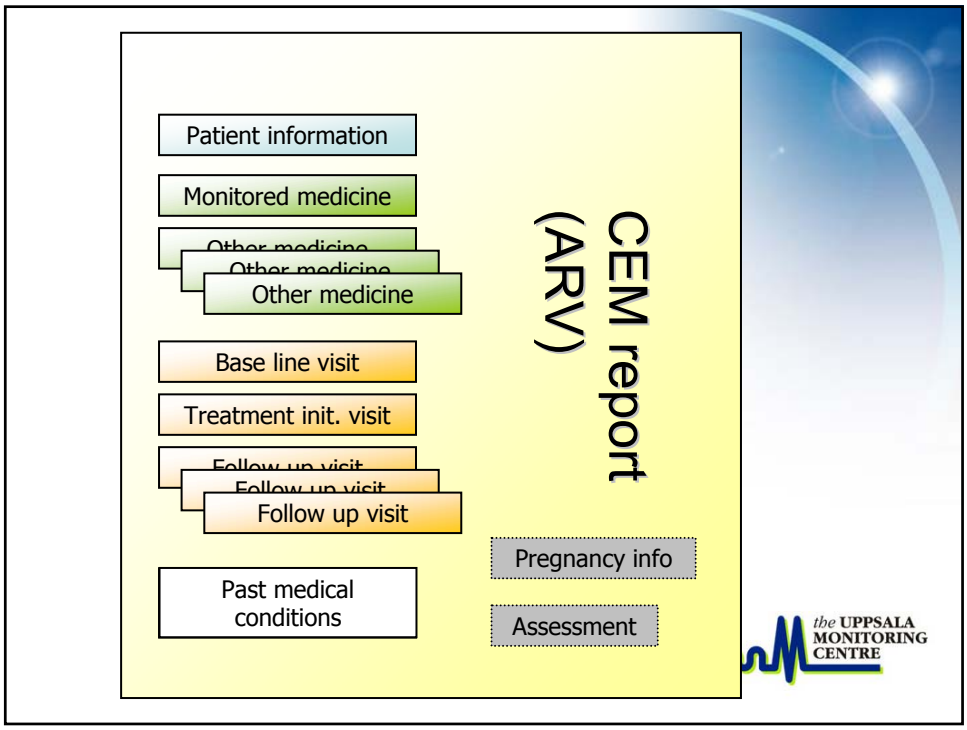
CEM report (ARV)
Patient information
Monitored medicine
Other medicine
Other medicine
Other medicine
Base line visit
Treatment init. visit
Follow up visit
Follow up visit
Follow up visit
Past medical conditions
Pregnancy info
Assessment
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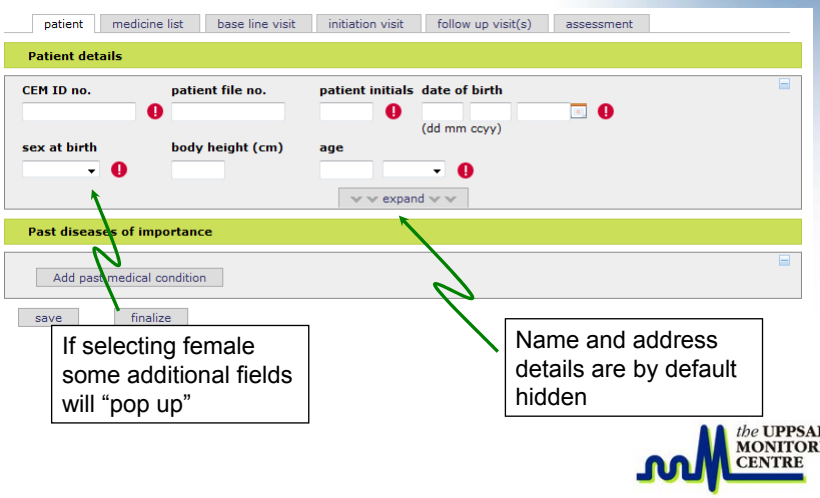
Patient details



If selecting female some additional fields will "pop up"

Name and address details are by default hidden

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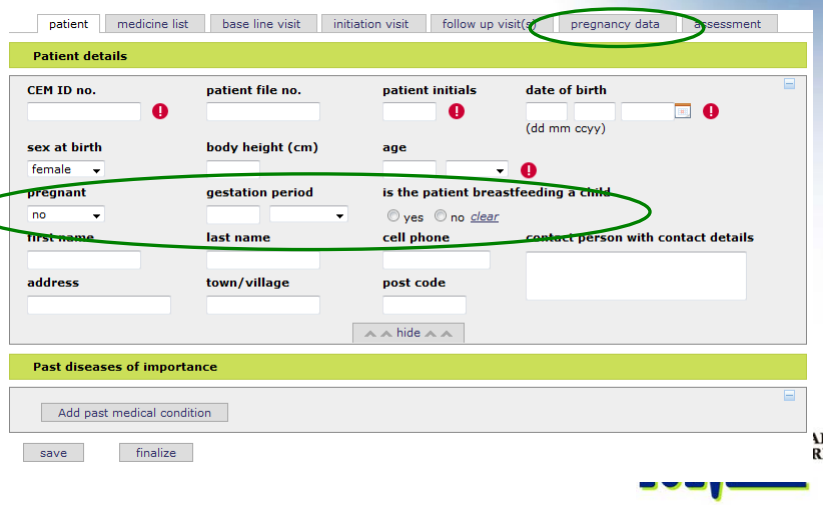
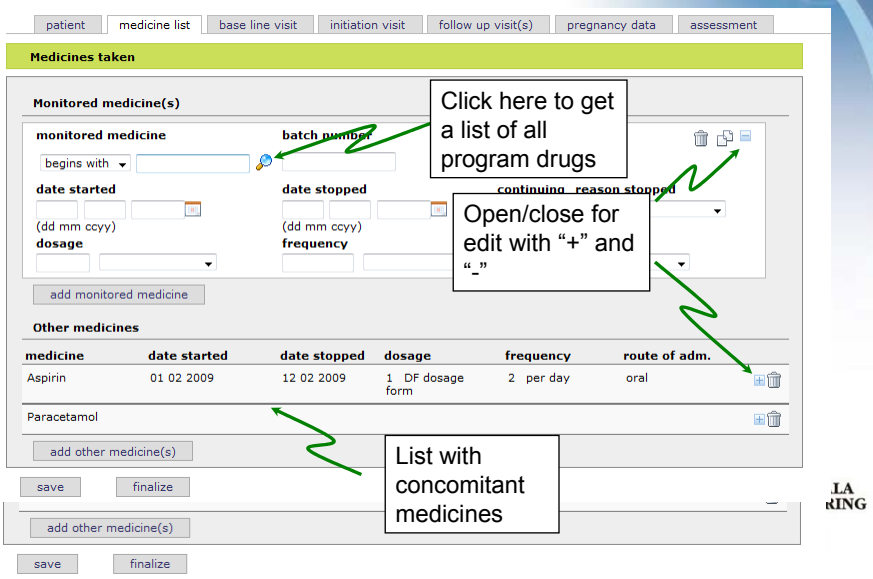
More information for females



Medicine list



Visits

- There are three types of visits
  - Base line visit – *only one*
    - Only used if "Use baseline visit" is ticked in the program administrator
  - Treatment initiation visit – *only one*
  - Follow up visit – more than one can be added
- The visits are ordered in separate tabs
  - Base line visit tab, treatment initiation visit tab and follow up visit(s) tab
- The most important is the follow up visit – shown on next slide

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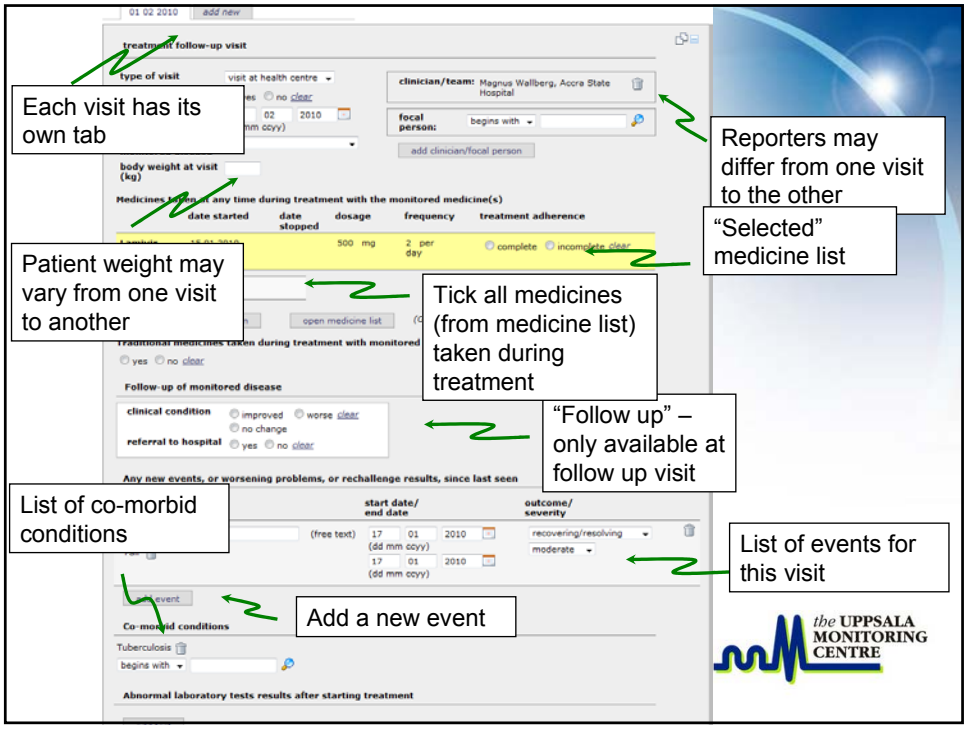
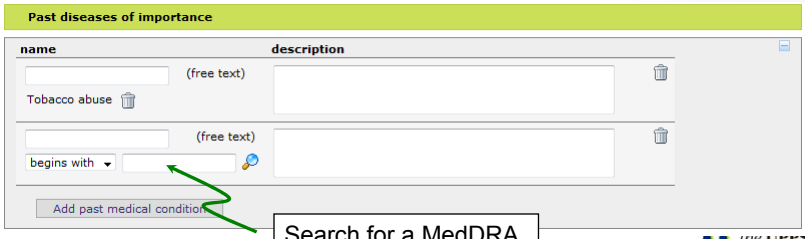
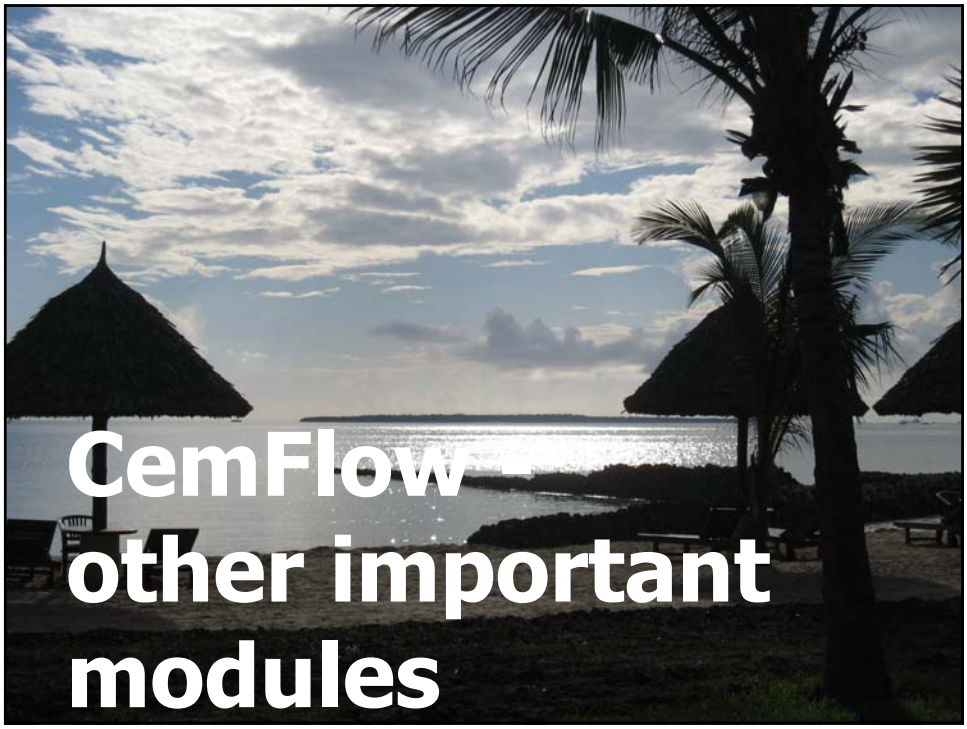


Past diseases of importance

- Significant past medical conditions
- Any number of conditions can be added
- Free text and coded values can be used





CemFlow – other important modules

Reporter

- A reporter is added to the system and referenced on the report via a reporter lookup tool
- A reporter should belong to a reporter organization/clinic
- A reporter can **not** log on to the CemFlow system – is **not** a CemFlow user

Shani Mwaluka – Mnazi Mmoja Health Centre, Dar es Salaam

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Reporter organization

- A reporter organization in CEM is for example a clinic/hospital where data for a CEM program is collected
- A reporter is connected to a reporter organization
- A reporter organization belongs to a CEM program

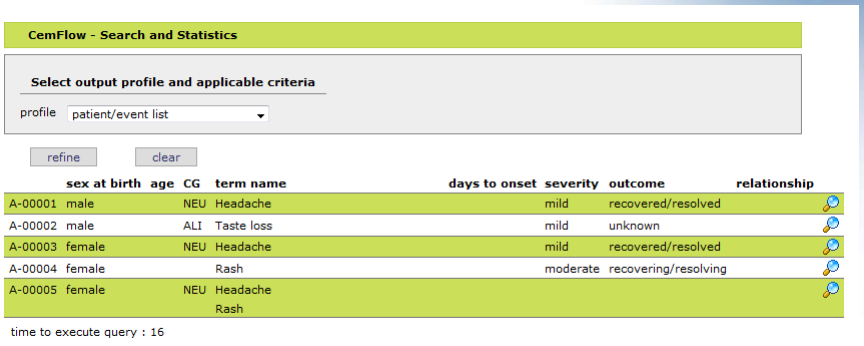
Search and Statistics

- The Search and Statistics tool provides standard analysis tools and export functionality
- Predefined profiles with different filters and stratifications are available
- Will need further research when more data is available

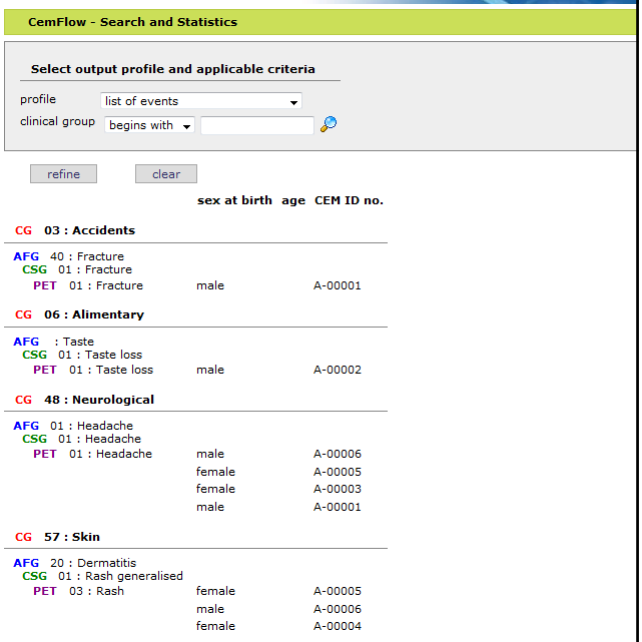
Profiles

- The different output types are available as profiles
  - Patient/event list
    - A simple patient list with all event listed
  - List of events
  - Stratification
    - An event list stratified by different strata
  - Summary by clinical category
  - … others to come

Patient/event list



List of events



Stratifications

- It is possible to stratify events based on
  - Sex
  - Age group
  - Monitored drug
  - Co-morbid condition
- In addition – statistics will be available based on
  - Concomitant medications
  - Lab values
  - …

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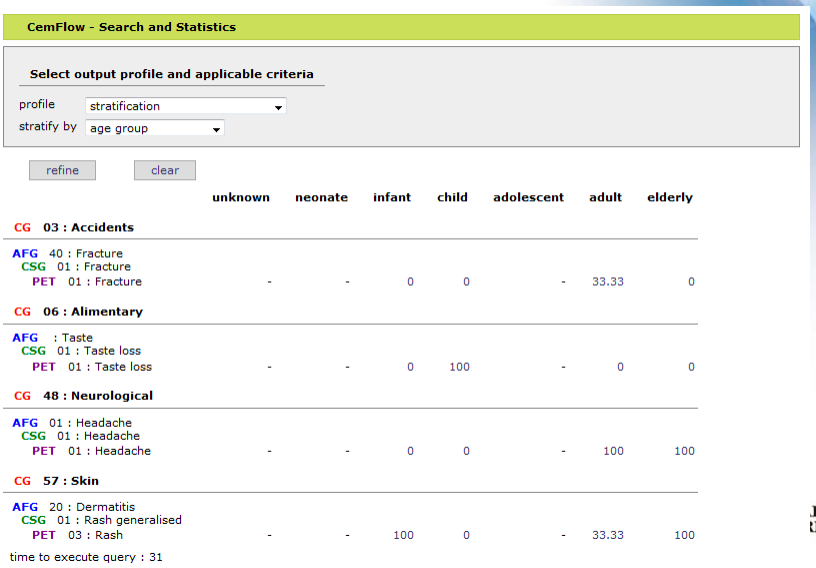
Stratification by age group



CemFlow - Search and Statistics

Select output profile and applicable criteria

profile: stratification

stratify by: age group

refine | clear

	unknown	neonate	infant	child	adolescent	adult	elderly
CG 03 : Accidents							
AFG 40 : Fracture / CSG 01 : Fracture / PET 01 : Fracture	-	-	0	0	-	33.33	0
CG 06 : Alimentary							
AFG : Taste / CSG 01 : Taste loss / PET 01 : Taste loss	-	-	0	100	-	0	0
CG 48 : Neurological							
AFG 01 : Headache / CSG 01 : Headache / PET 01 : Headache	-	-	0	0	-	100	100
CG 57 : Skin							
AFG 20 : Dermatitis / CSG 01 : Rash generalised / PET 03 : Rash	-	-	100	0	-	33.33	100

time to execute query : 31

Search and Statistics – cont

- Search results are currently presented as figures
- In the future statistics will also be:
  - Represented in graphs
  - Possible to export as Excel for local refinement

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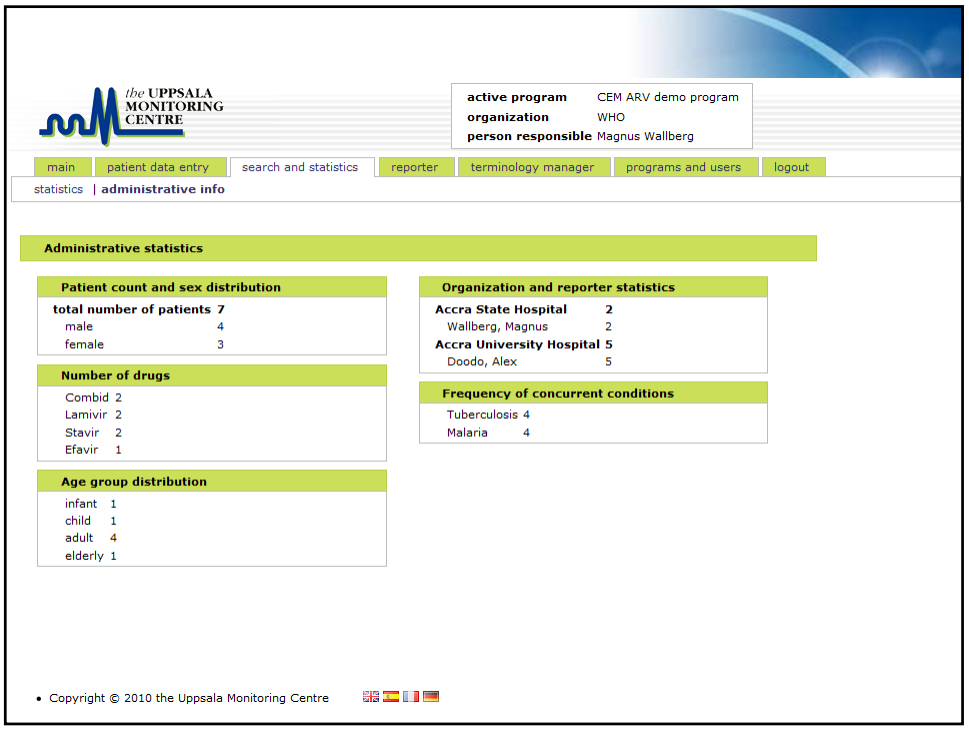
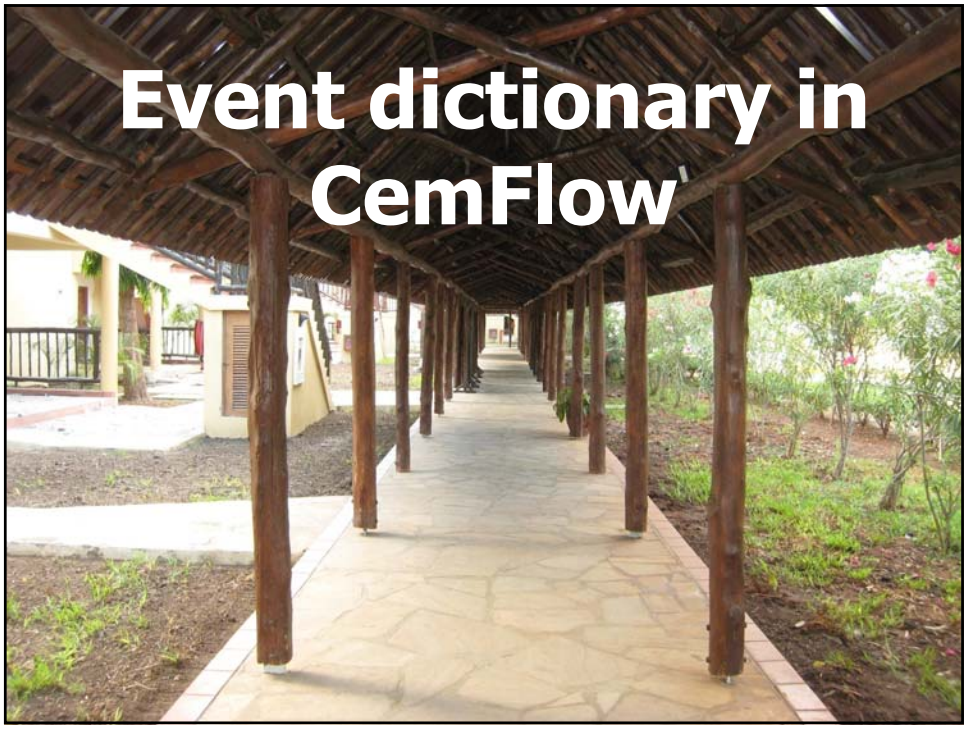
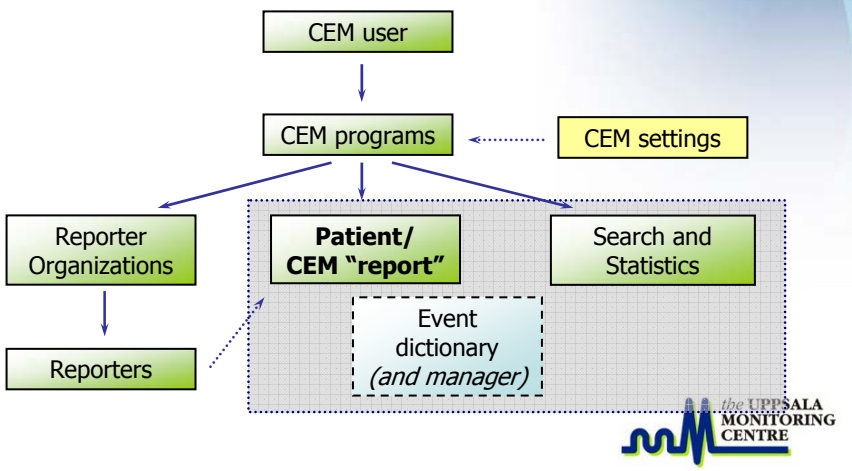
Administrative statistics

- A sub section of the Search and Statistics tool will provide administrative statistics like:
  - Reporting per clinic and reporter
  - Number of reports in the database
  - Number of reports per drug
  - General distribution of co-morbid diseases
  - …

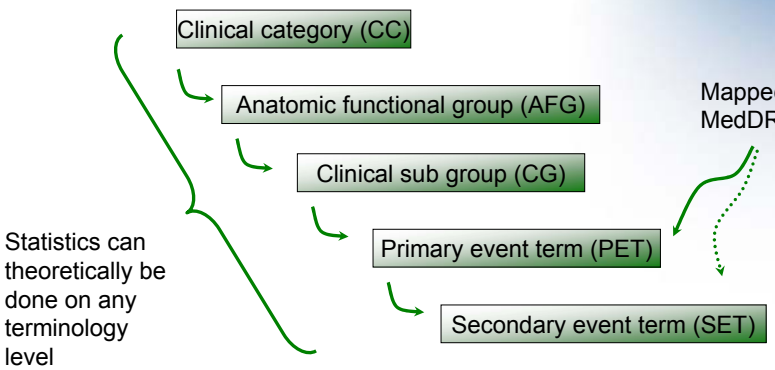




CemFlow structure – event dictionary



CEM event hierarchy



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Why not use MedDRA or WHO-ART 'as is'

- Another type of grouping adds value
  - Different levels
  - One term can belong in different Clinical Categories
    - And where it is placed is important
- Terms are ordered in a way that makes sense to clinicians
  - Can highlight problem "areas" in a simple way
- In the CemFlow event dictionary each individual term can have a definition attached to simplify the selection process
  - Definitions will be continuously added and modified

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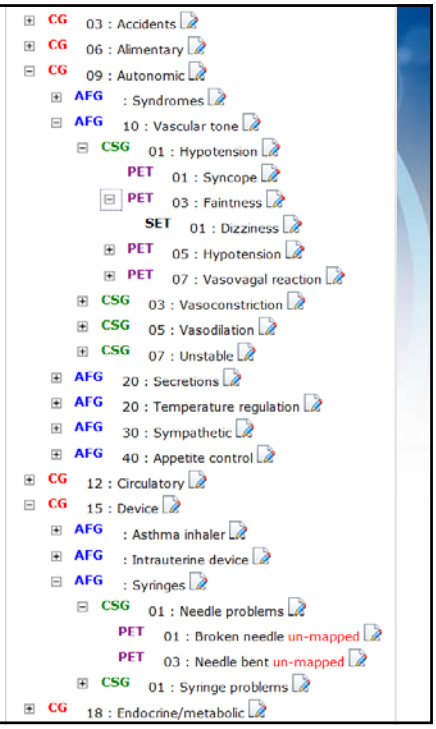
An example of the CEM event hierarchy in CemFlow



CEM event coding

- The event will be entered as free text by the reporter and connected to a term in the events dictionary by an assessor or reviewer
- Coding of the events is crucial for the statistical methods to work
- It is important that events are coded in "the same way" by all assessors/reviewers
  - term definitions will aid this

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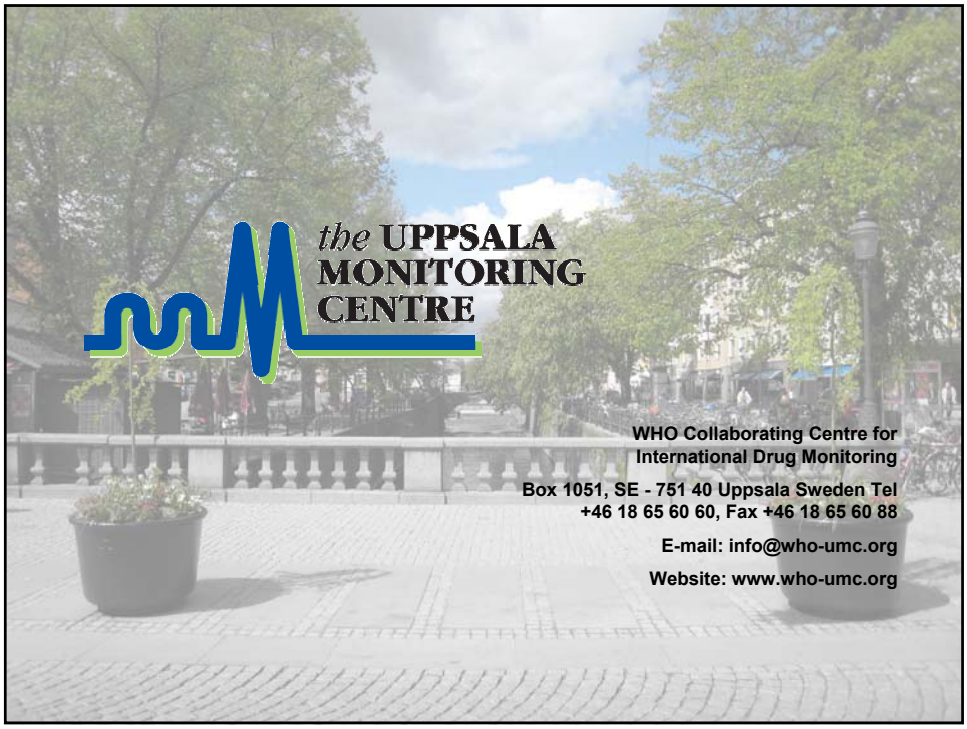
Event dictionary manager

- To allow for easy maintenance and flexibility of the CEM event dictionary a dictionary manager is available within CemFlow
  - Available for users with special access
  - Allows for:
    - Restructuring of available terms
    - Addition of new terms
    - Mapping of terms to MedDRA
    - Editing of definitions

Coding of "non event terms"

- To code other data items on the CEM report, apart from the event terms, MedDRA*) can be used for
  - Indications
  - Past medical conditions
  - Co-morbid conditions/concomitant diseases
  - Tests
- Often used terms can be added to a quick list through the program manager
  - like standard tests and important concomitant diseases

*) Subject to appropriate and valid licence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