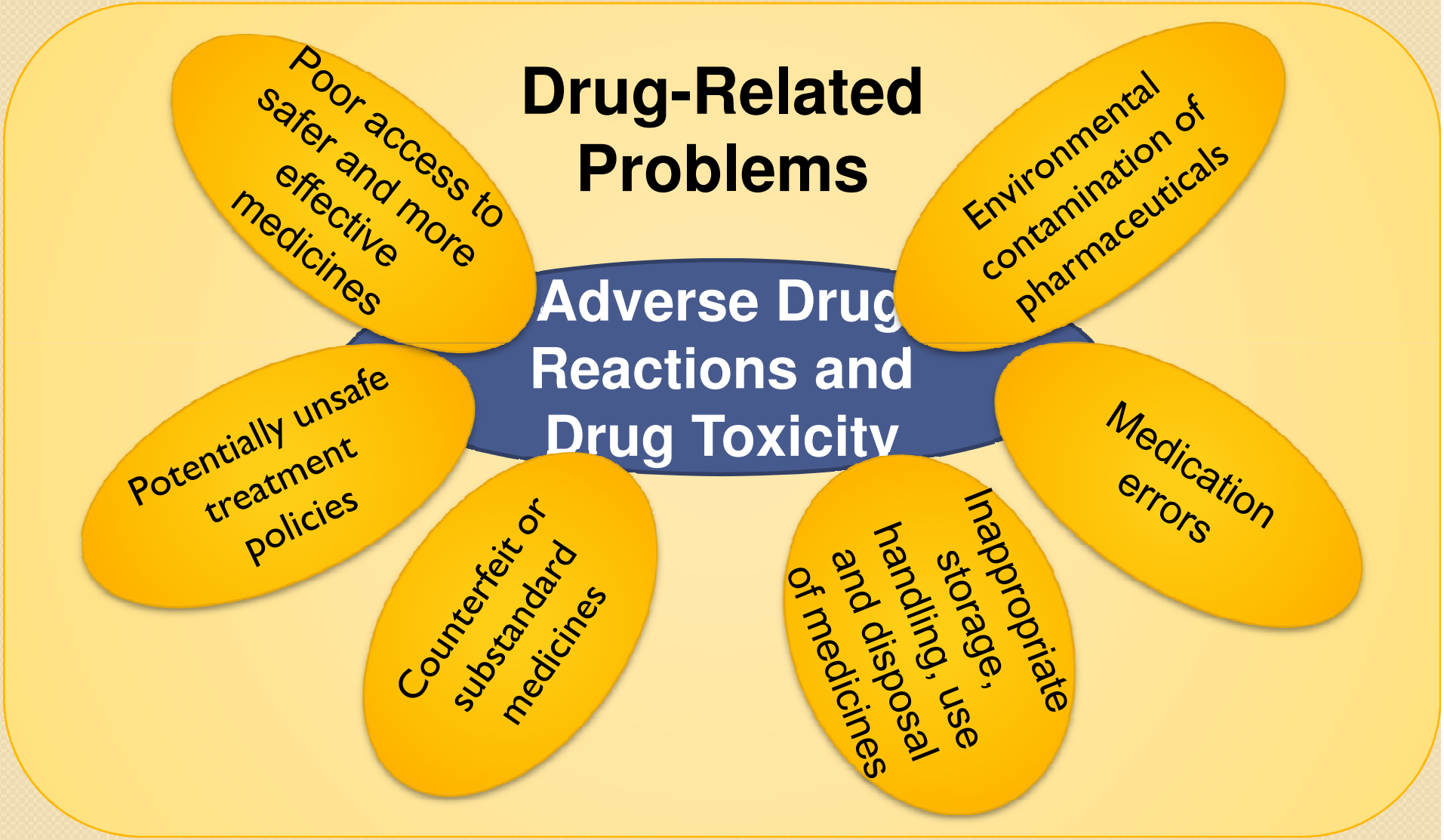
ARV Pharmacovigilance in S. Africa

- What is the scope of pharmacovigilance?
- Why ARV (HIV) Pharmacovigilance?
- What is the status of pharmacovigilance in SA?
- ARV pharmacovigilance projects currently underway in SA

Pharmacovigilance: The science and activities concerned with the detection, assessment, understanding and prevention of adverse reactions and other drug-related problems.



ARV Pharmacovigilance: What is worth knowing?

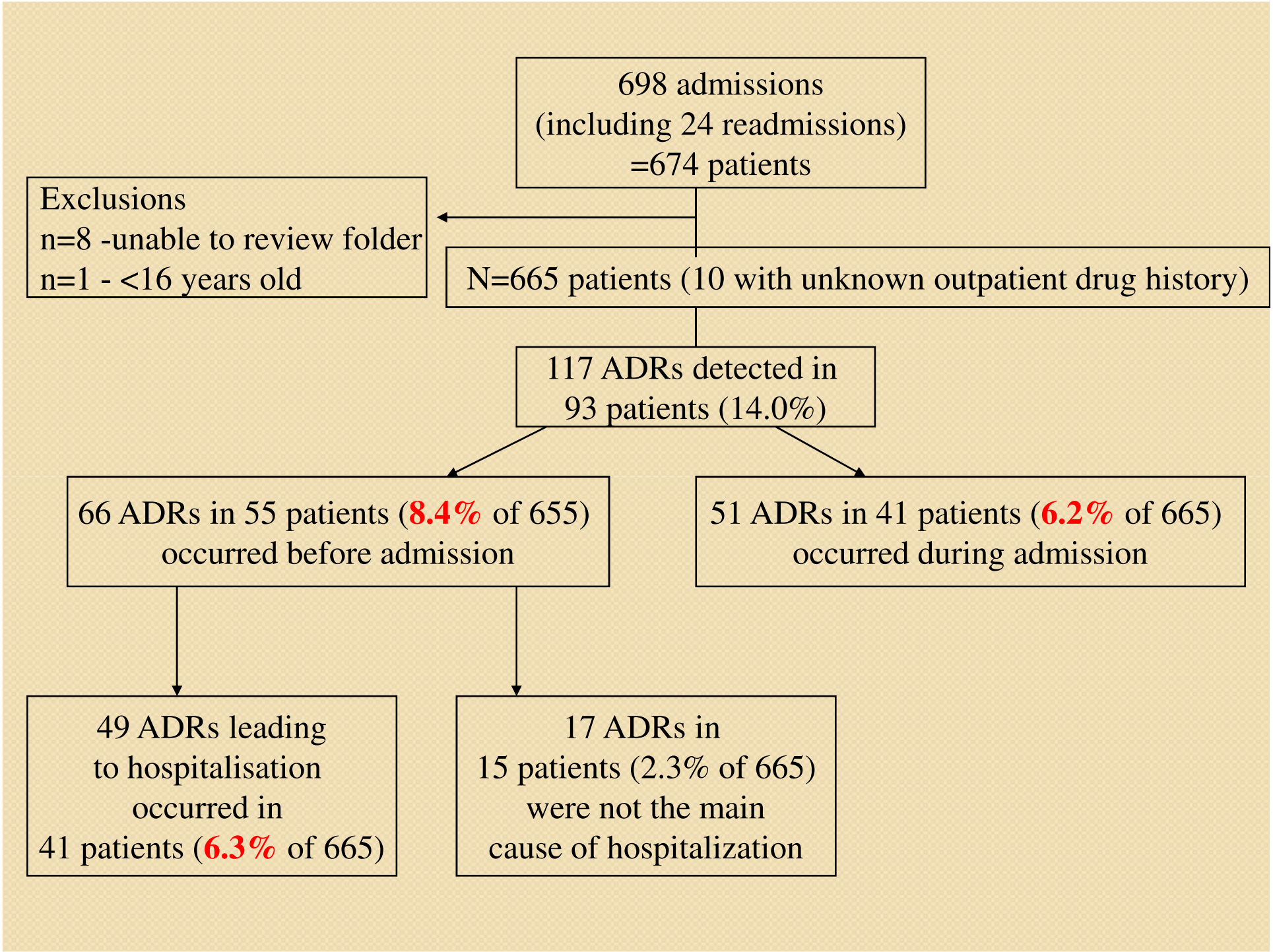
- What is the burden of toxicities on patients (tolerability, morbidity, mortality)?
- What is the burden (and cost) of ADRs on the health system?
- What proportion (and which) of toxicities are preventable?
- How can these known toxicities be prevented?
- What are the comparative risk profiles of available regimens and individuals drugs?
- ??

The PV approach should be governed by the objectives that need to be met.

What is the burden of ADRs on healthcare system in SA? The Somerset Hospital Study

- 3 month prospective observational study of 665 adults admitted to 2 medical inpatient wards at Somerset Hospital in 2005
- Objective:
  - Describe the frequency, nature and preventability of community-acquired and hospital-acquired ADRs in a SA hospital serving a community with a high prevalence of HIV/AIDS

Mehta U et al. Br J Clin Pharm 2007


698 admissions
(including 24 readmissions)
=674 patients
Exclusions
n=8 -unable to review folder
n=1 - <16 years old
N=665 patients (10 with unknown outpatient drug history)
117 ADRs detected in
93 patients (14.0%)
66 ADRs in 55 patients (8.4% of 655)
occurred before admission
51 ADRs in 41 patients (6.2% of 665)
occurred during admission
49 ADRs leading
to hospitalisation
occurred in
41 patients (6.3% of 665)
17 ADRs in
15 patients (2.3% of 665)
were not the main
cause of hospitalization

Somerset Hospital Study: Results

- 46.2% of ADRs were preventable
- Patients admitted with ADRs were older than patients not admitted with an ADR (median 53 vs. 42 years, p=0.003).
- Among those <60, HIV-infected were more likely to be admitted with an ADR.
- Among HIV-infected patients, those receiving antiretroviral therapy (ART) were more likely to be admitted with an ADR than those not receiving ART (the stavudine era).
- No ART-related ADRs were fatal. Antibiotics and drugs used for opportunistic infections were implicated in two-thirds of hospital-acquired ADRs.

Regulatory vs. Institutional vs. Programmatic PV

Activity/ Characteristic	Regulatory	Institutional /Clinical	PH Programmes
Focal Point	MRA, pharmaceutical manufacturers	PTC, researchers, hospital QA department, pharmacy departments	PH programmes (with MRA and disease surveillance units)
Medicines under focus	All drugs, particularly newly-marketed drugs.	Targeted drugs used by health institutions and lower levels of care – e.g. EDL meds	Meds used within the programme to treat disease under surveillance
Objectives	Ensure marketed medicines are safe, effective and of good quality.	Understand and minimise drug-related morbidity, mortality and cost at institutional level.	Minimise preventable harm Maintain public trust in programme and its drugs
Example in SA	MRA PV Unit and NADEMC	Hospital surveillance study (UCT) Dermatology study	ARVs, TB, vaccines Targeted Spont reporting, Cohorts

PV in SA – An online survey
Survey Objectives and Methods

Objectives

- To obtain a clear overview of all pharmacovigilance activities being conducted in the public sector at a national and provincial level in South Africa.

Methods:

Online survey for PV programmes in SA – primarily public sector.

Focus :

- to determine objectives, activities, collaborations, areas of focus, infrastructure, resources and methods of PV activities in South Africa.

Not a focus:

- successes and challenges in achieving the goals and objectives
- Impact of programme on patient care and informing policy

Funded by US CDC and conducted by Div of Clin Pharmacology -UCT

Type of PV system (n=11)	Targeted Spontaneous Reporting (n=6)	Disease-based observational cohorts (n=1)	Cohort Event Monitoring (n=2)	Hospital Surveillance (n=2)
National/Provincial/Institutional	2/4/0	1/0/0	1/1/0	1/0/1
Medicines/Patient Population in Focus				
All medicines	0			2
HIV/AIDS patients	2	1	2	
TB patients only	0			1**
Both HIV and TB	3			
Vaccines	1			
Adult*	4		2	1/ 1 NOS
Paediatric*	5	1	1	
Outputs				
Verbal/telephonic	3		1	1
Periodic reports	4		1	1
SOPs	1		2	
Training manuals	1		1	
Abstracts	1			
Newsletters	1			
Scientific Publications	1		2	2

Survey Conclusions

"Start where you are. Use what you have. Do what you can"

- Innovative PV approaches have been developed in SA
- Improved co-ordination between programmes.
- Compatible data management systems:
  - e.g. standardised terminologies, case definitions, etc. to allow for pooling of data.
- More efficient feedback and communication between systems to improve impact.

Key Safety issues identified at National PV Workshop 7-8 August 2012

- TDF safety – nephrotoxicity and bone/skeletal toxicity as a first line option
- Paediatric Pharmacovigilance – safety of regimens e.g. long term effects of PIs
- Pregnancy exposure –EFV, NVP and other ARVs
- Drug resistance – early warning indicators
- Safety of antidiabetic and other common co-morbidities / co-medication in HIV-infected
- Traditional medicines – cross-cutting issue
- Serious skin reaction with TB, HIV meds – focussed surveillance
- Other treatment-related safety concerns?

In the pipeline…..A National Pregnancy Register
- a platform for improving maternal/child care

- Lack of background data on birth defects - only have estimates
- Unprecedented roll out of ARVs in Africa
- HIV-Malaria-TB overlap - compounds the potential for treatment benefit or risk of harm in pregnancy
- Unresolved drug safety concerns in pregnancy (TDF, EFV, HAART with option B+):

  a silent epidemic? or denying treatment access to
  - women of childbearing age
  - pregnant women
  - fetus?
- Need large cohorts that incorporate exposed, unexposed, infected and uninfected pregnant women to estimate risk

The WHO Pregnancy Registry

1. To build capacity to obtain **reliable information on obstetric, medical, and drug history during pregnancy** and **diagnose, assess, monitor and manage** pregnancy and the **outcomes** of pregnancy including congenital malformations, stillbirths and prematurity.

2. To quantify the **baseline risk of major congenital malformations** in the absence of drug exposure in the first or other trimesters of pregnancy.

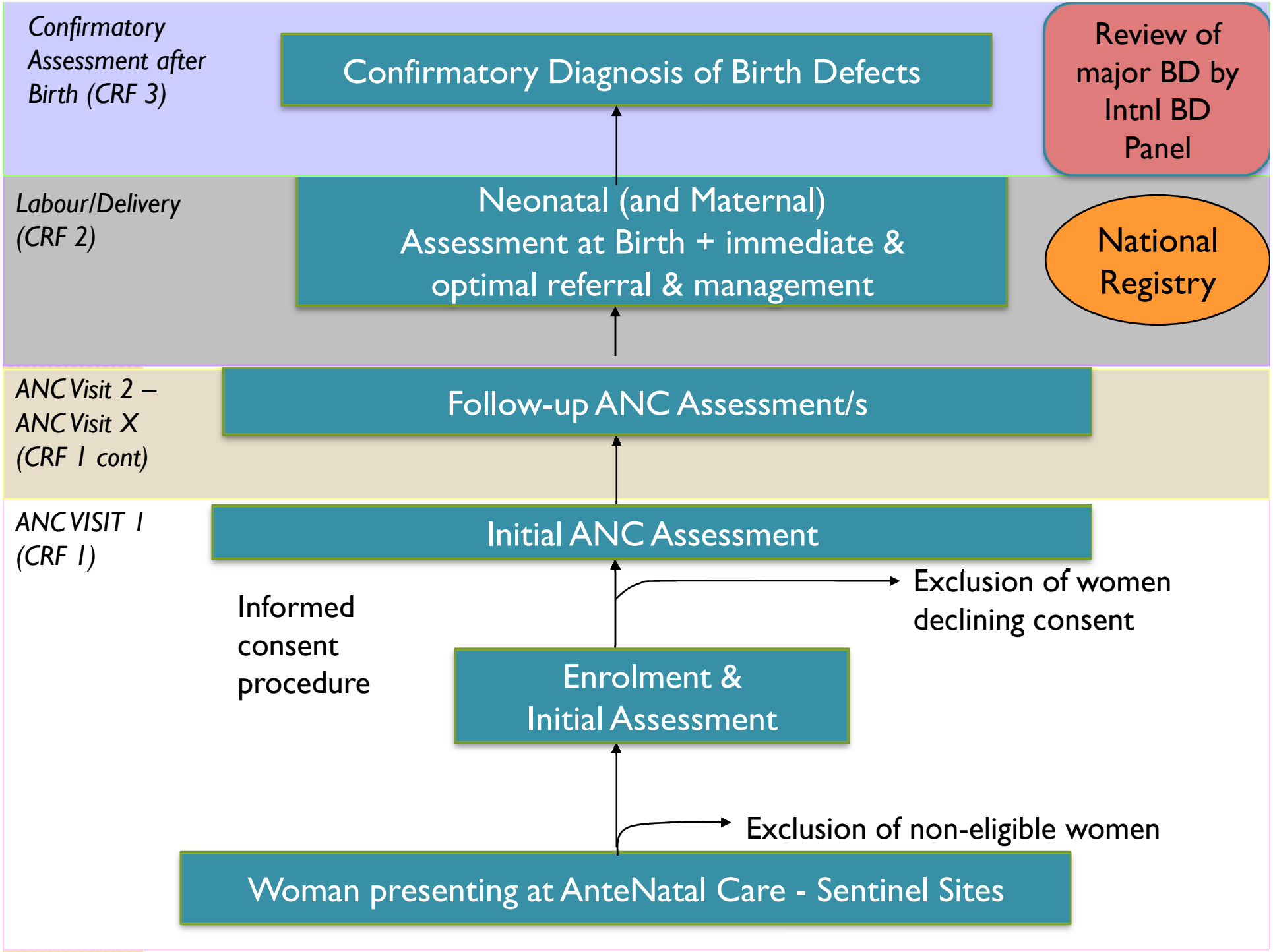
3. To **quantify the risk of major congenital malformations associated with exposure to medicines** in the first or other trimesters of pregnancy.

4. To **identify other factors that may contribute to the risk of major congenital anomalies** and other adverse birth outcomes in pregnant women.

5. To support a **culture of drug safety awareness** among women and their providers in participating countries to avoid preventable adverse drug-related pregnancy outcomes.

6. To develop an **ongoing surveillance system** of maternal and newborn health that strengthens the health system to improve maternal and neonatal outcomes.

Mehta U et al, BMC Pregnancy and Childbirth 2012


Confirmatory Assessment after Birth (CRF 3)
Confirmatory Diagnosis of Birth Defects
Review of major BD by Intnl BD Panel
Labour/Delivery (CRF 2)
Neonatal (and Maternal) Assessment at Birth + immediate & optimal referral & management
National Registry
ANC Visit 2 – ANC Visit X (CRF 1 cont)
Follow-up ANC Assessment/s
ANC VISIT 1 (CRF 1)
Initial ANC Assessment
Exclusion of women declining consent
Informed consent procedure
Enrolment & Initial Assessment
Exclusion of non-eligible women
Woman presenting at AnteNatal Care - Sentinel Sites

Conclusions

- PV has evolved in SA from being a purely regulatory activity
- SA has developed innovative approaches to PV since rollout of ARVs
- PV needs to be better integrated into clinical practice to optimise benefits to patients
- The system is only as good as the extent of its "extroversion"
- Ultimately the quality of PV system should be measured by the extent to which it improves patient care and informs policy.

ARV PV – Discussion

- What are the key drug safety challenges facing clinicians?
- Can PV surveillance be integrated into your practice? How? What are the opportunities/challenges/frustrations?
- How can existing ARV PCV activities in SA better benefit patients and providers?
- What platforms can be used to improve feedback and knowledge transfer on toxicities of treatments in HIV-infected?
- How can we streamline ARV PV to improve clinical care?