Long-Term Monitoring of ARV Treatment Related Adverse Events

Pharmacovigilance and Regulatory Considerations in the South African Programme

Meeting on Long-Term Monitoring of Treatment Related Adverse Events in Resource Limited Settings
Dublin, 13th November 2005

Aims of Pharmacovigilance

- improve patient care and patient safety in relation to the use of medicines, and related medical and paramedical interventions;
- improve public health and safety in relation to the use of medicines;
- contribute to the assessment of risk and benefit of medicines, encouraging their safe, rational and more effective (including cost-effective) use; and,
- promote understanding, education and clinical training in this field of medical science, and its effective communication to the public[1].

[1] WHO report: The Importance of Pharmacovigilance. 2002

Objectives

- **To determine the burden of drug-related morbidity and mortality in patient with HIV/AIDS, particularly associated with ARV use.**
- **To identify and develop measures to minimize drug-related morbidity and mortality in patients with HIV/AIDS**
- **To provide information support to health personnel and patients on the safe use of antiretrovirals.**
- **To identify, assess and communicate any new safety concerns associated with the use of antiretrovirals.**
- **To support regulatory and public health decision-making through an efficient, national post-marketing surveillance system, monitoring the benefits and risk of harm associated with ARV's in particular but also of other drugs currently used in the health sector.**
- **To minimize the negative impact of misleading information or unproven associations between adverse events and ARV therapy.**

Programme Activities

- Enhanced national spontaneous reporting system with active feedback to decision-makers, prescribers, reporters, patients and the public.
- Development of a sustainable, functional, user-friendly database to support the spontaneous reporting system.
- Develop regulatory procedures to support the defined objectives
- Provision of unbiased, evidence-based information on the safety profile of ARV's, the safe and effective use of ARV's and the management of potential complications.
- To introduce targeted sentinel surveillance systems to evaluate signals of safety issues of potential public health importance (e.g. high risk groups such as pregnant women, infants, HIV-TB co-morbidity).
- Develop novel pharmacovigilance methods to complement and support spontaneous reporting and sentinel surveillance systems.
- Develop key indicators for estimating the prevalence of drug-related morbidity and mortality.

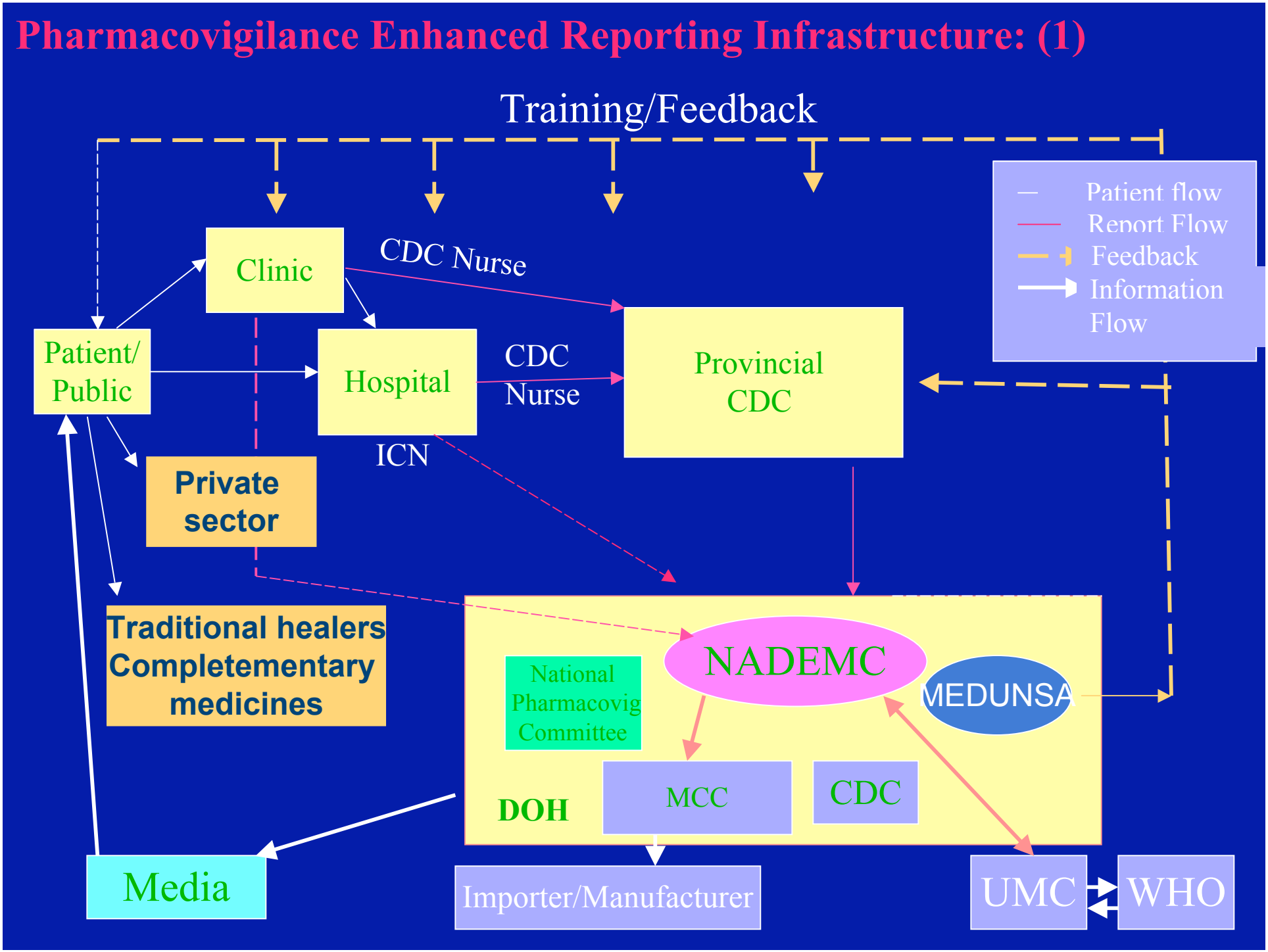
Activity 1: Enhanced National Spontaneous Reporting System

- Measures to improve national awareness and understanding of ADR reporting and to encourage reporting
  - Weakest area
  - Integrate reporting into provincial drug distribution system or other existing infrastructure
- Widespread distribution of the ADR reporting form
  - Needs to be done in conjunction with training
- System of evaluation
  - National Adverse Drug Event Monitoring Centre
  - Pharmacovigilance committee
- System of feedback and acknowledgement to individual reporters
  - Acknowledgement in place but not always feedback
- System of feedback to health professionals and public
  - Drug alerts – system already in place – need to increase frequency

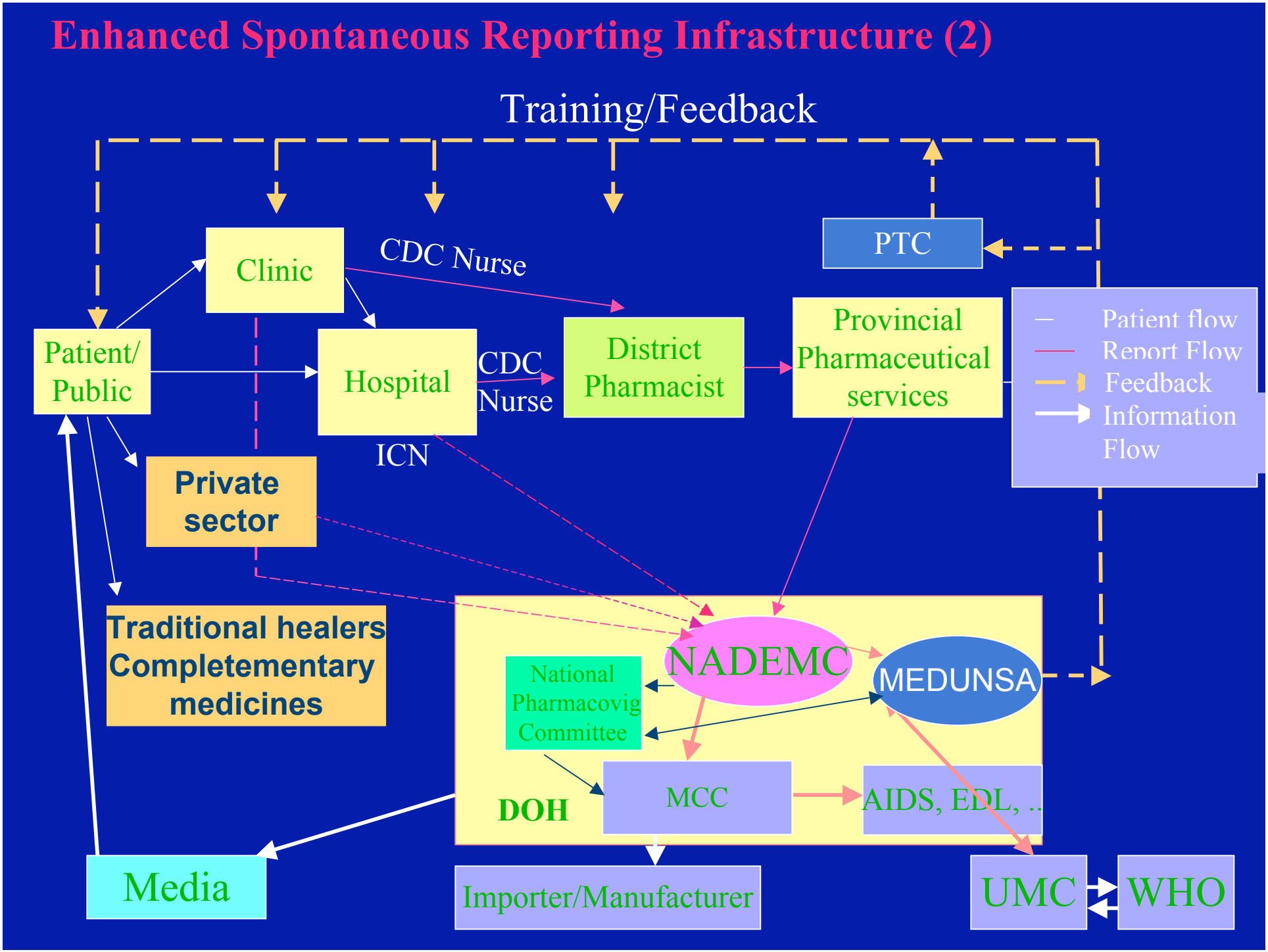
Rationale for Strengthening General Spontaneous Reporting

- Improve awareness of importance of ADR reporting in general
- Improve the ability to detect ADRs associated with ARVs
- Prevent undue concern among the community and healthcare personnel about the safety of newly introduced ARV regimens.
- Allow for comparison of reporting rates among various therapeutic classes of medicines including ARVs
- Assess the possible contribution of underreporting to lack of detection of adverse drug reactions associated with ARVs

Pharmacovigilance Enhanced Reporting Infrastructure: (1)



Enhanced Spontaneous Reporting Infrastructure (2)



Activity 2: Develop Regulatory Procedures

- **General**
  - Media communications plan & training of personnel for dealing with public safety concerns
- **Complementary medicines**
  - Provision of information on complementary medicines commonly used in HIV, particularly the potential for drug interactions with ARV's
- **Clinical**
  - Monitor and respond to safety-related regulatory actions taken in other countries.
  - Publish and distribute Drug Alerts and public health advisories in local health profession journals and media
  - Standardized product labeling and patient information
  - Translation of patient information into local languages and use of pictograms
  - Timely review and communication of safety-related labeling amendments (web-based)
- **Inspectorate**
  - Ensure compliance (e.g. GMP) of ARV products in the marketplace
  - Action against unregistered products falsely claiming benefit for HIV/AIDS
  - Review of advertising materials for false or misleading claims or irresponsible advertising

Activity 3: Database to Support Spontaneous Reporting

- Primarily concerned with the detection of new signals and important drug-related problems
- Compatible with WHO Uppsala Monitoring Centre database
- Easy data capture and evaluation
- User-friendly
- Robust search capabilities and ability to provide useful statistics and signal detection capabilities
- Partially automated acknowledgement and feedback system to reporters

Activity 4: Provision of Information

- Overview of safety profile of selected regimens
  - epidemiology, case definitions clinical presentation, diagnosis, Mx & prevention.
  - Guidelines on clinical management of known reactions e.g.
    - Management of NVP skin reactions
    - Approach to lactic acidosis diagnosis and management
    - Clinical management of peripheral neuropathy
    - Management of suspected drug-induced hepatotoxicity
- Specific pharmacovigilance training for healthcare personnel
- Training materials & guidelines for HIV/AIDS counselors and educators
- Booklet on core information for basic health workers on HIV/AIDS and the use of ARV's (e.g. clinic nurses etc.)
- Posters and booklets on drug interactions for ARVs and other medicines commonly used in HIV/AIDS patients.
- Patient/consumer information booklets with basic facts on HIV/AIDS and ARV regimens

Activities 5&6: Focused Surveillance Activities

Guided by a clear agenda of safety concerns requiring monitoring and evaluation

- Sentinel Surveillance systems e.g.
  - Lactic acidosis
  - Serious skin reactions
  - Grade III/IV Hepatitis (particularly TB patients)
  - Cardiac safety
- Pregnancy Registry
  - Follow-up of pregnancy outcomes and patients on ARVs
- Pediatric Pharmacovigilance Unit
- Other novel pharmacovigilance methods
  - Enhanced signal detection through prescription event monitoring
  - Confidential enquiry into deaths in patients on ARVs
  - Record Linkage studies – managed care organisations
  - Case control studies

Activity 7: Key indicators for estimating the prevalence of drug-related morbidity and mortality

- System to track patient outcomes
- Identify diseases likely to be drug-induced
- Assess impact of these diseases on patient care

Challenges

- How to integrate with ARV roll-out?
- Who are the partners likely to effectively support this process?
- Timing and prioritizing
- What is our role in actual training?
- Lessons learnt from other programmes (e.g. vaccines and malaria)
- Identifying critical success factors
- Relationship of programme versus regulatory pharmacovigilance activities
- Adequate resources and planning
- Collaboration and critical partnerships

Needs Assessment and Planning

- Audit of locally available resources that will assist in supporting safe use of medicines
  - Consumer advocacy groups
  - Drug information centres
  - Early roll-out sites
  - Academic institutions
- Identify resources for promoting ARV safety within the national health care infrastructure in which ARV's will be introduced.
  - AIDS directorate, EDL
  - Health Professions Council, Pharmacy Council
  - NHIS
- Determine the minimum infrastructural needs to ensure proper safety monitoring of ARV by prescribers.
  - Monitoring equipment
  - Proformas and monitoring charts

Support Structure

- Develop of an up-to-date resource centre for information on HIV/AIDS therapeutics with a strong focus on ARV's.
- Design and pilot a training programme in ARV therapeutics and optimal HIV/AIDS patient management.
- Strengthen collaboration and partnerships.
- Advocacy and awareness-building in pharmacovigilance
- Develop and expand Regulatory website and information services
  - Drug alerts
  - Safety-related package insert amendments for ARVs
  - "Dear health professional" letters
  - Core safety information to be reflected in ARV PIs
  - Electronic bulletin for new warnings – sent as distribution list