The ACT Consortium and the Centralized Drug Safety Repository

RBM CMWG-7, Annecy, France

Cheryl Pace
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ACT Consortium Overview

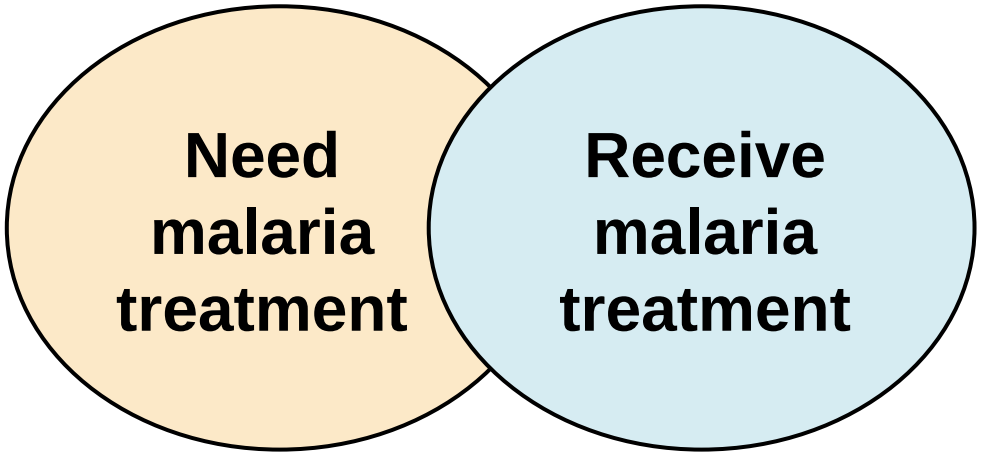
The ACT Consortium is an international research collaboration aiming to maximize the public health impact of artemisinin-based combination therapy (ACT) through high quality, policy driven, multidisciplinary research

ACCESS

TARGETING

QUALITY

SAFETY



Funded by the Bill and Melinda Gates Foundation

ACTc Safety Activities

Quality of source safety data
- Methods for evaluating harms
- Data capture forms
  - Clinicians
  - Non-clinicians

Evaluating safety in specified populations
- HIV (interactions)
- (Pregnancy (MiPc))

Evaluating safety in practice
- Repeated treatment
- Ototoxicity

Centralized Drug Safety Repository

Outputs

Products
- Repository

Tools
- Data capture tools
- Data evaluation methods

Guidelines
- Influencing malaria and HIV guidelines

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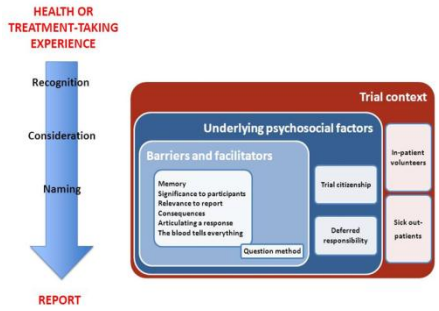
Methods for evaluating harm associated with antimalarial drugs

1) Mixed-method study in two antimalarial drug safety trials[1]

- Optimal methods for collecting harms data unclear
- Evidence that questioning methods influence outcomes (participant-reported AEs, previous & concomitants meds etc.)



2) Survey with antimalarial drug clinical researchers

- Range of methods used to elicit, assess (for severity/causality) and record AEs and related data could impact on ability to pool data (preliminary results)

3) Cochrane systematic review

- Eliciting adverse effects data from participants in clinical trials

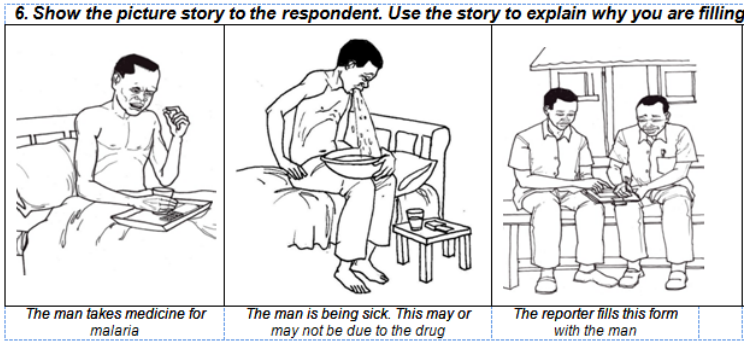
4) Delphi

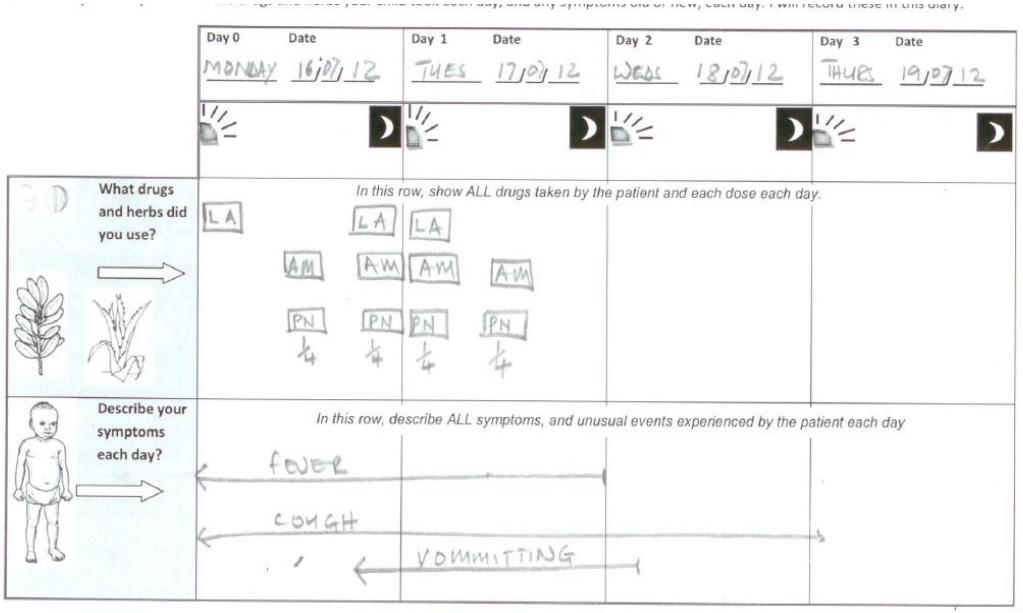
- Reflect on above & work towards consensus on whether, and if so how, there could be harmonisation as to appropriate methods and/or tools used

[1]**Allen et al**. Eliciting harms data from trial participants: how perceptions of illness and treatment mediate recognition of relevant information to report. Trials 2011, 12(Suppl. 1):A10. Oral Presentation.

Non-clinician data capture forms

Established drug safety surveillance systems have limited effectiveness and in low resource settings, treatment provision is often undertaken by non-clinicians





Davies EC, Chandler CIR, Innocent SHS, Kalumuna C, Terlouw DJ, et al. (2012) Designing Adverse Event Forms for Real-World Reporting: Participatory Research in Uganda. PLoS ONE 7(3): e32704. doi:10.1371/journal.pone.0032704

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InterACT and SEACAT

The efficacy, safety and pharmacokinetics of artemether-lumefantrine for the treatment of uncomplicated malaria in Tanzanian adults receiving first-line antiretrovirals: a clinical controlled study (InterACT) (nevirapine or efavirenz)

Vestergaard L, Lemnge M, Bygbjerg I et al

Study Groups	Description
Group A	HIV +ve, ARVs, malaria +ve
Group B	HIV +ve, no ARVs, malaria +ve
Group C	HIV –ve, malaria +ve
Group D	HIV +ve, ARVs, malaria –ve

Pharmacokinetic interaction between the antimalarial combination artemether-lumefantrine and combination antiretroviral therapy including nevirapine in HIV-infected adults (SEACAT)

Barnes K, Kredo T et al

Study Groups	Description
Group A	HIV +ve, ARVs, malaria –ve
Group B	HIV +ve, no ARVs, malaria –ve

ACTc SEACAT study

ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 2011, p. 5616–5623 Vol. 55, No. 12
0066-4804/11/$12.00 doi:10.1128/AAC.05265-11

Interaction between Artemether-Lumefantrine and Nevirapine-Based Antiretroviral Therapy in HIV-1-Infected Patients[▽]

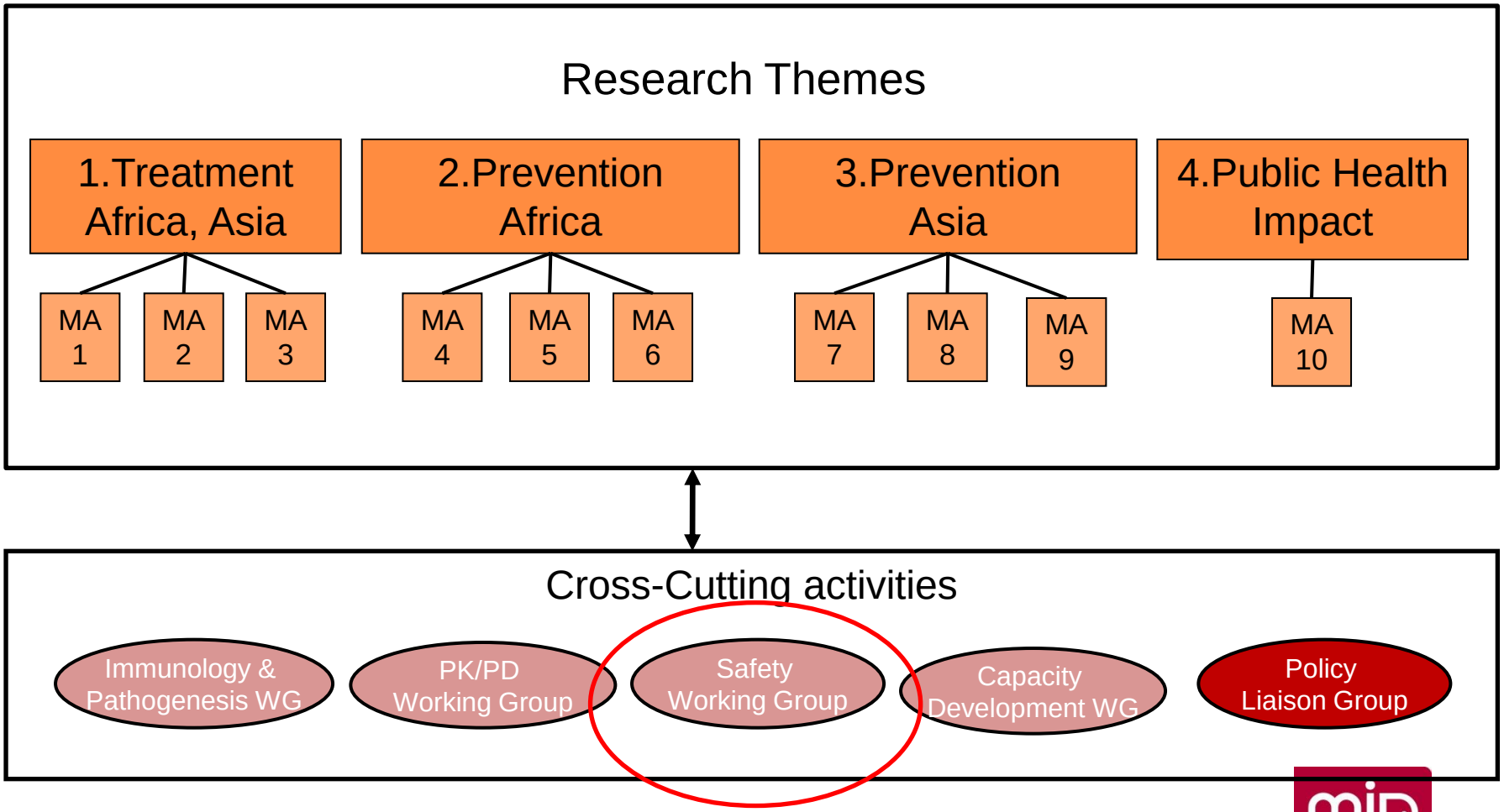
T. Kredo,[1,5]* K. Mauff,[1,3] J. S. Van der Walt,[1,4] L. Wiesner,[1] G. Maartens,[1,2] K. Cohen,[1,2] P. Smith,[1,2] and K. I. Barnes[1]*

Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, Cape Town, South Africa[1]; Groote Schuur Hospital, Cape Town, South Africa[2]; Department of Statistical Sciences, University of Cape Town, Cape Town, South Africa[3]; Pharmacometrics Research Group, Department of Pharmaceutical Biosciences, Uppsala University, Uppsala, Sweden[4]; and South African Cochrane Centre, South African Medical Research Council, Cape Town, South Africa[5]

Received 11 July 2011/Returned for modification 1 August 2011/Accepted 19 September 2011

MiP Consortium

Aim: To identify & evaluate new ways of preventing and treating malaria in pregnancy to improve the evidence base for its control



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ACTia: safety and effectiveness of ACTs with repeated use in programmatic settings (Malawi)

- Safety of repeated treatment in young children with artemether-lumefantrine vs DHA-piperaquine over 3 years
- Phase IV effectiveness trial, real life
  - Weight-based dosing as per recommended regimen
  - Only 1st treatment observed - adherence

Main research questions

Safety of repeated Rx	• Remaining concern ototoxicity • Pharmacovigilance model Phase IV • AE detection by clinician and non-clinical fieldworkers
Effectiveness vs efficacy	• DHA-PPQ vs artemether-lumefantrine • Difference in malaria incidence? • Adherence tool • Rapidly changing background burden

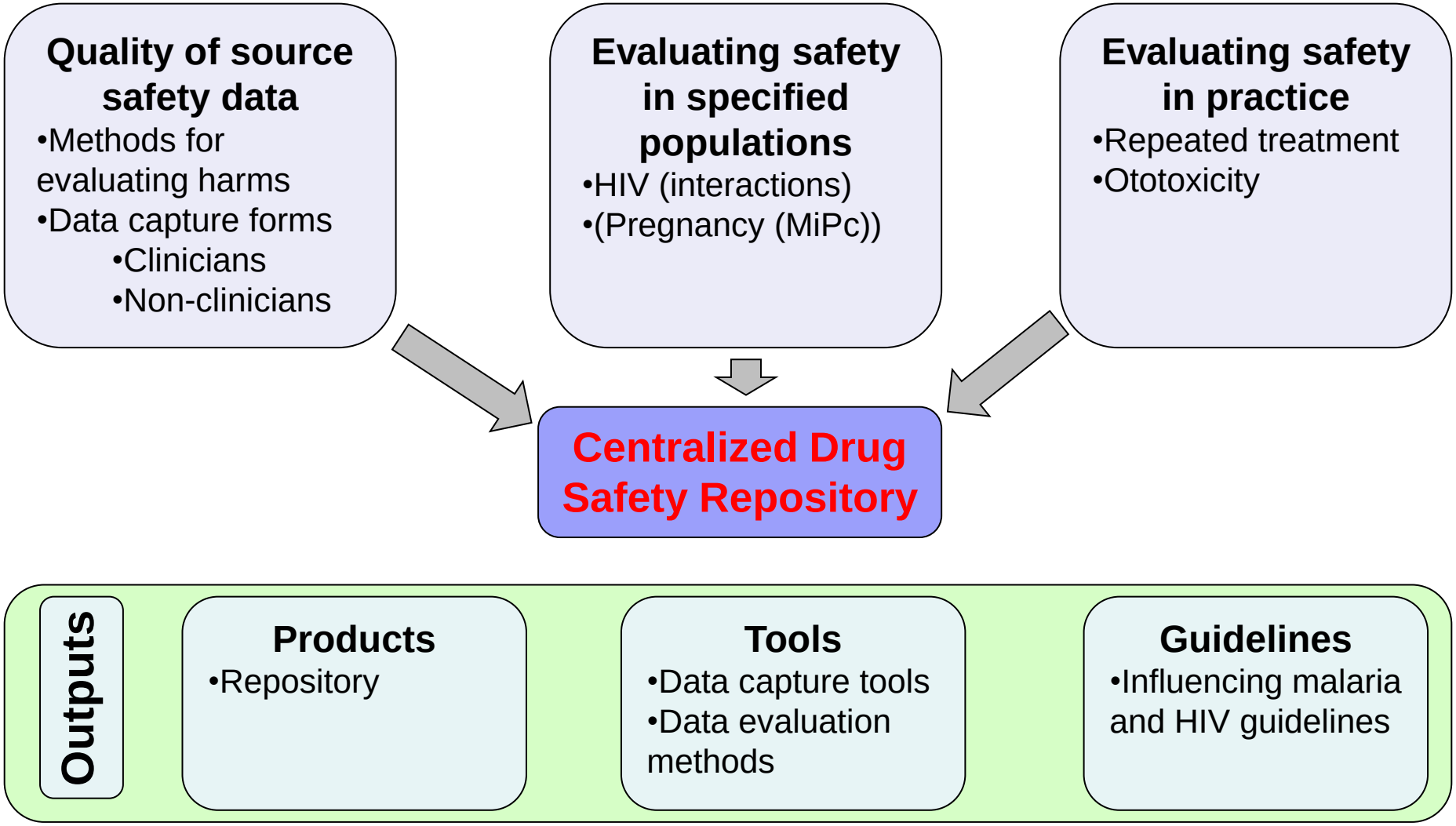
Lalloo D, Phiri K, Terlouw D et al.

PRIME – Evaluating the impact of enhanced health facility-based care vs standard care for malaria and febrile illnesses (Uganda)

- AE monitoring of cohort over 18 months
- Artemether-lumefantrine
- Monthly household visits
- AE detection by fieldworkers (reviewed by clinicians)

Staedke S, Kamya M, Dorsey G et al

ACTc Safety Activities



Centralized Drug Safety Repository (DSR)

Collaboration between the ACT Consortium and MiP Consortium

Aim

- To collect and collate safety data from a variety of sources to inform on the incidence of known adverse reactions and identify new signals of potential harms

Key features

Anti-malarial specific dataset

- Approx. 2000 case reports of serious adverse events

Strengthen in-country pharmacovigilance capacity

- Infrastructure developed to facilitate reporting of events to national centres

Diverse dataset

- Trials
  - Observational/Interventional studies
- Prevention vs treatment
- Clinician vs non-clinician reporting

Aggregation of data

- Increased power to detect signals and inform on known harms

Key features

Integrated standardized dictionaries to aid data retrieval, presentation and analysis

- MedDRA (Medical Dictionary for Regulatory Activities)
- WHO Drug Dictionary

Ability to use Standardized MedDRA Queries

- To aid identification and retrieval of potentially relevant individual case safety reports
  - e.g. using ‘extrapyramidal syndrome’ SMQ to identify case reports that may be relevant to emerging signal with AS-AQ

In-depth analysis of sub-groups to identify risk factors

- Dose to onset time, age, concomitant drugs

Countries (no. of serious reports)

- Kenya (80)
- Uganda (105)
- Mozambique (260)
- Malawi (301)
- Tanzania (144)
- Zambia (105)
- The Gambia (21)
- Mali (40)
- Burkina Faso (63)
- Ghana (135)
- Gabon (98)
- Benin (288)
- Papua New Guinea (262)
- India (13)
- Afghanistan
- South Africa
- Indonesia

Data

Drug	No. of serious cases (possibly/probably related to drug)
Amodiaquine-artesunate	54 (9)
Artemether-lumefantrine	224 (12)
Artesunate-SP	8 (0)
Azithromycin-SP	137 (0)
Chloroquine-SP	125 (2)
Dihydroartemisinin-piperaquine	188 (9)
Mefloquine	440 (19)
Mefloquine-artesunate	60 (7)
Sulphadoxine-pyrimethamine	351 (1)
Blinded	328 (7)
Total	**1915 (66)**

Acknowledgements

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ACT Consortium
Secretariat
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Munir Pirmohamed
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MiP Consortium

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