Evaluation of 4 artemisinin-based combinations for treating uncomplicated malaria in African children

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Objectives

- Main
  - To compare the safety and efficacy of 4 ACT, i.e. AQ+AS, AL, DHAPQ, CDA, for single and repeat treatments of uncomplicated malaria
- Specific
  - To evaluate the efficacy of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria (first active follow-up);
  - To determine after the first active follow-up the incidence rate of a second clinical episode of uncomplicated *P. falciparum* malaria

Objectives (continue)

- Specific
  - To evaluate the efficacy of treating the second clinical episode of uncomplicated *P. falciparum* malaria with the same ACT used for the first one (second active follow-up);
  - To evaluate during the active and passive follow up the safety of the 4 ACTs for the treatment of children with uncomplicated *P. falciparum* malaria;
  - To establish the impact of using CDA on the selection of *P. falciparum* genotypes linked to SP resistance.

Study design

- 3-arm multicentre, randomised, open label trial;
- First follow up of 28 days;
- Beyond 28 days:Passive follow up for detection of a second clinical episode within 6 months;-> re-treatment;
- Second follow up of 28 days;
- 510 patients per site/ 170 per arm

Study treatments by country

Country	***Numb. sites***	***Affiliation***	***Study treatments***		
Burkina Faso	1	Centre Muraz/IRSS	AQ+AS	DHAPQ	AL
Nigeria	1	TDRI	AQ+AS	DHAPQ	AL
Zambia	1	TDRC	AQ+AS	DHAPQ	AL
Gabon	1	HAS/Tubingen	AQ+AS	DHAPQ	AL
Uganda	1	EANMAT	DHAPQ	CDA	AL
Uganda	2	EANMAT/EPICENTRE	AQ+AS	CDA	DHAPQ
Rwanda	2	EANMAT	DHAPQ	CDA	AL
Mozambique	1	Manhiça	AQ+AS	CDA	DHAPQ

End points

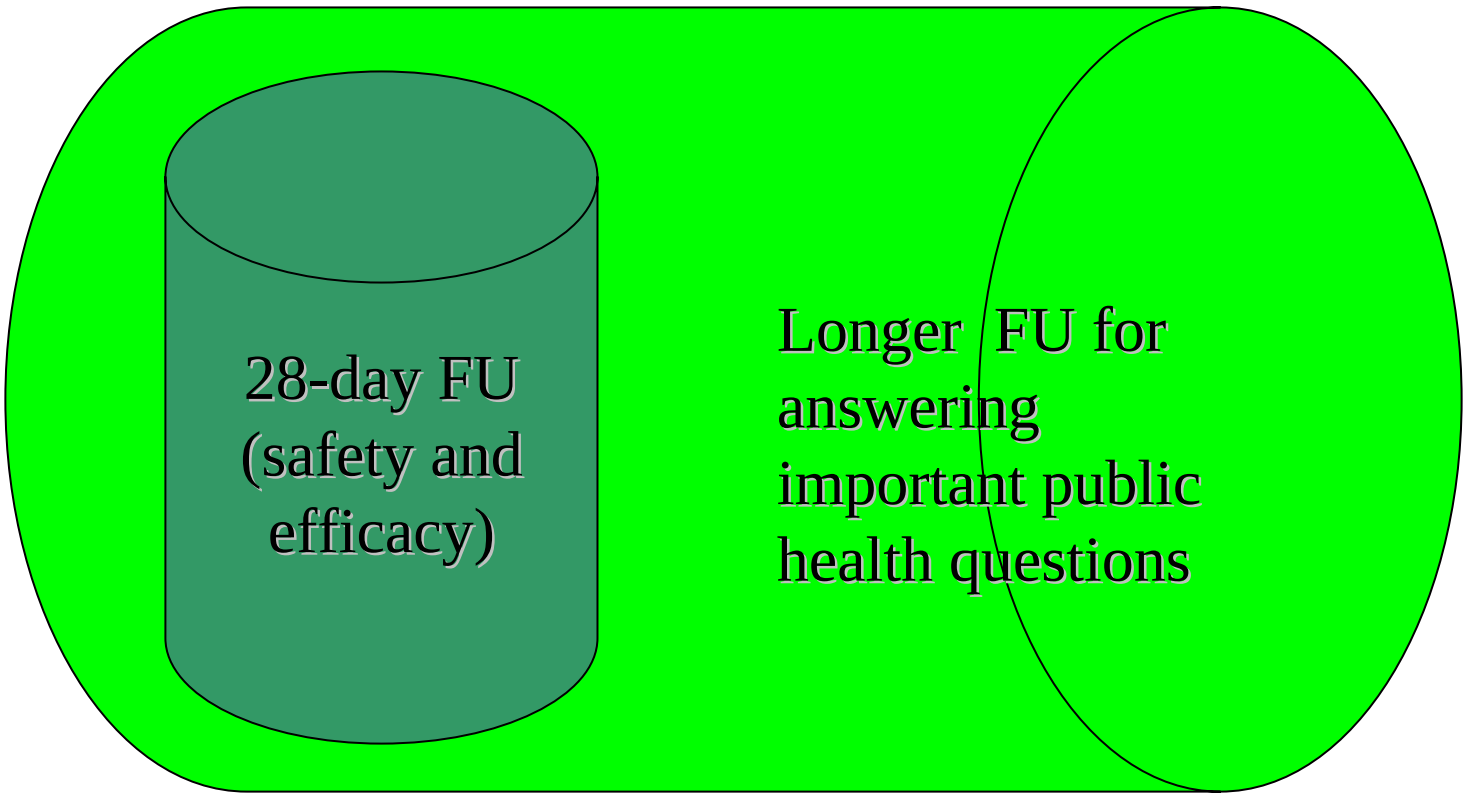
- **Primary**
  - PCR unadjusted treatment failure (TF28U):
  - PCR adjusted treatment failure up to day 28 (TF28A)
- **Secondary**
  - PCR unadjusted treatment failure up to day 63 (TF63U)
  - PCR adjusted treatment failure for the whole period of passive surveillance

End points (continue)

- Secondary
  - Fever clearance time.
  - Asexual parasite clearance time.
  - Gametocytaemia at day 7, 14, 21 and 28.
  - Hb changes day 3, 7, 14 and 28.
  - Clinical malaria after first active follow-up;
  - Clinical malaria after second active follow-up;

End points (continue)

- Secondary
  - TF second clinical episode (D28 and D63);
  - Changes in the frequency of mutations in the dihydrofolate reductase (DHFR) (for patients treated with CDA).
  - Safety profiles including significant changes in relevant laboratory values.


28-day FU
(safety and
efficacy)
Longer FU for
answering
important public
health questions

First and second follow up

Day	0	1	2	3	4	5	6	7	14	21	28	Any other day[1]
History	X							X	X	X	X	X
Examination (clinical)	X	X	X	X				X	X	X	X	X
Temperature	X	X	X	X				X	X	X	X	X
Blood film	X		X	X				X	X	X	X	X
Filter paper PCR	X							X	X	X	X	X
Treatment	X	X	X									
Adverse drug reactions		X	X	X				X	X	X	X	X
Haematology	X	X	X	X				X	X		X	X
Biochemistry	X							X	X[2]		X	

[1] Spontaneous attendance to health facility [2] If abnormal at day 7.

Inclusion criteria

- Age 6 months and 59 months inclusive
- Body weight ≥ 5 Kg
- Monoinfection of *Plasmodium falciparum* (parasitaemia ≥ 1,000/µL to 200,000/µL).
- Fever/history of fever
- Haemoglobin value ≥ 7.0 g/dl
- Signed informed consent

Exclusion criteria

- Participation in any investigational drug study during the previous 30 days.
- Known hypersensitivity to the study drugs.
- Severe malaria or danger signs
- Presence of intercurrent illness
- Severe malnutrition
- Ongoing prophylaxis with drugs having antimalarial activity

Passive follow up

- Parents/guardians asked to attend for any illness;
- Monthly visits at home to keep contact without collecting blood samples unless sick;
- When atteding HC, blood slides, BT and Hb/PCV collected systematically;
- If inclusion criteria included in the second follow up;
- If malaria not fulfilling criteria, treated with I line treatment;

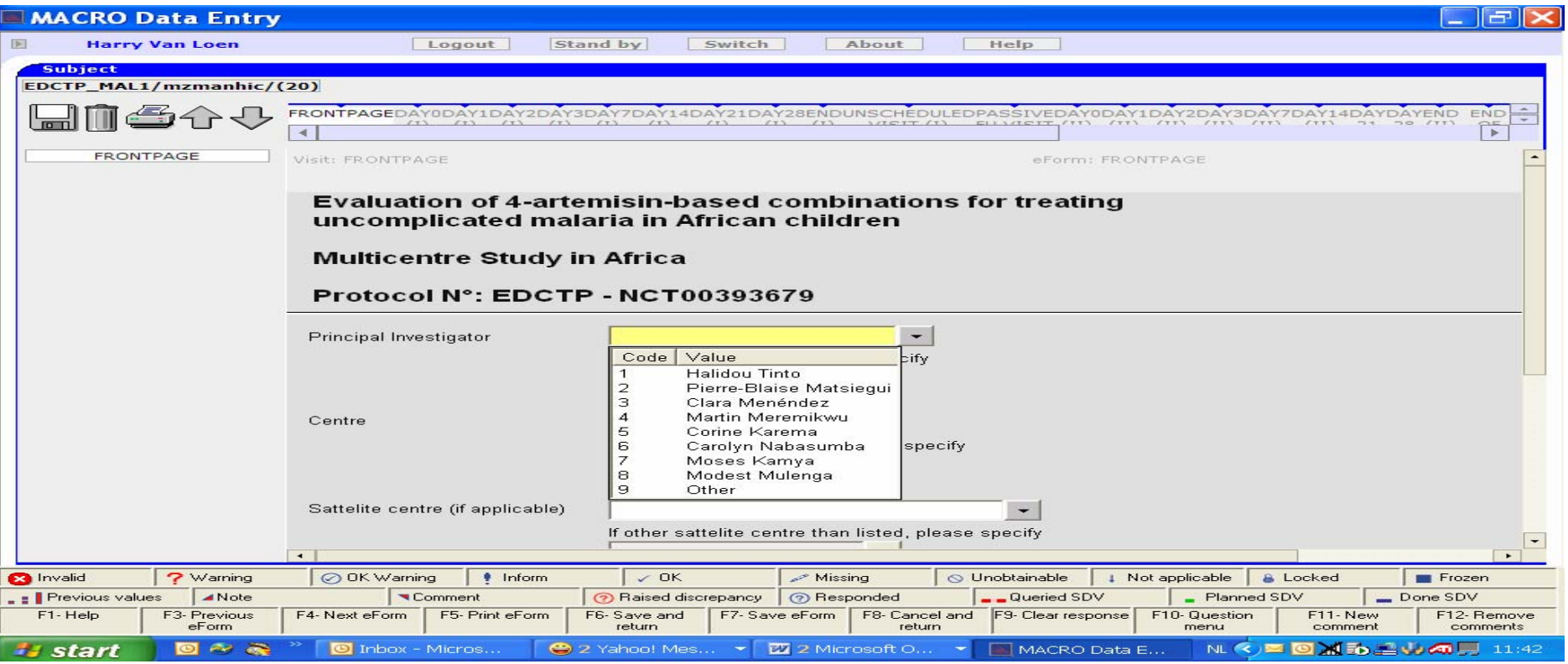
Current situation

- All treatments secured from the pharmaceutical companies
  - DHA-PPQ donated by Sigma Tau
  - AQ-AS donated by Sanofi Aventis
  - CD bought from GSK and artesunate bought from Sanofi Aventis
  - AL bought from Novartis
- All sites able to carry out biochemistry tests (last machine shipped to Nigeria some weeks ago)
  - Many administrative problems

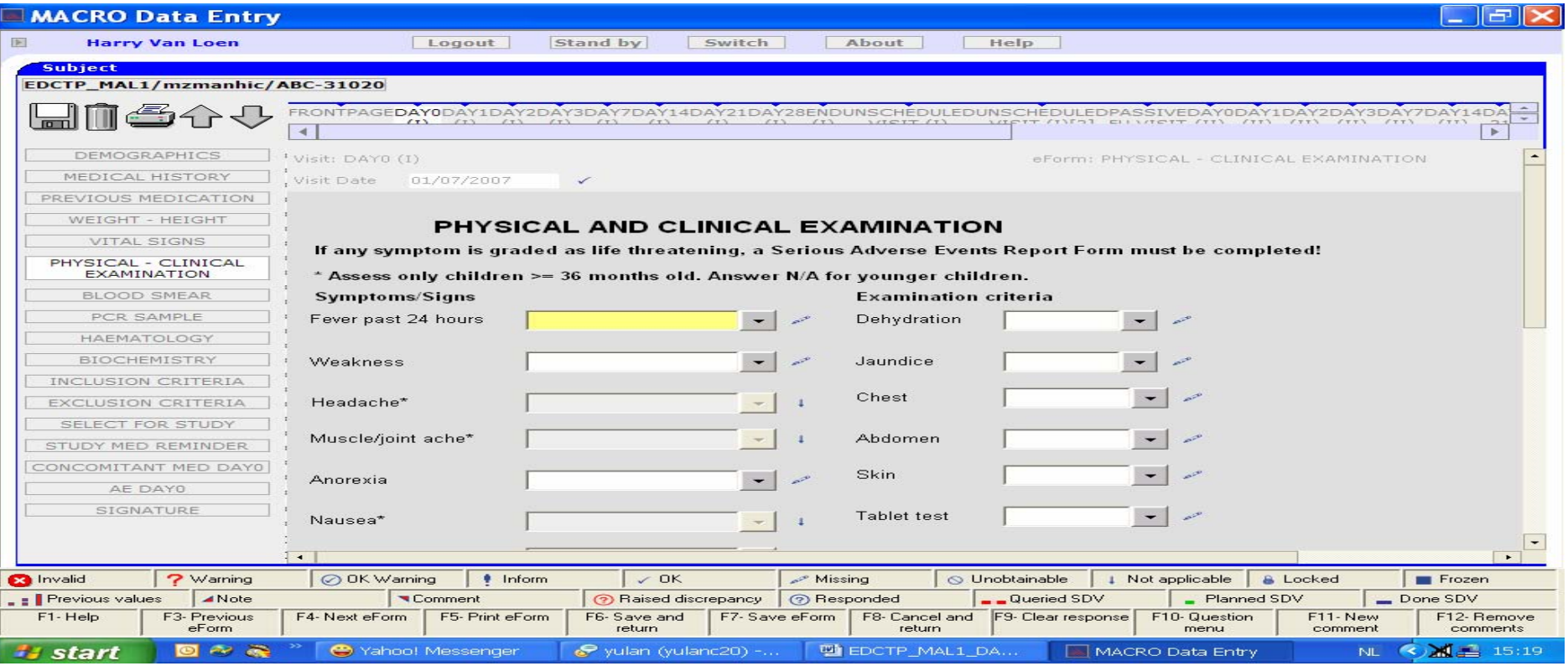
Current situation

- eCRF in use
  - Standard source document produced
  - eCRF data entry guidelines and training package developed
  - All sites equipped with laptops with MACRO software and eCRF
  - Sites regularly enter data from the source document and send them to Antwerp by internet
  - Data manager in Antwerp continuously checking the consistency and the quality of data

Front page eCRF



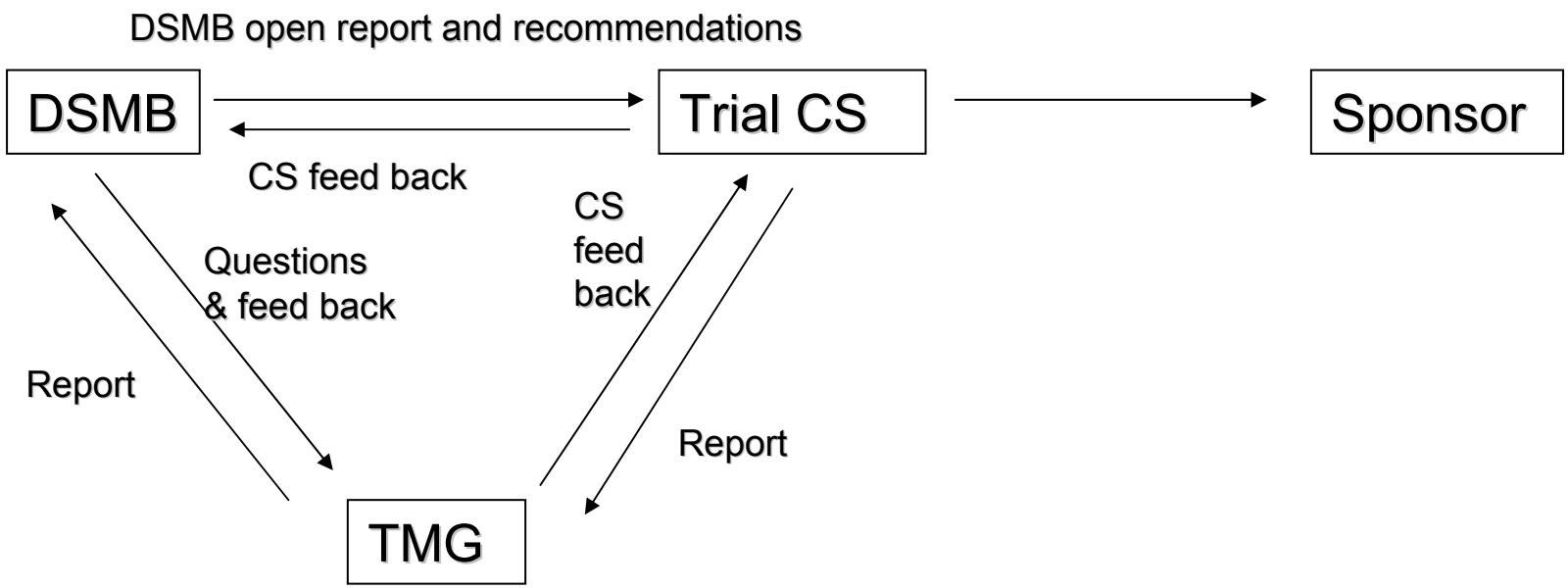
Physical and clinical examination



DSMB

- Members: Prof Bernard Brabin, LSTM (Chair), Prof Abdel Babiker, MRC clinical trial unit London, Dr Anja Terlouw , LSTM
- Aims of the DSMB
  - The DSMB will be established for the purpose of providing independent advice on the quality of the data produced, the efficacy and safety of the treatments tested, so contributing to safeguarding the interests of the trial participants.
- The DSMB will be asked to consider patient safety, particularly any Sudden Unexpected Serious Adverse Reactions (SUSARs) leading to death, alongside treatment efficacy when making their recommendation regarding continuation, amendment or discontinuation of the trial.

Relationship between DSMB, Trial Management Group, Consortium Secretariat and Sponsor



Interim analyses

- the Haybittle-Peto approach will be employed for 3 equally spaced interim analyses
- Planned after approximately 1300, 2600 and 3900 children have been randomised, with 99.9% confidence intervals calculated for the difference between each pair of drugs.
- The final analysis will be undertaken after the final child has completed 28 days follow-up (5100 randomised in total) and 95% confidence intervals will be calculated.)

15/10/2007

Sites	Date I in	Screened	Recruited	
Manhiça	09/07	106	84	
Lambarene	19/07	219	9	2 SAEs
Fougamu	29/08	133	5	
Nanoro	07/09	285	117	
Ndola	02/10	?	?	Started recruitment
Mbarara	28/08	124	43	2 SAEs
Jinja	?	5	5	Started recruitment
Tororo	?	?	?	Started recruitment
Rukara	NA	0	0	Initiation visit done
Mashesha	NA	0	0	“
Calabar	NA	0	0	Initiation end Oct
Total		872	263	

Institutions involved

- Institute of Tropical Medicine, Antwerp, Belgium
- Liverpool School of Tropical Medicine and Centre for Medical Statistics and Health Evaluation, University of Liverpool, UK
- East African Network for Monitoring Antimalarial Treatment (EANMAT).
- Centre Muraz, Bobo Dioulasso, Burkina Faso.
- Department of Paediatrics, University of Calabar, Cross River State, Nigeria.
- Tropical Diseases Research Centre, Ndola, Zambia
- Institute of Tropical Medicine, Department of Parasitology, University of Tuebingen, Germany and Medical Research Unit,
- Albert Schweitzer Hospital, Lambaréné, Gabon.
- Uganda Malaria Surveillance Project (UMSP), Kampala, Uganda.
- Epicentre, Paris, France and Mbarara University of Science and Technology, Faculty of Medicine, Mbarara, Uganda
- Programme National de Lutte contre le Paludisme, Kigali, Rwanda.
- Fundacio Clinic per a la Recerca Biomèdica/Centre for International Health, University of Barcelona, Spain and Manhiça Health Research Center, Mozambique.

Trial Management Group

- UDA, **Coordinating Investigator**
- Ambrose Talisuna, **Field Coordinating Investigator**
- Raffaella Ravinetto, **Coordinator of the Clinical Trial Unit**
- Harry van Loen, **Data Manager**
- Paula Williamson, **Statistical Team Leader**
- Daniel Kajungu, **Study statistician**

Some issues to be discussed

- Decreasing trend in Africa is good news but…increases the time and cost of reaching the sample size target;
- Reviewers of proposals and budgets should be aware of additional costs involved in carrying out GCP/GLP compliant trials (e.g. human resources for sponsor (academic) and coordinator)