

# **Establishing a malaria clinical research site in Africa: experience from Bagamoyo Tanzania**

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# Outline

- Development of clinical trial sites in Africa
- Issues in the implementation of phase II/III evaluation of malaria drugs and vaccines
- Challenges for sustaining clinical trial capacity

# **Clinical trial sites: Capacity strengthening in Africa**

# Background

- Increasing pipeline of both new drugs and vaccines for malaria, HIV & TB
- Clinical research sites are needed in Africa to evaluate new interventions in endemic populations
- Different stakeholders are currently investing in the set up of such sites
- Poor health infrastructure in most developing countries and limited skilled human resource makes the establishment and maintenance of these sites challenging.

# Bagamoyo set up-I

## 1. Infrastructure

- Expansion of the waiting area and OPD clinic
- Expansion of the inpatient facilities
- Dedicated research laboratory that is quality controlled
- Communication and referral facilities

## 2. Personnel

- Identification of the team & build a research culture
- Training in GCP and various aspects of clinical trials

## 3. Procedures

- Development of SOPs (clinical, laboratory & field)
- Training and standardisation of clinical procedures
- Development of study specific procedures

# Bagamoyo set up-II

4. Community involvement
  - Characterisation of the burden of diseases
  - Community views and concerns
  - Appropriate mechanisms for continuous interaction
5. Administrative, Ethics and Regulatory oversight
  - Formal agreements with District authorities and MoH
  - IRB restructuring and procedures
  - Dialogue with the regulatory authority
6. Support structures and stakeholders
  - Local technical support in maintenance/troubleshooting
  - Sponsors assistance in quality development
  - Partnerships with established sites & Investigators



Sentinel dispensaries

Trained staff

PDA based PCD

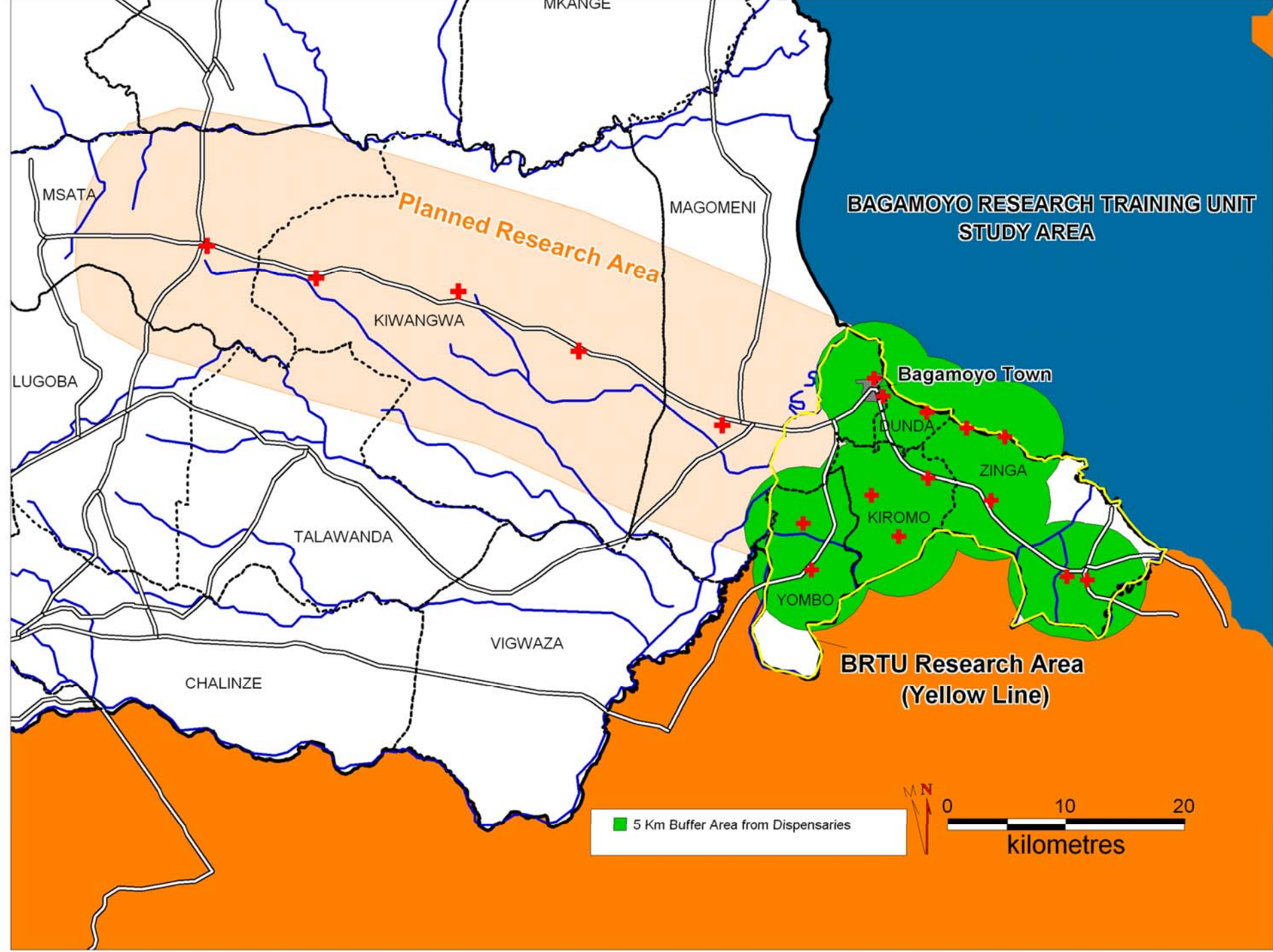
Diagnostic with RDT

Vaccination facilities

System for Supervision

Referral

Communication



# Community Participation



Need Cooperation for

- Concerns communication
- Consent process
- Referral of AEs
- Complete Follow up
- Manage “activists”
- Crisis management

*Community advisory board not political community representatives nor village healthcare workers*

**General community outreach**

**Support dissemination of information,**

**Feedback on criteria for participation, ICFs, volunteer retention**

## Studies: 2006-7

1. Phase IIb RTS,S vaccine- (MAL040 & MAL050) -MVI/GSK
2. Phase II/III Coartem paediatric formulation – MMV/Novartis Pharma
3. Phase II RBx11160- MMV/Ranbaxy
4. Phase III CDA – MMV/GSK
5. Assessment RDTs Phase III – WHO

# **Design issues in the conduct of Phase II/III Trials in Africa**

# Appropriate end points in clinical studies

Easiest to Measure

<i>Infection</i>
<i>Genotypic breakthrough</i>
<i>Parasite density</i>
<i>Multiplicity of Infection</i>
<i>Anemia</i>
<i>Clinical malaria</i>
<i>Severe malaria</i>
<i>Death</i>

Most difficult to measure

What will we know when about the impact of malaria vaccines? The WHO recommendation on endpoints

# Choice of primary efficacy objective: Clinical malaria versus severe disease

- Clinical malaria disease
  - Important disease entity on pathway to severe disease
  - Can be achieved reliably in a smaller trial
  - Suitable licensure endpoint
- Severe malaria disease
  - Rates are falling in study centers with improvements in malaria control and treatment
  - Remains important secondary objective required by health policy makers



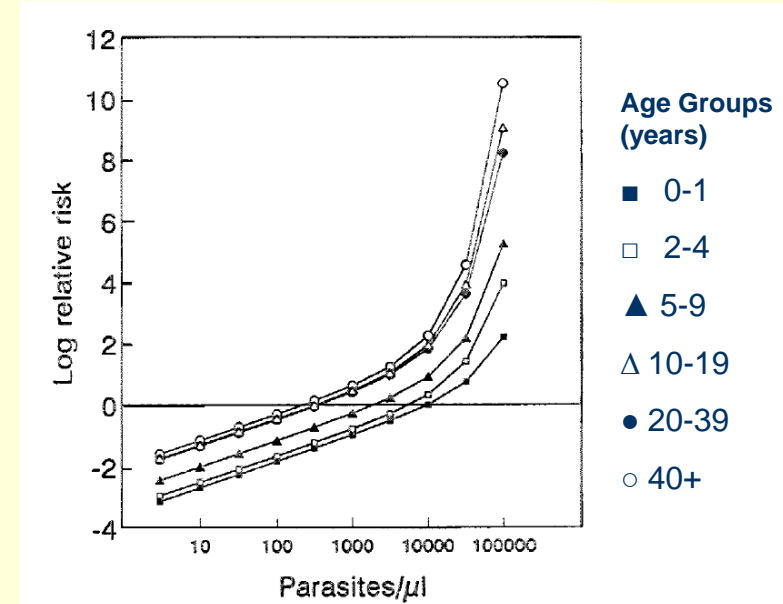
# Different primary case definition of clinical malaria disease

A specific case definition of malaria disease in endemic countries is challenging because:

- symptomatology of malaria overlaps with other childhood infections
- AND asymptomatic infection with *P. falciparum* is common

There is a positive relationship between parasite density and likelihood of clinical disease:

- This can be used as basis to model the specificity and sensitivity of case definitions with differing threshold values of parasitemia [Smith, 1994]



From: Smith T, Genton B, Baea K, Gibson N, Taime J et al. Relationships between *Plasmodium falciparum* infection and morbidity in a highly endemic area. *Parasitology* 1994; 109:539-549

*WHO recommends to use a cut off parasite density threshold predicted to have a specificity of at least 80% in all transmission settings and age groups*

# **Implementation issues in the conduct of RTS,S Phase II/III Trials in Africa**

# Implementation issues

- Training and harmonisation of the procedures
- Quality control: Lab, Clinical and field.
- Skill mix

# Implementation and Operational issues in Phase III RTS,S trial



# Blood slide reading and validation

- Harmonization of the malaria parasite quantification:
  1. Counting parasites against WBC and RBC counts
  2. Counting parasites in a measured blood volume
- All slides read by two independent readers and a third reader if not meeting agreement criteria
- Reference panel to be read every 4 months by each reader at each site (WHO methodology with defined criteria for agreement and competency)
  - To ensure comparability of methodologies
  - To ensure consistency across sites
  - To maintain standards throughout the trial by implementing regular re-accreditation of each reader

# WHO methodology for competency assessment

- Reference panel of 3 recognized expert microscopists
- Referee laboratories selected on the basis of experience and peer acknowledgement of excellence
- WHO Informal consultation on quality control of malaria microscopy 3 March 2006

<b>Grading</b>	<b>Species identification (% accuracy)</b>	<b>Quantitation: % slides within 25% of true count</b>
<b>Expert</b>	90 %	50%
<b>Reference</b>	80%	40%
<b>Competent</b>	70%	30%
<b>In training</b>	<70%	<30%

# Challenges in sustaining clinical trial sites

# Sustaining clinical capacity

- Changing epidemiology of malaria
- Pipeline of products
- Networking of sites
- High attrition of personnel hence expanding the pipeline
- Personnel retention schemes especially for local talent
- Adherence to GCP versus focus on care of participants

# Clinical Trial Partnership Committee (CTPC)



**CTPC is a committee of members from African centers GSK and MVI which was chartered at a meeting in September 2005 for the phase 2/3 program for RTS,S**

# Take home messages

# Experiences so far

- Enrolment of volunteers and follow up very good very low refusal/withdrawal rates.
- Systems for tracking of adverse events and study outcomes were appropriate for the rural communities.
- Good Quality assessments reports
- The improvement of quality of care in the health facilities appreciated by the whole community.
- The site's northern partners, sponsors and other stakeholders were critical in ensuring success.
- The biggest challenge is maintaining the activities and high quality implementation over time.

# Studies 2008-9

1. Pre 55 and MAL55 RTS,S vaccine
2. Pyronaridine artesunate assessments
3. 2 Phase II-III Antimalarial drug studies
4. Phase I Vaccine trial (PMAL03)
5. Diagnostics for Malaria, HIV & TB
6. Surveillance of infectious diseases in children on including TB.

# Take home messages

- Capacity is being developed across Africa to support clinical trials and offer improved quality of care
- Capacitating local investigators has a better prospects for sustainability and success of the product development programmes
- Establishment of networks of site/investigators/stakeholders will speed up the process of evaluation and uptake of new products
- Work is ongoing on harmonization and quality control of methodologies and procedures
- Community concerns for development need to be addressed with the work



# Acknowledgements

# Research

# Malaria Vaccine Pipeline

Source: World Health Organization, Initiative for Vaccine Research, "Portfolio of candidate malaria vaccines currently in development, July 2004" at [http://www.who.int/vaccine\\_research/documents/en/malaria\\_table.pdf](http://www.who.int/vaccine_research/documents/en/malaria_table.pdf)

