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SEMA ReACT
SEVERE MALARIA IN REMOTE AREAS
CLOSING THE EVIDENCE GAP

Generating evidence for the pre-referral use of rectal artesunate, combined with Injectable artesunate and artemisinin-based combination therapies, as part of the continuum of care for severe malaria patients in remote areas

Timely access to effective antimalarial therapies has been proven to save young lives. For instance, treatment with pre-referral rectal artesunate capsules (RAS), followed by injectable artesunate (Inj AS) and 3-day treatment with artemisinin-based combination therapies (ACTs) leads to an observed 96% reduction in mortality in trials settings. Although recommended by the WHO for years, RAS deployment has been limited. The full treatment paradigm is not always feasible when access to primary healthcare facilities is inadequate due to lack of transport, non-availability of services, and/or other resources. Rollout of RAS was temporarily paused as of January 2022, as analysis of observational outcome data seemed disappointing in these contexts. As of July 2023, after a careful in-depth review, the temporary moratorium on scale up of RAS deployment was lifted though the need to develop best practice recommendations remains high and challenging.

The project and its objectives

The 4-year SEMA ReACT project (April 2023 – March 2026) aims to generate data on treatment strategies that openly acknowledge and address the challenges faced by rural and vulnerable communities at risk of severe malaria infection. In doing so, the study can help reduce the burden of severe malaria, malaria mortality and morbidity in Africa, particularly in the youngest and most vulnerable members of society. It will thus directly contribute to the delivery of Sustainable Development Goal (SDG) #3 as well as SDGs #1, 2, 4, 10, 16.

We hypothesize that deployment of RAS in the health system improves access to health care by community members who would have otherwise sought care from elsewhere and may point to a decreased mortality at population level. And that RAS plus ACT can be implemented in remote areas in children 6 months to ≤5 years and is not inferior to RAS plus Injectable artesunate plus ACT in terms of effectiveness in remote areas.

The main goals of the study are categorised on the clinical assessments and on the implementation evaluation. This gives an opportunity to evaluate the best way to assess the proposed intervention (SEMA ReACT) in terms of its clinical effectiveness as well as its implementation feasibility aiming at saving lives of children 6 months to 5 years in places where referral for follow up treatment has been a problem.

Primary clinical evaluation objective:

- To evaluate the clinical outcomes of RAS plus ACT treatment for patients 6 months to 5 years in areas where referral for follow-up treatment with injectable artesunate is not feasible, compared to outcomes obtained after full referral is completed.

Primary implementation evaluation objective:

- To evaluate feasibility of provision of rapid treatment of severe malaria with RAS in children 6 months to 5 years not able to access a referral health facility, by a community health worker or in health facility where there is no injectable artesunate available.

The project will also assess operational and institutional facilitators and work towards mitigating barriers at the level of all stakeholders (patients, caregivers, health care providers, regulators, malaria experts).

Expected outcomes

Output data generated from the SEMA ReACT study will enable national and international policy makers and treatment guideline developers to decide how best to address severe malaria and realize the potential impact of RAS plus ACTs in rural settings. Increased evidence and understanding will ensure that normative treatment guidance addresses the needs of all patient populations and allows countries to maximize the impact of current tools in the face of rising death tolls.

SEMA ReACT partners and funders

The SEMA ReACT Consortium brings together partners experienced in the rollout and deployment of RAS, study design and execution, social science research, data collection & management, stakeholder engagement, and translation of research results into clinical practice.

The SEMA ReACT project is funded by The European and Developing Countries Clinical Trials Partnership (EDCTP3) and the Swiss State Secretariat for Education, Research and Innovation (SERI).

SEMA ReACT Work Packages

The SEMA ReACT Consortium workplan comprises five Work Packages (WPs), each responsible for well-defined aspects of the project and its delivery. A multi-national **Consortium Steering Committee (CSC),** will direct and oversee the project's scientific and technical decision-making, make provisions for the achievement of milestones and deliverables, and define budget allocations.

Work Package 1: Management and coordination

Led by Professor Jean-Pierre Van geertruyden, Global Health Institute, University of Antwerp (UA), Belgium.

WP1 will ensure the overall coordination and administration of the study and execute the decisions made by the CSC. Among its many responsibilities, WP1 will oversee and support the progress of other WPs, ensuring timely compliance with the grant agreement including financial and technical reporting.

Work Package 2: Study operations

Led by Dr Christine Manyando, Tropical Diseases Research Centre (TDRC), Ndola, Zambia

WP2 is responsible for operational execution, including study site assessments and enrolment, site-readiness activities, capacity building to support high-quality data capture, and patient monitoring. It brings together research institutes from Zambia, DRC and Tanzania and will be coordinated by local malaria experts well versed in the challenges of malaria case management in rural districts. Dr Manyando also serves as the scientific lead of the Consortium.

Work Package 3: Social science research
Led by Prof Aimé Kakudji Kyungu, University of Kinshasa (UNIKIN), DRC

WP3 will provide expertise in social science research and trial ethics and support all social science aspects of the study design and delivery. WP3 results will enable an understanding of community responses to RAS administration, especially factors that facilitate or hinder adherence to the strategy. These will be vital for future implementation in other similar settings. WP3 also seeks to understand the major political and sociological barriers for wider implementation of RAS in high burden areas.

Work Package 4: Data management and analysis
Led by Tafadzwa Maseko, University of Antwerp (UA)

WP4 will oversee data management and analysis of clinical data within the standards recognised by stringent regulatory authorities. It will be responsible for handling all sensitive patient data and overall data quality; and will help identify and support delivery of any training required to upskill clinical site staff and local doctoral students. This support will extend to training in data analysis and population statistics for principal investigators (PIs) and authors of any resulting publications.

Work Package 5: Communication, dissemination and exploitation
Led by Hans Rietveld, Medicines for Malaria Venture (MMV)

WP5 will work with the partners and national malaria control programmes of Zambia, DRC and Tanzania to ensure regular and timely communication of information about the study and its findings to key stakeholders. It aims to exploit the research results to their full potential, and support uptake, so that people at risk of severe malaria in sub-Saharan Africa have access to safe health technologies of proven efficacy.

Expected impact

Timely access to effective antimalarial therapies can be the difference between life and death, especially in rural areas where referral health facilities are only accessible by travelling long or geographically challenging distances. Thirty to 80 percent of Africa's population live in such remote communities where the deployment of RAS has the potential to save the lives of numerous children at risk of malaria infection. The SEMA ReACT study's outputs will not only improve severe malaria case management in rural settings, but will also have significant societal, economic, and scientific impact (link to web page on SMO).