



Investing in our future

The Global Fund

To Fight AIDS, Tuberculosis and Malaria

tel +41 (0)22 791 1700
 fax +41 (0)22 791 1701
 email info@theglobalfund.org

Chemin de Blandonnet 8 • 1214 Vernier • Geneva, Switzerland

www.theglobalfund.org

IMPLEMENTATION SCIENCE PRIORITIES FOR THE AFFORDABLE MEDICINES FACILITY-MALARIA (AMFm)

Needs and Opportunities to Learn From and Inform Implementation of Approaches to Scale-up Access to ACTs and Crowd-Out Undesirable Anti-malarial Treatment

Version of 30 November 2009

Please note: This document builds on bi-lateral and multi-lateral discussions with various partners and draws on materials from: (i) the AMFm Phase I Monitoring and Evaluation Technical Framework; and (ii) the Clinton Foundation’s June 2009 draft paper entitled Operational Research Needs and Opportunities to Increase Access to and Targeting of Effective Malaria Treatment.

1. INTRODUCTION

The Affordable Medicines Facility - malaria (AMFm) is a financing mechanism designed to make artemisinin-based combination therapies (ACTs) a more accessible treatment for malaria, and by so doing to reduce the use of less-effective treatments. The AMFm involves negotiating a reduced price for ACTs, and then making a co-payment towards the cost of ACTs purchased by eligible first-line buyers to further lower their sales price to end-users in malaria-endemic countries. These subsidized ACTs will then be distributed through providers across the public, private for-profit and not-for-profit sectors. By reducing the cost of ACTs available across all providers, the AMFm aims to serve as a platform for scaling up access to ACTs and curtailing emerging resistance to artemisinin exacerbated by the use of artemisinin monotherapies. In order to support the implementation of the co-payment for ACTs, as part of the AMFm, countries are required to implement supporting interventions to improve malaria case management and ensure safe and effective scale-up of ACT use. The AMFm is expected to represent one key component in a comprehensive global response to malaria.

The purpose and structure of implementation science opportunities in the Affordable Medicines Facility-malaria (AMFm) Phase 1 have been described in the AMFm Phase 1 Monitoring and Evaluation Technical Framework. In brief, implementation science provides a vehicle via which countries can investigate, test and build evidence for effective program activities that are applied to their specific country contexts. It generates lessons and provides opportunities for “learning by doing.” This includes an emphasis on “why and how” of implementation, unintended effects of the AMFm and how to mitigate them; implementation science provides an opportunity for understanding reasons why things are, or not are, progressing as expected and how to improve them.

Crucial considerations: Implementation science studies for the AMFm should: (i) be selected to address issues of strategic relevance and importance to the Global Fund Board, and (ii) be conducted in time for the findings to feed into the Phase 1 independent evaluation report, which will inform the Global Fund Board’s decision on the future of AMFm beyond Phase 1.

Some questions of potential importance to the Global Fund Board will not fit under implementation science. These may be appropriately examined through the independent evaluation of AMFm and complementary exercises in modeling of alternative scenarios. Readers are referred to the AMFm Phase 1 Monitoring and Evaluation Technical Framework for more details.

AMFm Phase 1 has two streams of implementation science activity which are explained below.

Importantly:

- It is essential that these implementation science studies are conducted; however, it is not key that the Global Fund be the financier. The Global Fund Secretariat is consulting with the Clinton Foundation, WHO's Special Programme for Research and Training in Tropical Diseases (TDR) and others to explore coordinated options for parallel or joint financing for this work stream.
- Coordination of research funding and activities will be central to ensuring that current key knowledge gaps are addressed. Whilst there will be a range of studies relevant to AMFm Phase 1, it is important to note that only a single report on the independent evaluation will be submitted to the Global Fund Board for its consideration.
- Given the timing of the Board decision, all activities must fit wholly or substantially within the duration of AMFm Phase 1.

1.1 Country-Specific Operational Research/Implementation Science

Countries are encouraged to undertake country-specific implementation science activities as part of their M&E grant activities during Phase 1. This means identifying and directly undertaking or commissioning implementation science work for their own use. AMFm application guideline to countries specified that operational research/implementation science questions should be directly relevant to the objectives of the AMFm and barriers to the achievement of these objectives. The guidelines also suggested that specific operational research/implementation science topics might be expected to fall into one of the following broad categories:

- Constraints on the availability of co-paid ACTs through public, private for-profit and not-for-profit channels;
- Factors that keep the retail prices of co-paid ACTs higher than those of chloroquine (CQ) and sulfadoxine-pyrimethamine (SP) (i.e., prices paid by patients in the private sector);
- Factors that prevent a significant increase in the market share of ACTs relative to monotherapies and other undesirable treatments (e.g., artemisinin monotherapies (AMTs), CQ, SP, amodiaquine (AQ));
- Barriers to access and use of co-paid ACTs by vulnerable socio-economic groups of interest to the AMFm (e.g., poor people, children and rural residents), including issues of the appropriate use of ACTs and compliance with the full course of treatment.

Some country-led studies could include randomization of alternative approaches to expanding access to co-paid ACTs, thereby strengthening the experimental evidence generated by AMFm Phase 1. However, local determination of the focus of country specific implementation science is important, given proposals are assessed to be relevant, feasible, technically sound and affordable.

There are a number of relevant source documents that countries may find useful for the identification and development of country-specific implementation science proposals.

- RBM AMFm Task Force. Operational Research Priorities for the AMFm, October 2008
- WHO. Partnerships for Malaria Control: Engaging the Formal and Private Sectors. 2006. www.who.int/tdr
- A Joint Publication: The Global Fund to Fight AIDS, Tuberculosis and Malaria, USAID, World Health Organization (Special Program for Research and Training in Tropical Diseases), UNAIDS, The World Bank Global HIV/AIDS Program, Framework for Operations and Implementation Research in Health and Disease Control Programs. 2008. <http://www.theglobalfund.org/me/FrameworkForOperationsResearch.pdf>

Countries were encouraged to develop implementation science proposals in line with the thematic areas listed above. However, other AMFm relevant ideas will be considered, where justified by countries (e.g., approaches to facilitate adherence to full treatment course regimens).

AMFm Phase 1 eligible countries intending to undertake implementation science work with Global Fund financing were required to provide a brief description of the concept and an estimated budget as part of the AMFm country grant application. The complete implementation science protocol (including methods) and budget will need to be shared with the Global Fund Secretariat upon grant amendment signature. Implementation science methods are determined by countries and described in the implementation science protocol submitted to the Global Fund Secretariat. If required, technical assistance to design implementation science protocols is available. Implementation science protocols are subject to scientific peer review and approval.

1.2 Multi-Country Implementation Science

Global Fund funded multi-centric implementation science activity will be determined on the basis of prior discussions with countries and multiple partners in the formative stages of the AMFm and through further consultations with partners who are planning a program of AMFm-related implementation science work. Discussions to date have led to the following thematic areas or “building blocks” of particular interest regarding existing knowledge gaps and the potential for extracting important lessons from the implementation of AMFm Phase 1. Please note that these priority “building blocks” are not mutually exclusive research areas. Multi-country implementation science to address the needs of Phase 1 of the AMFm should be designed to realize the aims identified below as key priorities. Priority research aims are those of strategic relevance and importance to the Global Fund Board decision that will be made regarding the future of the AMFm beyond Phase 1. It will be important to review effective practices and to understand what works, how and under what circumstances. These research aims may need to be further prioritized given financial resource constraints.

Priority aims of Phase 1 AMFm related multi-country implementation science, by thematic area:

1) Rational use of diagnostics and prescription of ACTs by frontline health workers (in both public and private sectors) alongside adherence to full treatment regimens by consumers

- (a) Inform approaches for scaling-up rational use of diagnostics and ACTs by frontline workers in both public and private sectors. This work area will take the approach of both/and, not either/or, regarding diagnostics and ACTs. It may include:
- i. Decision analysis to assess trade-offs, in terms of lives and money, between “treatment of false-positives” and “failure to treat false-negatives”¹ under different circumstances (e.g., levels of malaria endemicity, service delivery capacity, socio-economic status and ease of access to services (in the case of severe illness after failing to treat a false negative)).
 - ii. Analysis of incentives/disincentives and a comparison of approaches for rational use of ACTs among frontline service providers (whether public or private) who rely on drug sales for profit and/or cost-recovery. It should be possible to better understand how to make use of the profit motive in the private sector (and in some public sector settings) to achieve desired ends with respect to universal access to and rational use of ACTs.
 - iii. Compare and inform alternative approaches across different population and sub-population groups for supporting both provider and consumer behavior that facilitates adherence to full treatment regimens. This will require examining what works, where, under what circumstances, etc. and at what cost. It should improve understanding of how best to make use of the profit motive in the private sector (and in some public sector settings) to achieve desired ends with respect to adherence to full treatment regimens. [Lessons learned from this work could have implications that extend far beyond malaria.]
 - iv. Assess and inform discussions of cost-quality trade-offs: what are the total, average and incremental costs of improving quality in different contexts, where quality is defined as a combination of the rational use of diagnostics, rational prescription of ACTs, and adherence to the correct dose of treatment.

2) Reaching the poor and other vulnerable groups

- (a) Inform approaches for reaching poor populations, those living in geographically remote areas and other vulnerable groups, including elucidating factors that both hinder and facilitate the update of ACTs by socio-economic quintile. This will require examining what works, where, under what circumstances, etc. for reaching the poor and other

¹ The terms “false positives” and “false negatives” in this context refer to results of symptomatic diagnosis as the screening test; diagnoses based on RDTs/microscopy are confirmatory tests in this context.

vulnerable groups and at what cost. [Lessons learned from this work could have implications for improving access to other health interventions among these typically “hardest to reach” population sub-groups.]

- (b) Inform discussions about the costs, effectiveness and, where appropriate, monetized benefits of alternative approaches to reaching the poor and other vulnerable groups with ACTs. Such discussions must cover both AMFm goals of “saving lives” (through expanded access to ACTs) and “buying time” (by displacing monotherapies).

3) ACT delivery models

- (a) Inform how implementation of the AMFm performs relative to other financing platforms to both “save lives” (i.e., by expanding access to and increasing use of effective treatments) and “buy time” (i.e., by displacing monotherapies from the market, helping to decrease use of those monotherapies).
- (b) Inform what may be the most effective package of supporting interventions, including training and communications, to ensure the desired effects of making subsidized ACTs available.

4) Public/private sector interactions

- (a) Inform how best to maximize synergies and complementarities between public and private sector distribution channels.

5) Supply chains

- (a) Identify approaches that support the consistent supply of subsidized ACTs in the public sector. [Apart from the AMFm, maintaining an efficient, consistent supply of ACTs in the public sector remains an outstanding challenge in many countries.]
- (b) Inform approaches to ensure the consistent supply of subsidized ACTs to private outlets in remote areas, including through the use of incentive schemes.

6) Drug quality

- (a) Assess the quality of ACTs in local supply chains (public, private for-profit and private not-for-profit), including pharmaceutical content relative to packaging claims. [It will be important to assess this prior to the arrival of co-paid ACTs in countries.]
- (b) Inform practical approaches to minimizing the supply and use of poor quality ACTs (i.e., beyond legislation alone). [This is a well-known, long-standing challenge with implications beyond malaria.]

2. CONSIDERATIONS FOR SCREENING PROJECT CONCEPTS

In prioritizing from among the above-mentioned possibilities, it will be important that implementation science to be conducted maintain a strong emphasis on improving understanding with a view of finding solutions. Some additional suggested considerations that may be taken into account for prioritizing research projects include the following:

- **Leveraged impact:** the results of the project could directly lead to broad changes in policy and practice and subsequent health impact;
- **Relevance:** the intervention being tested and potential outcomes are relevant to the objectives of the AMFm;
- **Robustness:** the project will produce sufficiently robust results to inform appropriate decision-making;
- **Gap filling:** the project fills a key gap in existing evidence and practice and is fully additional to other research;
- **Efficiency:** the project achieves the necessary impact with as little as possible money and with robust initial results in time for the Global Fund Board decision on the AMFm, presently scheduled for November 2011; and
- **Country priority:** the area has been identified as a priority or area of strong interest by national governments or other local groups.

3. SOME EXISTING RELEVANT RESEARCH CURRENTLY FUNDED

There are a number of currently funded initiatives exploring issues related to malaria treatment access which may help expand the knowledge base and inform malaria treatment policy and implementation decisions. Information on these efforts available through public access websites is summarized below, by implementing organization. Whether findings from this work will be available in time to inform the Global Fund Board decision regarding the evaluation of Phase 1 of the AMFm is not specified in most cases.

3.1 ACT Consortium

The ACT Consortium is a global research partnership formed in November 2007 to answer key questions on malaria drug delivery in Africa and Asia. The Consortium aims to improve access, targeting and safety and to provide useful information to policy makers for planning and implementing the delivery of ACTs for the treatment of malaria.

The ACT Consortium is funded by the Bill and Melinda Gates Foundation and has partners throughout Africa, Asia, Europe and the United States. It is coordinated through the London School of Hygiene and Tropical Medicine. In March 2008, ACT Consortium announced a US\$ 39.7 million grant from the Bill & Melinda Gates Foundation through October 2012 to conduct a coordinated research program to identify how best to optimize the delivery and cost-effectiveness of combination drug treatment for malaria in Africa and Asia, and across a range of epidemiological and healthcare settings. This includes work on improving access to antimalarials, better targeting and diagnosis, determining drug side-effects and detecting counterfeit drugs.

The research coordinated from LSHTM is being undertaken by a consortium of academic institutions including Dangwe West Research Centre in Ghana, International Health Research Development Centre in Tanzania, the Karolinska Institute in Sweden, the Liverpool School of Tropical Medicine, the National Institute of Medical Research at the University of Copenhagen, and the University of Cape Town. The ACT Consortium currently has 14 projects (13 in Africa) in numerous sites across 11 countries. These countries include: Afghanistan, Cameroon, Ghana, Laos, Malawi, Mozambique, Nigeria, Rwanda, South Africa, Tanzania, and Uganda.

Studies address one or more of the following research themes: **access, targeting, longitudinal studies, safety and quality**. Below are specific research questions to be addressed and target outputs by theme. Although some projects address multiple themes, they are listed below under a single primary theme. Additional information can be found at <http://www.actconsortium.org/>.

3.1.1 ACCESS

Project 1: Comparison of home-based management of fever/malaria to enhanced health facility-based care in Tororo, Uganda.

Projects 2 and 3: Strategies to improve malaria diagnosis and use of ACTs in the home management of malaria (HMM) in Uganda: randomized trials to evaluate the role and cost-effectiveness of RDTs in HMM (Studies 1 and 2).

Project 4: IMPACT 2: Monitoring Interventions to Improve ACT Access and Targeting.

Project 5: An equity and cost-effectiveness analysis of alternative strategies for the deployment of artemisinin-based combination therapy (ACT) at the community level.

Research questions

- How can ACT delivery through health care facilities be optimized, and does this lead to increased uptake and access?
- What is the appropriate role of community management in ACT delivery outside the formal healthcare sector?
- What is the appropriate role of the private and non-governmental sector, including private drug retailers in ACT delivery, and how can this be best utilized to deploy ACTs and other new antimalarials?

Target outputs

- To determine, in terms of healthcare systems and epidemiology, where community-based management of malaria is effective and cost-effective as a way of improving access.
- To determine appropriate drugs for use within a community-based management system where ACTs are being deployed in the formal healthcare sector
- To define the role of the private sector in increasing access to new antimalarials
- To determine under what conditions, if any, in which rapid diagnostic tests used outside the formal healthcare sector, and especially in the private sector, can improve targeting of antimalarials to patients with malaria.

3.1.2 TARGETING

Projects 2 to 5 above

Project 7: Rapid Diagnostic Tests in patients with fever attending primary health care facilities. Adherence to test results and health outcome

Project 8: Effects of restricting the use of Artesunate plus amodiaquine combination therapy to malaria cases confirmed by a dipstick test: A cluster randomized control trial

Project 9: A cluster-randomised trial of health worker and community interventions to improve adherence to national guidelines for the use of ACTs in Tanzania: The TACT trial: (Targeting ACT)

Research questions

- Will the deployment of RDTs lead to an improvement in case identification and rational prescription of antimalarials and antibiotics at an individual level where microscopy already exists, but is ignored? This needs to be addressed in settings with different transmission intensities and healthcare systems, and can be addressed using relatively simple individually-randomized trials.
- Will the deployment of RDTs lead to an improvement in case identification and rational prescription of antimalarials and antibiotics at an individual level where microscopy does not exist and diagnosis is currently syndromic (e.g., most dispensaries)?
- Does using RDTs to limit prescriptions of antimalarials have a positive or negative impact on morbidity, both malaria-specific (such as anaemia) and from other causes of febrile illness (eg bacterial diseases) at the population level? This will need to be addressed using cluster randomized trials.

- Can rational prescribing of antimalarials be improved by behavioural interventions targeting both patients and healthcare workers? This will need to be addressed using cluster randomized trials.
- What is the impact of RDTs on prescribing rationally for falciparum malaria in settings where vivax malaria is the predominant species? This is a major problem in much of South Asia and parts of the Horn of Africa.
- How cost-effective are these diagnostic interventions?

Target outputs

- Quantification of the impact of deploying RDTs on the proper targeting of antimalarials for individuals in different healthcare settings and transmission intensities.
- Assessment of the impact of RDTs on malaria-specific and general morbidity at population level.
- Assessment of the relative impact on appropriate use of antimalarials of strategies that target both prescriber and patient behavior
- Quantification of the cost-effectiveness and acceptability of these approaches.

3.1.3 LONGITUDINAL STUDIES

Projects 6 and 11 (see below)

Research questions

- What is the impact of treatment with the same antimalarial combination (randomized to the combination to be prescribed for each episode of malaria) on treatment incidence density?
- When given repeatedly for treatment of uncomplicated malaria, how do different antimalarial combinations compare in terms of efficacy, safety, cost-effectiveness and measures of drug resistance?
- Does repeated treatment with an antimalarial combination change its safety profile or increase the risk of adverse events?

Target outputs

- Quantitative evidence of the impact of using one of the new combinations repeatedly within the same individuals on the burden of malaria for an individual, in comparison to other drug combinations under consideration.
- Data which can be used to calculate the cost-effectiveness of different drug combinations.
- Comparative safety data for the drug combinations under consideration.

3.1.4 SAFETY

Project 10: InterACT: Interactions between artemisinin-based combination treatment for malaria and antiretrovirals for HIV/AIDS in co-infected patients in Muheza, Tanzania

Project 11: Programmatic implementation of ACTs in Malawi: Safety and effectiveness of combination therapies with repeated treatments for uncomplicated *P. falciparum* malaria over a three-year period

Project 12: Establishment of a drug safety register for the ACT consortium

Project 13: Pharmacokinetic interaction between the antimalarial combination artemether/lumefantrine and antiretroviral therapy including nevirapine or lopinavir/ritonavir in HIV-infected adults.

Research questions

- How can existing networks and trials best be utilized to collect data on adverse events? This will include setting up an antimalarial adverse event database
- What is the frequency within the target population of adverse effects occurring with the different antimalarial combinations?
- What is the comparative tolerability of the different ACTs?
- What factors (e.g. age group, co-morbidity, repeated administration) predispose patients to developing adverse drug reactions?
- Are there any signals of new or unreported adverse events occurring with the ACTs or other new combination antimalarials?
- Are ACTs equally safe and efficacious in HIV-positive individuals, and are there clinically significant drug interactions between ACTs and antiretrovirals?

Target outputs

- Comprehensive reports, and regular policy briefs, on comparative safety of combination antimalarials in terms of the frequency and severity of different adverse drug reactions (ADRs) to ACTs (and other combination antimalarials)
- Testable hypotheses on the causation of adverse effects, and suggestions of possible interventions to minimize these risks that could be subject to trials.
- Determining risk factors associated with these ADRs, including data on the safety and efficacy of ACTs in those with HIV and on antiretrovirals.

3.1.5 QUALITY

Project 14: A surveillance system and drug forensic network to monitor the quality and authenticity of artemisinin combination treatments in Africa

Research questions

- To identify and develop inexpensive and easily deployed tests for fake or sub-optimal drugs that can be used near point-of-sale of antimalarial drugs.
- To develop and test an effective and sustainable sampling panel for early identification of fake and substandard drugs entering the market.
- To set up a network to detect fake antimalarial drugs and support the work of individual countries' drug regulatory authorities.

Target outputs

- Methods of testing for fake and substandard ACTs which can be easily and practically deployed in the field.
- Methods of sampling for ACTs which maximize the chance that any fake or substandard drugs will be rapidly detected.

3.2 The Catalytic Initiative to Save a Million Lives

As part of the multi-partner Catalytic Initiative, the Canadian International Development Agency (CIDA) is funding a 15 country home management of malaria project through Population Services International, Save the Children, the Malaria Consortium and the International Rescue Committee. The projects vary in breadth from simple presumptive treatment of malaria to community-based integrated management of childhood illness (C-

IMCI). The purpose of these projects is to demonstrate the impact and cost-effectiveness of community case management (CCM) of malaria (and other childhood diseases) in reducing child mortality.

- **Diagnosis/Drug Provision & Sale:** Comparison with control areas will allow an assessment of the impact of CHW programs on access to diagnosis and ACTs.
- **Treatment Seeking Behavior; Selection of Health Provider:** Assesses the impact of CCM on prompt access to treatment and use of CCM vs. facility-based care vs. retail sector.
- **Demand for/Acceptability of Diagnosis:** Assesses the impact of CCM on patient/caregiver acceptance of diagnosis.

3.3 ACTwatch

An initiative led by Population Services International (PSI) to monitor the availability, price, volume, perceptions and knowledge of anti-malarials in the public and private sectors. ACTwatch is active in 6 African countries (i.e., Benin, DRC, Madagascar, Nigeria, Uganda and Zambia) and Cambodia and includes household, outlet, and supply chain surveys. Outputs from the ACTwatch aim to inform policy in the following ACT supply/demand chain categories:

- **Importation and Distribution/ Stock Management:** Explores the functionality of the entire supply chain from importers to retailers and facilities, including mark-ups at each stage in the supply chain. Outlet survey explores inventory & stock outs of ACTs at public and private facilities.
- **Diagnosis:** Outlet survey collects information on the availability of RDTs in public and private outlets.
- **Drug Selection and Provision/Sale:** Outlet survey asks providers questions about ACT knowledge and promotion.
- **Treatment seeking behavior; Selection of Health Provider:** Household survey asks questions about treatment seeking behavior and health provider selection.

3.4 Medicines for Malaria Venture (MMV)

Building on its leading role in developing new anti-malarial treatments, MMV has recently expanded its work to facilitating increased access to ACTs and other effective treatments. Its access work is broad, with the most relevant activities for AMFm implementation science including support for a pilot ACT subsidy in Uganda (the Consortium for ACT Private Sector Subsidy (CAPSS)) and indepth surveys in other high burden countries, including Malawi, Mozambique, and Senegal. The targeted relevant outcomes include:

- **Importation and Distribution; Stock Management:** Examines current practices and breakdowns in the public and sector supply chains and impact on availability of products.
- **Drug Selection and Provision/Sale:** Surveys examine existing use of anti-malarials use in the private sector while CAPSS explores how selection and pricing of anti-malarials with introduction of subsidized ACTs and a package of supporting interventions.

- **Treatment seeking behavior; Selection of Health Provider:** Surveys explore current treatment seeking behavior, with CAPSS detecting potential changes in behavior following introduction of interventions.

3.5 **INDEPTH Effectiveness and Safety Studies of Anti-malarial Drugs in Africa (INESS)**

A project led by the INDEPTH network to monitor the safety and efficacy of anti-malarial use in the field. The project is currently being set up in Ghana and Tanzania and is expected to play a leading role in assessing the ongoing safety of ACTs. The limited relevance to AMFm implementation science includes:

- **Instructions/follow-up:** Assessing the frequency of adverse events associated with ACTs and the follow up of health providers.

3.6 **Special Program for Research and Training in Tropical Diseases (TDR)**

The UN-sponsored TDR is one of the leading research bodies on infectious disease issues in the developing world, with significant work on development and research of malaria interventions. Currently, TDR has a number of strategic focus areas within malaria, ranging from case management to vector control and integrated community interventions. The two most relevant for the AMFm are the areas of building evidence for access to anti-malarial treatment and supporting accessible quality assured diagnosis. Specific priorities and work within these areas that relate to the AMFm include:

- **Diagnosis:** Helping to drive the first-ever robust assessment of the quality and performance of malaria RDTs to support country and partner decision-making.
- **Treatment seeking/selection of health provider:** Assessing the feasibility and impact of home management of malaria programs in increasing access to effective treatment.
- **Drug selection:** Leading the evaluation of and policy guidance use of ACTs in home management of malaria programs; also, testing impact of rectal artesunate as a prereferral treatment for severe malaria.