UNITAID

END OF PROJECT EVALUATION OF THE "IMPROVING SEVERE MALARIA OUTCOMES" PROJECT

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Final Report

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CONTENTS

ACRONYMS AND ABBREVIATIONS

Acronym	Full description
AFI	Area for investment
BE	Bioequivalence
CEPA	Cambridge Economic Policy Associates
CHAI	Clinton Health Access Initiative
CHW	Community health worker
DALY	Disability-adjusted life year
ERP	Expert Review Panel
Global Fund	The Global Fund to Fight AIDS, Tuberculosis and Malaria
HCF	Health care facility
HCW	Health care worker
Inj AS	Injectable Artesunate
Ir AS	Intra-rectal Artesunate
ISMO	Improving Severe Malaria Outcomes
KPI	Key performance indicator
M&E	Monitoring and evaluation
MC	Malaria Consortium
MMV	Medicines for Malaria Venture
MoU	Memorandum of Understanding
MTE	Mid-term evaluation
NMCP	National Malaria Control Programme
PMI	US President's Malaria Initiative
ToR	Terms of Reference
UNICEF	United Nations Children's Fund
US FDA	United States Food and Drug Administration
VfM	Value for money
WHO	World Health Organization
WHO GMP	WHO Good Manufacturing Practice
WHO PQ	WHO Prequalification

EXECUTIVE SUMMARY

Background to the ISMO project

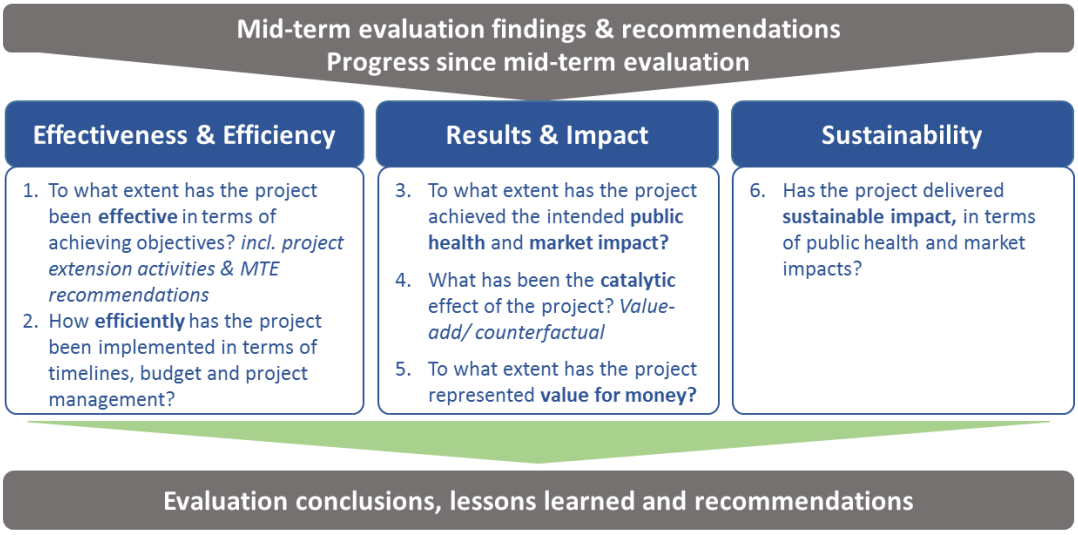
The "Improving Severe Malaria Outcomes" (ISMO) project was commissioned by UNITAID in June 2013 to address the limited availability and uptake of quality Injectable Artesunate (Inj AS) for treating severe malaria and lack of quality assured Intra-rectal Artesunate (Ir AS) for the pre-referral treatment of severe malaria in children, despite a revision of the WHO guidelines in April 2011.[1] For Inj AS, the project aimed to increase the proportion of severe malaria cases treated by Inj AS as compared with quinine, through supporting generic manufacturers to pre-qualification (PQ), funding commodity procurements and increasing country-level demand through updating guidelines and training health workers. For Ir AS, the project aimed to provide access to quality assured Ir AS for pre-referral treatment for severe malaria, by supporting manufacturers to PQ and conducting operational research.

Project implementation was led by Medicines for Malaria Venture (MMV), with Clinton Health Access Initiative (CHAI) and Malaria Consortium (MC) responsible for country-level activities. It was implemented over a period of three years from June 2013 to 2016 and with a budget of US$34m across six countries (Cameroon, Ethiopia (two regions), Kenya, Malawi, Nigeria (13 states) and Uganda. A four-month project amendment was agreed until September 2016 to effectively close-out activities.

Evaluation objectives and methods

This end of project evaluation has been conducted by Cambridge Economic Policy Associates (CEPA) during January-March 2017, and builds on our previous mid-term evaluation (MTE) of the project. The evaluation framework is structured around three key dimensions (Figure 1), and is based on document review, stakeholder consultations and quantitative analysis.

Figure 1: Evaluation framework



[1] WHO (2011), World Health Organization Guidelines for the treatment of malaria, 2nd edition – Rev 1.

Key findings by evaluation dimension are provided below, followed by overall conclusions, lessons learnt and recommendations.

Dimension 1: Effectiveness and efficiency

At the start of the project, there was mostly non-existent uptake of Inj AS. As such, the project goal of increasing the use of Inj AS for the treatment of severe malaria was extremely ambitious, requiring a radical change in policies, guidelines and behaviours. Given that by the end of the project supported countries had, for the most part, switched from quinine to Inj AS and that quality-assured Ir AS is now available are substantial project achievements. However the pathways to achieving these results for Inj AS have been more effective for demand creation activities than planned supply side activities, as discussed below.

Achievement of supply side activities

The supply side project interventions faced several issues in terms of manufacturer mobilisation and procurements, largely due to unrealistic timeframes in project planning. At project close, the Inj AS monopoly supply situation continued. However, the submission of two Ir AS dossiers to WHO PQ is a significant achievement of the project.

In terms of **WHO PQ dossier submissions**, we note the following project achievements:

- **Inj AS:** Ipca submitted their dossier to WHO PQ in December 2016, after the end of the project. This delay was largely due to factors beyond the control of the project, reflecting the complexity and high risk nature of UNITAID investments. However, with the benefit of hindsight we assess that it may have been more effective to support more than one manufacturer to balance risks and consider more realistic timeframes.
- **Ir AS:** The project target of two dossiers submitted for WHO PQ was achieved in December 2015 by Cipla and Strides. This is a key project success, which is unlikely to have been achieved without the support provided by MMV.

Regarding **Inj AS procurement**, we note the following achievements and key issues:

- **Price and procurement approach:** Significant efforts were accorded to price negotiations, despite UNITAID senior management noting this was not an intended key focus area. Whilst the project prices obtained from Guilin were the lowest prices offered (US$1.42 per vial for 80% of project orders), the target price of US$1.04 was not achieved. This has been due to the inability to bring in a second supplier, challenges with price negotiation strategies and continued use of monopoly power by Guilin. However, the pooled procurement approach adopted with the Global Fund helped build an important partnership and coordination between the organisations.
- **Procurement quantities:** The project procured a total of 5.6m Inj AS vials, representing 38% of the planned amount. This was largely attributed to higher than expected vial price, project delays with the initial procurement and changing country

needs with procurement from other donors. In most countries UNITAID-funded procurements served more as a "gap-filler", although in Kenya UNITAID was more catalytic, playing a "front runner" role. Nevertheless, country needs appear to have largely been met.

- **Procurement management:** Whilst concerns were raised on Missionpharma's appointment as the procurement agent, no major issues have been identified during the project. However, delays have been flagged in terms of long procurement lead times and long UNITAID approval processes, as well as cost and time implications from having removed in-country support from Missionpharma's contract.

Achievement of demand side activities

The project made significant achievements in terms of demand generation, through supporting procurement planning, health worker training and guidelines development. Indeed, this is an area of UNITAID's value-add, that it is able to "push" country demand, as compared to the Global Fund, who responds to country needs. Achievements include:

- **Country level demand quantification and procurement planning**: The project achieved its aim of having functioning quantification committees, as well as fully achieving the aim of zero stock-outs in four out of the six countries.
- **Health care worker training and use of guidelines**: The project has exceeded targets for training, thereby enabling a "*complete switch in mind set"* regarding severe malaria treatment. By the end of the project, health care workers from 2,082 health care facilities have received training (67% above target). However, there is evidence that continued efforts are required to ensure that these achievements are sustained given issues on staff attrition and effectiveness of extending training to other facility staff.
- **Operational research studies**: Four studies were completed, albeit with delays of at least twelve months and one study having been denied ethical clearance. Study results have been published and presented at an international conference.

Project efficiency

Overall the project has been well managed with effective partner selection, performance and coordination. However, we note the following in terms of issues and inefficiencies:

- **Timelines**: The project has been beset by a number of delays, including PQ dossier submissions, signing of country memoranda of understanding, and procurement, suggesting the need for better project planning and more realistic timelines.
- **Budget**: 59% of the budget has been expended, with the majority of the underspend due to lower levels of procurement than budgeted. A complete budget revision may therefore have been appropriate to more closely monitor budget efficiency.

- **Project structure**: MMV's coordination role for country-level activities without country presence has not been an optimal model, creating some inefficiencies in terms of communicating country-level information to UNITAID.
- **Monitoring and reporting:** There have been inefficiencies and inaccuracies in project reporting due to lack of clarity in indicator definitions and inappropriate reporting tools. These could have been mitigated through closer monitoring and dialogue between parties.
- **Collaboration and communication:** There is a need for greater and more effective collaboration between UNITAID and the project implementers, particularly for UNITAID to ensure common understanding of priorities, and roles and responsibilities.

Dimension 2: Results and impact

The project has had a positive public health impact, with approximately 85.5% of severe malaria cases reported as being treated with Inj AS by December 2015. Based on the 5.6m vials of Inj AS procured by the project, it is estimated that an additional 40,200 deaths and 660,300 DALYs were averted over the project period.[2] Through the provision of 12.6m vials from other sources in project countries and other African counties, the indirect impact is estimated to be much higher.

Whilst the planned market impact was not achieved for Inj AS, due to the continuation of a monopolistic market, the project did contribute to the increase in global procurement of Inj AS, from 1.6m vials in 2011 to 27m in 2015. Financial savings for the project and the Global Fund through pooled procurement are estimated at US$2.8m and US$3.6m respectively, when project prices are compared with UNICEF procurement prices over the period.

In terms of market impact for Ir AS, there is high potential to achieve the intended outcome of affordable quality-assured Ir AS on the market, with Cipla and Strides successfully submitting their Ir AS WHO PQ dossier and ERP approval being granted for Cipla.

Dimension 3: Sustainability

The project has supported sustainability by conducting activities focusing on systemic change, selecting partners with an ongoing focus in the area and emphasising transition planning. However, the project only supported manufacturers to PQ submission, rather than supporting through the approval and registration processes, raising potential sustainability issues.

There has been a notable increase in funding for Inj AS from the Global Fund and PMI since 2014, with a positive picture of donor commitments in the immediate future. However, we note potential risks in terms for Inj AS results as whilst there is an expectation that Ipca will receive WHO PQ approval and will adhere to the prices discussed, there are no assurances

[2] Please refer assumptions and limitations to these calculations in the main report and annexes.

that these will indeed be the case. The sustainability of results is promising for Ir AS, particularly given current discussions on follow-on support from UNITAID.

Conclusions, lessons learned and recommendations

In conclusion, the project was much needed and has been greatly valued by all stakeholders, with significant successes achieved in terms of supporting the development of quality assured Ir AS, increasing demand for Inj AS in focus countries, and enabling the appropriate use of Inj AS through a substantial training element. However, the supply side interventions for Inj AS have had limited impact, with delayed procurements reducing the intended catalytic role of the project and continuation of a monopoly supply situation as at project end.

Based on the lessons learned, we provide the following recommendations for UNITAID.

Recommendation 1: UNITAID should encourage reasonable flexibility and revision of approaches/ targets/ budgets based on learnings and developments in grant implementation, through ongoing dialogue between UNITAID and the grantee. Grant "trigger points" may be developed that merit re-scoping or revision of activities/ objectives.

Recommendation 2: UNITAID should develop a more collaborative approach with project grantees, moving away from a traditional "funder-grantee" relationship, to one that is partnership-based and reflective of UNITAID's engaged approach towards achievement of project objectives. This would entail a clearer definition of UNITAID's role within the project and that this role is well-communicated and understood by the grantee, open-dialogue and joint commitment to project results, and improving predictability of funding by ensuring clear and timely communication on potential extensions and/ or amendments.

Recommendation 3: There should be greater alignment between the project scope/ activities and the grant structure, considering project management structure and different elements of the project scope as separate grants or agreements with the most relevant parties.

Recommendation 4: Appropriate and realistic timeframes for project targets should be developed (recognising that this is challenging), drawing on wider stakeholder views and market intelligence.

Recommendation 5: Project logframes need to be developed in a robust manner, particularly in terms of clearly defining market terms (e.g. "access", "market stability"), including baselines, milestones and targets for indicators, and effective reporting formats.

Recommendation 6: UNITAID should take relevant measures to ensure the sustainability of project outcomes, with continuity of grants where there are follow-on grants and systematic tracking of achievements where there are no follow-on grants.

Recommendation 7: Project evaluations should be leveraged, by providing a management response for improved accountability and post-evaluation meetings to share grantee learnings.

1. INTRODUCTION AND EVALUATION APPROACH

Cambridge Economic Policy Associates (CEPA) has been appointed by UNITAID to undertake an end of project evaluation of the "Improving Severe Malaria Outcomes" (ISMO) project. This evaluation builds on the mid-term evaluation (MTE), which CEPA conducted during August-November 2015.

This introduction section provides a brief description of the UNITAID ISMO project (Section 1.1), evaluation objectives (Section 1.2), evaluation framework and methodology (Section 1.3) and structure of the report (Section 1.4).

1.1. Background to the ISMO project

The ISMO project was commissioned by UNITAID in June 2013 with the goals of increasing the proportion of severe malaria cases treated by Injectable Artesunate (Inj AS) as compared with quinine and providing access to quality assured Intra-rectal Artesunate (Ir AS) for pre-referral treatment for severe malaria. The project context was limited availability and uptake of quality Inj AS and lack of quality assured Ir AS despite a revision of the WHO guidelines in April 2011 recommending the use of Inj AS for treating severe malaria and Ir AS for pre-referral treatment of severe malaria in children.[3] The project outcomes were therefore to create a stable market to catalyse the use of quality-assured Inj AS and improve the availability of affordable quality-assured Ir AS for pre-referral treatment. The project goals, outcomes and outputs are presented in Table 1.1.

Table 1.1: Project goals, outcomes and outputs

Injectable Artesunate	
Goal	To increase the proportion of severe malaria cases treated by Inj AS as compared with quinine[4]
Outcome	Creation of a stable market for quality assured Inj AS
Outputs	1. Increased use of (appropriately used) Inj AS for severe malaria 2. Generic manufacturers producing quality assured Inj AS 3. Other global donors/ funders commit to funding procurement of Inj AS 4. Procurement planning for stabilization of the market for Inj AS
Intra-rectal Artesunate	
Goal	Access to life saving quality assured Ir AS for pre-referral treatment for severe malaria
Outcome	Affordable quality assured Ir AS on the market
Outputs	1. Securing of Prequalification of Ir AS 2. Optimise use of Ir AS in low resource settings

[3] WHO (2011), World Health Organization Guidelines for the treatment of malaria, 2nd edition – Rev 1.

[4] Revised from "to reduce case fatality rates for severe malaria" due to measurement challenges for this indicator.

The project budget was US$34m for three years between June 2013 and June 2016 across six countries (Cameroon, Ethiopia (two regions), Kenya, Malawi, Nigeria (13 states) and Uganda). Key planned activities included updating of treatment guidelines, development and delivery of training materials for Inj AS, training of health workers in the appropriate use of Inj AS, support to country quantification committees, procurement and delivery of Inj AS and support for the preparation and submission of the pre-qualification (PQ) dossier for a second Inj AS product and at least two Ir AS products. In addition, there was an operational research component with four studies around the use of Inj AS and Ir AS in low resource settings.

Project implementation was led by Medicines for Malaria Venture (MMV), with Clinton Health Access Initiative (CHAI) and Malaria Consortium (MC) responsible for in-country activities. The procurement agent selected for Inj AS procurements was Missionpharma. Following an analysis of potential manufacturers, MMV agreed to support Ipca for Inj AS and Cipla and Strides Arcolab (Strides) for Ir AS PQ submissions.

In October 2015, MMV requested an 18 month project extension from July 2016 to December 2017 using the unspent budget.[5] This request was not approved by UNITAID as they viewed the project to have succeeded in achieving its catalytic impact in line with its objectives, as well as on account of commitments to Inj AS procurement having been made by other donors. Instead, a project amendment was agreed for four months until September 2016 to effectively close-out activities, with a budget of $111,592.

1.2. Evaluation scope and objectives

Based on the Terms of Reference (TOR) and discussions with the UNITAID Secretariat, the evaluation objectives are as follows:

- To provide UNITAID with an assessment of the programmatic implementation of the project, with a particular focus on the market and public health impact.
- To assess project results and sustainability, as well as identify key lessons learned from project implementation.
- To build on the value for money (VfM) analysis of the project conducted by CEPA previously, in terms of direct, indirect and long term impact.

The evaluation covers the full period of the project, including the extension, and builds upon the analysis and findings of the MTE.

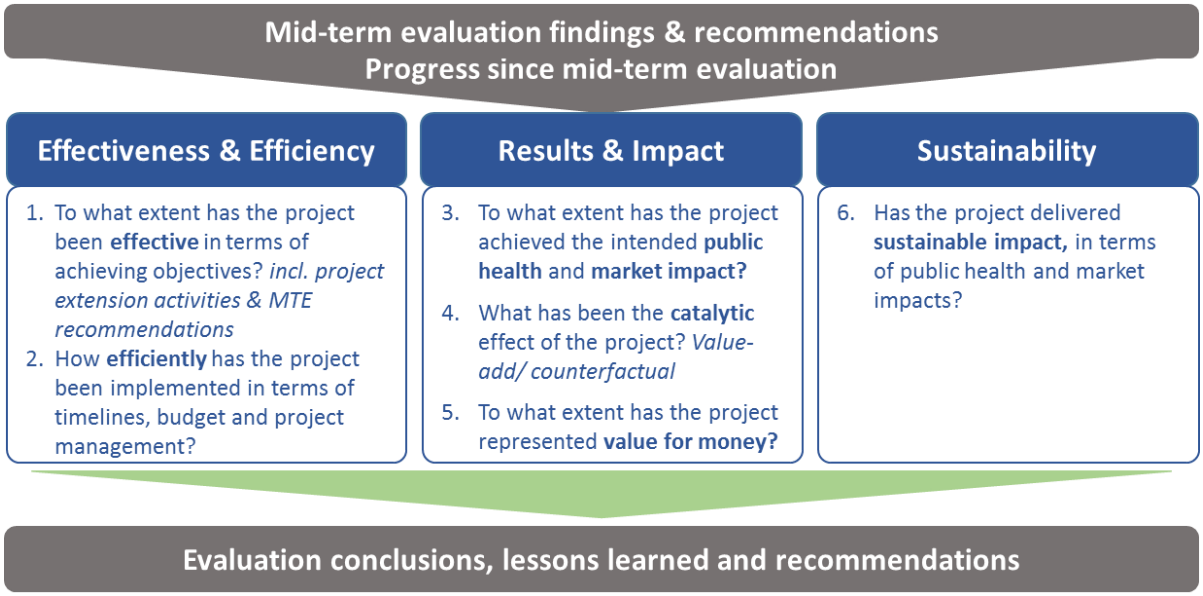
[5] Drawing on ongoing discussions at that time with project stakeholders, an extension had also been recommended in the mid-term evaluation.

1.3. Evaluation framework and methodology

1.3.1. Evaluation framework

The evaluation framework (Figure 1.1) has been structured along three inter-related dimensions of: (i) effectiveness and efficiency of implementation; (ii) results and impact; and (iii) sustainability. Specific evaluation questions have been developed for each dimension, under which we have assessed issues related to Inj AS and Ir AS in turn. Our analysis across these evaluation dimensions informs the evaluation conclusions, lessons learned and recommendations.

Figure 1.1: Evaluation framework



1.3.2. Evaluation methods

Key methods for the evaluation include a review of documentation, stakeholder consultations and quantitative analysis, as detailed below.

The comprehensive **desk-based review of project documents** included applicable information shared for the MTE, as well as progress reports since the MTE, ISMO transition plan, contract amendments, papers from the operational research, end of project letters to countries, site visit audits, logframe updates and budget documentation. Annex 1 provides the list of documents consulted.

Stakeholder interviews comprised an important source of information for this evaluation, and were conducted by telephone. Interviewees have included UNITAID Secretariat, project implementers (MMV, CHAI, Missionpharma), MoH in select project countries, pharmaceutical manufacturers and other donors. Annex 2 provides a list of interviews conducted and Annex 3 provides corresponding interview guides.

Quantitative analysis has been conducted on data including: indicator results against targets set out in the project logical framework; key metrics on efficiency and efficacy of procurement

activities, including volumes, prices, lead-times and stock-outs; project budget and expenditure; and data analysis relevant for the impact and VfM assessment.

1.3.3. Evaluation limitations

The limitations of our evaluation methods are noted below.

- **Availability of detailed progress data until end-2015 only:** The 2016 Final Report provides the most up-to-date source of information available for the evaluation, but does not include detailed data for 2016 (as per the agreed project reporting approach). As such, project progress has only been analysed in detail until 2015, whereas the project closed in September 2016.
- **Stakeholder bias:** Stakeholder consultations with UNITAID and project implementers have formed the key evidence base but have been impacted by the relative bias implicit in the role of each stakeholder (i.e. funder, implementer). Several project developments have had conflicting viewpoints from these stakeholders, rendering challenges in making unbiased conclusions.
- **Limited review of country activities:** Country visits were not included in the evaluation methodology. As such, country-level activities and country stakeholder perceptions have been gathered through a very limited number of phone consultations, although we have drawn on the country visit findings during the MTE. Further, consultations were only held with one of the two country-level project implementers, as it was not possible to contact MC, despite several attempts.

1.4. Structure of the report

The report is structured as follows:

- Sections 2 to 4 provide an analysis and assessment of the three evaluation dimensions of effectiveness and efficiency, results and impact, and sustainability; and
- Section 5 presents evaluation conclusions, lessons learned and recommendations.

The report is supported by the following annexes: bibliography (Annex 1); list of stakeholders consulted (Annex 2); interview guides (Annex 3); analysis of the extent to which the MTE recommendations were implemented (Annex 4) and data and assumptions for the value for money analysis (Annex 5).

2. DIMENSION 1: EFFECTIVENESS AND EFFICIENCY

The first evaluation dimension, focussing on the implementation experience, assesses the effectiveness and efficiency of the project. This assessment focuses on the extent to which project *activities* and *outputs* have been completed/ achieved thereby supporting planned objectives, noting progress made since the MTE and factors that have supported or impeded progress.

2.1. Project effectiveness

Q1: To what extent has the project been effective in terms of achieving objectives?

The context at the start of the project was one of severe malaria treatment not adhering to the WHO guidelines, with mostly non-existent uptake of Inj AS. The project goal of increasing the use of Inj AS for the treatment of severe malaria therefore required a radical change in policies, guidelines and behaviours that had remained unchanged for decades. As such, the project was extremely ambitious, and the fact that by the end of the project, supported countries had for the most part switched from quinine to Inj AS is a substantial achievement. The project contribution towards making available quality-assured Ir AS is also another key project legacy.

Nevertheless, the project faced several issues in successfully completing the intended pathways for these results in terms of manufacturer mobilisation and project procurements, largely due to unrealistic timeframes in the project planning; although was more successful with demand generation and policy change activities at the country level. In this first question, we consider these pathways in detail, from the perspective of:

- **Supply side activities**, in terms of: (i) Inj AS WHO PQ dossier submission; (ii) Ir AS WHO PQ dossier submissions and (iii) Inj AS procurement and price negotiations; and
- **Demand side activities,** in terms of: (i) country level demand quantification and procurement planning, (ii) health worker training and (iii) operational research.

2.1.1. Achievement of supply side activities

We first discuss the above-noted supply side activities (i) and (ii) in terms of Inj AS and Ir AS dossier submission, followed by (iii) on Inj AS procurement and pricing.

Inj AS and Ir AS WHO PQ dossier submission

The project outputs for Inj AS and Ir AS were to enable generic manufacturers to produce quality assured Inj AS and to secure the prequalification of Ir AS respectively.[6] Table 2.1 below presents the extent to which project targets have been achieved for Inj AS and Ir AS and Table

[6] As per the revised project logframes for Inj AS and Ir AS (23 May 2013)

2.2 provides an overview of progress by supported manufacturers during the project and since project close, based on the 2016 Final Report and our consultations with the project implementer and manufacturers.

Table 2.1: Achievement of project targets for PQ dossier submission and stringent regulatory approval[7]

Product	Indicator target	Achievement
Inj AS	At least one dossier submitted to WHO PQ (Baseline of Guilin having submitted a dossier prior to project start)	One dossier submitted since project close (Ipca).
Ir AS	At least two dossiers submitted to WHO PQ	Two dossiers submitted during the project.[8]
	At least two products prequalified	No products WHO prequalified, but one product received Expert Review Panel (ERP) approval since project close.

Table 2.2: Overview of progress towards WHO PQ dossier submission during and post-project

Manufacturer	Progress during project	Progress since project close
Ipca (Inj AS)	• Factory upgrades and generating six months of stability data • Technical project support provided by MMV, including mock inspections	• Dec 2016: WHO PQ dossier submitted • July 2017: WHO GMP site inspection planned
Cipla (Ir AS)	• Dec 2015: WHO PQ dossier submitted • Technical and financial project support provided by MMV	• Q3 2016: ERP approval received • Procurement discussions with donors and intention to bid on upcoming Global Fund tender
Strides (Ir AS)	• Dec 2015: WHO PQ dossier submitted • Requirement to re-conduct the bioequivalence (BE) study, as WHO had not considered original results to be demonstrative • Technical and financial project support provided by MMV	• Q1 2017: BE study report re-submitted to WHO PQ

These results are considered in further detail below.

Support to manufacturers for Inj AS

Whilst the project target of a dossier submission for WHO PQ was not achieved during the project lifetime, Ipca submitted their dossier in December 2016, shortly after project close. This delay was largely on account of factors beyond the control of the project and reflects the complexity and high risk nature of UNITAID investments. However, with the benefit of

[7] Legend for colour coding – Green: target fully achieved; orange: target partially achieved; red: target not achieved. Information on achievements since project close were provided by MMV, Ipca, Cipla and WHO PQ.
[8] ISMO End of Project report, p.38. We note the dossiers were submitted later than originally planned.

hindsight there is learning that it may have been effective to support more than one manufacturer to balance risks and consider more realistic timeframes.

At the start of the project, MMV conducted discussions with a number of manufacturers to determine potential for Inj AS PQ dossier submission. Ipca, whom MMV had been providing technical support to previously, was deemed as the most viable partner to submit their dossier by end 2013, and a Memorandum of Understanding (MoU) was signed to this effect.[9] The MoU required Ipca to submit to the ERP by end of 2014, therefore enabling procurement of a quality-assured product by early 2015. However, Ipca's dossier development was beset by delays, mainly unforeseen, throughout the process, including:

- United States Food and Drug Administration (US FDA) import warning and the need for Ipca to deploy internal resources to manage the issue. In January 2016 a further warning letter was issued by FDA and the import alert remains in place.[10,11] However, given demonstrated progress, Ipca are now exporting some API products to the US and the ban is therefore not expected to impact the clearance of the WHO PQ dossier.
- Ipca conducted factory upgrades, including to the sterile API block, the filling line and a new water system, which had not been discussed with MMV. These delays had therefore not been factored in to the anticipated timelines.

As such, Ipca's dossier was submitted almost three years later than planned.

Based on our consultations, we understand that two other manufacturers have since made progress with WHO PQ dossier submission for Inj AS – Mylan and Macleods – both of whom are looking to submit dossiers by the end of 2017. Mylan has recently received MMV support outside of the UNITAID project and Macleods stated during our interview that technical support from MMV would have been beneficial.

Whilst the decision to support one manufacturer only was also based on funding availability through the project, with the benefit of hindsight there is learning that it may have been beneficial to support more than one manufacturer for WHO PQ submission. Indeed, this was also flagged in the MTE and supporting an additional manufacturer for the final year of the project may have sped up outcomes, also given available budget within the project. Further, we assess that the project timeframes were unrealistic, particularly those within Ipca's MoU, therefore suggesting the need for greater market review and intelligence by UNITAID and project implementers to define project parameters.

In spite of these delays, consultations have reported positively on MMV's support to Ipca, with Ipca noting that their support helped speed up the process for dossier submission, through appropriately supporting the dossier development process, providing insight into

[9] ISMO Project Plan 1s (Inj AS), p.40. We understand that MMV also prepared an MoU to provide support to Mylan. However, this MoU was not signed and support not provided due to Mylan subsequently failing an FDA inspection.

[10] www.fda.gov/ICECI/EnforcementActions/WarningLetters/2016/ucm484910.htm

[11] www.accessdata.fda.gov/cms_ia/importalert_189.html Published date 28th February 2017

how to navigate the interagency network, and negotiating a date for WHO to conduct the good manufacturing practice (GMP) inspection, as required for ERP application.

Whilst MMV's proposed project extension (that was not approved by UNITAID) would have entailed additional support to Ipca, it is not clear if this would have substantially brought forward the timing of the Ipca PQ dossier submission or helped reduce prices eventually (see below on procurement analysis). Discussions with Ipca indicate that the support MMV has been able to provide since project close has been sufficient to support dossier preparation. Nevertheless, our view is that there is a potential risk that intended project benefits may not be realised (e.g. should Ipca run into issues during WHO PQ approval), but also recognise that UNITAID investments need to be time-bound.

Support to manufacturers for Ir AS

For Ir AS, the project target of submission of at least two dossiers for WHO PQ was achieved in December 2015 by Cipla and Strides. This is one of the biggest project successes, particularly noting that when the project started, there was no quality-assured product on the market. The broader target of having at least two Ir AS products prequalified has not yet been achieved, but Cipla received ERP approval in December 2016, since project close.

MMV provided both technical and financial support to Cipla and Strides, which has been viewed very positively and seen as having played a critical role in achieving WHO PQ submission, through:

- **Accessing TDR reference capsules -** MMV were able to provide evidence to WHO that the TDR capsules were representative of those used to generate clinical trial data and then, following several months of negotiations with WHO, were able to make these capsules available to Cipla and Strides. This enabled both manufacturers to conduct bioequivalence (BE) studies, rather than new clinical trials that could take around three years to conduct, thus significantly speeding up the process and reducing costs. Cipla and Strides both stated not being able to achieve this without MMV's support. Indeed, Cipla had started Ir AS product development prior to MMV support, but were struggling to access the comparator product.
- **Financial support to act as a needed subsidy -** Ir AS is not viewed as a particularly profitable commodity by the two manufacturers, with the financial support provided by MMV viewed as acting as an incentive to invest. For example, the cost of BE studies was noted as being higher than anticipated.[12] Several stakeholders also viewed this as being a key factor for ensuring the product dossier received due priority over others.
- **Dedicated and engaged support -** Having a focal point at MMV to provide technical assistance, liaise with WHO and project manage the PQ dossier preparation was

[12] We note that Macleods are currently developing a WHO PQ dossier for Ir AS without external support, implying that financial incentives are not essential. However, Macleods are unlikely to be able to progress without external support in obtaining TDR reference samples.

viewed as being particularly helpful in speeding up the process and having a better understanding of WHO requirements.

Procurement of Inj AS

The final aspect for review of supply side activities covers the procurement of Inj AS, including planned versus actual prices and quantities secured.

Price and procurement approach

One of the two project indicators to measure progress towards the project outcome of creating a stable market for quality assured Inj AS was related to price reduction. UNITAID senior management have commented that this was not intended to be the project focus, however we assess that this focus was not clearly communicated or well understood within UNITAID and by project implementers, given the significant effort accorded to price negotiations during the project.

The project target was to achieve a median price of US$1.04 per vial by the end of the project, representing a 20% reduction against the 2012 UNICEF reference price of US$1.30.[13] This target was not achieved, with 80% of project orders purchased at US$1.42 (following lengthy negotiations) and the remainder at US$1.56 (which is 50% higher than the project target). However, the prices obtained by the project were reported by Guilin as being the lowest price offered.

The poor performance against the pricing targets and high transaction costs in price negotiations have been on account of several factors, including:

- **Inability to bring in a second supplier** during the project timeframe, as discussed above.
- **Challenges with negotiation strategies** – As indicated in the MTE, a pre-agreed pricing agreement with Guilin may have reduced transaction costs associated with negotiations during the project. There was also the challenge that the project could not commit to larger or longer term procurements, given UNITAID is relatively small and short term buyer. Further, we understand that at the start of the project, Missionpharma commenced price negotiations with Guilin to obtain a price of US$1.45, which according to UNITAID set the bar high for further reductions.
- **Continued use of monopoly power by Guilin** – Guilin reported the price increase, to US$1.56, for the final project procurement as being due to the project not having ordered in the volumes originally discussed, the Yen having devalued against the USD, and increased cost of labour and power. Furthermore, one of Guilin's two plants was closed due to GMP requirements, thus reducing the capacity Guilin was expecting to be able to manufacture and therefore a greater need to recoup costs.

[13] We note the logframe target is measured against either the UNICEF reference price or Global Fund price.

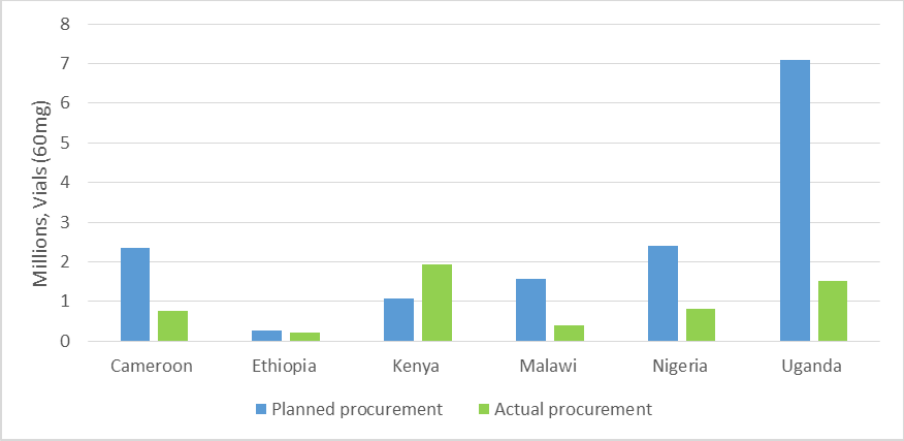
However, we also question the accuracy of the project benchmark of US$1.30, the 2012 UNICEF reference, which does not seem indicative of the market at that time. For example, in 2012/13 Global Fund had paid US$1.35, UNICEF US$1.66 and PMI up to US$1.90.[14] A more accurate assumption may have been to take an average of different prices achieved by large institutional buyers, rather than opting for the lowest value.

A strength of the project procurement approach was the pooled procurement arrangements with the Global Fund. In an attempt to secure price reductions by leveraging larger volumes, UNITAID and MMV adopted a pooled procurement approach with the Global Fund. Through joint negotiations, a final price of US$1.42 was agreed in June 2014, albeit after a delay of four months. However, this helped build an important partnership between the two organisations, as well as improved coordination.

Procurement quantities

The project procured a total of 5.6m Inj AS vials, representing 38% of the planned amount of 14.8m vials.[15] As such, most countries, apart from Kenya, received significantly lower volumes from UNITAID than planned, as reflected in Figure 2.1.

Figure 2.1: Actual procurement volumes compared with planned procurement[16]



The following reasons were provided for this lower than anticipated procurement:

- **Higher than expected vial price**: The total number of planned vials had been based on a lower price per vial than was achieved, meaning with the agreed price of $1.42, fewer vials would be able to be purchased with the project budget.
- **Delayed initial procurement:** Following prolonged price negotiations described above and delays in signing country MoUs (lasting from November 2013 – February 2014),[17]

[14] ISMO 2013 Annual Report, p.30
[15] ISMO Procurement plan (pp. 14-15)
[16] Based on cumulative procurement figures presented in the ISMO End of Project Report, as data for 2016 results has not been made available to the evaluation.
[17] Signature of the MoU for Malawi was postponed until parallel distribution challenges had been resolved in November 2014, though the text of the agreement had been finalised in February. The ISMO 2014 Annual Report

the first order was placed in June 2014, seven months later than originally planned.[18] As such, by the end of 2014, UNITAID had procured 2.7m vials, compared with the planned 6.3m vials.[19]

- **Changing country needs with procurement from other donors:** Procurement forecasts were based on the hypothesis that UNITAID would initially fulfil most of country needs, before other donors gradually increased their commitments. Whilst this hypothesis may have held true at the time of project design in 2012, given initial project procurement delays, by the time of the first UNITAID procurement other donors (e.g. the Global Fund and PMI) were already procuring significant amounts. This was spurred in part by the successful demand creation activities of the project, as discussed in the next section. In Uganda, for example, the first UNITAID delivery was postponed until July 2015 as other donors had already committed to meeting Uganda's need until that time.

As such, in most countries the UNITAID project procurements served more as a "gap-filler", although there were country exceptions, such as Kenya, where UNITAID played more of "front runner" and catalytic role. Importantly, despite these lower than anticipated volumes, country needs appear to have largely been met, with the only country to show a gap in needs for 2016 being Uganda.[20]

Procurement management

In terms of procurement management, whilst concerns were raised on Missionpharma's appointment as the procurement agent, no major issues have been identified in their management of the procurement process.[21] The MTE also notes that initial issues were also resolved in discussion with MMV.

Initial issues regarding clarity of roles and responsibilities were rectified through regular meetings with MMV, weekly shipment updates and a set of key performance indicators (KPIs), which were reported on regularly and showed mainly positive results. Areas where performance issues were raised, such as receipt of timely cost estimates, were noted as being due to unrealistic targets which had not been jointly agreed upon.

However three key issues have been flagged on procurement management more generally:

- **Long procurement lead-time:** The project anticipated a lead time of 140 days (from date of quantification to delivery at central medical store). However, the average lead time during the project was around six months (or 180 days), due to a shortage of

does not include the months between February and November in its assessment of "delays caused by MoU signatures".

[18] ISMO 2014 Annual Report, p.18

[19] ISMO End of Project report (p.21) and Procurement plan (p.14).

[20] ISMO Project transition plan reports Uganda having a gap of 187,854 vials for 2016.

[21] Whilst UNITAID questioned the performance of Missionpharma, a KPMG audit in 2015 evaluated the quality and delivery of supply management and distribution as robust and efficient, highlighting only minor issues for improvement on length of decision making processes. KPMG (November 2015), Field Visit, Missionpharma.

refrigerated containers for transportation, delayed production by Guilin (for the last order) and delays to clear customs.

- **Long procurement approval process:** Following UNITAID rules, every project procurement order had to be approved by UNITAID, which lengthened the process time. Whilst it was noted in the MTE that UNITAID was reviewing these processes in order to enhance efficiency, changes were not made before the end of the project. Further, UNITAID was keen to closely monitor procurement, possibly due to the higher than planned unit price, and project implementers reported that only orders which would otherwise have resulted in country stock-out were approved.
- **Ineffective role definition:** We found that the decision to remove in-country support from Missionpharma's contract in exchange for a reduced fee has created substantial difficulties for implementing partners in Kenya. For example, our analysis of import waiver processes in Kenya suggests that decision increased rather than lowered overall project costs.[22] This also led to the project using the central medical stores trust in Malawi, which other donors had boycotted due to accountability concerns.

Project stakeholders have flagged other issues throughout the procurement process, including one procurement arriving during the extension period raising questions around whether this was effectively managed given reduced staff presence. However, due to evaluation limitations in gaining a clear picture from the country perspective, it is not possible to comment further on these.

2.1.2. Achievement of demand side activities

The project made significant achievements in terms of demand generation. Indeed, this is an area of UNITAID's value-add, that it is able to "push" country demand, as compared to the Global Fund, who responds to country needs. This has been achieved through conducting a broad range of awareness raising and demand generation activities, working with MoH and National Malaria Control Programmes (NMCP). This is evident from the fact that all six project countries included Inj AS in their concept notes to the Global Fund in 2014.[23] Given that the CHAI malaria programme only have a presence in Malawi and Cameroon through ISMO funding, this achievement can be largely linked to the project.

Many of the key demand side project objectives had already been achieved at the time of the MTE, in terms of supporting procurement planning, health worker training and guidelines development. This section therefore assesses additional progress since that point, as well as how key issues raised in the MTE have been addressed.

[22] CEPA (2015) Mid-term evaluation of the ISMO project, p.20

[23] Malawi submitted their concept note in 2015. Uganda's concept note also included Ir AS.

Country level demand quantification and procurement planning

The project aimed to have **functioning quantification committees** in all project countries (output indicator 4.2), which was achieved by 2014. Their main achievement has been the coordination across donor procurements, development of a supply plan and conducting gap analyses. Whilst these committees often existed prior to the project, support has ensured that Inj AS has been a key focus area. For example, Cameroon, the last country to meet this target, already had a general quantification committee within its Department of Pharmacy and Medicines, but established a severe malaria sub-committee supported by CHAI from Q1 2014.

The project also aimed for **zero stock-outs at the central warehouse** in each country (output indicator 4.1). This objective has been fully achieved in four countries (Cameroon, Ethiopia, Malawi and Uganda). However, stock-outs were observed in:

- **Kenya:** Due to delayed UNITAID deliveries in Q3 2014, with the Kenyan MoH lacking funds to re-stock in the interim.
- **Nigeria (three states):** Due to delays in obtaining waivers following presidential elections.

Given the focus of project interventions, stock-outs are only measured at the central level, which we consider appropriate. However, to assess overall project impact, we also note that there have been some stock-out issues at district and health facility levels, highlighting broader health systems issues of supply chain and stock reporting.

- **Ethiopia** - stock outs were experienced due to a shift in supply chain management responsibilities from regional health bureaus (RHBs) to the government agency PFSA (Pharmaceuticals Fund and Supply Agency).
- **Malawi** - experienced stock outs in the first half of 2016 due to issues with distribution from the central medical storage to health facilities, also linked to quantification challenges during the rainy season.
- **Uganda** – experienced a month of stock-outs due to a malaria epidemic in 2015, which UNICEF was able to address through an emergency order.

Health care worker training and use of guidelines

The substantial progress made in terms of designing and implementing health worker trainings by the time of the MTE has been further capitalised on by the end of the project. As one stakeholder noted, this thereby enabled a *"complete switch in mind set"* regarding severe malaria treatment. We note the following key achievements:

- Training modules have been designed and developed in collaboration with country NMCPs. All six countries have developed and are utilising case management training materials, which are aligned with WHO guidelines on administration of Inj AS.[24]
- In collaboration with country NMCPs, 1,243 health care facilities (HCFs) were identified from which to train health care workers (HCWs). By the end of the project, HCWs from 2,082 HCFs have received training through a training of trainers approach (67% above target). This approach, as well as cascade training, has resulted in over 18,000 HCWs being trained on the appropriate administration of Inj AS for severe malaria.
- In several countries, the project provided supportive supervisions, which were seen as beneficial to improving health worker practices.
- We understand from MMV that the training tool kit (posters, job aids and videos) have also been used outside of the six ISMO project countries in Cape Verde, DRC, Namibia, South Africa, Swaziland, Togo and Zambia.

However, an issue with the trainings was that in some countries, training was provided prior to Inj AS being available in countries (on account of the procurement delays discussed previously), resulted in the need for refresher training.

We note the positive effects of these trainings on demand generation. For example, the operational research component provides strong evidence of the positive effect that the existence of a malaria treatment policy chart has on the appropriateness of treatment provided.[25] However, results from the operational research also note challenges with the cascade training model, which was not effective at extending training to other facility staff as planned and has been further exacerbated by high staff attrition rates.[26]

In summary, although project objectives for training have been exceeded, there is evidence that continued efforts are required to ensure that these achievements are sustained. We note this was included in MMV's request for a project extension, although assess that UNITAID's rejection of this request was justified given its role is not to provide ongoing funding for these activities.

Operational research studies

As part of the project, four operational research studies were conducted in Ethiopia, Nigeria and Uganda.[27] All studies were completed, with the exception of one study in Uganda, for

[24] 5 of the 6 countries had achieved this by 2013, with Cameroon finalising training materials by November 2014. In Ethiopia, project materials used in the supported states are now being incorporated into national training material.
[25] Malaria Consortium (September 2016). ISMO Operational Research Study Report. P.33
[26] Ibid.
[27] The lack of consultations with Malaria Consortium, who were responsible for this project aspect, has been a key limitation for this evaluation. This section therefore presents an overview of the key issues.

which ethical clearance was denied.[28] However, there were significant delays of at least twelve months for all studies, largely due to longer than planned ethics review processes. It is not clear what actions Malaria Consortium could have taken to expedite these processes, though this experience underlines the need to incorporate potential ethics review delays into project planning and increase dedicated staff time to this activity. The need to complete the operational research was one of the reasons for UNITAID to approve the project extension, which enabled results to be disseminated in the three research countries. Two manuscripts from one study have been published to date and results from other studies were presented at the American Society of Tropical Medicine and Hygiene (ASTMH) in 2015, with further manuscripts being prepared for publication.[29,30]

2.2. Project efficiency

Q2: How efficiently has the project been implemented in terms of timelines, budget and project management?

The second evaluation question seeks to assess whether the resources have been used efficiently/ productively to achieve the desired targets. Our review includes: (i) the timelines in which activities were delivered as compared to the project plan; (ii) expenditures for project implementation, comparing planned budget versus actual expenditure; and (iii) project management, including monitoring and evaluation (M&E) and coordination between project partners. An in-depth analysis of these aspects has been conducted in the MTE and our endeavour is to update this assessment for the full project term.

2.2.1. Timelines

The project has been beset with delays, a number of which we assess to have been on account of unrealistic timelines. In particular, delays have included:

- **Inj AS dossier submission:** Ipca submitted their dossier to WHO PQ in December 2016, after project close. Whilst it is acknowledged that this three year delay cannot be attributed to the project, it has significantly impacted many of the market impact goals of the project.

[28] Although the protocol for this study was accepted in Nigeria and Ethiopia, the ethics review board in Uganda considered it to be unethical and instead requested the protocol to be amended to a knowledge, attitude and practices study. However, this was not possible due to requiring an increased budget.

[29] Kefyalew et al., *Health worker and policy-maker perspectives on use of intramuscular artesunate for pre-referral and definitive treatment of severe malaria at health posts in Ethiopia*, Malaria Journal (2016) 15:507; Adesoro et al., *Health worker perspectives on the possible use of intramuscular artesunate for the treatment of severe malaria at lower-level health facilities in settings with poor access to referral facilities in Nigeria: a qualitative study*, BMC Health Services Research (2016) 16:566

[30] 64th ASTMH meeting, Philadelphia. Abstract number LB-5346

- **Ir AS dossier submission:** Cipla and Strides submitted in December 2015, slightly delayed from the planned Q3 2015, and Strides has been further delayed due to dossier resubmission.
- **Signing of country Memorandums of Understanding (MoUs):** Only two countries (Uganda and Cameroon) signed MoUs for the project in 2013, as planned.[31] MoUs for Kenya, Ethiopia, Nigeria and Malawi were signed in January, February, April and November 2014 respectively.[32] The process took longer than expected due to the number of stakeholders involved, degree of legal complexity, and the structure of the MoH in some countries.
- **Project procurements:** As discussed previously, there were delays in lengthy price negotiations and procurement approvals resulting in delayed procurement, with the first procurement only occurring in June 2014, seven months later than planned.
- **Country specific issues during project implementation:** For example, in Kenya, the roll-out of training and data collection was slowed down by the need to communicate and seek approval from county level health departments.
- **Operational research approvals:** Delays were also experienced in receiving ethical approval for operational research, which affected the overall project timeline and was one reason for granting the project extension.

Many of these delays were not anticipated under the "Risk Assessment and Management" section of the project plan, suggesting the need for better project planning.

However, we also note that while PQ dossier submission has been later than planned, the project's work has also helped further the process which would otherwise have been even more delayed. For example, it is estimated that MMV support enabled Strides to submit their dossier 9-12 months earlier. Cipla estimate they were able to submit their dossier three years earlier, as access to the comparator product would not have been possible without MMV's support, meaning a clinical study would have been required. Stakeholders also noted that the increased quality of a WHO PQ dossier could significantly reduce time to approval.

As a final point we flag that the MTE was conducted around half a year before project end. This limited the extent to which lessons learned or recommendations could be incorporated into the project, although we note that some revisions had been made prior to the MTE.

2.2.2. Budget

The project had a total budget of US$34m, for the period of June 2013 to June 2016, majority of which was for the purchase and freight of Inj AS (US$21m or 62% of the total budget). At project close, 59% of the overall budget had been used. Figure 2.2 presents an overview of budget analysis.

[31] 2013 Annual Report, p.7
[32] 2014 Annual Report, p.11

Figure 2.2: Budget analysis of actual spend as a % of budget, by (a) output, (b) expense type, (c) implementing partner and (d) commodities [33]

By way of analysis, we note:

- Majority of the project underspend was due to lower levels of procurement than budgeted, with $11.9m (or 57%) remaining on this budget line. However, staff costs were almost fully utilised, with 96% of the budget spent, implying a planned versus actual programmes to overhead budget of 85% and 76% respectively.[34]
- Country level implementing partners utilised all or nearly all of the dedicated budget, but MMV used less than two thirds. The majority of MMV's underspend (86%) was programmatic and consultancy expenses linked to the project activities on Ir AS manufacturer support due to savings from having worked closely with Cipla and Strides previously and negotiating better value contracts.
- On commodity costs we note that despite only 38% of vials procured, 95% of the freight budget has been used. This high spend is partly due to the project budget not having anticipated refrigerated shipping containers. Further, customs, storage and distribution costs, representing 8% of drug costs, were paid by the project in Kenya and Uganda, but covered by the government in other project countries. Given that 50% of this budget line was used, despite only 38% of planned number of vials being

[33] "Staff costs" include indirect costs. "Other" includes travel, consultancies and telecom expenses.
[34] An overspend in Nigeria staff was reported in the financial narrative, due to higher time input required than planned, however further analysis is not possible due to only aggregated staffing costs per partner reported.

procured, this represents a high spend. Procurement agent fees correctly represent the proportion of vials procured.

We therefore note that whilst there was a significant budget underspend, due to fewer vials procured, several aspects of the budget have continued to be fully spent (staffing costs and country implementation) and other costs have been substantially higher than planned (supporting commodity costs). We comment that given this budget underspend had been anticipated during the MTE, a complete budget revision may have been appropriate in order to more closely monitor the efficiency of budget spend against project objectives.

2.2.3. Project management

The final section of the first evaluation dimension assesses the extent to which project management has been satisfactory in terms of partner structure and reporting approaches.

Project partner structure and performance

This is discussed in detail in the MTE and we provide additional salient points below:

- Project implementers have been well selected given MMV's extensive experience supporting manufacturers and CHAI and MC's country-level expertise.
- In general, all project partners performed their roles well throughout the project, including effective leadership by MMV through their dedication to resolving project issues (e.g. implementing regular meetings with Missionpharma given concerns raised by UNITAID) and country programme management by CHAI and MC (e.g. we note that audits conducted by KPMG did not highlight any significant issues).
- The project structure has not been optimal in terms of MMV's coordination role for country-level activities without country presence or responsibility for delivering country activities. This also created some inefficiencies e.g. extended communication timeframes when UNITAID requested country-specific information. As such, a model with co-leads based on areas of focus was suggested as being more efficient.
- Project implementers have coordinated well throughout the duration of the project, including regular cross-country meetings to share operational research information.

Further, discussions have indicated the need for greater and more effective collaboration between UNITAID and the project implementers. In particular, project implementers have noted that there was a need for UNITAID to:

- Provide clearer communication to ensure common understanding of project priorities (e.g. project focus on price negotiations) and roles and responsibilities (e.g. for procurement);[35] and

[35] It was suggested that given multiple stakeholders for procurement, two separate agreements may have been more effective, a grant agreement for project objectives and a commercial agreement for procurement.

- Provide timely communication (e.g. in response to the project extension decision, where we understand UNITAID took four months to decide not to accept MMV's request and was only formally communicated after project close on 15th July 2016).

Monitoring and reporting

The MTE flags a number of issues with the project logframe in terms of lack of a logical flow of activities to outputs, outcomes and finally impacts, with a mix of output and outcome indicators accorded to the four project outputs. Further, the list of outputs is not comprehensive with several country-level activities not being included.

As per the agreed contract, MMV reported semi-annually to UNITAID, with some indicators reported on an annual basis. As the project ended part way through 2016, no detailed data was provided on the 2016 annual indicators, although consolidated achievements were included in the final report. We note the following issues and inconsistencies in reporting:

- **Project goal** – proportion of severe malaria cases treated with Inj AS – is only reported on until 2015. Given that the majority of project procurement was only received in country in 2015, it would have been beneficial to view these results for 2016. Also there is no defined target for this indicator.
- **Project outcome** – median price paid for Inj AS. There was lack of clarity in the indicator definition, as to whether it covered all Inj AS procurements or only project procurements, leading to a misunderstanding between UNITAID and MMV. This lack of clarity led to differing interpretations, with MMV initially reporting on the former and, following the 2015 report, UNITAID understanding the latter. Furthermore, the baseline from which the target is calculated is not specific, referring to two separate price points (UNICEF and Global Fund reference pricing).
- **Reporting templates:** Implementing partners are required to complete the UniPro reporting template. For this project, the locked excel document provided to MMV double counted some results, with both the country total and sub-totals per Nigerian states/ Ethiopian regions included in the automatic total calculation. These issues were not rectified despite several requests to amend the template. This resulted in some errors, for example, the figure noted in the 2016 Final Report for the proportion of all severe malaria treatments procured that are Inj AS in 2013 includes this double counting and therefore overstates the project results. Furthermore, the report narratives do not clearly present project achievements, with considerable repetition.
- **Poor data quality** – Notwithstanding challenges in accessing data and limited funds for data collection, 2015 M&E narrative shows that no facility-level data was reported from Kenya for all of 2015 and only six months of data have been provided for Malawi. This brings into question the quality of overall reporting.

These issues have led to inefficiencies and inaccuracies in project reporting, which could have been mitigated through closer monitoring and pro-active dialogue between parties.

3. REVIEW DIMENSION 2: RESULTS AND IMPACT

This evaluation dimension focuses on whether the project has achieved its goals, both in terms of public health and market impact, as well as its catalytic impact and value for money. The specific evaluation questions, approaches and assessments are outlined below.

3.1. Public health and market impact

Q3: To what extent has the project achieved the intended public health and market impact?

The project plan outlines the public health and market impact related goals and outcomes, as summarised in Table 3.1 below. Our assessment as to whether the targets have been met draws on information provided in final, annual and semi-annual reports, consultations and findings from the operational research.

Table 3.1: Project public health and market impacts for Inj AS and Ir AS

Project goal/ outcome	Inj AS	Ir AS
Project goal (public health impact)	To increase the proportion of severe malaria cases treated by Inj AS, as compared with Quinine	To give access to life-saving Ir AS for pre-referral treatment of severe malaria
Project outcome (market impact)	Creation of a stable market for quality assured Inj AS	Affordable quality assured Ir AS on the market

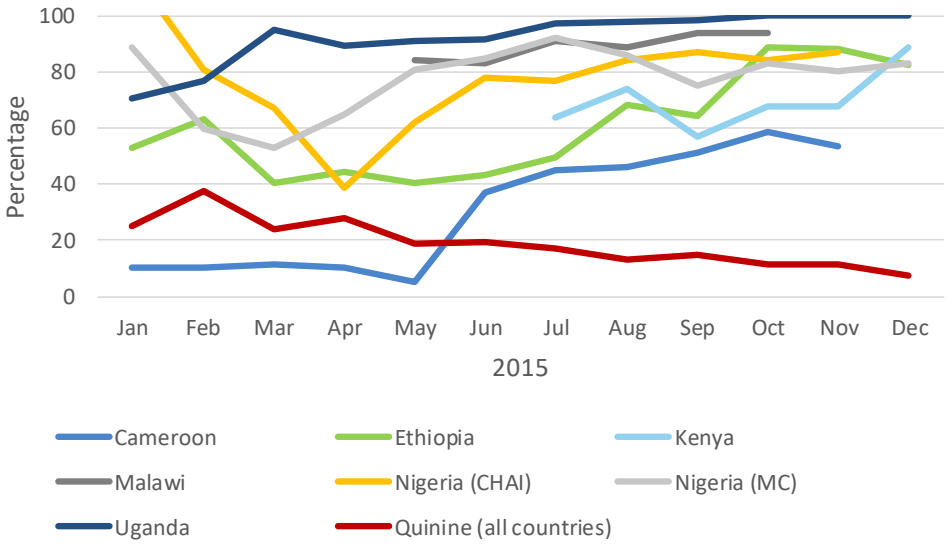
3.1.1. Public health impact

Inj AS

In terms of the impact the project has had on public health with regards to Inj AS, we have primarily assessed the extent to which project countries have switched to Inj AS from other anti-malaria treatments, in line with the logframe. Additionally, we provide high level comments on the broader public health impacts in terms of deaths averted, reduced recovery times, etc.

There is data for one year only on the switch from quinine to Inj AS (as the indicator was introduced in 2015 and not reported on in 2016) and no target has been defined in the logframe, limiting our assessment of progress made by the project. Nevertheless, Figure 3.1 shows positive results during 2015, with all countries reporting an increase in Inj AS use and a corresponding decline in quinine use.

Figure 3.1:Percentage use of Inj AS for the treatment of severe malaria over 2015, as compared with quinine[36]



In general, the use of Inj AS gradually increased over the year and as at December 2015, approximately 85.5% of severe malaria cases were reported as treated with Inj AS, although we note substantial country variations in Ethiopia and Nigeria:

- **In Ethiopia**, the decrease in Q1 was reportedly due to stock-outs at the health facilities that occurred due to a change in the procurement channel, noted previously.[37] This was resolved and usage increased by the end of the year.
- **In Nigeria**, Q1 and Q2 uptake were lower than anticipated due to the dependence on the project monitoring and support supervision visits for drug distribution. In Q3 and Q4 requisition for Inj AS had been incorporated into the routine health facility requisition for drugs leading to a significant reduction in stock-out from an average of seven stock-out days/ month in January to less than an average of two.[38]

Notably, in **Uganda,** a complete switch to Inj AS was made in 2016 and the central warehouse stopped procuring quinine.

Box 3.1 presents information on the broader public health impact.

[36] The January 2015 figure 116% for Nigeria (CHAI) is under investigation for correction of the error (ISMO M&E report narrative, 2016)
[37] Data and information taken from ISMO End of Project report.
[38] ISMO 2015 Annual report.

Box 3.1: Broader public health impacts

- **Deaths and DALYs averted**. Based on the SEAQUAMAT trial[39] which showed that Inj AS reduced severe mortality by 34.7% in adults and the AQUAMAT[40] trial which showed that Inj AS was 22.5% more effective than quinine in reducing severe malaria mortality, it can be expected that the project has had a positive effect on patient outcomes (discussed in Section 3.3). However, as 5.6m vials were procured through the project, instead of the planned 14.8m vials, the direct public health impact of the project has not been as large as expected.
- **Reduction in malaria mortality.** Uganda and Ethiopia received the 2017 ALMA Award for Excellence for their impact on malaria incidence and mortality.[41] Anecdotal information from Uganda notes that this is due in part to the introduction of Inj AS.
- **Evidence of inappropriate administration of Inj AS** from the operational research includes: i) low prevalence of uncomplicated malaria cases treated with Inj AS (4.2% in Uganda and 0.7% in Ethiopia); and ii) fewer than 80% of cases received the correct antimalarial drug, despite over 90% of facilities having Inj AS in stock (Nigeria and Ethiopia). Anecdotal negative impact of effective treatment from Inj AS is that when HCWs know Inj AS is a "super drug", they may be inclined to also use for non-severe malaria treatment.
- **Anecdotal evidence gathered during the MTE country visits on health systems and patient experiences being improved:**
  - **Recovery times**: The speed at which patients recover is much quicker with Inj AS than quinine (2 hours for Inj AS compared to 24 hours for quinine).
  - **In patient stay duration**: Patients are able to travel home soon after receiving Inj AS as it requires less surveillance.
  - **Burden on staff**: Because of the reduced length of stay in hospital, and less burdensome drug administration and monitoring, there is a reduced burden on staff.
  - **Reduced overall costs:** Hospital store manager noted that Inj As reduced overall costs, due to reduced consumable need.

Ir AS

Given that the project did not specifically fund the introduction and access to Ir AS nor intend to establish an integrated pathway for the management of severe malaria, having a direct public health was not within the project scope for the Ir AS component. As such, this aspect is not included in the evaluation.

3.1.2. Market impact

The ISMO project aimed to create a stable market for Inj AS and bring affordable quality assured Ir AS to market, through the PQ of (additional) manufacturers.

[39] South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group (2005), Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

[40] Dondorp et al. (2010), Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial

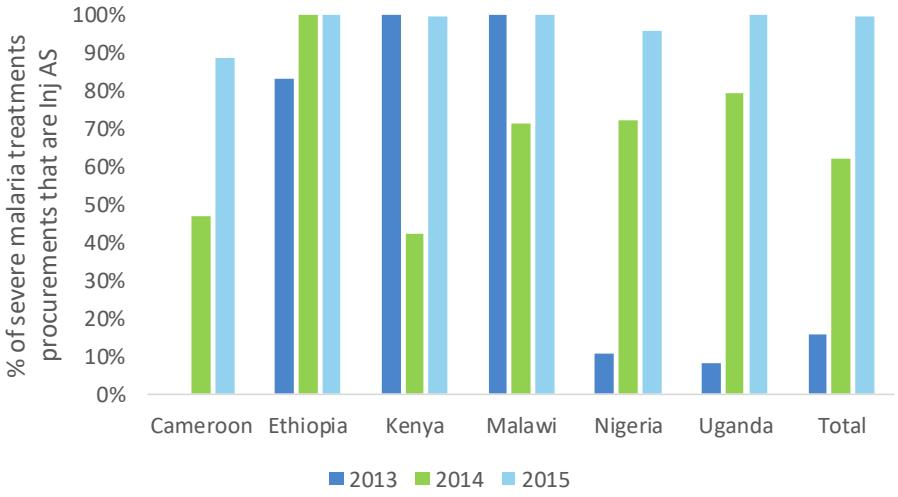
[41] http://alma2030.org/content/african-leaders-hailed-countries-make-gains-against-malaria

Inj AS

The project logframe measures market impact in terms of a stable market for quality assured Inj AS through price declines and extent of public procurements. As noted previously, targets for price declines were not achieved during the project timeframe, with the market continuing to be monopolistic and prices higher than anticipated. Stakeholders generally agree that no further actions could have been taken to mitigate the increase in price from US$1.42 to US$1.56 and actions to try to reduce the price may have jeopardised the sustainability of the only supplier. However, the December 2016 Ipca dossier submission to WHO PQ suggests the potential for price declines (and other characteristics of a stable market such as supply security, etc.) to be achieved soon, and it would be critical for UNITAID to continue to monitor achievements in prices and market stability following Ipca's entry into the market.

The progress in terms of share of Inj AS in public procurements for severe malaria treatments has however been positive – the final project report notes that Inj AS made up only 15.6% of treatment procurements in 2013, but this increased to 61.9% in 2014 and to 99.5% in 2015 (Figure 3.2).

Figure 3.2: Proportion of all severe malaria treatments procured that are Inj AS[42]



The project has been an enabler and contributed to the increase in global procurement of Inj AS, from 1.6m vials in 2011 to 27m in 2015.[43] Between 2013 and 2016, 18m vials of Inj AS were procured across the six implementing countries, of which 31% was procured by UNITAID. It was noted that because UNITAID, the Global Fund and PMI were jointly able to meet the majority of country needs, this enabled a switch from quinine to Inj AS. Without this fully funded situation, it is unlikely that countries would have switched.

[42] Data includes all vials procured, including non-project funded vials.
[43] MMV (October 2016) MMV APMAC Improving Severe Malaria Outcomes (ISMO) powerpoint presentation

Ir AS

In terms of market impact for Ir AS, there is high potential to achieve the intended outcome of affordable quality-assured Ir AS on the market, with Cipla and Strides successfully submitting their Ir AS WHO PQ dossier and ERP approval being granted for Cipla. We understand that Cipla has now begun the process of product registration in several countries.

3.2. Catalytic effect

Q4: What has been the catalytic effect of the project?

UNITAID funding aims to be catalytic, in terms of changing market conditions and increasing the availability and affordability of health products, amongst others.[44] In assessing the extent to which the project has achieved this aim, we consider the counterfactual, adopting OECD DAC's definition: *"the situation or condition, which hypothetically may prevail for individuals, organisations, or groups were there no development intervention"*[45] and the extent to which the project has represented *added value*, in terms of "more/ additional", "improved", "unique", "faster" or "new and innovative" approaches and results. We assess this from the perspectives of manufacturers (section 3.2.1) and countries (section 3.2.2).

3.2.1. Manufacturers

From a manufacturer perspective, the project has represented considerable added value and, specifically for Ir AS, has also been particularly catalytic. The project has enabled each of the following aspects:

- **Faster –** All three supported manufacturers noted project support having sped up the development of their WHO PQ dossier, including through providing a dedicated project manager to push the process forward and, for Inj AS, receiving agreement from WHO PQ that dossiers could be submitted for pre-review with three months' stability data, rather than six.
- **Innovative –** The project has provided support to enable quality Ir AS to be brought to market. Whilst WHO Guidelines issued in 2011 recommended this product, prior to the project support manufacturers were not investing in developing a pre-qualified product.
- **Unique** – MMV enabled the submission of WHO PQ dossiers for Ir AS through providing access to the comparator product. Manufacturers would not have been able to access this without MMV's direct negotiations and legal discussions with WHO.

[44] We note that catalysing equitable access to better health products now forms a key aspect of the mission of UNITAID's 2017-2021 Strategy.
[45] OECD-DAC (2004): "Glossary of Key Terms in Evaluation and Results-based Management"

Without this product, manufacturers would have had to conduct a clinical trial, thus adding significant time and costs to the development process.

- **Improved –** MMV provided technical experts to conduct audits and site inspections, which improved the quality of WHO PQ dossier submissions for both Inj AS and Ir AS.
- **More/ additional** – For Ir AS, MMV provided financial support to Cipla and Strides. This additional funding covered the majority of upfront investment costs, thus reducing risks and thereby enabling both manufacturers to reach agreement from their respective Boards to invest resources in Ir AS. Without this additional funding, manufacturers stated it would have been difficult for them to proceed in developing a product that has a minimal return on investment.

In terms of the counterfactual, we assess progress made by manufacturers who did not receive support through the project, specifically:

- **Mylan (Inj AS):** expect to submit their dossier to WHO PQ by the end of 2017, following the production of 6-months' stability data. Mylan received some technical assistance from MMV outside of the project, in terms of production development and making the process affordable. This support consisted of two consultant visits and some phone calls. Whilst this support was viewed as beneficial, it was not seen as having been critical to product development.
- **Macleods (Inj AS):** have tested three different approaches to ensure sterility over a period of three years. However, had technical support been received initially, they would unlikely have attempted the first two technologies, thus reducing the overall process by 1.5 years. Plant validation is now expected to be finished in April 2017, after which they aim to submit the WHO PQ dossier by end 2017.
- **Macleods (Ir AS):** Macleods are also developing a dossier for Ir AS. However, the main challenge has been in accessing the comparator product with which to conduct a bioequivalence study. In spite of this, Macleods intend to start collecting 6 months' stability data, in the hope that comparator samples can be obtained. However, without this bioequivalence data, a WHO PQ dossier cannot be submitted or country registration completed.

Given this progress, we assess that the project has added significant value to the development of the Ipca Inj AS WHO PQ dossier, but may not be viewed as catalytic per se, particularly given progress made by non-supported manufacturers, albeit at a slower rate.

In terms of Ir AS however, it is clear that the project has had an important catalytic effect, with non-supported manufacturers being more disadvantaged.

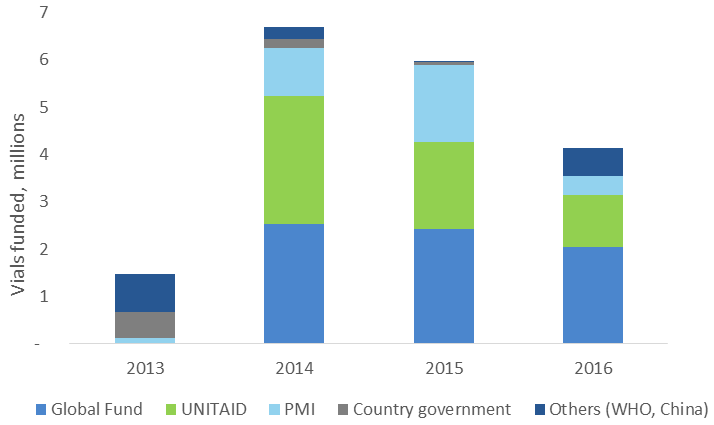
3.2.2. Countries

From a country perspective, we assess that certain project activities have been particularly *catalytic,* while other aspects have *added value*, but may not be viewed as catalytic per se.

Specifically, the demand generation activities have been particularly catalytic, with limited efforts from other actors in this area in advance of the project (although with some variance by country). In fact one consultee commented that the same achievements would have taken around nine years without the project support. As such, this support enabled project countries to include Inj AS in their 2014 Global Fund concept notes, in a context where using donor funding for severe malaria commodities had not happened before (as donors did not usually procure quinine). The ISMO project funding could also be used to meet Global Fund co-funding requirements.

Where the project has been less catalytic, although still of added value, is with regards to procurements where initial delays resulted in limited need for project funded procurements given entry by other donors (Figure 3.3).

Figure 3.3: Inj AS procurement in project countries, by purchaser[46]



It is difficult to assess "spill-over" effects of the project to other countries in Sub-Saharan Africa, given the role of multiple actors and country-specific factors. However, we note that whilst in 2011 nine African countries had changed their severe malaria policy in favour of Inj AS[47], by 2016, this number had increased to 30 African countries for Inj AS.[48] Additionally, by project close, 19 countries had included Ir AS in their severe malaria policies.

3.3. Value for money

Q5: To what extent has the project represented value for money?

The third question within this evaluation dimension aims to assess the value for money (VfM) of the ISMO grant, drawing on the results of the previous two questions and building on the work carried out by CEPA during both the MTE and the multi-grant VfM analysis undertaken

[46] Data taken from ISMO End of Project Report p.21. However, we note that these figures do not tally with those provided in the excel data.
[47] ISMO Project Plan (Inj AS), p.11
[48] WHO, World Malaria Report, 2016

in May-June 2016. We base our assessment on ISMO VfM on key performance indicators (KPIs) included in UNITAID's current 2017-21 Strategy, as follows:

- KPI 1.1. Increasing public health impact – number of lives saved
- KPI 1.2. Generating efficiencies and savings – financial savings and health system efficiencies ($ values)
- KPI 1.3. Delivering positive returns – returns on investment ($ benefit/ $ cost)
- KPI 5.1. Securing funding – proportion (%) of project countries where future funding has been secured at grant closure through partners and countries
- KPI 5.2. Scaling-up coverage – additional number of people who benefit from a better health product or approach

Our approach to estimating these KPIs is based on available data from project progress reports and publicly available sources, such as the World Malaria Report and academic literature. In addition, stakeholders' views on relevant assumptions and likely projections have been factored into the analysis, which are also reflected in sensitivities for key metrics.

Performance against KPIs 1.1 and 1.2 has been estimated from the perspective of the direct and indirect impacts of the project through the enabling effect on i) project countries and ii) African countries.[49] KPI 1.3 has been estimated using the direct impact of the project investment. Looking at the long term impact of the project, performance against KPIs 5.1 and 5.2 has been assessed for two years using projected forecasts (based on data availability and as per UNITAID's measurement approach). We also provide a discussion for the longer term of five years, drawing largely on forecasted demand by UNITAID and consultations with suppliers on expected capacity and pricing.

Key limitations include: (i) poor availability of data, especially with regards to statistics on severe malaria burden; (ii) unclear and inconsistent data provided in the project progress reports; (iii) use of imperfect assumptions and proxies given lack of robust and reliable data; amongst others. It is important to note that several of the assumptions reflect views that are relevant today and may need to be revised with ongoing changes in the market and country landscape. Assessment of the longer term results are less reliable given these are mostly based on assumptions.

We first present results relating to Inj AS for each of the five KPIs in turn (sections 3.3.1-3.3.5), before discussing the longer term effects (section 3.3.6). We then provide a discussion on the impact and VfM relating to Ir AS (section 3.3.7). Annex 5 provides more details on the calculations, sources of information and assumptions.

[49] Estimates on deaths and disability-adjusted life year (DALYs) averted are represented in comparison to quinine being used in treatment of severe malaria.

3.3.1. KPI 1.1. Increasing public health impact – Number of lives saved

Direct project impact[50]

Based on the 5.6m vials procured by the project, it is estimated that through the treatment of Inj AS instead of quinine, an additional 40,200 (39,700 – 47,400) deaths and 660,300 (628,800 – 808,500) DALYs were averted over the project period. These estimates draw on the findings from Lubell et al (2011),[51] Dondorp et al (2010)[52] and the SEAQUAMAT group (2005).[53] The sensitivities are based on variations in assumptions on number of vials use per treatment and proportion of adults and children treated.

Based on an estimated need of 1.9m treatments per year in 2011 for severe malaria in project countries (as per the project plan, and assumed to be the same during the project period given lack of updated data), the project directly met approximately 17% (16 – 20%, based on varying assumptions on vials per treatment) of the need.

These results are lower than expected had all of the 15m vials been procured, which would have resulted in an estimated 107,200 additional deaths averted and 1.76m additional DALYs averted.

Indirect impact – project countries

Based on similar calculations as above, it is estimated that through the provision of 12.6m vials from other sources (Global Fund, PMI, country governments) in project countries over the project period, an additional 89,400 (88,300 – 105,300) deaths and 1,468,200 (1,398,300 – 1,797,800) additional DALYs were averted in project countries.

This is an estimated 37% (35% – 45%) of the need in project countries met by other donors. Together with the estimated direct impact of the project, this represents 53% (51% – 65%) of the need in project countries.

Indirect impact – Africa

Based on data from Guilin on annual sales of 60mg Inj AS vials over 2013-16, with 90% of sales to Africa, a total of 50.4m vials were procured in Africa over the project period. Based on similar calculations as above, and using additional data from MMV and the World Malaria Report on malaria incidence, it is estimated that through the treatment of Inj AS instead of quinine in Africa, 358,200 (354,000 – 422,000) deaths and approximately 5,883,900

[50] We understand that UNITAID intends to present this indicator for the project period and for a certain number of years thereafter. However, we recommend the presentation adopted here where direct impacts during the project are presented separately as these metrics have greater robustness than longer term metrics.
[51] Lubell et al (2011) Cost-effectiveness of parenteral artesunate for treating children with severe malaria in sub-Saharan Africa. Bull World Health Organ 2011;89:504–512
[52] Dondorp et al. (2010), Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial
[53] South East Asian Quinine Artesunate Malaria Trial (SEAQUAMAT) group (2005), Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial

(5,603,800 – 7,204,800) additional DALYs were averted, relative to treatment with quinine. This is an estimated 54% (52% – 67%) of the need in Africa. Whilst acknowledging that these results be attributed to the project, given the project has contributed by way of "demonstration effects", these are viewed as positive results.

3.3.2. KPI 1.2. Generating efficiencies and savings – Financial savings and health system efficiencies ($ values)

Direct project impact

The **financial savings** of the project are estimated to be US$2.8m. This is estimated by comparing the UNICEF supply catalogue prices for each year of the project with the prices achieved under the project.[54]

Regarding **heath system efficiencies,** we present results from the Lubell et al, 2011 study where the estimated cost per death averted of Inj AS relative to quinine is US$123. We view the costs included in this measure as representing costs largely from a "provider" (i.e. health systems) perspective and hence present this metric as a measure of the health system efficiency under the project.[55,56] As this study was conducted between 2009 and 2010, certain costs such as drug prices may have increased (and indeed the prices obtained under the project are substantially higher than that assumed in the study). However, Lubell et al notes that *"even if the cost of artesunate were substantially higher, it would remain a cost-effective option*", as the main cost driver was the duration of in-patient stay.

If the patient/ societal perspective is adopted, then further efficiencies are obtained. Quinine requires greater surveillance and longer administration times, as it is administered as a slow, rate-controlled infusion, usually over four hours and at eight-hour intervals.[57] Therefore, some health workers have anecdotally reported that their patients have been able to travel home between doses on Inj AS rather than be admitted as an in-patient.[58] For these reasons, the costs borne by the patient may be lower with Inj AS as they are able to return home quicker.

Indirect impact – project countries

Through the pooled procurement arrangement between UNITAID and the Global Fund for the project countries, the Global Fund has secured US$3.6m in financial savings on account of the lower prices as compared to that achieved under UNICEF procurements.

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[54] 2015 price was not available and therefore assumed as an average of 2014 and 2016.
[55] Lubell et al (2011)
[56] Furthermore, the country costs utilised in this study have been obtained from health facilities in Tanzania, Uganda and Nigeria and therefore are highly generalizable to the project.
[57] World Health Organization (2015) Guidelines for the treatment of malaria, 3rd edition
[58] CEPA (2015) Mid-term evaluation of the ISMO project

3.3.3. KPI 1.3. Delivering positive returns – Returns on Investment = $ Benefits/ $ costs

The project expenditure per death averted is US$418 and the expenditure per DALY averted is US$25. However, we note that this is a substantial underestimation of the total costs per death or DALY averted as it does not include other costs incurred by MMV/ other partners or by countries.[59]

3.3.4. KPI 5.1. Securing funding – Proportion (%) of project countries where future funding has been secured at grant closure through partners and countries for a period of two years i.e. 2017-2018

According to the transition plan, 100% of the estimated requirement for project countries was committed for the rest of 2016. For 2017, four out of six (67%) of the countries had the required vials committed. Whilst funding commitments had been made for some countries for 2018, this represented only 21% of the predicted need (based on gap analyses and other quantification methods), and no country had their full needs met.[60] Malawi and Kenya had the most funds committed over 2017-2018.

3.3.5. KPI 5.2. Scaling-up coverage – Additional number of people who benefit from a better health product or approach for a period of two years i.e. 2017 – 2018

Based on the transition plan, the estimated number of vials has been projected for project countries for 2017 and 2018.[61] If this need is met by donors, approximately 3.2m treatments could be administered and an estimated additional 134,600 (133,000 – 158,600) deaths and 2,211,500 (2,106,200 – 2,708,000) DALYs would be averted if Inj AS is utilised instead of quinine. However, as per the results for KPI 5.1, as at project close, funding has been committed for approximately 1.4m treatments only, implying an estimated additional 60,600 (59,800 – 71,300) deaths and 994,800 (947,400 – 1,218,100) DALYs averted. Further details regarding the funding commitments from donors such as PMI or Global Fund was not available in the project progress reports and could not be obtained at the time of writing this report.

[59] As quantification of benefits is beyond the scope of this evaluation, further analysis cannot be conducted on this KPI.

[60] ISMO Transition plan March 2016. Note information for Nigeria and Ethiopia is specific to project regions. Nigeria had more than 100% of the estimated need committed for 2016 which could assist to meet the 2017 estimated need.

[61] ISMO Transition plan March 2016. Note information for Nigeria and Ethiopia is specific to project regions.

3.3.6. Forecasted longer term impact – five years

In terms of demand, the UNITAID malaria forecasting report (2016-19) provides estimates for Inj AS procurements in the public sector in Africa as 29m in 2016 and going down to 25.5m in 2019.[62,63]

In terms of supply, our consultations with the range of existing and potential Inj AS suppliers suggests the following capacity over the next five years (Table 3.2), assuming the continued relevance of Inj AS (i.e. no revisions in treatment guidelines, artemisinin resistance, etc.).

Table 3.2: Inj AS supply capacity (in millions)

Supplier	2016	2017	2018	2019	2020	2021	Notes
Guilin	20	25	30	30	30	30	• Expected max capacity of 30m by 2018
Ipca	-	2.5	12	15	15	15	• Expected to enter the market by Q4 2017 following ERP approval • Capacity of 10-12m, which can be extended to 15m
Macleods	-	-	6	12	12	12	• Expect to submit PQ dossier Q3/4 2017 and apply for ERP approval; assume supply from mid-2018 (assume ERP takes 6 months)
Mylan	-	-	6	12	12	12	• Expect to submit dossier Q4 2017, therefore assume being able to supply from mid-2018 (assume ERP takes 6 months)
Total	**20**	**27.5**	**54**	**69**	**69**	**69**	

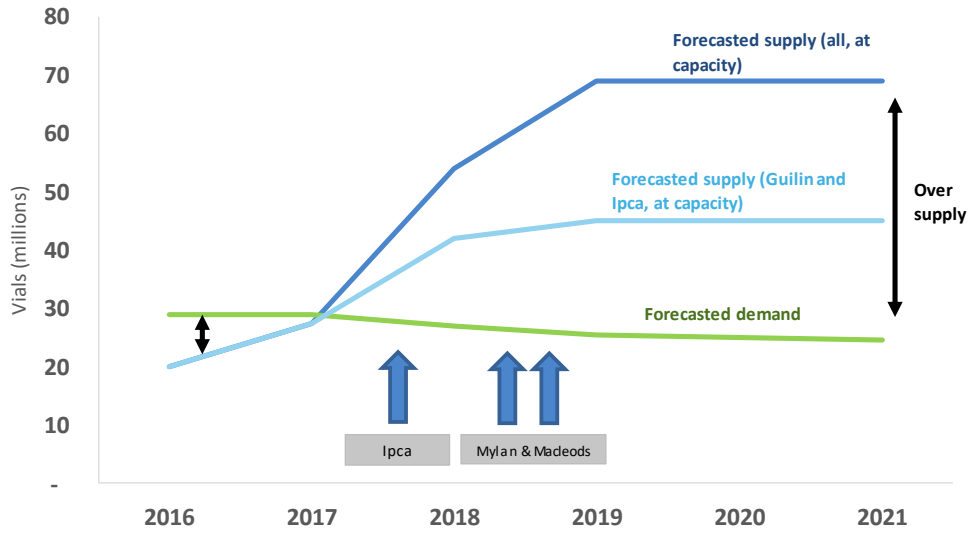
As such, given supply limitations at 20m in 2016, the demand of 29m could not be satisfied. In 2017, if Ipca ERP approval is received, as per current expectations, there will still be an expected gap in satisfying demand in Africa (of around 1.5m vials). From 2018 however, Guilin and Ipca would be able to fully satisfy the demand, with their supply capacity exceeding demand.[64] As such, should Macleods and Mylan also join the market, there would be a situation of over supply or all suppliers not functioning at capacity which would impact potential price reductions that can be achieved. Figure 3.4 provides a presentation of this discussion.

[62] UNITAID (Dec 2016) Global Malaria Diagnostic And Artemisinin Treatment Commodities Demand Forecast 2016 – 2019.

[63] The World Malaria Report states that there were 5.6m severe malaria cases globally in 2012 (Ref: MMV powerpoint presentation (29 October 2016), ' MMV APMAC Improving Severe Malaria Outcomes (ISMO), and assuming 92% of these are in Africa (based on 92% mortality rates for malaria in Africa as per the WMR 2016), there are 5.1m severe malaria cases in Africa. At 6 vials per treatment, an estimated demand of 30.9m vials is calculated, which is close to the figure quoted in the UNITAID report.

[64] Given lack of data availability on expected demand for 2020 and 2021, we have assumed a slightly lower level than that estimated by UNITAID for 2019 (i.e. the last data point available).

Figure 3.4: Potential market situation over 2016-21



On pricing, our discussions with suppliers indicate a slightly higher price for the Guilin product given its better quality in terms of longer shelf-life (three years compared to two years for other products). However, the current expectation from stakeholders consulted is that competitive pressures would drive the prices down to around US$1/ 60mg vial, especially if additional suppliers come on board and there are large volume commitments from the Global Fund (although as noted above, not functioning at capacity may impact this price achievement). Assuming a certain price profile, based on the indications provided from the different stakeholders consulted during the evaluation, an estimated US$51m of financial savings could be achieved through price declines with competition over the five year period from 2017-21. We strongly caveat this number as it is based on the above described profile of the supply market and an indicative profile for price changes (which may not bear fruition).

Drawing on calculations used previously to estimate additional deaths and DALYs averted through use of Inj AS over quinine, we estimate an additional 919,700 (908,900 – 1,083,600) deaths and 15.1m (14.4 – 18.5m) DALYs averted over the period 2017-21.

3.3.7. Ir AS impact and VfM

As previously noted, without support provided to Cipla and Strides, it is unlikely that the Ir AS product would have been brought to market, or at least not as quickly. Cipla reports not expecting restrictions regarding producing capacity and therefore the main constraint is demand rather than supply capacity. Based on the William Davidson Institute forecast, the expected demand for 2016, 2017 and 2018 is 1.5m, 2.5m and 3.6m vials respectively.[65] However, if demand is increased through guideline changes, then the return on investment in bringing this product to market may be much higher.

[65] William Davidson Institute (2014). Global Demand Forecast for Intra-Rectal Artesunate 2016-2018

4. REVIEW DIMENSION 3: SUSTAINABILITY

The final evaluation dimension takes a longer-term view on the project results to assess sustainability.

Q6: Has the project delivered sustainable impact, in terms of public health and market impacts?

The project aims of changing treatment practices and creating a stable market were long term in nature, as such the extent to which the project impact has been sustainable is a key component of this evaluation.

By design, the project has supported sustainability in a number of ways by conducting activities focusing on systemic change, selecting partners with an ongoing programme focus in the area and emphasising transition planning. However, one project design aspect in which sustainability has not been adequately addressed is that the project only supported manufacturers to PQ dossier submission, rather than also supporting through the approval and registration processes. This creates a risk of project efforts not being sustained should issues be flagged during WHO PQ dossier review for which a manufacturer requires technical assistance or if prices do not decline significantly with entry of the second manufacturer. We understand some safeguards were put in place through the inclusion of indicative pricing guidance in the MoU, but this is an important area for continued review to ensure the benefits of the project are materialised.[66] We also note that UNITAID is currently discussing two follow-on grants, although it is unclear whether any aspects relating to continued support of Inj AS will be included.

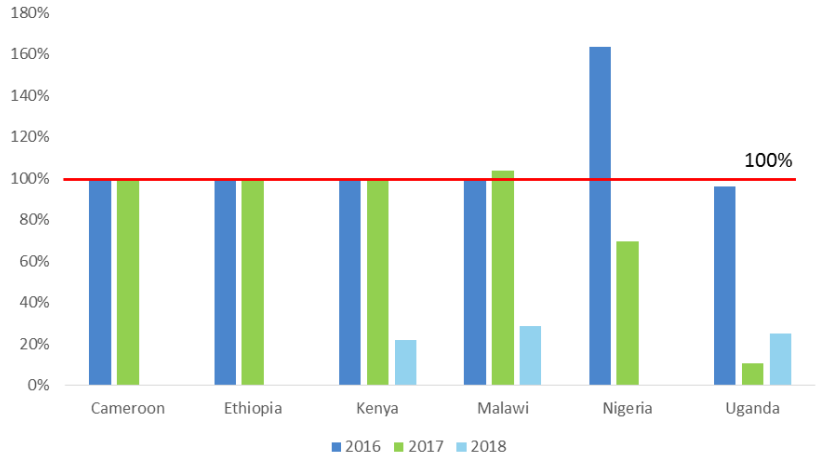
By the end of the project, we note the following aspects in terms of sustainability of results (marked as positive (+), negative (-) or mixed (±)):

- ± **Inj AS procurement commitment by other donors:** There has been a notable increase in funding from the Global Fund and PMI since 2014, with project transition planning presenting a fairly positive picture of other donors committing funding for Inj AS in the immediate future (Figure 4.1). However, currently only limited commitments have been made for 2018, although this does not yet take into account figures countries are expected to include in their forthcoming Global Fund concept notes. This gap between project close-out and other donor procurements may present a risk for continued Inj AS procurements and hence the need for UNITAID to closely monitor country prioritisation of Inj AS. We understand that several countries (Ethiopia, Uganda and Malawi) were left with less than six months of Inj AS stocks at project close, causing a risk of stock-outs that may have been avoided with an additional

[66] We have been unable to confirm this, as manufacturer MoUs have not been shared.

order. However, we understand that UNITAID had not accepted buffer stocks to be included in the final order.[67]

Figure 4.1: % future Inj AS country needs met[68]



± **Project focus on lessons learned:** Several activities have been conducted in country to share lessons learned from the operational research, as well as presenting at an international conference and publishing papers. In addition, CHAI published a case study on Inj AS, outlining impact and lessons learned.[69] We also understand that MMV has recently started to engage with stakeholders and WHO on developing the Severe Malaria Observatory in order to share lessons learned. However, there was limited awareness of this learning from broader stakeholders and given the project focus on long term change, it would have been appropriate to include a greater focus on advocacy and sharing lessons from the project as a whole.

\+ **Ir AS follow-on grants:** We understand UNITAID is currently discussing two follow-on grants for Ir AS: (i) a "supply grant" with MMV focusing on Ir AS product development; and (ii) a project to roll out Ir AS in four countries in 2017, to be implemented by UNICEF and CHAI and to increase the evidence base by capturing lessons learned along the way. This will help ensure that the gains from the ISMO project are taken forward.

\- **Project extension communication:** We understand that UNITAID took a long time to officially respond to MMV's request for a project extension. This caused issues from the point of view of sustainability in that project implementers were not able to effectively plan close-out activities or to fully capitalise on the extension period.

In summary, the sustainability of results differs for Ir AS and Inj AS. This is promising for Ir AS, particularly given current discussions on follow-on support from UNITAID. However, we note potential risks in terms for Inj AS results.

[67] MMV had requested buffer stocks of three months for Cameroon, Malawi and Uganda, and six months for Ethiopia, Kenya and Nigeria, to avoid possible stock-outs prior to planned Global Fund procurements.
[68] Data from ISMO transition plan, with 2018 needs projected for Malawi and Nigeria.
[69] www.clintonhealthaccess.org/content/uploads/2015/08/Case-Study_Inj-AS-Uptake.pdf

5. CONCLUSIONS, LESSONS LEARNED AND RECOMMENDATIONS

This final section presents conclusions and lessons learned from the project, as well as recommendations for UNITAID for the development and implementation of future projects.

5.1. Conclusions and lessons learned

The project to improve severe malaria outcomes was much needed and has been greatly valued by all stakeholders. The project has achieved significant successes, particularly in terms of supporting the development of quality assured Ir AS (which is unlikely to have been achieved without the project), increasing demand for Inj AS in focus countries leading to a notable increase in use over quinine, and enabling the appropriate use of Inj AS through a substantial training element. However, the supply side interventions for Inj AS have had limited impact, with delayed procurements reducing the intended catalytic role of the project and continuation of a monopoly supply situation as at project end. While the supply situation remains uncertain, there is promise given the recent WHO PQ dossier submission from Ipca and that nearly all project countries have their Inj AS procurement needs met for 2017 by other donors.

By way of lessons learned, we note the following:

- **Complementarity of supply and demand activities:** The project design of supporting both the supply and demand side of the Inj AS market has been an effective approach and provided positive results. This is recognised as a unique focus of UNITAID and would be an appropriate model to replicate.
- **Review of project focus and revisions in line with market developments:** The project approach in view of a continued monopoly for Inj AS was not appropriate and should have been amended once delays to the second manufacturer entering the market became clear. The methods used to address the monopolistic market did not reach the intended project outcomes, with considerable wasted time on negotiations with a monopoly supplier. The project therefore did not achieve the correct balance of focus between the supply and demand aspects.[70]
- **Risk management in relation to supplier support:** Given the high risk nature of this project and the potential for PQ dossier submission delays as well as supplier attrition, it was appropriate for the project to support multiple manufacturers for Ir AS. Similarly, it would have been more effective had the project supported more than one manufacturer for Inj AS.

[70] We assess that this is partly due to the focus of the previous UNITAID Strategy, which emphasised impacting market dynamics through engagement on supply-side issues. Therefore, we view the current 2017-21 Strategy shift to a more comprehensive, multi-dimensional approach as more appropriate and comprehensive.

- **Alignment of project management structure with activities:** MMV have performed well as the project lead. However, given the multi-faceted project scope, the project organisational structure has not been efficient.
- **Realistic timelines:** Planned timelines have not always been realistic and there is a case for stronger risk/ contingency planning. A three year timeframe for UNITAID market shaping projects is considerably challenging.
- **Improvement of reporting systems:** Project issues have highlighted a strong need for UNITAID to develop a more streamlined grant reporting system and format, with better management of content and feedback loops for appropriate course correction.
- **UNITAID project engagement and management:** Delayed communication by UNITAID to grantees on project extension decisions has impacted the effectiveness of project close-out. UNITAID should improve communication to grantees, providing clear deadlines by which information on project close will be provided.
- **Links to health systems partners:** Introducing a new product is challenging without a full health systems approach that incorporates broader systemic change, including its incorporation in health management information systems (HMIS), supply chain and ongoing quality assurance. Whilst addressing health systems challenges is not in line with UNITAID's mandate, projects could aim to establish complementary links with other implementers.
- **Increased focus on lessons learned:** The operational research aspect of the project included the sharing of lessons learned. However, given the intended catalytic nature of UNITAID investments, it would have been beneficial to increase sharing of best practices and lessons learned to all aspects of the project.
- **Enhancement of sustainability potential:** There is promising potential for sustainability of Inj AS in project countries. This could be further increased were UNITAID to align project timing with Global Fund funding cycles, thereby enabling support to prioritise the inclusion of Inj AS in concept notes and secured continuation of funding.

5.2. Recommendations

Based on the learnings from the ISMO end of project evaluation, we provide the following recommendations for UNITAID.

Recommendation 1: Encourage reasonable flexibility and revision of approaches based on learnings and developments in grant implementation

Whilst focused implementation of project plans and agreed approaches is important, also from an accountability perspective, given that UNITAID interventions are in mostly unchartered territory and high risk, an increased degree of flexibility in grant implementation,

within reason, would support more effective achievement of objectives. Amendments to project approaches, targets and budgets should be encouraged where planned results are not being achieved and/ or stalled, based on ongoing dialogue between UNITAID and the grantee (and possibly also drawing on external expert views). Recognising the high risk and innovative nature of UNITAID investments, consider prioritising certain project activities and outcomes over others and thereby allocating the balance of efforts on these. These should also be well documented to support mutual understanding and accountability.

This may be facilitated through a continually updated "theory of change" for projects that tracks the logical flow of results, risks and assumptions as well as introducing certain "trigger points" (i.e. a lower bound on certain results, identified risks occurring in practice, etc.) that merit re-scoping or revision of activities/ objectives during the project lifetime to ensure effective use of UNITAID monies.

Recommendation 2: Develop a more collaborative and partnership-based/ joint working approach with project grantees, wherein grantees are also well-aware of UNITAID's role in the project

Given UNITAID's role as a "mandated funder" with specific objectives and priorities (i.e. different from a standard funder that mainly serves as an additional source of funds to its grantees), we recommend that UNITAID further adapts its approach of engaging with grantees to move from a traditional "funder-grantee" to a more partnership-based approach and relationship that is reflective of UNITAID's engaged approach towards achievement of project objectives. This would entail, for example:

- A clear definition of UNITAID roles and responsibilities for a project, including outlining the extent of UNITAID engagement and better management of grantee expectations/ clearer communication on UNITAID's role.
- More open dialogue between UNITAID and the grantee on what is working well and not so well, and a commitment to jointly resolve issues.
- Greater predictability on grant funding from UNITAID, including clear and timely communication on potential extensions and/ or amendments.

Recommendation 3: Ensure alignment of project scope and activities with grant structure

For projects with a broad focus and multi-dimensional activities, UNITAID should critically consider the most appropriate grant structure and management arrangements. In some cases this may require separating out different aspects of the project, for example:

- Different project co-leads within one grant, each with clear responsibilities and deliverables for discrete objectives and activities. However, this would require effective coordination mechanisms between the co-leads for overall grant objectives.

- Separate grants, each focusing on different project elements (e.g. for supply and demand side elements respectively). However, this would likely increase transaction costs for UNITAID to ensure effective coordination between grants.
- Separate agreements, with a grant to focus on project activities and a commercial agreement for procurement or price negotiations. This model would be pertinent and increase effectiveness should UNITAID continue to preclude project implementers from approving procurements directly.

A range of structures would enable increased project efficiencies and effectiveness, allowing the skills and experience of implementers to be best aligned with each project aspect.

Recommendation 4: Consider appropriate timeframes for achievement of project targets

UNITAID projects need to realistically consider the time required to achieve certain market outcomes or country-level activities, notwithstanding the challenges with accurate forecasting/ predictability. Unrealistic timelines provide a misguided view of project delays. Greater engagement with key stakeholders, further consultations and gathering of market intelligence may facilitate development of more realistic timeframes.

Recommendation 5: Develop robust project logframes and reporting formats

UNITAID should ensure that projects have quality logframes or results frameworks, with:

- a logical progression between activities, outputs, outcomes and impacts;
- clearly defined results indicators that are "SMART", with baselines, interim milestones and final targets;
- use of a standardised/defined set of market terms (e.g. terms such as "availability", "access", "stability", "supply security", etc.) to ensure a clear vision and mutual understanding between project partners of results;
- detailed risk matrices and mitigation strategies; and
- clear and simple reporting formats, with the ability to be tailored for specific projects, supported with effective narrative formats that bring out salient features of project progress rather than lengthy details.

Recommendation 6: Establish mechanisms to ensure sustainability of project outcomes

UNITAID should take relevant measures to support the achievement of "incomplete" project objectives and continuity of project benefits, both directly and indirectly.

Directly, in terms of projects with a follow-on grant (where appropriate), UNITAID should consider continuity between grants. This would increase efficiency and effectiveness, in terms of continuity of project staff and activities, as well as likely increase the catalytic potential. As

such, the planned follow-on grants for Ir AS access objectives should be suitably timed to ensure they leverage from the ISMO project.

Indirectly, for projects without a follow-on grant, we recommend that UNITAID track post-project achievements in a systematic manner and consider whether further interventions may be required by UNITAID or other stakeholders (e.g. for the ISMO project, UNITAID should closely monitor the outcomes of the Ipca PQ dossier review process and supply to the market). This would also entail alignment with Global Fund funding cycles for country-level activities and commodity funding.

Recommendation 7: Leverage project evaluations further

UNITAID should maximise the use of its project evaluations through the following approaches:

- Introduce a management response to external evaluations for improved accountability, outlining steps and a timeframe to action recommendations.
- Arrange post-evaluation meetings between UNITAID and project implementers to discuss evaluation findings and lessons learned, in order to jointly agree on appropriate next steps.
- Incorporate formal processes to track the implementation of relevant and agreed-upon recommendations.
- Share final evaluations, along with the management response, with key project stakeholders.
- Consider conducting a meta-review of evaluations to gather broader lessons learned and develop strategic policy recommendations.

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ANNEX 2: LIST OF STAKEHOLDERS CONSULTED

This annex presents the list of stakeholders consulted.

Table A2.1: Consultee list

Stakeholder group	Organisation	Name	Position
UNITAID	UNITAID	Philippe Duneton	Deputy Executive Director
		Ambachew Yohannes	Malaria Portfolio Officer
		Ombeni Mwerinde	M&E Officer
		Nargiza Mazhidova	Data Analyst M&E
		Jemmy Dopas	Grants Finance Officer
		Lorenzo Llewellyn Witherspoon	Procurement Officer
MMV	MMV	Pierre Hugo	Director, Access and Delivery Africa
		George Jagoe	Executive Vice President
		Alexis Kamdjou	Country and Procurement Liaison Manager
Other project implementers	CHAI Global	Luke Rooney	Global Malaria Program Manager
	CHAI Kenya	Patricia Njiri	Senior Program Manager, Kenya
	CHAI Uganda	Alex Ogwal	Malaria Program Manager, Uganda
	Missionpharma	Jens Rasmussen	Sales Manager, Development Aid
		Michaela Nielsen	Key Account Administrator, Development Aid
Donors	Global Fund	Mariatou Tala Jallow	Acting Chief Procurement Officer, Sourcing and Supply Management Department
	PMI Global	Jennifer Wray	Senior Malaria Advisor/Commodities
		Eric Halsey	Co-lead of Case management technical group
	PMI Ethiopia	Matthew Murphy	Program Centers for Disease Control and Prevention, Ethiopia
	PMI Malawi	Peter Troell	Resident Advisor, Malawi
Pharmaceutical companies	Guilin Pharmaceutical Co. Ltd.	Lily Su	General Manager

Stakeholder group	Organisation	Name	Position
	Cipla Ltd.	Sharadd Jain	Global Institution Business
		Sweety Thoppil	Business development
		Vaishali Shridhankar	Regulatory team
	Strides Ltd.	Vinod Nair	Vice President - (Marketing)
	IPCA	Sohrab Mulla	Dy. General Manager - Generics
	Mylan	Kedar Madhekar	Senior Manager Infectious Diseases/Business Development
	Macleods	Vijay Agarwal	Director
WHO PQ	Prequalification Team - Medicines	Matthias Stahl	Group Leader Medicines Assessment
Ministry of Health	National Malaria Control Programme (NMCP)	John Sande	Head Case Management

ANNEX 3: CONSULTATION INTERVIEW GUIDE

This annex provides the interview guides used for global and country stakeholders respectively. Consultations were based around the following high level questions, though questions were tailored appropriately for each consultee.

Interview guide – global consultees

1. What have been the key project achievements and how effective has the project been at meeting the stated objectives, from both the supply and demand side? What have been major enabling factors that have supported successful implementation of activities and what, if any, have been barriers to implementation?
2. How has the project enabled each of the following and would these have progressed in the absence of the project:
    a. Second manufacturer PQ dossier submission for Inj AS
    b. Increase in country demand and procurements for Inj AS
    c. Increased demand and procurement for Inj AS in non-project countries
    d. PQ dossier submission for Ir AS
3. Did the four month project extension adequately enable the project to complete activities and fully achieve objectives? Could more have potentially been achieved with a different focus or longer period for the extension?
4. How have recommendations and lessons learned from the mid-term evaluation been incorporated into the project, and if these have not, why not?
5. How has the project performed in terms of timeliness, coordination/ advocacy and budget management? Have the project partners (UNITAID, MMV, CHAI and MC) delivered on their roles and responsibilities? What have been key issues in this regard and has the project adopted appropriate risk mitigation strategies to address these?
6. How effective have quantification committees and project-initiated monitoring systems been and have these supported a reduction in stock-out levels, including since project close? What has been the impact of health worker trainings? Have these activities supported health systems strengthening in country?
7. Recognising the different product challenges, what have been the relative costs and benefits of the different models MMV used to engage with manufacturers?
8. *Relating to Inj AS:* What has been the public health impact of the project and how have project M&E efforts contributed to the measurement of this? To what extent has health worker training and supervision been effective in improving appropriate use of Inj AS?
9. *Relating to Ir AS:* What have been the key project areas of progress and challenges with regards to this project component? What issues will need to be taken into consideration to maximise impact now that the product is being brought to market?

10. What lessons have been learned from the operational research and how has this information been shared with key stakeholders?
11. To what extent have project activities been sustained after project close? What processes have been implemented to support continued sustainability of project activities and achievements?

Interview guide – country-level consultees

1. To what extent is Inj AS replacing quinine as the main treatment for severe malaria?
2. Has the uptake of Inj AS by staff (administrative/procurement and health staff) gone according to plan? What have been the main challenges and what has worked well?
3. To what extent has health worker training and supervision been effective in improving appropriate use of Inj AS? Have training and supervision activities continued since project close?
4. To what extent has the project been well coordinated with other donors/ partners active in the rolling-out of Inj AS/ malaria treatment more generally in country?
5. Did the procurement agent (Missionpharma) deliver quality goods in a timely manner as per expectations? What has worked well and not so well?
6. Have there been any issues with the in-country procurement process? Have there been any regional variations/challenges and if so, why and what was done to address those?
7. How effective have quantification committees and project-initiated monitoring systems been? Have these supported a reduction in stock-out levels, including since project close?
8. Were the country's supply needs of Inj AS met during the project? Has there been an adequate level of Inj AS procurement since project close and who has procured this? Have existing quinine stocks in-country had an effect on Inj AS procurement needs?
9. To what extent differences been observed between Inj AS and quinine with respect to patient outcomes, in-patient stay duration, and burden on staff?
10. *Relating to Inj AS:* What has been the public health impact of this project?
11. *Relating to Ir AS:* What have been the key project areas of progress and challenges with regards to this project component? What issues will need to be taken into consideration to maximise impact now that the product is being brought to market?
12. What have been the lessons learned from the operational research? Have these been communicated to country stakeholders and what actions have subsequently been taken?
13. What has been the *added value* of the project, in terms activities and results which would not have happened without project support?
14. To what extent have the achievements of this project been sustained since project close? What systems have been put in place to promote sustainability? What more is required for countries to increase uptake of Inj As and introduce Ir AS?

ANNEX 4: IMPLEMENTATION OF MTE RECOMMENDATIONS

Table A4.1 compares the recommendations made in the mid-term evaluation (MTE) and the associated outcomes completed between the MTE (November 2015) and project close (September 2016). These are assessed in terms of the extent to which recommendations have been implemented *(Green – implemented; orange – partially implemented; red – not implemented).*

Table A4.1: Recommendations made in the MTE and associated outcomes

Relevance of MTE recommendations	Outcome/responses to MTE recommendations
1: UNITAID and MMV should discuss and agree a clearly defined no-cost extension for the project	It was determined by UNITAID that this project did not warrant a no-cost extension as it was considered that the overall grant objectives had been met. The following reasons were provided: • UNITAID considered that the project had succeeded in achieving its catalytic impact. This was due to the increasing funding support for the procurement of Inj AS from other donors, as well as the increase in demand from countries. • Other grant objectives had broadly been met including: i) accelerating implementation of the new WHO treatment guidelines for severe malaria approved in 2012 in the beneficiary countries; ii) training of health workers on the correct use of Inj AS, including the development of training materials; iii) coordinating Inj AS demand forecasting and procurement planning; and iv) submission of two dossiers to WHO PQ for Ir AS.
2: Explore the possibility of expanded pooled procurement and further price negotiation for the planned 2016 procurement	In June 2014, a joint pooled procurement price of US$1.42 was reached between UNITAID, MMV, Global Fund and Guilin for one year. In the final procurement, the price increased to US$1.56. Although this was a price increase, it was better than the price that other institutions (including PMI and Global Fund Principal Recipients in non-ISMO countries) paid, which was up to US$1.80. There were unexpected reasons for the price increase including increasing costs for Guilin and the Yen having devalued against the USD. However, it was still a monopolistic market.
3: Emphasise donor coordination of procurement and delivery of Inj AS	Between 2013 and 2016, UNITAID procured 31% of the vials for the six project countries whilst the Global Fund procured 38%, PMI 17% and the remainder was procured through country governments, Chinese government and others.[71] Improved coordination was achieved through pooled procurement and transition planning.[72]
4: Focus on fast-tracking the prequalification process for Ir AS and explore new support to encourage demand creation for the product	The following outcomes were achieved regarding Ir AS dossier submission: • Cipla: Submitted to WHO PQ (December 2015) and received ERP approval in Q3 2016 (after project close).

[71] ISMO End of project report
[72] ISMO Transition plan submitted March 2016

Relevance of MTE recommendations	Outcome/responses to MTE recommendations
	• Strides: Submitted the dossier WHO PQ (December 2015), but have been further delayed with their dossier submission due to a requirement to repeat the bioequivalence study. MMV is continuing to support manufacturers during the WHO PQ review stage which might decrease the time manufacturers take to respond to WHO PQ clarification requests, therefore potentially fast-tracking the process to some extent.
5: Ensure adequate emphasis is placed on improving M&E systems for data on the need for and use of Inj AS	This recommendation was relevant to Inj AS as a whole, and it was noted that whether UNITAID should fund this directly or support the work of other partners was a higher-level strategy question for UNITAID. Whilst health system strengthening activities fall outside of UNITAID's current mandate, it would be beneficial for linkages to be formed in these areas to ensure better results from UNITAID funding of procurements. We are not aware of any attempts to form linkages.
6: Consider and disseminate key country-level learnings and best practice.	MC conducted four operational research (OR) studies, and the results have been disseminated in the three participating countries (Ethiopia, Nigeria, Uganda).[73]

[73] ISMO End of Project report

ANNEX 5: VALUE FOR MONEY ASSESSMENT – ASSUMPTIONS AND CALCULATIONS

The embedded Excel document in this annex shows the data, assumptions and calculations for the value for money analysis.

CEPA VfM_analysis_ISMO