Research Protocol

Assessing Health System Readiness for Scaling Antenatal MMS in Cambodia: A Mixed-Methods Assessment

Executive Summary

Background: Malnutrition among pregnant women in low- and middle-income countries (LMICs) can cause micronutrient deficiencies that result in adverse maternal and neonatal health outcomes. The World Health Organization has recently recommended antenatal multiple micronutrient supplementation (MMS) that includes iron and folic acid (IFA) to improve maternal and neonatal health outcomes. MMS likely provides additional antenatal benefits over IFA supplementation alone. The Cambodian government, in partnership with Helen Keller International, is piloting MMS implementation in Takeo Province, which will inform nationwide scale-up of MMS.

Study Purpose: The Takeo implementation must be evaluated to understand context-specific implementation of MMS and health system readiness for scale-up. This study assesses system readiness through four domains from the Intervention Scalability Assessment Tool (ISAT): (1) fidelity and adaptation, (2) reach and acceptability, (3) delivery setting and workforce capacity, and (4) implementation infrastructure.

Population: The pilot involves transitioning to MMS from IFA across all 86 health centers, all 6 referral hospitals, and the provincial hospital in Takeo province. This study includes pregnant women receiving antenatal care, antenatal healthcare providers and facilities, and hospital managers in Takeo. The study also includes national governing bodies for MMS delivery.

Methods: This mixed-methods study uses ISAT as a framework for developing data collection methods. Sampling strategies emphasize urban and rural representation across all operational districts in Takeo and diverse stakeholder perspectives at multiple levels of the health system. Data collection includes:

1. **12 focus group discussions** (FGDs) with health center providers to assess provider adherence to MMS delivery guidelines, perspectives on the transition to MMS, and additional resources needed for MMS delivery
    a. **Workload assessment surveys** at FGDs to quantify any burden on providers and resource gaps to deliver MMS
2. **MMS stockout monitoring** at 18 health centers and 7 hospitals to assess supply chain reliability
3. **15 key informant interviews** with hospital managers to assess perspectives on the integration of MMS into antenatal services and facility readiness for MMS delivery
4. **Phone surveys** with 630 pregnant women to assess acceptability and adherence to MMS at 90- and 180-days after MMS distribution
5. **1 FGD** with national-level stakeholders to assess national-level readiness, economic planning, and resource planning for sustainable MMS implementation and scale-up
6. **Rapid economic evaluation** to estimate the cost of nationwide scale-up

Potential Impact: This study will generate insights into real-world implementation of MMS in Cambodia. It will identify context-specific adaptations, implementation gaps, and resource planning frameworks needed for nationwide scale-up of MMS. Successful scale-up is anticipated to improve maternal and neonatal health in Cambodia. Findings can also be used to guide other LMICs seeking to transition to and sustainably implement MMS.

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1. Background and Rationale

Malnutrition and micronutrient deficiencies during pregnancy have significant consequences for maternal and neonatal health, particularly in low- and middle-income countries (LMICs). Dietary diversity and quality in LMICs are often limited. Micronutrient deficiencies can result in low birthweight, preterm birth, stillbirth, and being born small for gestational age. Micronutrient deficiencies can increase the risk of maternal mortality and obstetric complications (Bourassa et al., 2019; Mei et al., 2017; UNICEF 2024).

To combat this, the World Health Organization (WHO) previously recommended iron and folic acid (IFA) supplementation as part of antenatal care (ANC) (Mei et al., 2017). However, since 2020, WHO has acknowledged the significant body of evidence that multiple micronutrient supplementation (MMS) results in improved health outcomes for pregnant women and their babies in low- and middle-income countries (Bourassa et al., 2019; Keats et al., 2019; WHO, 2020). Now, WHO guidelines include MMS as an essential antenatal medicine (WHO, 2021). WHO has urged countries to conduct implementation research to drive feasible, acceptable, and context-specific MMS implementation (WHO, 2020).

The UNIMMAP MMS formulation recommended by WHO contains 15 vitamins and minerals, including iron and folic acid, in the recommended safe doses for pregnant women. The formulation was developed in 1999 through a collaboration between WHO, the United Nations University, and UNICEF, and then tested rigorously through randomized controlled trials for safety and effectiveness. In 2021, UNIMMAP MMS was officially included in the World Health Organization's Model List of Essential Medicines based on evidence that it is effective and safe (WHO, 2021). We have summarized a list of the key references highlighting publications that confirm UNIMMAP MMS's safety, efficacy, and cost-effectiveness as Appendix A.

Helen Keller Intl (Helen Keller) has been working with the Cambodian Ministry of Health (MoH) to conduct MMS implementation research in the Cambodian context. The Cambodian MoH will use MMS implementation studies in Cambodia to inform scale-up strategies for transitioning from IFA to MMS as a key part of ANC. In 2023, Helen Keller conducted a randomized cluster non-inferiority trial in Kampong Thom province to assess pregnant women's adherence and acceptability to IFA compared to MMS (Hoang et al., 2024). This study found that adherence to MMS was superior to IFA, and pregnant women found MMS to be highly acceptable, thereby supporting the transition to MMS (Sauer et al., 2024). With this evidence, the Cambodian national guidelines for ANC are being updated to include antenatal MMS, which includes 15 micronutrients, including iron and folic acid, versus IFA alone.

To advance the transition from IFA to MMS in Cambodia, the MoH, in collaboration with Helen Keller, Vitamin Angel Alliance, and Kirk Humanitarian, has designed a phased implementation approach beginning with a province-wide pilot in Takeo. This strategic pilot represents the first province-wide implementation of MMS in Cambodia, covering all 6 operational districts and 86 health centers. This pilot will generate critical evidence on implementation feasibility and offer insights on system readiness and how to prepare for national expansion. Helen Keller presents this protocol as a tool to assess implementation readiness for MMS scale-up. The assessment employs a mixed-methods approach to examine four critical dimensions of implementation quality and health system readiness for scaling:

1. Fidelity and adaptation
2. Reach and acceptability
3. Delivery setting and workforce
4. Implementation infrastructure

In this context, the assessment will help assess the scalability of antenatal MMS delivery, identify contextual factors facilitating or hindering scale-up, and provide a structured mechanism for working

through key gaps to facilitate a smooth rollout. Study findings will make recommendations for future scale-up and inform the national strategic planning process. The quality of the MMS rollout and the health system's readiness will ultimately determine the extent to which Cambodian pregnant women receive the intended health benefits of MMS.

The Cambodian government will use these findings to identify critical areas for adaptation when scaling MMS in other provinces to ensure a seamless transition to MMS. Strategies for adaptation may be related to cost, funding, healthcare provider training, national ANC guidelines, supply chain strengthening, planning for other resources, and individual- and household-level characteristics of pregnant women and their families. Importantly, the results from this context-specific protocol may inform implementation practices in other low- and middle-income countries that aim to transition to MMS to improve birth outcomes globally.

2. Objectives

This study aims to systematically evaluate the following key dimensions of MMS implementation in Cambodia:

1. **Fidelity and adaptation**
    a. Assess implementation fidelity to the Cambodia Interim National Micronutrient Guidelines during MMS rollout and identify context-specific adaptations for optimal MMS delivery in the Cambodia healthcare system
2. **Reach and acceptability**
    a. Determine the reach and perceived acceptability of the MMS intervention among healthcare providers and the pregnant women as well as their level of satisfaction with the implementation
3. **Delivery setting and workforce**
    a. Evaluate the capacity of health workforce to deliver MMS effectively; specifically assessing health system infrastructure readiness, adequacy of healthcare provider training, resource availability, and supply chain reliability
4. **Implementation infrastructure**
    a. Model the implementation infrastructure and resource requirements for nationwide MMS scale-up
        i. Cost analysis: Compare the economic implications of transitioning from IFA to MMS
        ii. Supply chain: MMS forecasting, procurement timelines, and considerations for a resource planning framework for sustainable implementation

3. Study Design

3.1. ISAT Framework

This protocol uses the Intervention Scalability Assessment Tool (ISAT) as a framework to guide the development of data collection methods. ISAT is an adaptable framework to help stakeholders assess intervention scalability, identify contextual factors impacting scale-up, and identify gaps in knowledge to determine scalability (Australian Prevention Partnership Centre, 2019). The ISAT framework contains several domains. The domains within ISAT Part B, Intervention Implementation Planning, are most relevant to the objectives of this study. By assessing factors that affect the four domains in Part B, the ISAT framework will help decision-makers in Cambodia evaluate health system readiness for scaling MMS based on the rollout in Takeo. **Table 1** summarizes the four ISAT domains and key considerations to guide data collection.

Table 1. ISAT domains and contextual considerations (Australian Prevention Partnership Centre, 2019).

Domain	Key Considerations
1. Fidelity and Adaptation	To what extent do healthcare providers adhere to the newly revised Interim National Micronutrient Guidelines regarding MMS dosage and distribution protocols?
	What mechanisms exist to monitor the implementation of fidelity?
	What context-specific adaptations should be made to the guidelines and training materials to optimize delivery in the Cambodian antenatal healthcare system?
	To what extent are the 15 micronutrients in MMS stable under field conditions?
2. Reach and Acceptability	What proportion of eligible pregnant women in Takeo province are taking MMS?
	To what extent do healthcare providers understand and accept their role in MMS distribution and counseling?
	How satisfied are pregnant women in Takeo with the organoleptic aspects of MMS?
	What percentage of pregnant women take MMS as prescribed throughout pregnancy?
3. Delivery Setting and Workforce	How well is MMS integrated into existing ANC services in health facilities?
	To what extent are healthcare providers adequately trained in MMS counseling and distribution?
	Are there sufficient material resources (job aids, counseling materials) to support MMS delivery?
	How reliable is the MMS supply chain across operational districts (frequency and duration of stockouts)?
	What is the health system's capacity to monitor MMS distribution and adherence?
4. Implementation Infrastructure	What are the economic implications (one-time and recurring costs) of transitioning from IFA to MMS nationwide?
	How would the national supply chain need to be adapted for reliable MMS procurement and distribution?
	What sustainable financing mechanisms exist or must be developed for long-term MMS implementation?
	What human resource considerations are necessary for a nationwide scale-up?

3.2. Setting

This study will be conducted in Takeo province, a coastal province in southern Cambodia's Mekong ecological zone. Takeo has 6 operational districts. A province-wide MMS rollout is planned to distribute MMS in all 86 health centers, 6 referral hospitals, and 1 provincial hospital across Takeo.

Takeo was chosen for Cambodia's first province-wide rollout to explore the translatability of previous implementation research (Hoang, 2024) to different provinces, generate a range of evidence for context-specific implementation, and use generalizable findings to inform a nationwide MMS rollout. Takeo has urban and rural characteristics. However, contextual factors in each province will affect the generalizability of findings from Takeo.

According to the 2019 national census, Takeo has a population of about 901,000 (Cambodia National Institute of Statistics, 2020). In 2024, Takeo was expected to have 19,837 pregnant women across all health facilities. See **Table 2** to compare ANC and sociodemographic characteristics of Takeo to rural and urban averages, ranges across all provinces, and total averages across Cambodia. In summary, Takeo is similar to national averages for the percentage of women (age 15-49) who received ANC from a skilled

provider, had at least 4 ANC visits, and took any iron-containing supplements (IFA) when pregnant for their last live or still birth in the last 2 years. Takeo is above national averages for the percent of women who had only 1 ANC visit and the percent of women who took IFA during pregnancy for 90-179 days. IFA adherence was relatively high in Takeo at 93.4%. Finally, Takeo is similar to national averages for female literacy rates and employment rates (both sexes) for people aged above 15.

Table 2. Comparison of ANC and sociodemographic characteristics of Takeo with other areas of Cambodia.

	% Women (ages 15-49) reporting these events for their last live or still birth in the last 2 years[1]					**Rate of characteristic for people aged 15+ [2]**	
Area	Received ANC from a skilled provider[1]	Had only one ANC visit[1]	Had at least four ANC visits[1]	Took any iron-containing supplements[1]	Took iron-containing supplements during pregnancy for 90-179 days[1]	Female literacy[2]	Employment (both sexes)[2]
Takeo	98.1	1.7	83.9	98.5	93.4	86.2	99.3
Urban average	99.1	0.6	91.3	97.7	87.4	91.4	98.2
Rural average	98.5	1.4	82.8	97.8	88.2	80.2	98.9
Upper value across all provinces	100	10	93.8	100	92.7	94.9	99.7
Lower value across all provinces	94.2	0	57.3	88	69.1	65.3	93.1
Total average across all provinces	98.7	1.1	86.1	97.8	87.9	84.8	98.7

[1] Indicator taken from Cambodia National Institute of Statistics (2020)
[2] Indicator taken from Cambodia DHS Program (2022)

3.3. Data Collection Methods and Tools

This **cross-sectional study uses quantitative and qualitative methods** to assess health system readiness for nationwide MMS implementation and scale-up based on the province-wide rollout of MMS in Takeo.

Before the study, MMS will have already been rolled out across all 86 health centers, 6 referral hospitals, and the only provincial hospital in Takeo. All healthcare providers (doctors, nurses, and midwives) will have been trained to provide and counsel on MMS. All pregnant women attending at least one ANC visit will receive one 180-count bottle of MMS pills. They will not be given IFA unless they are anemic (hemoglobin level below 11.0 g/dL).

Figure 1 and **Table 3** present summaries of the data collection methods.

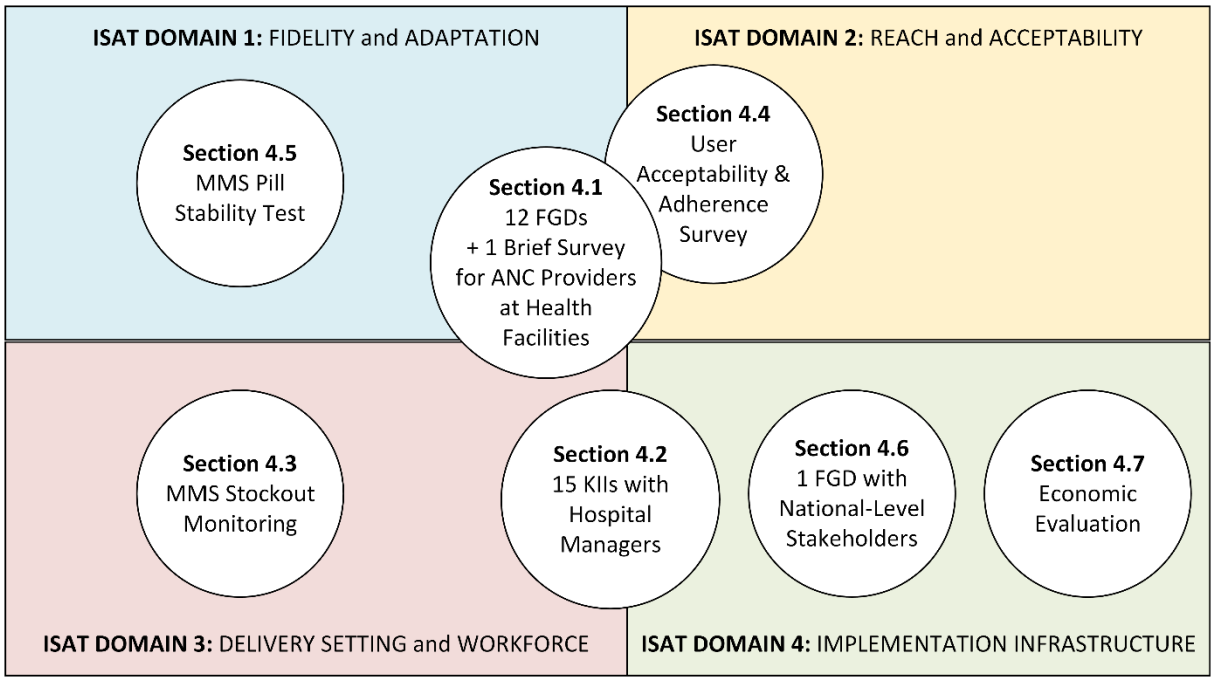


Figure 1. Summary of study methods (organized by section) and aligned ISAT domain.

Table 3. Key questions, data collection tools and approaches, and metrics per ISAT domain.

Key Question	Data Collection Tools	Collection Approach	Metrics
Domain 1: Fidelity and Adaptation			
To what extent are healthcare providers adhering to MMS dosage and distribution protocols as specified in the Cambodia MoH's draft Micronutrient Guidelines?	FGD guide for healthcare providers (provider adherence to protocols and training effectiveness)	12 facility-level FGDs (2 per operational district) with 6-8 healthcare providers each	Provider perceptions of training and resources to deliver and counsel on MMS Provider perceptions of ability to implement MMS per national guidelines
	Pill collection form for stability test (evaluate MMS stability under field conditions)	200 pill samples collected from pregnant women's homes at 90- and 180-days post-distribution	Percent deviation of analyzed nutrient content per tablet in distributed ("field") MMS supplements compared to labeled nutrient content
	Phone survey questionnaire for pregnant women (user adherence to MMS)	Phone surveys with 630 pregnant women at 90 and 180 days after first ANC visit, with verification through real-time pill counts during calls	Percent of pregnant women receiving the correct MMS dosage Percent of women receiving key MMS counseling messages Percent of pregnant women adhering to taking MMS as prescribed for 90 to 180 days
	Informed consent forms (2 forms)	-	-
Domain 2: Reach and Acceptability			
What is the coverage and	Phone survey questionnaire for pregnant women (user	Phone surveys with 630 pregnant women at 90	Average score of user acceptability toward sensory

acceptability of MMS among healthcare providers and pregnant women?	acceptability of MMS)	and 180 days after first ANC visit	aspects of MMS Percent of pregnant women reporting acceptability-related barriers to taking MMS
	Recall phone survey questionnaire for user acceptability and adherence (quality assurance)	Recall phone surveys with 10% of the population that participated in the acceptability and adherence surveys	
	Brief provider workload assessment survey questionnaire (quantify provider changes in workload and acceptability of transition)	Workload assessment survey given to all participants at facility-level FGDs with healthcare providers	Average score of provider acceptability of transition to MMS Average score of additional workload burden on providers to deliver MMS
	Enrollment form		
	Informed consent form (2 forms)		
Domain 3: Delivery Setting and Workforce			
How ready is the health system infrastructure and workforce for MMS implementation?	FGD guide for healthcare providers (perspectives on training adequacy and resource needs)	12 facility-level FGDs with 6-8 healthcare providers each	Degree to which providers understand MMS guidelines, dosage, and counseling Provider perceptions of the sufficiency of training, job aids, and ongoing support for MMS implementation Provider perceptions of infrastructure readiness (i.e., MMS supply and stockouts), integration of MMS into routine ANC, and alignment with existing protocols
	Brief provider workload assessment survey questionnaire (quantify provider changes in workload and acceptability of transition)	Workload assessment survey given to all participants at facility-level FGDs with healthcare providers	Average score of changes in provider workload or perceived burden to transition to and deliver MMS
	KII guide for hospital managers (perspectives on implementation and resource needs)	15 KIIs with high-level management officials from 6 referral hospitals and 1 provincial hospital	Manager perceptions of infrastructure readiness (i.e., MMS supply and stockouts), integration of MMS into routine ANC, and alignment with existing protocols Perceptions of policy support and coordination for MMS rollout

	MMS stockout data collection form (monitoring supply chain reliability)	Monthly stockout monitoring and health facility data review at 18 health centers (20% sample), 6 referral hospitals, and the provincial hospital	Percent of health facilities without MMS stockouts in the last month MMS coverage (women receiving MMS/women in need)
	Informed consent forms (2 forms)		
Domain 4: Implementation Infrastructure			
What are the required resources and economic implications for nationwide MMS scale-up?	MMS cost data collection forms (rapid economic evaluation including procurement, workforce training, and supply chain costs)	Health facility data review, health department records analysis, national government data review	Average MMS unit cost compared to IFA unit cost Average MMS transition cost, including training, advocacy, and policy updates Average recurring MMS costs, including procurement, distribution, and monitoring Average financing gap for long-term sustainability of MMS implementation Proportion of projected MMS costs financed through domestic versus international means
	FGD guide for national-level stakeholders (to assess infrastructure and resources needed to transition to MMS and sustainably implement MMS nationwide)	1 FGD with National MMS Steering Committee (6-8 members)	Perceptions of MMS integration into existing ANC services Degree of alignment on additional resources, systems, and capacity needed to scale-up and sustainably implement MMS nationwide Degree of alignment on long-term financing mechanisms for MMS Willingness to adopt MMS into national essential medicines lists and approve as final the Interim Micronutrient Guidelines
	Informed consent forms (1 form)		

The protocol uses 17 unique data collection tools across all domains, including:

- 7 informed consent forms for different participant groups
- 1 enrollment form (for user acceptability and adherence survey)
- 2 FGD guides (for providers at health facilities and national-level stakeholders)
- 1 brief survey instrument for workload assessment (for healthcare providers at FGDs)
- 1 KII guide (hospital managers)

- 1 stockout monitoring form
- 3 survey instruments for pregnant women (acceptability, adherence, and recall surveys)
- 1 pill collection form for stability testing
- 1 economic data collection form

4. Study Procedures

4.1. Focus Group Discussions and Workload Survey: Health Center Providers

4.1.1. Overview and ISAT Domain Alignment

There will be 12 FGDs with healthcare providers from 12 health centers. Participants will complete a workload assessment survey at each FGD.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 1: Fidelity and Adaptation
Health facility providers FGDs	Provider adherence to specified MMS dosage and distribution protocols
	Provider adherence to counseling content and frequency as outlined in Cambodia's draft Micronutrient Guidelines
	Mechanisms to monitor and ensure fidelity to implementation guidelines
	Context-specific adaptations made to accommodate resource constraints
	Appropriateness of adaptations in maintaining essential intervention components
	Domain 2: Reach and Acceptability
Health facility providers FGDs	Provider understanding of their role in MMS counseling and distribution
	Provider assessment of pregnant women's receptivity to MMS
	Perceived barriers affecting provider ability to effectively reach all eligible women
	Provider observations of patient adherence patterns and influencing factors
	Strategies employed by providers to enhance acceptability and adherence
Provider survey (workload assessment)	Provider acceptability of and agreement with transition to MMS (Likert scale)
	Provider level of commitment to transitioning to and providing MMS counseling (Likert scale)
	Domain 3: Delivery Setting and Workforce
Health facility providers FGDs	Integration of MMS into existing ANC services and workflows
	Adequacy of provider training on MMS counseling and distribution
	Availability of supporting materials (job aids, counseling tools) for MMS delivery
	Interest in or need for exploring task-shifting for MMS delivery
	Time and resource implications of transitioning from IFA to MMS distribution
	Supply chain reliability at facility level and frequency of MMS stockouts
	Capacity to monitor MMS distribution and patient adherence
Provider survey (workload assessment)	Change in provider workload (i.e., time spent in training) to transition to MMS (hours of time per week or Likert scale of level of increased burden)
	Change in provider workload to counsel on and deliver MMS (hours of time per week or Likert scale of level of increased burden)
	Provider perception of added burden of MMS delivery (Likert scale)

4.1.2. Study Population
Healthcare providers (doctors, nurses, midwives) with direct involvement in MMS distribution or counseling at the health facility level and who are willing to participate and available to attend. The population excludes personnel from referral hospitals and the provincial hospital.

4.1.3. Sampling Approach
From each operational district, one urban and one rural health center will be randomly selected (total of 12 health centers). From each of the 12 health centers, 6-8 personnel will be invited to participate using convenience sampling, with 8-10 people initially approached to account for a 20% non-attendance rate.

4.1.4. Data Collection
FGD: A trained moderator and notetaker will conduct each 70-minute FGD in a private, comfortable location using a structured guide aligned with the 4 ISAT domains. All discussions will be audio-recorded after obtaining written informed consent. The moderator will ensure balanced participation while the notetaker will document contextual factors and non-verbal cues that may inform interpretation of findings.

Survey: Survey instruments will be developed in English and translated into Khmer using forward and backward translation. The survey will be kept brief (5-7 questions) so that completion does not take longer than 3-5 minutes. Finalized surveys will be on paper and self-administered due to time constraints.

The FGD moderator will provide all participants with the survey at the end of each FGD. Participants will complete the survey and return it to the moderator.

4.1.5. Data Analysis
FGD: Audio recordings will be transcribed verbatim into English. Local language recordings will be translated and transcribed into English. Transcripts will undergo quality checks against the audio and notetaker notes. After transcription, transcribers and coders will clean the data, and final transcripts will be reviewed for completeness and clarity.

Qualitative analysis experts will conduct thematic content analysis. Coding schemes will be refined after reviewing a sample of transcripts. Lead researchers will verify coder accuracy through interrater reliability before finalizing the scheme, which will then be shared with the study team. Assigned coders will analyze transcripts using QSR NVivo. NVivo will be used to identify patterns in code summaries (context, descriptions, language, narratives) to extract common themes, opinions, and perspectives.

Survey: Surveys will be analyzed by calculating mean scores related to provider acceptability of the transition to and delivery of MMS and increases in provider burden to transition to and deliver MMS.

Integrated Analysis: Findings will be triangulated with (1) delivery setting assessments and (2) user reach and acceptability assessments (Section 4.4) to identify resource implications of overcoming barriers.

4.2. Key Informant Interviews: Hospital Managers
4.2.1. Overview and ISAT Domain Alignment
15 KIIs will be conducted with high-level management officials at the 6 referral hospitals and 1 provincial hospital.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 3: Delivery Setting and Workforce
Hospital manager KII	Integration of MMS into existing ANC services and workflows
	Time and resource implications of transitioning from IFA to MMS distribution

	Supply chain reliability at facility level and frequency of MMS stockouts
	Capacity to monitor MMS distribution and patient adherence
	Domain 4: Implementation Infrastructure
Hospital manager KII	Economic implications of transitioning from IFA to MMS at facility level
	Additional costs (one-time and recurring) associated with MMS implementation
	Human resource considerations for scalable facility-level implementation
	Supply chain strengthening needs for reliable MMS procurement and distribution
	Barriers to feasibility and sustainability of facility-level MMS implementation

4.2.2. Study Population

High-level management officials with direct involvement in MMS management at referral hospitals and the provincial hospital and who are willing to participate and available to attend. This population excludes personnel from health centers.

4.2.3. Sampling Approach

For each referral hospital and the provincial hospital, 6-8 personnel will be invited to participate using convenience sampling, with 8-10 people initially approached to account for a 20% non-attendance rate.

4.2.4. Data Collection

A trained interviewer will conduct each 60-minute KII in a private, comfortable location using a structured guide aligned with the ISAT domains. All discussions will be audio-recorded after obtaining written informed consent. The interviewer will take notes to document contextual factors and non-verbal cues that may inform interpretation of findings.

4.2.5. Data Analysis

Audio recordings will be transcribed verbatim into English. Local language recordings will be translated and transcribed into English. Transcripts will undergo quality checks against the audio and notetaker notes. After transcription, transcribers and coders will clean the data, and final transcripts will be reviewed for completeness and clarity.

Qualitative analysis experts will conduct thematic content analysis. Coding schemes will be refined after reviewing a sample of transcripts. Lead researchers will verify coder accuracy through interrater reliability before finalizing the scheme, which will then be shared with the study team. Assigned coders will analyze transcripts using QSR NVivo. NVivo will be used to identify patterns in code summaries (context, descriptions, language, narratives) to extract common themes, opinions, and perspectives.

Integrated Analysis: Findings will be triangulated with delivery setting assessments to understand health system readiness.

4.3. Stockout Monitoring: Health Facilities

4.3.1. Overview and ISAT Domain Alignment

Monthly MMS stockout frequency and duration will be collected from a random sample of 18 health centers across all operational districts, 6 referral hospitals, and 1 provincial hospital.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 3: Delivery Setting and Workforce
Stockout monitoring	Supply chain reliability at facility level and frequency of MMS stockouts

4.3.2. Study Population

Health centers, referral hospitals, and the provincial hospital (all will receive MMS to distribute) that are willing to participate.

4.3.3. Sampling Approach

18 health centers will be randomly selected (~20% of the total number of health centers). All 6 referral hospitals and the 1 provincial hospital will be included for data collection. A total of 25 health centers and hospitals will be included.

4.3.4. Data Collection

Monthly stockout data will be collected. Health centers and hospitals already conduct monthly inventory checks and documentation, so data can be pulled from existing sources.

Missing Data: Reasons for missed data should be documented by data collectors. Depending on the amount and nature of missing data, imputation strategies or a sensitivity analysis may be considered during data analysis.

4.3.5. Data Analysis

Stockout data will be analyzed to assess: (1) percentage of facilities and hospitals reporting stockout within the past month and (2) percentage of MMS coverage (pregnant women received MMS / pregnant women in need of MMS).

Integrated Analysis: Findings will be integrated with other delivery setting assessments to understand the effect of supply chain readiness on health system readiness.

4.4. User Acceptability and Adherence Survey: Pregnant Women

4.4.1. Overview and ISAT Domain Alignment

Home visits will be conducted with pregnant women at 90- and 180-days after first ANC visit (where they first received MMS) to assess user acceptability and adherence using a structured acceptability and adherence survey.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 1: Fidelity and Adaptation
Household survey	Pregnant women receiving correct MMS dosage at ANC visits
	Pregnant women receiving correct MMS counseling (benefits of MMS, how to take MMS) from healthcare providers
	Pregnant women adhering to taking MMS as prescribed
	Domain 2: Reach and Acceptability
Household survey	Satisfaction level among pregnant women with the sensory aspects of MMS
	Barriers that affect uptake and continued use among the target population

4.4.2. Study Population

Inclusion criteria: Women who are (1) at least 18 years old, (2) able to provide informed consent, (3) have attended at least one ANC visit at a health center or hospital in Takeo during the study period, and (4) can provide a functioning phone number for follow-up contact.

Women will be enrolled regardless of gestational age to evaluate acceptability and adherence patterns across different pregnancy stages and reflect the real-world setting. This will provide insights into potential timing-related barriers to MMS use.

Exclusion criteria: (1) Women with diagnosed anemia who require IFA supplementation instead of MMS, (2) women unable to communicate via telephone, (3) women who withdraw consent at any point.

During informed consent, the participants will have the opportunity to learn about the study and will have full decision to participate. If they decide not to participate in the study, they will have the opportunity to take IFA instead of MMS. Therefore, yes, there will be a choice for all pregnant women to participate in the study and to take the MMS.

4.4.3. Sampling Approach

Sample Size and Power: The sample size of 630 women was calculated to allow for detection of a minimum difference of 10% in the primary outcome measure (MMS adherence rate) with 95% confidence level and 80% power, accounting for the cluster sampling approach across health centers and hospitals. This includes a 30% margin for potential loss to follow-up between enrollment and the 180-day assessment point. The sample size is sufficient to generate province-representative estimates of intervention reach and acceptability across rural and urban settings and all six operational districts.

Sampling Approach: A stratified random sampling approach will be employed to ensure balanced representation across all six operational districts and between urban and rural health centers and urban hospitals.

Enrollment: Eligible women will be recruited during their first ANC visit at participating health centers and hospitals. Healthcare workers will be trained in the standardized protocol for enrollment, including obtaining written consent and recording registration data.

Follow-up sample selection: For each assessment timepoint (90 and 180 days), data collectors will be provided with a randomized list of enrolled women due for follow-up. The lists will be stratified by health center or hospital and date of first ANC visit to ensure representative sampling.

4.4.4. Data Collection

Survey Parameters:

- **Reach**
  - Verification of MMS receipt at ANC visit
  - Timing of MMS distribution relative to pregnancy stage
  - Quantity of MMS received
- **Acceptability**
  - Sensory evaluation using Likert scales (taste, smell, swallowability, appearance)
  - Overall satisfaction with MMS supplementation
  - Cultural appropriateness and fit with daily routines
- **Adherence**
  - Household survey and pill count at participant's home
  - Consistency of usage patterns since first receiving MMS
  - Calculation of adherence rate (tablets consumed/days available for consumption)
  - Social and cultural factors influencing adherence (role of husbands, mother-in-law, community leaders, other pregnant women)
- **Barriers and facilitators**
  - Reported side effects or concerns
  - Storage and handling practices
  - Quality of counseling received from healthcare providers
  - Knowledge of MMS benefits
  - Social support for supplement use
  - Suggestions for improving MMS delivery

Survey instruments will be developed in English and translated into Khmer using forward and backward translation. They will be validated through cognitive interviews with 5-10 women similar to the target

population. Surveys will then be pilot tested with 20 women to assess comprehension and administration time.

Finalized surveys will be programmed into electronic data collection forms for standardized administration. For acceptability and adherence monitoring will take place at the participants' homes. Tablet counts will be conducted at the 90-day and 180-day time-points post enrollment.

Side Effect Monitoring. Monitoring of all side effects associated with MMS is a critical aspect of the study and is included in the household visit questionnaire and will also be included in the following procedures.

- **Health Provider Training:** All health providers involved in MMS distribution will receive targeted training to actively encourage pregnant women to report any adverse side effects they experience.
- **Clear Reporting Channels:** Health providers will be instructed to promptly report any adverse events to the designated provincial project coordinator.
- **Dedicated Provincial Oversight:** Each province will have a dedicated, trained provincial project coordinator responsible for collecting and escalating reports of adverse impacts to the central research team.
- **Participant Education:** Pregnant women will be informed about the importance of reporting any side effects, and will be reassured that many symptoms such as nausea, dizziness, and fatigue are common in early pregnancy.

These measures are designed to ensure that any potential side effects are detected and addressed in a timely manner, safeguarding participant well-being and maintaining the integrity of the study.

Quality Assurance: To ensure data quality and reliability, 5% of participants will receive a household recall survey conducted by a different data collector within 48-72 hours of their original survey.

All data collectors will receive standardized training on survey administration, including role-playing exercises and observed practice calls. The first five surveys conducted by each data collector will be monitored in real-time by a supervisor.

Weekly data quality checks will be performed to identify and address potential systematic errors or biases. Data collectors will document call quality, participant engagement, and any technical issues encountered.

Participant Contact Protocol: Data collectors will make up to three household visits to each selected participant. Household visits will be separated by at least 1 week and scheduled between 7:00 AM and 7:00 PM to maximize response rates. Non-responsive participants after three attempts will be documented, and the data collector will proceed to the next individual on the randomized list.

Upon successful contact, data collectors will verify participant identity, reconfirm consent verbally before data collection, and proceed with the survey administration.

Missing Data: Reasons for missed data should be documented by data collectors. Depending on the amount and nature of missing data, imputation strategies or a sensitivity analysis may be considered during data analysis.

4.4.5. Data Analysis

- **Reach**
    - Proportion of eligible women who received MMS (calculated using health facility ANC attendance as denominator)

    - Geographical and demographic patterns in MMS coverage
    - Proportion of women receiving adequate MMS counseling
- **Acceptability**
    - Mean scores for each sensory parameter (taste, smell, swallowability, appearance)
    - Overall acceptance rate (proportion of women reporting satisfaction)
    - Thematic analysis of qualitative responses regarding barriers and facilitators
- **Adherence**
    - Mean adherence rate at 90 and 180 days
    - Proportion of women adherent above the threshold of 76%, in alignment with the adherence threshold used in the Hoang *et al.* (2024) study in Cambodia
    - Correlation between self-reported adherence and pill count verification
    - Factors associated with higher/lower adherence (demographic, geographic, implementation factors, social, cultural)
- **Integrated analysis**
    - Changes in acceptability and adherence between 90 and 180 days
    - Correlation between acceptability ratings and adherence rates
    - Relationship between quality of counseling and adherence
    - Key barriers affecting MMS uptake and continued use

4.5. Focus Group Discussion: National-Level Stakeholders

4.5.1. Overview and ISAT Domain Alignment

One FGD will be conducted with members of the National MMS Steering Committee to assess national MMS scalability.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 4: Implementation Infrastructure
National-level FGD	Integration of MMS into existing ANC services and workflows
	Availability of supporting workforce and materials for MMS delivery
	Implications on time, resources, and human resources for national transition to MMS from IFA and scale-up
	Supply chain reliability and strengthening for national procurement and distribution
	National capacity to monitor MMS distribution, delivery, and coverage
	Barriers to feasibility and sustainability of national MMS implementation
	Economic implications of transitioning to MMS from IFA at the national level (one-time and recurring costs)

4.5.2. Study Population

Members of the National MMS Steering Committee with direct involvement in MMS program planning, implementation, supply chain management, or delivery at various administrative levels. Participants must be willing to participate and available to attend.

4.5.3. Sampling Approach

6-8 personnel will be invited to participate using convenience sampling, with 8-10 people initially approached to account for a 20% non-attendance rate.

4.5.4. Data Collection

trained moderator and notetaker will conduct each 70-minute FGD in a private, comfortable location using a structured guide aligned with the 4 ISAT domains. All discussions will be audio-recorded after obtaining written informed consent. The moderator will ensure balanced participation while the notetaker will document contextual factors and non-verbal cues that may inform interpretation of findings.

4.5.5. Data Analysis

Audio recordings will be transcribed verbatim into English. Local language recordings will be translated and transcribed into English. Transcripts will undergo quality checks against the audio and notetaker notes. After transcription, transcribers and coders will clean the data, and final transcripts will be reviewed for completeness and clarity.

Qualitative analysis experts will conduct thematic content analysis. Coding schemes will be refined after reviewing a sample of transcripts. Lead researchers will verify coder accuracy through interrater reliability before finalizing the scheme, which will then be shared with the study team. Assigned coders will analyze transcripts using QSR NVivo. NVivo will be used to identify patterns in code summaries (context, descriptions, language, narratives) to extract common themes, opinions, and perspectives.
Integrated Analysis: Economic probes from this FGD will be triangulated with (1) implementation infrastructure assessments and (2) MMS stockout data to inform supply chain strengthening needs.

4.6. Economic Evaluation

4.6.1. Overview and ISAT Domain Alignment

This is an evaluation of the economic and resource needs to scale and implement MMS nationwide. It builds on and integrates methods in other sections of this protocol. This will guide the development of an evidence-based resource planning framework for sustainable MMS scale-up beyond the Takeo pilot.

Data Collection Tool	Data to be collected related to ISAT Domains
	Domain 4: Implementation Infrastructure
Economic evaluation	Economic implications (one-time and recurring costs) of transitioning from IFA to MMS nationwide
	National supply chain strengthening needs for reliable MMS procurement and distribution
	Sustainable financing mechanisms that exist or need to be developed for long-term MMS implementation
	Human resource considerations for nationwide scale-up

4.6.2. Study Population

Inclusion criteria: Institutions and individuals with direct involvement in MMS-related financial planning, budgeting, supply chain management, or resource allocation, including (1) health facilities across all six operational districts in Takeo province, (2) district health departments and Takeo provincial health department representatives, (3) national government agencies (Ministry of Health Finance Department, Central Medical Stores), (4) National MMS Steering Committee members, and (5) development partners and NGOs contributing to MMS financing or implementation.

Exclusion criteria: Institutions without direct financial involvement in MMS implementation or individuals without authority to provide financial or resource utilization data.

4.6.3. Sampling Approach

A stratified purposive sampling approach will be employed to ensure comprehensive representation

across all levels of the health system (facility to national), urban and rural contexts, different operational districts with varying resources.

Facility-Level Economic Data: All health facilities involved in the facility-level FGDs (Section 4.1) and an additional 12 randomly selected facilities (2 per operational district) for a total sample of 24 health facilities (28% of all facilities).

District- and Province-Level Economic Data: All six operational district health offices in Takeo and the Provincial Health Department Finance and Planning Division

National-Level Data: Members of the National MMS Steering Committee and the Ministry of Health Maternal and Child Health Division, Finance Department, and Central Medical Stores.

4.6.4. Data Collection Dimensions

Cost Data Collection: Cost data collection forms will be used to collect detailed financial information through administrative record reviews. Data will be collected across seven dimensions:

- **MMS Procurement Costs**
  - Unit costs under different procurement scenarios (international/local)
  - Comparison with historical IFA procurement costs
  - Volume-based price modeling for nationwide procurement
  - Foreign exchange and importation considerations
- **Training Implementation Costs**
  - Personnel time (trainers and trainees)
  - Training venue and materials
  - Per diems and transportation
  - Follow-up supervision costs
- **Material Development Expenses**
  - Development costs for training manuals/materials
  - Job aid production and distribution
  - Counseling materials development
  - Printing and distribution expenses
- **Supply Chain Management Costs**
  - Storage requirements and costs
  - Transportation expenses from central to health facility level
  - Inventory management systems
  - Quality assurance mechanisms
- **Human Resource Requirements**
  - Additional staff time for MMS-related activities
  - Opportunity costs of existing staff reallocation
  - Supervision and monitoring expenses
- **Infrastructure Adaptations**
  - Storage facility modifications
  - Distribution system adjustments
  - Information system updates for tracking
- **Recurrent and One-time Costs**
  - Clear disaggregation of transitional (one-time) versus recurrent costs
  - Annual recurrent cost projections for different scale-up scenarios

Economic Assessment within National-Level FGD: An economic component will be included in the national-level FGD with specific probes on:

- **Budget Planning and Financial Sustainability**
  - Government budget allocation processes for MMS
  - Donor transition planning for sustainable financing
  - Integration with existing health financing mechanisms
- **Supply Chain Readiness**
  - Central Medical Stores capacity for nationwide MMS distribution
  - Inventory management system strengths and limitations
  - Risk mitigation strategies for supply disruptions
- **Resource Planning Framework**
  - Human resource allocation mechanisms
  - Equipment and infrastructure needs
  - Monitoring and supervision systems

- **Coordination Mechanisms**
  - Inter-ministerial coordination structures
  - Public-private partnership opportunities
  - Development partner engagement processes

Economic Assessment within Facility-Level FGD: An economic component will be included in the facility-level FGDs with specific probes on:

- **Implementation Costs**
  - Additional time burden for healthcare providers
  - Storage and inventory management challenges
  - Administrative requirements
- **Resource Constraints**
  - Perceived resource gaps affecting implementation
  - Opportunity costs and trade-offs
  - Suggestions for efficiency improvements

4.6.5. Data Collection

Economic Data Collection at Health Facilities:

- Data collectors with financial/economic training will visit selected health facilities and review records using data collection forms
- Health facility administrators will be interviewed to validate/contextualize financial data
- Healthcare providers will be interviewed to collect data on time allocation

District and Provincial Data Collection:

- Meetings with finance officers at district and provincial health departments
- Structured review of budgetary allocations, expenditure reports, and financial projections
- Documentation of financing mechanisms and fund flows
- Assessment of financial management capacity for scale-up

National-Level Data Collection:

- Review of national financial records related to maternal health commodity procurement
- Documentation of budget allocation processes and financial sustainability strategies
- Assessment of Central Medical Stores capacity and supply chain costs
- Collection of cost data from previous health program scale-up efforts as benchmarks

Integration of FGD Economic Data:

- Economic components from national and facility-level FGDs will be appropriately coded
- Qualitative cost descriptions will be quantified where possible

- Resource constraints and opportunities noted in FGDs will be incorporated into analysis

4.6.6. Data Analysis
Cost Analysis:

- **Ingredient-based Costing**
  - Detailed itemization of all resources required for MMS implementation
  - Valuation of each ingredient at current market prices
  - Sensitivity analysis for price fluctuations

- **Comparative Cost Analysis**
  - Direct comparison of MMS versus IFA costs across all dimensions
  - Incremental cost calculation for transition
  - Cost projections for nationwide scale-up using demographic data
- **Scale-up Modeling**
  - Development of three scale-up scenarios (rapid, phased, and capacity-contingent)
  - Cost projections for each scenario with 5-year time horizon
  - Identification of efficiency gains possible at scale
- **Budget Impact Analysis**
  - Assessment of fiscal implications for national and provincial health budgets
  - Funding gap analysis for different implementation scenarios
  - Identification of sustainable financing options

Supply Chain Analysis:

- **Capacity Assessment**
  - Quantification of storage capacity requirements at each level
  - Transportation and logistics capacity mapping
  - Identification of supply chain bottlenecks
- **Risk Assessment**
  - Vulnerability analysis of the supply chain
  - Stockout probability modeling
  - Mitigation strategy development

Resource Planning Framework Development:

- **Gap Analysis**
  - Identification of critical resource gaps for nationwide implementation
  - Prioritization of gaps based on impact on implementation
  - Development of phased approach to address gaps
- **Sustainability Assessment**
  - Evaluation of long-term financial sustainability options
  - Assessment of integration potential within existing systems
  - Development of resource transition plan, policy development plan, and timeline from donor to government funding

Sensitivity Analysis:

- Compare findings against national cost-effectiveness analysis that is being led by Vitamin Angels as part of their Transforming Lives Through Nutrition consortium

Integrated Analysis: This assessment will be triangulated with (1) results from Sections 4.1, 4.2, and 4.6, (2) MMS stockout data (Section 4.2) to inform supply chain strengthening needs, and (3) user

acceptability and adherence findings (Section 4.4) to identify resource implications of overcoming barriers.

5. Data Management

Data will be linked to identifiers to track participants and prevent duplication. Identifiable data will be securely stored at Helen Keller offices, accessible only to PIs and Co-PIs. Designated personnel will clean and de-identify the data using anonymous ID numbers for analysis, with the process documented. All results will be de-identified.

Only authorized research staff with human subjects training will access the data. Paper notes from FGDs and KIIs will be securely stored until final analysis. Electronic data will be password-protected, stored on ONA, managed in SPSS, and uploaded to secure storage within six months of collection. At project completion, electronic data will be transferred to Helen Keller's country offices, with other copies deleted. Hard-copy data will be retained for up to three years before being shredded.

6. Stakeholder Involvement and Dissemination Plan

The National MMS Steering Committee will vet this research protocol before implementation. Throughout protocol implementation, the committee will be engaged at key decision points and regularly updated on the progress and findings. They will receive quarterly progress reports, presentations, meetings, and updates on MMS guidelines. They will be able to vet all study findings.

To disseminate study results (i.e., implementation successes, challenges, and health system readiness for scale-up) a roundtable discussion can be held with the Helen Keller team, National MMS Steering Committee members, and representatives from Takeo provincial and district health departments. Participants should have direct involvement in MMS program planning, implementation, supply chain management, or delivery at various administrative levels.

Opportunities for community dialogue can be held to share the findings with study participants, including pregnant women in Cambodia and their families.

The Helen Keller team can work with the National MMS Steering Committee to create a template to translate findings into actionable policy guidance. Together, they can use the ISAT domains to facilitate discussion around policy recommendations and sustainability planning to address adaptations for MMS scalability and feasibility before it can be rolled out across Cambodia.

7. Risks and Benefits

This study has minimal risks for participants. MMS is proven to improve health outcomes for mothers and babies, and it is recommended by the World Health Organization. The research methods do not pose risk of adverse events.

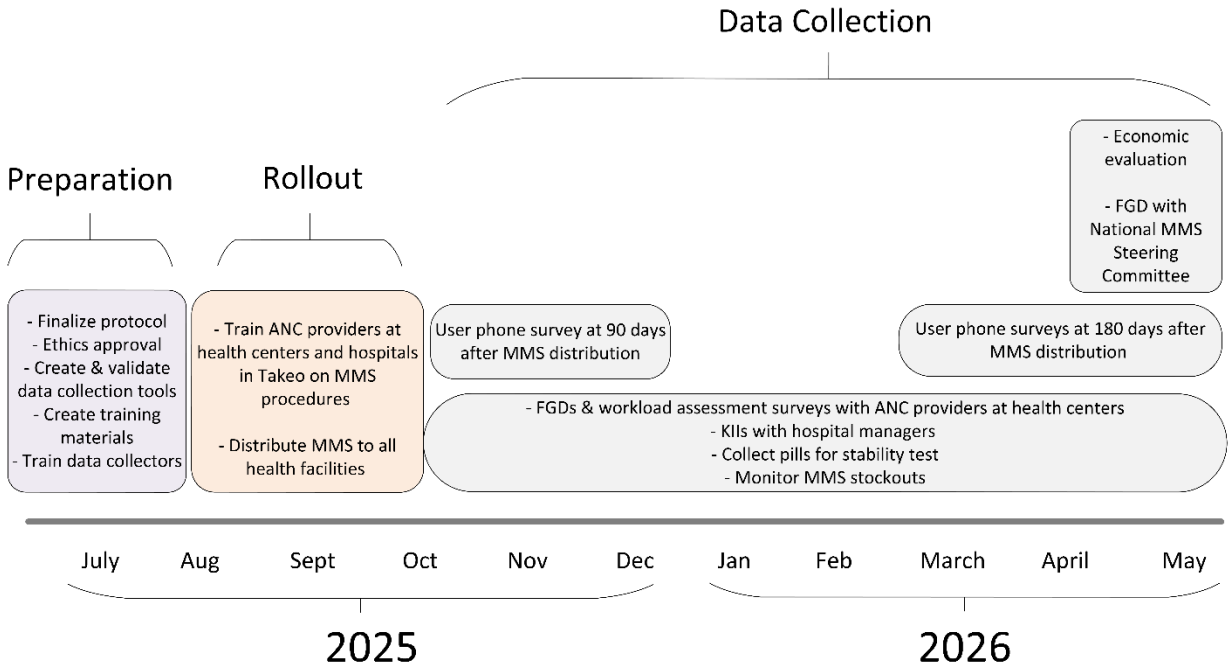
8. Ethics and IRB

Ethical clearance will be sought from the Ministry of Health, National Ethics Committee for Health Research. Ethical issues will be considered very carefully throughout the research. Before conducting the surveys, participants will receive a clear verbal and written explanation of the research's aim, objectives, and purpose. Participants will be informed of their rights, i.e., to participate or not to participate, or to drop out from the study or request for their responses not to be used even at the end of the interview if they wish. Consent forms will be required for all study participants. All study activities will be done in Khmer. The research participants' dignity, rights, value, and safety will be considered carefully during

the study process. Privacy and confidentiality of the participants will be maintained throughout the study using personal de-identifiers and password-protected data storage and analysis.

9. Timeline

Figure 2. Proposed timeline of MMS pilot in Takeo province.



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