STUDY PROTOCOL

A Randomized Controlled Trial in Lombok: Assessing Factors Influencing Adherence to Multiple Micronutrient Supplementation (MMS) Using Digital Tools

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EXECUTIVE SUMMARY

Background

Adherence to iron and folic acid supplementation (IFAS) remains a major challenge in Indonesia, as reflected in persistently high rates of maternal anemia (1-2). Although the government has begun adopting Multiple Micronutrient Supplementation (MMS) for pregnant women, similar adherence barriers observed with IFAS continue to pose a problem. National data indicate that only about half of pregnant women consume IFAS for at least 90 days, with adherence rates notably higher in urban areas (59.0%) compared to rural areas (47.8%) (3). This highlights the urgent need for strategies that can effectively improve adherence to supplementation programs across different settings.

In parallel, several studies have shown that calcium supplementation during pregnancy can significantly reduce the risk of hypertensive disorders of pregnancy (4-6). The World Health Organization recommends a daily calcium intake of 1,500–2,000 mg, administered in three divided doses (7). Given this recommendation, it is important to evaluate the feasibility and optimal strategy for co-administering calcium with multiple micronutrient supplements (MMS), particularly if calcium supplementation is to be integrated into the existing national MMS program.

Given these challenges, digital technology offers a promising solution for improving adherence to supplement consumption. Its use in public health has expanded rapidly, including in adherence monitoring (8). In this study, digital technology will be utilized to support and monitor pregnant women's adherence to MMS. Despite its potential, there is still limited evidence assessing the effectiveness of digital approaches in improving supplement adherence among pregnant women, creating a critical research gap this study seeks to address.

Rationale

The adherence to pregnancy supplementation in Indonesia remains suboptimal. This study aims to evaluate the factors influencing the adherence to Multiple Micronutrient Supplementation (MMS) consumption among pregnant women through a digital intervention. Furthermore, it will identify key determinants that support effective implementation and ensure the long-term sustainability of MMS supplementation programs within the national health system.

Objective

The primary objective of this study is to generate robust evidence on the factors influencing adherence to MMS and calcium intake among pregnant women. The study outcomes are expected to enhance program implementation of supplementation among pregnant women, inform national policies and guide the implementation of sustainable MMS programs in Indonesia.

Primary Objective

1) This study aims to determine the factors associated with adherence to MMS consumption through digital intervention.

Secondary Objective

1) To assess the association between MMS adherence and pregnancy outcomes, comparing intervention and control groups.
2) To further analyze factors influencing adherence to MMS by examining pregnancy birth outcomes.
3) To examine the relationship between MMS adherence and neonatal anthropometric outcomes, including birth weight and birth length.
4) To evaluate the impact of MMS adherence on early infant growth indicators.
5) To evaluate adherence to MMS and calcium when co-administered within routine antenatal care services.
6) To evaluate the cost-effectiveness of the digital MMS intervention to inform MMS program implementation, future policy decisions and potential scale-up strategies in Indonesia.

Methods

This study is designed as a two-stage randomized controlled trial conducted in Lombok Island, Indonesia. The first stage involves cluster randomization at the Puskesmas level, where clusters will be allocated into one of four MMS arms. In Stage 2, a cluster randomized trial at the integrated health post (posyandu) level will evaluate the addition of calcium supplementation to MMS, compared with MMS alone. This design allows assessment of implementation effectiveness, adherence, and program feasibility, while generating evidence to inform potential integration of calcium supplementation into the national MMS program.

Participants

The inclusion criteria for participants will be:

- Pregnant women in any trimester ≤ 32 weeks gestation
- Pregnant women stay in the site for the duration of the study

The exclusion criteria will include:

- Lost to follow-up
- Relocation out of the study area during the study period
- Death
- Miscarriage

All participants will be provided with study information and will sign informed consent prior to participation.

Sample Size

This study will use a two-stage randomized design. Sample size calculations were primarily based on the primary outcome of MMS adherence, accounting for cluster-level effects. Considering the supplement distribution system, anticipated program completion rates, annual birth volume, and statistical parameters (including clustering and power assumptions), approximately 10,012 pregnant women will be enrolled across 60 puskesmas clusters in Stage 1. In Stage 2, approximately 900 pregnant women will be recruited across 128 posyandu clusters to evaluate the addition of calcium supplementation to MMS.

Enrollment and Follow Up

Eligible participants will include all pregnant women at any gestational age who meet the inclusion criteria and provide informed consent. Enrollment will take place at participating health facilities through antenatal care (ANC) services. Upon enrollment, participants will be assigned according to their respective intervention arms based on the cluster and individual randomization schemes. All participants will be followed prospectively from the time of recruitment until 42 days postpartum to monitor adherence to supplementation, pregnancy outcomes, and potential side effects. Follow-up visits will be synchronized with routine ANC schedules, ideally conducted monthly or according to national ANC guidelines.

CHAPTER 1
INTRODUCTION AND LITERATURE REVIEW

1.1 Background

1.1.1 SUMMIT's Background

For over 25 years, the Summit Institute for Development (SUMMIT) has engaged communities to enhance public health. SID is also a founding partner of the Open Smart Register Platform (OpenSRP), which is currently used in 17 countries and recognized by the WHO as one of the top 10 innovations in global healthcare. Recently, using Fast Healthcare Interoperability Resources (FHIR), SID developed a team-based care model in four districts in Indonesia (with plans to expand to ten districts by 2027), covering 10 million people.

As a key partner of the Ministry of Health in accelerating integrated primary health services (ILP), SID collaborates with the Center of Data and Information (Pusdatin)-Digital Health Transformation Team (TTDK), formerly known as the Digital Transformation Office (DTO). We digitize frontline health workers' workflows and connect communities with facilities through the FHIR data ecosystem, including SATUSEHAT, the national platform. This system enables a dashboard for local monitoring and decision-making, used by primary healthcare managers and district health offices.

1.1.2 Importance of MMS

SUMMIT has also conducted large-scale randomized controlled trials (RCT) involving 42,000 pregnant women in Lombok, Indonesia. The results demonstrated that maternal micronutrient supplementation reduced infant mortality by 18%, with a 38% decrease in infant deaths among anemic pregnant women. These significant findings have shaped global policies and actions regarding the provision of MMS. The success of the SUMMIT trial also investigated factors contributing to low birth weight, small-for-gestational-age babies, and preterm births in Lombok, identifying maternal anemia, poor nutritional status, and inadequate prenatal care as primary determinants. This study highlights the need for focused interventions, emphasizing that improving maternal nutrition and access to healthcare can significantly reduce adverse pregnancy outcomes (9).

Further studies have investigated how MMS during pregnancy affects maternal and child biomarker patterns and nutritional status. These studies showed that supplementation significantly influenced maternal inflammatory markers and metabolic indicators. At ages 9–12 years, children of mothers who received supplementation exhibited 20% higher levels of essential micronutrients and a 15% improvement in overall nutritional status compared to children of non-supplemented mothers (10). These findings underscore the long-term benefits of prenatal micronutrient interventions.

Additionally, a review of MMS effectiveness during antenatal care in low- and middle-income countries indicated that micronutrient supplementation reduced the incidence of low birth weight by 14% and preterm births by 8%. Another study assessed the impact of maternal MMS on the stability of mitochondrial DNA copy number during

pregnancy in Lombok, showing that supplementation maintained mitochondrial DNA copy number within normal ranges and significantly reduced DNA variability by 10% compared to the unsupplemented control group. This stabilization was associated with better maternal health outcomes and suggested that micronutrient supplementation supports mitochondrial function and overall cellular health during pregnancy (11).

Adherence to iron and folic acid supplementation (IFAS) remains a major challenge in Indonesia, reflected in persistently high rates of maternal anemia (1-2). Although the government has begun adopting MMS for pregnant women, adherence barriers similar to those seen with IFAS remain unresolved. National data show that only about half of pregnant women consume IFAS for at least 90 days, with adherence higher in urban (59.0%) than rural areas (47.8%). Factors significantly associated with adherence include maternal age, education, occupation, parity, internet access, decision-making autonomy, husband's education, household wealth, ANC visits, and place of residence. These factors interact within a broader web of socioeconomic inequalities affecting supplement use (3).

Evidence suggests that program success in improving IFAS adherence depends on sustained engagement of community health volunteers, skill-based training for ANC promotion, reliable supplement supply, supervision and monitoring, consistent messaging on anemia prevention, and continuous operational research to guide scale-up. Context-specific implementation strategies, such as ongoing education, structured motivation and training of health workers, and clear, standardized information materials, have been particularly effective (12).

A study from Vietnam reported high adherence to preconception (82%) and prenatal (78%) supplementation, strongly linked to higher socioeconomic status (OR = 2.71, 95% CI = 2.10–3.52). First-time pregnancies were associated with lower adherence compared to multiparous women. Each visit from a village health worker increased adherence odds by 3–5% before pregnancy and 18% during pregnancy, underscoring the importance of community outreach (13). Program outcomes included increased skilled birth attendance, reductions in early infant mortality, and improved early ANC attendance. Effective strategies included evidence-driven implementation, recruitment and training of skilled community facilitators, and regular performance evaluation and certification (6) (9).

In Indonesia, the current adherence benchmark for micronutrient supplementation is defined as the consumption of 90 tablets during pregnancy (14). However, this standard represents only 50% of the total recommended MMS intake, meaning that many women are categorized as "adherent" despite not reaching the optimal level of consumption required to achieve full nutritional benefits (15). Several studies conducted in Indonesia have shown that even with this relatively low threshold, adherence rates remain suboptimal. Among the 655 women (53.9%) who started MMS intake in the first trimester, approximately 90% continued using MMS in the following trimesters and 75.3% consumed MMS $\geq$ 90 tablets. Implementation of MMS via community health centers resulted in high adherence once supplementation started (16).

In contrast, a systematic review indicates that to gain the significant benefits of MMS, such as increased birthweight and reduced risk of low birthweight (LBW) and small-for-gestational-age (SGA) births, pregnant women need to consume at least 70% of the total MMS capsules. A meta-analysis revealed compared to those receiving only iron-folic acid (IFA), while women with adherence below 60% showed no measurable benefit. Moreover, adherence below 75% was linked with higher risks of stillbirth and maternal anemia (17). These findings emphasize the need for Indonesia's supplementation programs to reassess adherence definitions and strengthen efforts to promote early initiation and consistent intake of MMS throughout pregnancy to achieve the intended health outcomes.

1.1.3 Importance of Calcium

Suggested scheme for calcium supplementation in pregnant women

Dosage	1.5–2.0 g elemental calcium/day[a]
Frequency	Daily, with the total daily dosage divided into three doses (preferably taken at mealtimes)
Duration	From 20 weeks' gestation until the end of pregnancy
Target group	All pregnant women, particularly those at higher risk of gestational hypertension[b]
Settings	Areas with low calcium intake

[a] 1 g of elemental calcium equals 2.5 g of calcium carbonate or 4 g of calcium citrate.
[b] Women are regarded as being at high risk of developing gestational hypertension and pre-eclampsia if they have one or more of the following risk factors: obesity, previous pre-eclampsia, diabetes, chronic hypertension, renal disease, autoimmune disease, nulliparity, advanced maternal age, adolescent pregnancy and conditions leading to hyperplacentation and large placentas (e.g. twin pregnancy). This is not an exhaustive list, but can be adapted/complemented based on the local epidemiology of pre-eclampsia.

Figure 1. Suggested calcium supplementation in pregnant women by WHO

The World Health Organization (WHO) recommends calcium supplementation for pregnant women, particularly those at high risk of developing gestational hypertension. The suggested dose is 1.5–2.0 grams of elemental calcium per day, equivalent to 2.5 grams of calcium carbonate or 4 grams of calcium citrate. This supplementation should be taken daily, with the total daily dose divided into three intakes, preferably with meals to enhance absorption. The supplementation is recommended to begin at 20 weeks of gestation and continue until the end of pregnancy to prevent pre-eclampsia and related complications (7).

The primary target group includes all pregnant women, especially those at high risk for gestational hypertension. Calcium supplementation is particularly recommended in areas with low calcium intake, as calcium deficiency can increase the risk of high blood pressure during pregnancy and other complications (7).

During normal pregnancy, the body undergoes adaptive cardiovascular changes to support increased maternal and fetal demands. There is a rise in vascular volume but a decrease in vascular resistance, largely due to reduced sensitivity to vasopressor agents and enhanced endothelium-dependent vasodilation. However, in pregnancies complicated by hypertensive disorders (HDP), these adaptive mechanisms are impaired. The increase in

vascular volume is not balanced by sufficient vasodilation, and vasoconstriction remains elevated, leading to increased systemic vascular resistance and higher blood pressure. A central mechanism involves intracellular calcium regulation, which controls both vasoconstrictive and vasodilatory pathways. Dysregulation of intracellular calcium may result in exaggerated vascular tone and impaired vasorelaxation, contributing to the vascular abnormalities observed in HDP (18).

Several randomized controlled trials have demonstrated that calcium supplementation can significantly reduce the incidence of gestational hypertension and preeclampsia. A Cochrane meta-analysis including 13 studies with a total of 15,730 participants showed that calcium supplementation lowered the overall risk of developing high blood pressure during pregnancy compared to placebo (12 trials, 15,470 women: risk ratio [RR] = 0.65; 95% confidence interval [CI]: 0.53–0.81; I^2 = 74%). Likewise, calcium supplementation was associated with a decreased risk of preeclampsia (13 trials, 15,730 women: average RR = 0.45; 95% CI: 0.31–0.65; I^2 = 70%; low-quality evidence). This protective effect was particularly evident among women with low dietary calcium intake (eight trials, 10,678 women: average RR = 0.36; 95% CI: 0.20–0.65; I^2 = 76%), but not among those with adequate calcium intake. The benefit also appeared more pronounced in women at higher risk of preeclampsia, although this finding may have been influenced by small-study effects (five trials, 587 women: average RR = 0.22; 95% CI: 0.12–0.42) (2). Calcium supplements may prevent preterm labor and delivery by reducing uterine smooth muscle contractility directly (7) and indirectly by increasing magnesium levels (19).

A study conducted in South Africa, Zimbabwe, and Argentina compared the effectiveness of low-dose and high-dose calcium supplementation in preventing pre-eclampsia and preterm birth. The study found that pre-eclampsia occurred in 23% of participants who received calcium supplements, compared to 29% in the placebo group (RR 0.80; 95% CI 0.61–1.06; p-value=0.121). Among participants with more than 80% adherence to supplementation, the risk was even lower—21% compared to 32% in those with poor adherence (RR 0.66; CI 0.44–0.98; p-value=0.037) (20).

Another study involving 11,000 pregnant women in India and Tanzania found similar rates of pre-eclampsia between groups taking 500 mg and 1500 mg of calcium. In India, the incidence was 3.0% in the 500 mg group and 3.6% in the 1500 mg group (RR 0.84; 95% CI 0.68–1.03), while in Tanzania, the rates were 3.0% and 2.7%, respectively (RR 1.10; 95% CI 0.88–1.36). These findings suggest that lower doses of calcium may be just as effective as higher doses in preventing pre-eclampsia (21).

Despite the acknowledged importance of calcium for pregnant women in various health resources, there is currently no specific guideline from the Indonesian government that clearly regulates calcium supplementation for pregnant women, including standardized dosage, administration schedule, or a structured distribution mechanism. While the Ministry of Health emphasizes the importance of micronutrient fulfillment, including calcium, as part of maternal health improvement efforts, available information remains general and is mostly delivered through educational programs such as Pregnancy Classes.

Furthermore, although the daily calcium requirement for pregnant women has been mentioned in various government publications, there is still no structured distribution system in place, unlike those implemented for iron and folic acid supplementation. This highlights the need for more targeted policies to ensure that pregnant women, especially those in areas with low calcium intake, can receive optimal supplementation to reduce the risk of pregnancy complications.

1.1.4 Type of packaging

Since the 19th century, glass and plastic bottles have been the primary choices for pharmaceutical packaging. Bottles remain widely used because they protect medications, are portable, flexible in size and labeling, and relatively affordable. However, blister packaging has become increasingly popular due to its child safety features, resistance to counterfeiting, better protection of medication quality, and its ease of use for patients. Blister packaging offers several advantages over bottles. It features an airtight seal that protects medication from contamination and prevents moisture from damaging the product. Each tablet or capsule is individually packaged, making it easier for patients to track their doses and know when to refill their medication. In contrast, medications in bottles are more likely to be jostled, increasing the risk of damage or breakage. With blister packs, each dose is individually protected, ensuring dosage accuracy and minimizing waste. Given these benefits, blister packaging has increasingly become the preferred option in the pharmaceutical industry to enhance safety, convenience, and sustainability (22).

In terms of adherence, a study conducted in Kampala, Uganda, showed that using blister packaging for iron and folic acid supplementation in pregnant women significantly improved medication adherence and hemoglobin levels. After four weeks, the average hemoglobin level in the blister group was higher than in the loose-pack group (11.9 ± 1.1 g/dL vs. 11.8 ± 1.3 g/dL; $p = 0.02$). By week eight, the hemoglobin levels in both groups were nearly the same (12.1 ± 1.2 g/dL vs. 12.0 ± 1.3 g/dL; $p = 0.23$). However, the increase in hemoglobin from baseline was significantly greater in the blister group (0.6 ± 1.0 g/dL vs. 0.2 ± 1.1 g/dL), with a mean difference of 0.4 g/dL (95% CI: 0.24–0.51 g/dL; $p = 0.001$). Additionally, medication adherence was higher in the blister group compared to the loose-pack group (52% vs. 47%), which likely contributed to the improved hemoglobin outcomes (23).

A study compared the cost-effectiveness of blister packaging versus traditional medication dispensing for outpatient care found that although blister packaging incurs slightly higher dispensing costs (estimated at 5% more than traditional methods), it offers benefits in improving medication adherence and overall health outcomes (24).

Furthermore, industry analysis indicates that while the initial production cost of blister packs is higher due to the use of specialized materials and equipment, this packaging format can result in long-term cost savings. These savings stem from reduced medication errors, improved patient adherence, and better product protection (25).

Another study developed an economic model to assess the impact of blister packaging on medication adherence and healthcare costs in a commercially insured

population. This randomized controlled trial evaluated the effect of daily-dose blister packs compared to traditional bottle packaging on medication adherence among elderly patients. The study concluded that blister packaging significantly improved both adherence and health outcomes in this population group (26).

Therefore, in this study, we aim to validate these findings while also comparing their effectiveness with digital interventions, which are the primary focus as a strategy to improve pregnant women adherence to MMS and calcium

1.1.5 SUMMIT's innovation

The upcoming MMS and calcium study will be integrated into the development of an artificial intelligence (AI)-based platform to enhance program efficiency and adherence monitoring. The SMART Supplement will provide several key features, including QR code scanning for each MMS blister or bottle, tracking of supplement consumption for adherence assessment, and integration with ANC services to enable tailored counseling at the point of care. This system represents a core component of our digital innovation strategy to improve maternal supplement adherence.

1.2 Problems

In Indonesia, pregnant women are required to consume iron and folic acid supplements (TTD). However, adherence to TTD supplementation remains low (3). Moving forward, the Indonesian government adopted UNIMMAP-based MMS, which contains various micronutrients, including iron and folic acid. Currently, the UNIMMAP formulation in MMS does not include calcium. Therefore, this study will incorporate calcium as part of the intervention alongside MMS. Previous studies have shown that adherence to TTD consumption is influenced by several factors, such as the frequency of antenatal visits, knowledge levels about TTD, and support from partners (27-30). Understanding the factors that affect adherence to MMS and calcium consumption is crucial for improving pregnancy outcomes.

Currently, the Ministry of Health of Indonesia does not have specific national guidelines on calcium supplementation during pregnancy. The existing concern relates to the WHO recommendation, which suggests a total daily intake of 1,500–2,000 mg of calcium, divided into three doses. When calcium is given in addition to MMS, pregnant women may experience a high pill burden, which can negatively affect adherence to both MMS and calcium supplements (31).

Calcium carbonate tablets are often unpalatable for some women because of their large size and powdery texture, leading to further reluctance in consumption (4). The high pill burden also makes calcium supplementation programs more costly, with an estimated cost of around USD 27 per woman from week 20 of pregnancy until delivery. These issues (acceptability, feasibility, and cost-effectiveness) pose significant challenges for scaling up calcium supplementation programs in low- and middle-income countries (LMICs) (32).

To date, there is limited evidence assessing adherence to MMS using digital intervention approaches. This study aims to evaluate factors influencing the adherence to MMS and calcium consumption among pregnant women. Additionally, it will identify key determinants that contribute to the effective implementation and long-term sustainability of MMS and programs.

1.3 Research Objectives

1.3.1 Primary Objective

1) This study aims to determine the factors associated with adherence to MMS and consumption through digital intervention.

1.3.2 Secondary Objective

1) To assess the association between MMS adherence and pregnancy outcomes, comparing intervention and control groups.
2) To further analyze factors influencing adherence to MMS by examining pregnancy birth outcome
3) To examine the relationship between MMS adherence and neonatal anthropometric outcomes, including birth weight and birth length.
4) To evaluate the impact of MMS adherence on early infant growth indicators.
5) To evaluate adherence to MMS and calcium when co-administered within routine antenatal care services.
6) To evaluate the cost-effectiveness of the digital MMS intervention to inform future policy decisions and potential scale-up strategies in Indonesia.

1.4 Significance of the Research

Research on digital interventions based on MMS and calcium has significant potential for various stakeholders to improve program implementation and policy recommendations.

1.4.1 Individuals/Patients

The implementation of digital interventions in the MMS program can directly enhance the quality of healthcare services for pregnant women and children (31). Through this approach, relevant information regarding nutritional needs, supplement consumption schedules, healthcare facility visit schedules, and the health benefits of MMS and calcium intake can be delivered more effectively. Thus, the use of this technology has the potential to improve pregnant women's knowledge and adherence to necessary supplementation through platforms such as WhatsApp API and Call Centers. Ultimately, this contributes to better health outcomes for both mothers and babies.

1.4.2 Healthcare Workers

For healthcare workers, digital interventions can serve as a support tool for providing more structured and efficient healthcare services. Digital applications can monitor patient adherence, provide supplement consumption reminders, and facilitate

communication between healthcare providers and pregnant women (8). With centralized and easily accessible data, healthcare workers can identify risks earlier, deliver more targeted education, and ensure the continuity of maternal and neonatal healthcare interventions.

1.4.3 Community

At the community level, this intervention can contribute to achieving maternal and child health (MCH) indicators, a key metric for assessing public health status. Digital service delivery can increase the accessibility of health programs, especially in regions with limited infrastructure or medical personnel. Moreover, with enhanced community awareness and participation in the MMS program, the impact can extend to achieving national health targets, such as reducing maternal and infant mortality rates and improving the overall nutritional status of the population.

1.4.4 Government

This research also has significant implications for policymakers at both national and subnational levels. The findings from this study can provide evidence-based recommendations regarding the implementation of technology-driven healthcare services, especially within the MCH program. Additionally, the results can support the development of more adaptable policies that cater to community needs, including the integration of MMS programs within broader healthcare systems. By leveraging digital technology, the government can enhance the efficiency and effectiveness of health programs and strengthen the overall healthcare delivery system.

CHAPTER 2
RESEARCH METHODOLOGY

2.1 Conceptual Framework

In this study, the dependent variable is the *adherence to MMS consumption* under two modes of care: Standard Care and Digital Care. The independent variables include *individual characteristics, socioeconomic status, and ANC service* that may influence adherence.

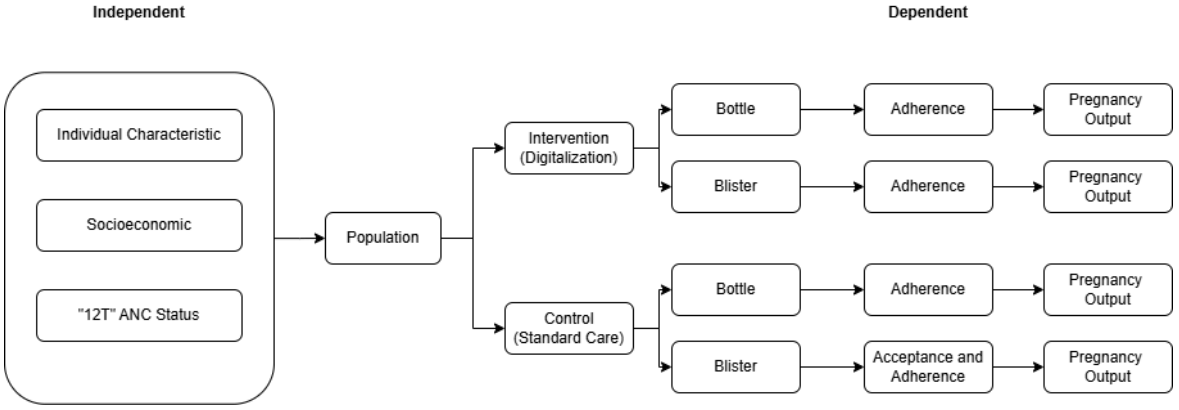


Figure 2. Conceptual Framework of Research

2.2 Research Design

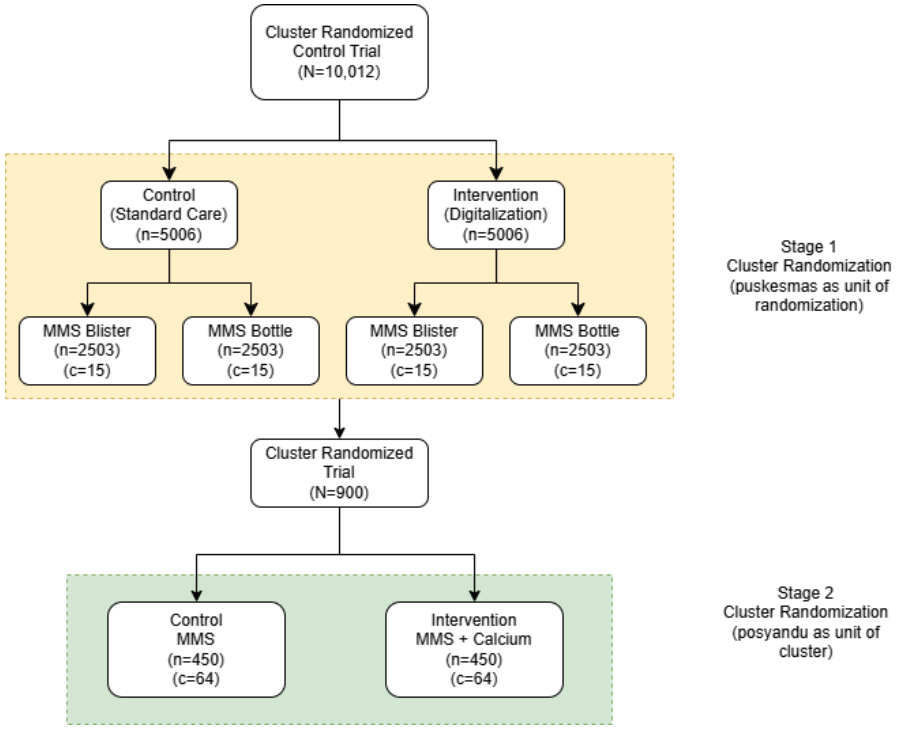


Figure 3. Research Design Staging (n= number of sample; c= number of cluster)

This study is a two-stage randomized controlled trial conducted in Lombok Island, Indonesia. The first stage is a cluster randomization at the Puskesmas (community health centers) level to allocate participants into one of four MMS arms. The intervention period will last for one year, with continuous follow-up from recruitment until delivery.

The study uses a nested (two-stage) randomization design, enabling simultaneous evaluation of MMS across four study arms that assess both digitalization and packaging strategies. First, a cluster randomized trial at the puskesmas level will evaluate MMS across four arms, incorporating different digitalization and packaging approaches. Second, a cluster randomized trial at the posyandu level will evaluate the addition of calcium supplementation to MMS compared with MMS alone.

The study will be conducted in selected Puskesmas across Lombok Island, West Nusa Tenggara, Indonesia. Posyandu (integrated health post) serves as the primary entry point for antenatal care and maternal health services in the Indonesian health system. Each participating Puskesmas will act as a randomization cluster for the MMS intervention.

2.3 Study Location and Duration

2.3.1 Study Location

The study will be conducted on Lombok Island, covering rural areas such as West Lombok, East Lombok, Central Lombok, and North Lombok, and urban areas such as Mataram. The total number of pregnant women in 2025 was 80.173 pregnant women.

2.3.2 Study Duration

The research will span around 2 years including preparation phase from April 2025, enrollment and monitoring starting in April 2026 and ending in June 2027.

2.4 Intervention Arms and Sample Size

2.4.1 Intervention Arms

The intervention will be evaluated for its impact and role in achieving the program's objectives. Randomized Controlled Trials (RCTs) will have a high level of validity due to their complex, detailed, and structured implementation, as well as their inclusion of a large population. One of the advantages of RCTs is their ability to provide strong responses in defining cause-and-effect relationships and offering insights for program or policy implementation. The differences between the standard care and digital care intervention packages will be explained as follows:

Table 1. Comparison Between Standard and Digital Intervention Package

Digital Group	Non-digital group
Standar Intervention - Standard service of ANC and PNC - Regular Health promotion and printed material **Tech Developed** - Whatsapp reminder - Call center - Personalized education via chatbot and consultations - Gamification and alert system **Tech Added Value:** AI monitoring and prediction	**Standar Intervention** - Standard service of ANC and PNC - Regular Health promotion and printed material
Operational optimization for both groups: - QR codes for every strip of supplement will be tracked and recorded to Kobo Form - Dynamic Worker Support (DWS): Field workers' (Community Health Promoters/CHPs) daily scheduling and field work optimization.	

Standard of Care (Non-Digital Group)

All participants will receive the Standard of Care (SoC) for maternal and child health services as implemented within the existing local health system framework. In this study, SoC refers to routine services delivered to pregnant women under national and district-level program policies, reflecting real-world variations in service delivery, resource availability, and operational priorities across facilities. This ensures that the study remains embedded within routine programmatic conditions rather than introducing externally controlled or idealized settings.

Under the Standard of Care, all Puskesmas will provide:

- Routine antenatal care (ANC) and postnatal care (PNC) services;
- Regular health promotion and counseling activities;
- Printed information materials to support maternal nutrition and supplement adherence.

No additional digital adherence tools or structured digital communication platforms will be introduced in this group.

Digital Care Group

Puskesmas assigned to the Digital Care arm will receive all components of the Standard of Care, complemented by an integrated package of digital innovations designed to

strengthen adherence support, improve monitoring systems, and enhance communication between providers and pregnant women.

Under Standard of Care:

- Routine antenatal care (ANC) and postnatal care (PNC) services;
- Regular health promotion and counseling activities;
- Printed information materials to support maternal nutrition and supplement adherence.

Digital Adherence and Monitoring Tools

- SMART Supplement Web Application for digital pill counting and real-time adherence tracking;
- QR code tracking for each supplement strip, linked to Kobo-based monitoring systems;
- AI-supported monitoring and predictive analytics to identify adherence risks.

Communication and Behavioral Support

- WhatsApp reminders for supplement intake and ANC/PNC attendance;
- Call center services to facilitate two-way communication, counseling, and rapid issue resolution;
- Personalized education delivered through chatbot-assisted consultation;
- Gamification features and automated alert systems to reinforce adherence behavior.

Operational Optimization for Both Groups

To ensure consistent implementation monitoring across study arms, selected system-level operational improvements will apply to both groups:

- QR codes for every supplement strip will be tracked and recorded using Kobo-based forms;
- Structured monitoring of supplement distribution and reporting mechanisms.

Each Puskesmas will be randomly assigned to one of four MMS arms:

1. Digital–Bottle: MMS provided in bottles, with adherence supported through a digital reminder and monitoring tool.
2. Digital–Blister: MMS provided in blister packs, with digital adherence support.
3. Non-Digital–Bottle: MMS in bottles without digital support
4. Non-Digital–Blister: MMS in blister packs without digital support.

This four-arm randomization allows assessment of both delivery format (digital vs non-digital) and packaging type (bottle vs blister). The allocation of supplementation type will be determined through a randomization process to ensure consistency in the type of supplement provided to all patients at each *puskesmas*.

2.4.2 Randomization and Allocation

A two-stage randomization will be implemented:

1. **Stage 1 (Cluster-level):** Puskesmas will be randomly assigned in a 1:1:1:1 ratio to the four MMS arms using computer-generated random sequences
2. **Stage 2 (Cluster-level)**: Within each selected Puskesmas, Posyandu will be randomly assigned to receive either MMS alone or MMS plus calcium supplementation. The allocation of calcium supplementation will be distributed

evenly across the four MMS arms established in Stage 1 to ensure balanced representation of calcium and non-calcium groups within each arm.

2.4.3 Inclusion and Exclusion Criteria:

The inclusion criteria for participants will be:

- Pregnant women in any trimester ≤ 32 weeks gestation
- Pregnant women stay in the site for the duration of the study

The exclusion criteria will include:

- Lost to follow-up
- Relocation out of the study area during the study period
- Death
- Miscarriage
- Stillbirth

2.4.4 Sample Size

This study applies a two-stage randomized design, consisting of (1) a cluster-randomized controlled trial (RCT) for MMS adherence, and (2) cluster nested randomization for calcium supplementation in posyandu level. The sample size calculation is based on the supplement distribution design, the likelihood that not all pregnant women will complete the program, the annual birth rate, and statistical calculations ensuring the results will be meaningful. Taking these factors into account, it is estimated that approximately **10,012 pregnant women** need to participate in the MMS program. Detailed calculations for sample size are as follows:

Table 2. Key parameter in sample size calculation

Parameter	Value	Source/Note
Randomization Unit	Cluster (Puskesmas) for MMS adherence; Individual (pregnant woman) for calcium dose	Two-stage randomization design: Stage 1 cluster-level, Stage 2 posyandu level
Effect Size	10% difference in MMS adherence (0.80 vs 0.90)	Based on expected adherence improvement with digital support (8)
Alpha (Type I Error)	0.05	Standard threshold for 95% confidence interval
Power (1–β)	0.80	To detect a significant adherence difference
Loss to Follow-Up (Attrition Rate)	32%	Based on previous SUMMIT Trial in Lombok
Intraclass Correlation	0.03	Estimated within expected

Coefficient (ICC)		range (0.01–0.05) for community-based studies
Average cluster size (n)	114.5	Average number of first-trimester pregnant women per cluster
Design Effect (DE)	4.41	DE = 1 + (n – 1) × ICC
Adjusted Design Effect (Adj DE)	4.28	Adj DE = DE / (1 + ICC)
Unadjusted sample size per group	397	Calculated using Lemeshow formula for two proportions (P_1 = 0.80; P_2 = 0.90)
Adjusted sample size per group (after DE)	1,702	397 × 4.28
Adjusted sample size per group (after attrition)	2,503	1,702 / (1 – 0.32)
Total sample size	10,012	2,503 × 4 groups (Bottle Intervention, Blister Intervention, Bottle Control, Blister Control)
Sub Sample Calcium	900 Calcium Carbonate (500 mg) and no calcium	Nested Cluster randomization by posyandu

Unadjusted Sample Size Calculation

Sample size calculation for proportion comparison, we will use the following formula (Lemeshow)

$$n = \frac{2\left\{Z_{1-\frac{\alpha}{2}}\sqrt{2P(1-P)}+Z_{1-\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)}\right\}^2}{(P_1-P_2)^2}$$

n = unadjusted minimum sample

$Z_{1-\frac{\alpha}{2}}$ = Z value with confident interval 95% (1,96)

$Z_{1-\beta}$ = Z value with power 80% (0,84)

P $= \frac{(P_1+P_2)}{2} = 0.85$

P_1 = Proportion in group 1 = 0.80

P_2 = Proportion in group 2 = 0.90

Unadjusted sample size per group as follow:

$$n = \frac{2\left\{1.96\sqrt{2\times0.85\times0.15}+0.84\sqrt{0.80\times0.2+0.9\times0.1}\right\}^2}{(0.1)^2}$$

n=397.47

Design Effect

Due to the clustering effect, it is necessary to account for the fact that individuals within the same cluster tend to have similar (homogeneous) characteristics compared to individuals from different clusters. This clustering effect is represented by the Design Effect (DE). The formula for calculating the design effect is as follows:

$$DE = 1 + (n - 1) \times ICC$$

ICC = Intracluster correlation coefficient, measures the correlation between individuals within the same cluster compared to individuals in different clusters. It represents the degree of similarity or homogeneity among individuals within a cluster. The ICC can be calculated from previous studies, if available. If no prior data is accessible, the ICC is typically estimated to fall within the range of 0.01 to 0.05. For this study, the ICC will be set at **0.03**.

n = Number of interquartile range of pregnant women in first trimester 114.5

$$DE = 1 + (n - 1)\times ICC$$

$$DE = 1 + (114.5 - 1)\times 0.03$$

$$DE = 4.41$$

Adjusted Design Effect

$$Adj\ DE = \frac{DE}{1+ICC}$$

$$Adj\ DE = \frac{4.41}{1+0.03}$$

Adj DE = 4.28

Number of Sample per Group

$$n_{group} = N \times DE$$

= 397.47 × 4.28 =1,702

Adjusted Sample per Group

The Attrition Rate (AR) is set at 0.32, based on previous MMS studies conducted in Lombok. This rate accounts for participants who are lost to follow-up, drop out, relocate, die, experience abortion, or stillbirth during the study period.

$$n_{adj} = \frac{n_{group}}{1 - AR}$$

$$n = \frac{1{,}702}{1-0.32}$$

n= 2,503

This study includes 4 groups (bottle intervention, blister intervention, bottle control, blister control). Thus, the total sample size for this study will be 2,503×4=**10,012**

Calcium (Sub-sample)

The total sample size for the calcium sub-study will be 900 pregnant women, equally allocated between intervention and control groups.

Participants will be divided as follows:

Table 3. Subsample calcium allocation

Type of Group	Calcium subsample	Number of Sample
Intervention	MMS + Calcium Carbonate (500 mg elemental)	450
Control	MMS + No Calcium	450

The intervention group will receive multiple micronutrient supplements (MMS) in combination with 500 mg of calcium daily, while the control group will receive MMS alone without additional calcium supplementation.

This sub-sample size was determined based on the adherence evidence reported on multidoses regiment (32), which demonstrated higher adherence with once-daily dosing compared to multiple daily dosing regimen.

2.5 Study Procedures

2.5.1 Training and Communication

Prior to study implementation, all field, IT, and data management staff will undergo initial training to ensure full understanding of the study protocol, *Good Clinical Practice (GCP)*, informed consent procedures, data collection, diagnostic procedures, safety monitoring, sample handling, and implementation of the intervention in accordance with the field manual procedures. Refresher training will be conducted every six months or as needed to maintain procedural consistency, ensure adherence to study standards, and uphold data quality across all study sites.

At the end of each training session, participants will be required to complete a competency assessment. Staff who do not pass the assessment will be required to retake the test after additional coaching or supervision. If the staff member fails the second assessment, they will be deemed unqualified to continue their role in the study and be replaced.

2.5.2 Pilot Study

Before the main study implementation, a pilot study will be conducted to ensure that all digital and field systems are fully functional, feasible, and acceptable for both participants and implementers. The pilot phase will last for four months, conducted approximately four months prior to the start of the main trial.

Objectives

The pilot study aims to:

1. Assess the feasibility, usability, and functionality of the digital systems, including the database, automated reminders, adherence monitoring tools, and AI-supported analytics.
2. Evaluate the field implementation procedures outlined in the field manual, ensuring that data collection, supplement distribution, and reporting workflows are operationally feasible.
3. Examine the acceptability and early adherence to supplement use (iron–folic acid and calcium) among pregnant women, as well as the effectiveness of digital adherence monitoring.
4. Assess participants' acceptability and comprehension of product information, including labeling, packaging, dosage, and usage instructions.

Design and Participants

The pilot study will enroll approximately 350 pregnant women, divided into two groups:

- Digital intervention group, receiving all supporting digital system, automated adherence reminders and follow-up monitoring through the digital system, such as reminder, supplement barcoding, education, and follow up
- Standard care group, following routine antenatal care (ANC) services at the *Posyandu* and *Puskesmas/Pustu*.

Each participant will receive standard iron–folic acid (IFA) supplements provided by midwives through *Posyandu* and a daily dose of calcium (500 mg calcium lactate). Adherence will be monitored digitally and verified through in-person follow-up.

2.5.3 Subject Screening and enrollment

2.5.3.1 Screening and Enrollment

Before the implementation of the intervention, the study will conduct a baseline data collection among all potential participants within the intervention area. This data will serve to establish a sampling frame that will guide the randomization process and ensure accurate identification of the target of the intervention.

The baseline demographic survey will systematically identify all pregnant women residing in the study area, using health facilities data such as village maternity posts (polindes) or auxiliary health services (pustu) and community health centers (puskesmas). All pregnant women at any trimester and residing in the study site for the duration of the study will be included. Pregnant women will be excluded if they are lost to follow up, relocate outside of the study site, or experience miscarriage, stillbirth, or death during the study period. The data collected will include each woman's name and address, gestational age, and place of residence. The resulting dataset will provide a comprehensive foundation for planning the intervention and evaluating its impact.

After compiling a complete list of pregnant women from each village within the study site, CHP will meet with all eligible participants during their scheduled posyandu visits. At these first encounters, the enrollment process will begin with a clear explanation of study objectives and procedures. Pregnant women who express interest and demonstrate understanding of the study will be given informed consent. Once consent is obtained, CHP will collect their ANC data, visit their homes to provide further information about the study, engage with family members for support, and perform household mapping. This approach ensures that participants are fully informed, their families are involved in supporting participation, and baseline household information is accurately documented to guide subsequent interventions.

2.5.3.2 Randomization

In the first stage, randomization is conducted at the puskesmas level, with a total of 60 puskesmas allocated into four intervention arms. The randomization process utilizes data management tools to generate randomization numbers, followed by stratification based on median, upper, and lower values of pregnancy rates to ensure balanced distribution across population characteristics. Following this process, the 60 puskesmas are assigned to four distinct intervention clusters: 1) Digital-Bottle (MMS provided in bottles, with adherence supported through a digital reminder and monitoring tool), 2) Digital-Blister (MMS provided in blister packs, with digital adherence support), 3) Non-Digital-Bottle (MMS in bottles without digital support, standard counselling only), 4) Non-Digital-Blister (MMS in blister packs without digital support). Puskesmas are randomly assigned in 1:1:1:1 ratio to these four MMS arms. The randomization schema is designed to be reproducible and minimize bias, providing a transparent framework for the assignment of interventions to each puskesmas cluster. This second-stage randomization is implemented to ensure balanced allocation of calcium supplementation across all four MMS arms from Stage 1. In other words, within each MMS intervention arm, posyandu are proportionally and randomly assigned to calcium or no-calcium groups to maintain comparability and avoid systematic imbalance across treatment combinations.

2.5.4 Data Management

Effective and secure data management is essential to maintain the integrity, accuracy, and confidentiality of study information. This study will implement a centralized data management system to ensure standardized and traceable handling of all data from

field collection to final analysis, in accordance with established Standard Operating Procedures (SOPs). The use of electronic data collection tools will enable CHP to capture data even in offline conditions, with automatic submission once a stable internet connection is available. Field data, laboratory sample data, and other data sources will be integrated into a single central database to facilitate comprehensive analysis.

A data processing pipeline will conduct data cleaning, transformation, and validation to ensure accuracy and consistency across datasets. To support uniform variable naming, clear definitions, and interoperability across platforms, a centralized data dictionary will be developed. All datasets will subsequently be converted to the FHIR standard to enhance compatibility and structured data exchange within the broader data ecosystem. The integrated data flow and transfer system will enable seamless linkage between field data, and monitoring dashboards, supporting efficient real-time analysis and reporting throughout the study.

Table 4. Integrated data flow and data transfer

Field Data (Baseline, Monitoring, Pregnancy Outcome)	**Analysis and reporting**
● CHP will collect participant data electronically using standardized digital forms during household and facility visits. ● Data collected will include demographic characteristics, antenatal care (ANC) visits, pregnancy outcomes, postnatal care (PNC), and supplement adherence. ● All entries will be recorded directly into the study's electronic data capture system to ensure accuracy and timeliness.	● The data analysis team will perform automated data processing and statistical analyses through the integrated data platform. ● Automation systems will also generate fieldwork schedules, WhatsApp messages, and call reminders to support real-time monitoring for pregnant women ● Dynamic worker support features will enable automated visit scheduling and progress tracking. ● dashboard will be established to provide daily insights, routine reports, and visual summaries of study progress and data quality

Data collection will be conducted using an electronic Case Report Form (eCRF) developed in KoboToolbox. The eCRF includes modules:

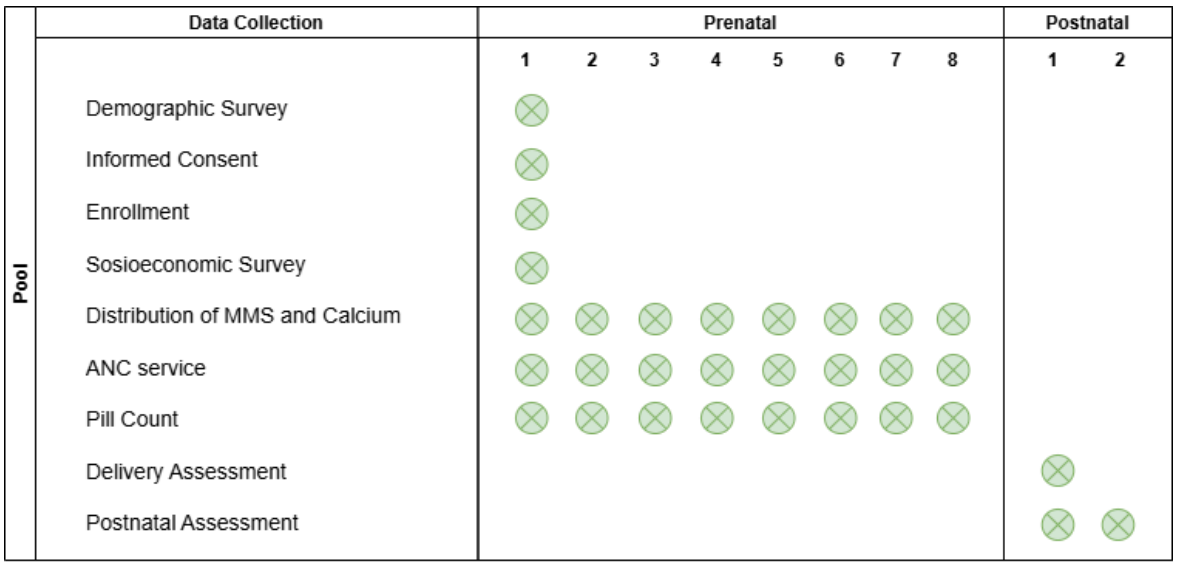
Table 5. Case Report Forms and Sources Documentation

Enrolment CRF	● Demographic survey ● Screening checklist and eligibility verification ● Individual and family informed consent documentation ● Assignment to study arm and randomization code generation
Baseline Assessment	● By name by address identification (geotag, phone number) ● Socioeconomic assessment ● Master database ● Baseline health indicator

Intervention and monitoring	• Supplement distribution and consumption monitoring (MMS + calcium) • Compliance verification via SMART MMS digital counting • Monthly field monitoring visits • Digital system logs for message reminders, chatbot interactions, and follow-up calls • ANC visit and service completeness
Pregnancy outcome	• Pregnancy outcome • Delivery details • Maternal Outcome • Infant outcome
PNC Module	• Postpartum visit • Infant feeding practice and growth monitoring • counseling and follow up

2.5.4.1 Data Collection

Figure 4. Data Collection Time Point



Demographic Survey

Prior to enrollment, CHPs will conduct a demographic survey at the *Polindes (Village Maternity Post)* to obtain the registry of pregnant women from the *Posyandu*. This registry will serve as the sampling frame for recruitment. All eligible pregnant women identified from the list will be approached and enrolled in the study.

Informed Consent and Enrollment

CHPs will visit the *Posyandu* to meet the identified pregnant women and provide an explanation of the study objectives, procedures, benefits, and potential risks. Pregnant women who agree to participate will sign the informed consent form in the presence of the midwife, who will serve as a witness. Following the *Posyandu* visit, CHPs will conduct home visits to obtain family consent and to provide regular reminders for pregnant women to consistently consume MMS and Calcium as instructed.

Pregnancy follow up procedures

CHPs will receive automated schedules indicating which *Posyandu* to visit for routine encounters with pregnant women. Each visit will capture *KIA* data, including ANC attendance, anthropometric measurements, supplement distribution, and relevant health indicators. QR codes will be used to link each participant's supplement adherence records across *Posyandu* visits and home follow-ups, ensuring data synchronization with the central database (BigQuery).

Data from *KIA* capture will be entered by trained data entry personnel using a double data entry system to ensure accuracy and consistency. Both entries will be automatically validated, and the final verified dataset will be connected to the central database (BigQuery) for integrated data management and analysis.

If a pregnant woman does not attend her scheduled *Posyandu* visit for ANC, the CHP will be rescheduled for a home visit to ensure follow-up.

Qualitative Assessment

Prior to the implementation of the main study, formative qualitative research was conducted to inform study design and operational planning. The activities included focus group discussions (FGDs) and simulation surveys with pregnant women to assess their preferences, perceptions, and acceptability toward supplementation. In addition, FGDs were conducted with midwives to understand field implementation workflows and to obtain their perspectives on potential challenges and facilitators of the intervention.

Socioeconomic Survey

A socioeconomic survey will be conducted through a home visit at the beginning of the study. During the visit, CHPs will conduct structured interviews and direct observations to collect information on household characteristics, living conditions, and assets. This data collection aims to assess the socioeconomic status of participating families, which will be used for subsequent analysis of factors influencing adherence and health outcomes.

Delivery assessment

Delivery outcomes will be assessed within 24 hours or at worst 3 days after birth, regardless of whether the delivery takes place at home, in a *Puskesmas*, or at a hospital. Prior to the estimated date of delivery, CHPs will conduct home visits to perform regular pill counts and to obtain information on the anticipated place and timing of delivery. Pregnant women will be encouraged to contact the study call center immediately on

delivery date to report the birth. Upon notification, CHPs will conduct a verification visit to collect detailed delivery outcome data. All delivery outcome data will be documented using standardized study forms and entered into the digital data collection system within 24 hours of verification.

Postnatal follow up

All study participants will be visited either at their homes or at the *posyandu* on days 3, 7, 28, and 42 postpartum to assess maternal and infant vital signs, health status, and anthropometric measurements. Infant immunization visits at six weeks will also be monitored to ensure adequate follow-up. Participants who are unavailable during scheduled visits, either at the *posyandu* or at home, will receive an additional home visit to confirm their pregnancy outcome and vital status.

Adherence to MMS and calcium supplementation

To further enhance the monitoring of MMS adherence, each MMS package, both in the control and intervention arms, is labeled with a unique QR code. This allows for traceability and accurate tracking of distribution and usage. In addition, the study develops image-based datasets to support the training of AI algorithms that estimate the number of MMS capsules consumed by pregnant women. Two specific types of datasets are being constructed:

a) A photo database of MMS blister packs to visually estimate pill consumption based on empty versus filled slots
b) A photo database of capsule piles from MMS bottles to predict remaining quantities using computer vision.

Conventionally, tablet consumption is estimated by manually counting or weighing the remaining pills and recording the data in electronic collection tools. This study introduces an AI-driven approach as an alternative to automate and scale adherence measurement. The AI algorithms derived from these datasets represent a key innovation of this study, contributing to the advancement of digital health monitoring tools for future MMS implementation programs.

Equipment Calibration and Measurement Standardization

All staff will receive initial and quarterly training to ensure standardization in anthropometric, scale, and blood pressure. For scale calibration, staff will conduct weekly calibration using standard weights and maintain logs, which will be reviewed during facility evaluations and supervised visits.

For blood pressure measurement, the same validated automated device will be used across all Posyandu. Staff will perform daily device checks (battery, air tube, cuff condition) and document the results. Initial and quarterly training will ensure consistent measurement practice.

2.5.4.2 Data Processing

Deep learning allows the system to analyze large datasets (big data) and predict health behaviors. Additionally, data from the MCH Handbook, digital forms, and primary healthcare services will be analyzed to predict adherence levels to MMS and calcium supplementation among pregnant women, and to identify service delivery gaps. This information will be used to improve healthcare service quality and adherence to MMS and calcium intake.

2.5.4.3 Data Utilization

This system is supported by a health communication platform integrated with the WhatsApp API, chatbot, and call center, specifically for the intervention group (digital services). Through this system, participants will receive automated reminders and health information. A data visualization dashboard is used to monitor MMS adherence levels in the study population. This dashboard presents data in real-time in an easy-to-understand format, such as maps, bar charts, and diagrams. Healthcare workers can monitor and evaluate health outcomes to make data-driven decisions to improve MMS adherence and service quality.

The system can also evolve to monitor interactions between communities and healthcare workers across various health facilities, as well as adherence to health recommendations. This aligns with the Integrated Primary Care (*Integrasi Pelayanan Kesehatan Primer/ILP*) model, which provides comprehensive healthcare as part of Indonesia's health system transformation. For successful implementation, continuous learning about AI, as well as its technical and ethical standardization, is essential. Data quality, OCR accuracy, and interoperability across health facilities must be optimized. More detailed explanations are as follows:

a) Dashboard, Analysis, and Reporting

   The dashboard is designed to present real-time data in a user-friendly and interactive format, such as maps, bar charts, and diagrams. With intuitive visualizations, the dashboard enables monitoring of various key aspects, including population characteristics, clinical status, ANC services, adherence levels, and pregnancy outcomes. Population characteristics help in understanding the profile of individuals participating in the program, while monitoring clinical status and ANC services allows evaluation of pregnant women's health conditions and the service coverage. The adherence monitoring feature ensures that participants are following the prescribed interventions, such as MMS and calcium intake. Information on pregnancy outcomes is also essential for assessing program results and identifying care gaps. This dashboard enables data-driven decision-making, allowing for more targeted interventions, quicker responses to changes, and enhanced quality of maternal and child health services.

b) Call Center, WhatsApp Communication, and Chatbot

   The study will utilize the WhatsApp API to provide health information, education, and consultations tailored to the needs of our beneficiaries. Additionally, the WhatsApp API delivers automated reminders related to health and adherence to MMS

and calcium. The SID call center also offers reminder services for mothers who cannot be reached via WhatsApp, sending automated health messages related to MMS and calcium adherence.

c) Dynamic Worker Support

Dynamic Worker Support (DWS) will be used to assist in scheduling CHPs. This scheduling includes structured visit packages for *posyandu* and home visits that must be completed daily. DWS allows teams to monitor CHP movements through a real-time GPS tracker and visualizer during ANC field activities, evaluate MMS adherence, and respond to community needs.

d) Knowledge Gateway

Knowledge Gateway is a curated online certification system developed by SUMMIT and has been used in various training that enables fair and massive assessments. Hundreds of bank questions have been developed, with a 5:1 ratio of questions with certain subject matters, random topic selections and various difficulty levels. KG is used to assess the performance and knowledge of CHPs, midwives, and other healthcare workers.

Through this comprehensive system, SUMMIT ensures effective and efficient monitoring of maternal and child health data, adherence to MMS and calcium intake, and improvement in the quality of healthcare services at the primary level.

2.6 Data Analysis

Data entered into the digital application in the MMS project will be stored on the local server of the Summit Institute of Development. Analysis will be conducted by the data analysis team of the Summit Institute of Development.

Data analysis will focus on the variables collected in the digital application, including individual characteristics, socioeconomic status, clinical status, knowledge, compliance with MMS consumption, and pregnancy outcomes for mothers and babies. The data analysis process will use leading statistical software such as SAS, STATA, or R. The choice of software is based on their flexibility and strength in handling complex data while meeting statistical analysis standards in public health research.

Definition of Study Variables

Tabel 6. Variable details

No.	Variable Group	Variable Details	Definition
Primary Outcome			
1.	Adherence to MMS	Mean Proportion of Recommended MMS Consumed from	Adherence is defined as the proportion of recommended daily MMS doses consumed over the total number of follow-up days, measured from enrollment until delivery

		Enrollment Until Delivery	(up to approximately 280 days of gestation). Adherence will be assessed using digital tracking data (QR code scans), self-reports, and/or supplement counts. Data will be collected monthly, and the final adherence value will be calculated as the mean of monthly adherence measurements per participant. Comparisons will be conducted across four study arms: (1) digital care with blister packaging, (2) standard care with bottle packaging, (3) standard care with blister packaging, and (4) digital care with bottle packaging.
Secondary Outcomes			
1.	Pregnancy and Birth outcome	Gestational Age at Birth	Gestational age (GA) will be calculated in completed weeks based on first-trimester ultrasound where available (preferred), or last menstrual period if ultrasound is unavailable. Mean GA at delivery will be reported.
		Preterm Birth	Proportion of live births occurring at <37 completed weeks of gestation.
		Very and Extremely Preterm Birth	Proportion of pregnancies delivered before these gestational age: at <34 weeks, <32 weeks, and <28
		Post-term Birth	Proportion of live births occurring at >42 completed weeks of gestation.
		Stillbirth	Proportion of pregnancies resulting in fetal death ≥28 weeks of gestation occurring before or during labor and before complete expulsion or extraction.
		Perinatal Mortality	Stillbirth (≥28 weeks gestation) or death of a liveborn infant within 7 completed days of birth.
		Neonatal Mortality	Death of a liveborn infant within 28 completed days of birth.

		Early Neonatal Mortality	Death within 7 completed days of birth.
		Late Neonatal Mortality	Death occurs after 7 days but within 28 days of birth.
2.	Neonatal Anthropometric Outcomes	Birth Weight	Mean birth weight (grams), measured within 1 hour of birth using calibrated mechanical or digital scales.
		Low Birth Weight (LBW)	Proportion of infants with birth weight <2500 g (≤2500 g if scale increments are 100 g).
		Small for Gestational Age (SGA, 3rd Centile)	Proportion of infants with birth weight <3rd centile of INTERGROWTH-21st standards by gestational age and sex.
		Large for Gestational Age (LGA, 90th Centile)	Proportion of infants with birth weight >90th centile of INTERGROWTH-21st standards by gestational age and sex.
		Birth Length	Mean birth length (cm).
		Short for Gestational Age (10th Centile)	Proportion of infants with birth length <10th centile of INTERGROWTH-21st standards by gestational age and sex.
		Short for Gestational Age (3rd Centile)	Proportion of infants with birth length <3rd centile of INTERGROWTH-21st standards by gestational age and sex.
		Head Circumference	Mean head circumference at birth (cm).
		Infant Sex	Proportion of male and female live births.
3.	Infant growth	Length-for-age z-score (LAZ)	Mean length-for-age z-score (LAZ)
		Weight-for-Length Z-score (WLZ)	Mean weight-for-age z-score (WAZ)

		Weight-for-Age Z-score (WAZ)	Mean weight-for-length z-score (WLZ)
		Stunting	Proportion of infants with LAZ < −2 at 1 months.
		Wasting	Proportion of infants with WLZ < −2 at 6 months.
		Underweight	Proportion of infants with WAZ < −2 at 6 months.
4.	Cost effectiveness	The total cost required for each treatment group divided by The number of pregnant women who adhere with supplementation consumption in each treatment group.	$Cost\ effectiveness$: $\frac{Total\ Cost}{Number\ of\ Adherence}$
5	Calcium adherence	Mean Proportion of Recommended Calcium and MMS Consumed from Enrollment Until Delivery	Adherence will be defined as the proportion of recommended daily doses consumed from week 20 until delivery. Dose consumption will be measured using digital tracking data (QR code scans), self-reports, and/or supplement counts where applicable. The outcome will be expressed as mean adherence proportion (%) per participant.
Independent Variables			
1.	Individual Characteristic	Age	Maternal age will be calculated as the difference between the date of interview/enrollment and date of birth (DOB), expressed in completed years.
		Occupation	Occupational status will be categorized based on the participant's primary employment at the time of enrollment
		Education status	Highest level of formal education completed
		Marital status	Marital status at the time of enrollment

		Number of pregnancy	Number of pregnancies (gravidity) will be defined as the total number of times the participant has been pregnant, including the current pregnancy, regardless of pregnancy outcome.
		Number of children	Number of living children will be defined as the total number of live-born children at the time of enrollment
2	ANC 12T Standard Care	Antenatal Care (ANC) Visit Frequency	Mean number of ANC visits attended per participant during pregnancy, and proportion of women attending ≥6 ANC visits from enrollment through delivery, following the national recommendation.
		Antenatal Care (ANC) Completeness	Proportion of pregnant women who complete the recommended minimum of six ANC visits from enrollment through delivery, including at least one visit in the first trimester, two visits in the second trimester, and three visits in the third trimester. Completeness will also include receipt of standardized ANC services ("12T" package), consisting of anthropometric assessment, blood pressure measurement, nutritional status assessment (MUAC), uterine fundal height measurement, fetal presentation and fetal heart rate assessment, tetanus-diphtheria immunization screening, provision of ≥90 iron-folic acid tablets, recommended laboratory testing (including hemoglobin and triple elimination testing for HIV, syphilis, and hepatitis B), counseling, limited obstetric ultrasound (first and third trimester), and mental health screening, following the national guideline.
		Antenatal Care (ANC) Timeliness	Proportion of women initiating ANC in the first trimester (≤14 completed weeks of gestation) and attending ANC visits according to the recommended trimester distribution (1 visit in first trimester, 2 visits in second trimester, 3 visits in third trimester). Timeliness will also include completion of first-trimester ultrasound

			screening and third-trimester ultrasound as recommended.
3.	Maternal Biomedical Status	Maternal Hemoglobin (Hb)	Mean maternal hemoglobin concentration (g/dL) measured in the first and third trimester.
		Maternal Anemia (Third Trimester)	Proportion of women with hemoglobin <11.0 g/dL during the first and third trimester.
		Maternal weight gain	Maternal weight gain during pregnancy
4.	Socioeconomic Status	Wealth Index	Household socioeconomic status will be assessed using a composite wealth index derived through principal component analysis of household assets, housing materials, water and sanitation facilities, energy source, crowding, livestock ownership, and income. The first principal component will be retained to generate standardized SES scores, which will be categorized into tertiles or quintiles for analysis.

We will conduct descriptive and inferential analysis:

2.6.1 Descriptive Analysis

Descriptive analysis provides an overview of the characteristics of the study population, helping to understand data distribution and variability. For continuous data, such as age and weight, the mean and standard deviation will summarize central tendency and variation, while the minimum, maximum, median, and interquartile range (IQR) will be used to describe the range and spread, especially for skewed or outlier-prone data. For categorical data, such as marital status and adherence to MMS, results will be presented as absolute frequencies and percentages, which help to clearly show the distribution across categories.

To enhance interpretation, the results will be visualized using bar charts or pie charts for categorical variables, and histograms or box plots for continuous variables. These graphical tools offer an intuitive understanding of the data, highlight patterns, and make it easier to identify trends and outliers, thus improving overall data communication..

2.6.2 Inferential Analysis

Inferential analysis is designed to answer the main research question, which is whether the digital MMS intervention has a significant impact on clinical outcomes, as well as to evaluate the relationship between certain factors and intervention outcomes.

To evaluate the relationship between various factors and intervention outcomes, a Generalized Linear Mixed Model (GLMM) will be used. This model is suitable due to the hierarchical structure of the data, where participants are nested within healthcare units or intervention clusters (33). The outcome variable, which could either be continuous (e.g., adherence to MMS measured by quantity consumed), will be modeled using the appropriate GLMM specification. Fixed effects will include individual-level covariates such as age, occupation, socioeconomic status, and clinical factors, as well as intervention-related factors such as the type of intervention (digital vs. control) and the form of MMS (bottle vs. blister) (34). Additionally, cluster-level covariates (e.g., healthcare unit characteristics like available resources, type of intervention provided, or geographic factors) will be included to account for variability between clusters (35). Random effects will be specified to model the variability between clusters (e.g., random intercepts for healthcare units), which will account for the fact that participants within the same healthcare unit are likely to be more similar to each other than to participants in other units (36). This approach allows for a more accurate estimation of the effects of the individual-level and cluster-level predictors on the intervention outcomes while controlling for the inherent clustering in the data.

2.6.3 Cost-Effectiveness Analysis

This study will measure cost-effectiveness by comparing the costs incurred for the intervention group (using digital intervention) and the control group (using standard care) to achieve MMS consumption adherence. The lower the cost-effectiveness value, the more efficient the program or intervention is considered in its budget utilization. The cost-effectiveness measurement will use the following formula:

$$Cost\ effectiveness: \frac{Total\ Cost}{Number\ of\ MMS\ Adherence}$$

Total cost = The total cost required for each treatment group.
Number of MMS Adherence = The number of pregnant women who adhere to MMS consumption in each treatment group.

Cost-effectiveness will be calculated for each of the following groups:

- Bottle group with digital intervention
- Blister group with digital intervention
- Bottle group with standard care
- Blister group with standard care

By comparing the cost-effectiveness values between groups, it can be determined which intervention method is the most cost-effective in increasing MMS consumption adherence.

2.7 Ethics Consideration

This study has been designed to adhere to the ethical principles of research involving human subjects, including respecting the rights, dignity, and welfare of participants. Prior to implementation, the study will obtain approval from the Ethics Committee of the University of Mataram to ensure that all aspects of the research comply with applicable ethical standards.

2.7.1 Informed Consent

Each participant will be provided with complete information about the study's objectives, benefits, potential risks, and procedures. This information will be delivered in both written and verbal forms in a language that is easy to understand for the participants. Participants will be asked to sign an informed consent form before participating, indicating that they have understood and voluntarily agreed to participate in the study.

2.7.2 Confidentiality and Privacy

Participants' personal data will be kept confidential using a coding system to protect their identities. Only the principal investigator and authorized team members will have access to the data, which will be stored in a secure system. Research findings will be presented in aggregate form without disclosing individual information. All study data, including electronic records, paper documents, images, and biospecimens, will be stored in a secure and confidential environment from collection through archiving, ensuring protection against unauthorized access, use, or disclosure in compliance with all ethical, legal, and regulatory requirements. Data security will be maintained through controlled-access data centers, surveillance systems, and regular security audits. All digital data will be encrypted, with user access restricted through role-based permissions, authentication, and detailed access logs. Participant information will be anonymized and de-identified using unique study codes, and any data shared externally will exclude direct identifiers, subject to Principal Investigator approval. Physical documents and storage media will be kept in locked facilities accessible only to authorized staff, with secure disposal procedures for materials no longer required. Regular data backups and a disaster recovery plan will ensure data integrity in case of system failure. Standard Operating Procedures (SOPs) will guide all data handling activities, and trained study personnel will adhere to periodic compliance audits. Data retention timelines will be defined to determine appropriate long-term storage or destruction of study materials.

2.7.3 Participant Safety

This study is designed to minimize the risks that participants may face. Before implementation, all procedures will be reviewed to ensure that any potential risks to participants are kept within acceptable limits. In the event of side effects or unexpected issues, the research team will be prepared to provide the necessary assistance and referrals.

2.7.4 Voluntary Participation

Participation in this study is voluntary. Participants have the right to refuse to participate or withdraw from the study at any time without any negative consequences regarding their access to healthcare or other benefits.

2.7.5 Transparency and Accountability

This study will be conducted with full transparency, and the results will be reported honestly and made accessible to relevant stakeholders. The procedures will comply with national and international research ethics guidelines, including the Declaration of Helsinki. By applying these principles, the study is expected to maintain scientific integrity while protecting the rights and welfare of the participants. Permissions in each region will also be processed according to the applicable licensing procedures. This study complies with the Personal Data Protection Act No. 27 of 2022 in the Health Sector to protect patients' personal data.

2.7.6 Safety Instructions

Participants will be provided with an informed consent form that includes information on what to do in the event of pregnancy-related side effects or adverse reactions to supplement consumption. Each supplement product will be accompanied by a label and instructions written in simple, easy-to-understand Indonesian language. Participants will be visited monthly, during which they will receive clear explanations on the correct method and timing of supplement consumption, ensuring proper adherence to the instructions. Participants will also be encouraged and guided on how to report any side effects they experience.

2.7.7 Labeling and Participant Instruction

Participants will be instructed to take one MMS tablet daily after meals. For participants who are also receiving calcium supplementation, MMS and calcium should not be taken at the same time and must be separated by at least a two-hour interval. Participants will be advised to take MMS in the morning and calcium in the evening whenever possible. If both supplements are taken in the evening, a minimum two-hour interval between MMS and calcium intake must be maintained.

Participants will also be instructed to store the supplements in a cool, dry place and to immediately report any unexpected or severe side effects to the Summit Health Communication team. Minor, self-limiting symptoms such as nausea or mild stomach discomfort may occur. Participants experiencing any concerning symptoms can seek care through contact of the Summit Health Communication call center or whatsapp who will be assisted by CHP in facilitating referrals to appropriate health facilities in accordance with standard practice.

2.7.8 Monitoring and Reporting of Side Effect

Monitoring of potential side effects related to the consumption of MMS and calcium will be conducted during routine monthly visits by CHP Staff in posyandu. During these visits, participants will be asked about any health complaints or symptoms experienced after consuming the supplements.

Participants will also be encouraged to report any unusual symptoms or health concerns at any time by contacting the HealthCom team through the communication channels provided during enrollment. Reported symptoms, including mild events such as nausea, dizziness, or stomach discomfort, will be documented and followed up by the research team as needed.

Pregnant women experiencing concerning symptoms are advised to seek medical care at the nearest health facility in accordance with routine health service procedures. The research team provides guidance and facilitates referral when necessary, but clinical evaluation and treatment will be conducted by qualified health care providers within the existing health system.

Any health events reported by participants will be documented in the study records. Information such as the type of event, timing, and actions taken will be recorded to support routine safety monitoring of the study implementation. All records will be securely maintained in the study database and periodically reviewed by the Principal Investigator and the study team to identify any issues that may require further attention. Relevant findings will be communicated to the Ethics Committee when necessary in accordance with applicable regulations.

2.7.9 Community Health Promoters (CHP) Responsibilities

Community Health Promoters (Field staff) are responsible for conducting demographic surveys to identify the total number of pregnant women within the intervention areas. They will then visit each posyandu to enroll eligible pregnant women into the study. Following enrollment, field staff will conduct regular home visits to monitor adherence to MMS and calcium supplementation among participants. During these visits, they will review supplement consumption records, remind participants about correct supplement intake including proper timing, dosage, and the importance of separating supplements from other medications and provide health education tailored to each woman’s gestational age and specific needs.

CHAPTER III
IMPLEMENTATION PROGRAM

3.1 Research Committee Structure

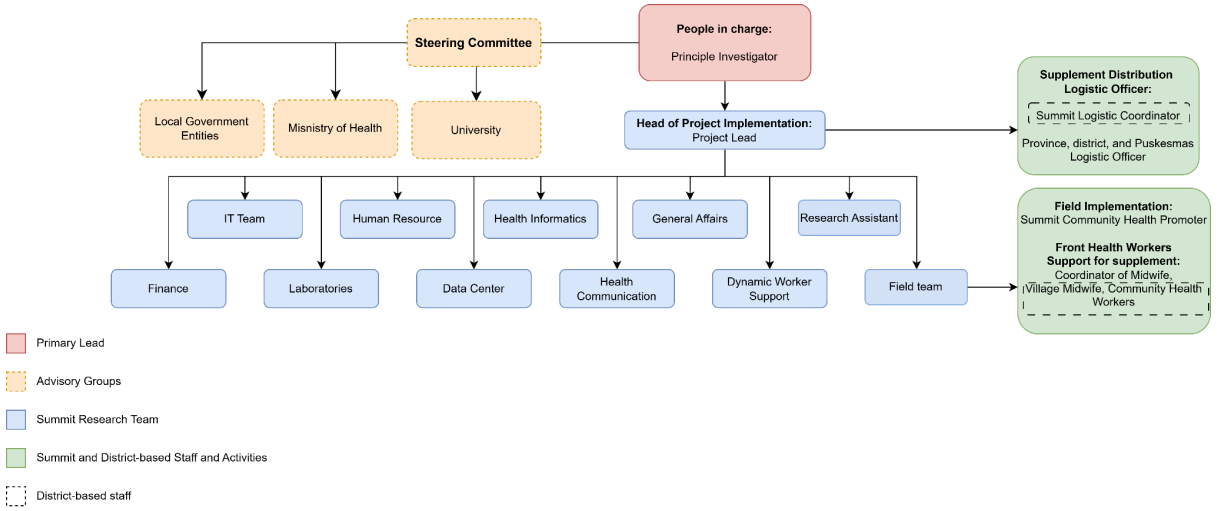


Figure 5. Research Committee structure

In this research, the SUMMIT team has established a close collaboration with the local government. This collaboration is crucial to ensure the sustainability of the implemented programs. Through the synergy between SUMMIT and the government, various policies and plans can be implemented more effectively and target the intended objectives. Additionally, the support from the local government strengthens the technical and managerial capacity in managing the study, ensuring that the study not only runs well in the initial stages but can continue to grow and provide long-term benefits to the community.

As part of its sustainability efforts, SUMMIT will establish a Steering Committee involving local government officials as the key policymakers for the MMS program going forward. This committee aims to ensure smooth implementation, monitoring, and evaluation of the program, as well as providing strategic guidance that aligns with the needs and priorities of the region (37). Through close collaboration with the local government, SUMMIT hopes to create strong synergy in achieving the success and sustainability of the MMS program in the future.

In preparation for the implementation of the MMS research in the community, coordination with the involved partners is necessary. The coordination flow presented in the diagram above is as follows:

3.1.1 Provincial and District Levels

- Socialization of MMS program implementation;
- Coordination with provincial and district health department heads for MMS storage and distribution flow from the province, district, to the community health center (Puskesmas);
- Coordination with provincial and district logistics staff regarding MMS storage and stocktaking;
- Coordination with provincial and district logistics staff concerning proper distribution for the four types of Puskesmas groups: 1) Puskesmas receiving bottled MMS with

digital intervention; 2) Puskesmas receiving bottled MMS without digital intervention (control); 3) Puskesmas receiving blister-pack MMS with digital intervention; 4) Puskesmas receiving blister-pack MMS without digital intervention (control);
- Communicating the need for population data according to the Puskesmas area, target populations, and Puskesmas's posyandu schedules.

3.1.2 Puskesmas Level

- Socialization of MMS program implementation;
- Coordination with Puskesmas head and logistics staff for MMS storage and distribution from Puskesmas to village midwives;
- Coordination regarding MMS storage and stocktaking;
- Requesting Puskesmas staff and cadres to assist with distribution and support the MMS program;
- Communicating the need for posyandu target data including: pregnant women, phone numbers of targets, posyandu schedules, and cadres.

3.1.3 Sub-district/Village Level

- Socialization of MMS program implementation;
- Coordination with sub-district heads and village heads to complete the target data for posyandu, including: pregnant women and phone numbers of targets;
- Coordination with village heads and hamlet heads regarding MMS monitoring through home visits to pregnant women.

3.1.4 Posyandu/Community Level

- SUMMIT team and village midwives are responsible for ensuring the availability of posyandu targets, including pregnant women;
- SUMMIT team and village midwives are responsible for ensuring the availability of MMS at the community health post or village health post for pregnant women;
- SUMMIT team and village midwives are responsible for ensuring that pregnant women receive MMS according to their needs.

3.1.5 The SUMMIT Team

a. Principal Investigator (PI)

- Focuses on the scientific and academic aspects of the research, directing and designing the study;
- Responsible for research design, methodology, and scientific validity;
- Makes key research decisions;
- Leads a team of scientists and researchers;
- Oversees the use of research data;
- Responsible for reporting research findings to sponsors or scientific journals.

b. Project Lead (PL)

- Focuses on project management and operational execution;
- Responsible for daily management, timelines, and project target achievements;
- Manages the budget within the project's scope;
- Coordinates the team to ensure the project runs as planned and on schedule;
- Reports project progress to partners and management.

c. Research Assistant (RA)

- Assists in technical and administrative research tasks;
- Collects data, conducts experiments, analyzes preliminary results, and supports research administration;
- Works under the supervision of the Project Lead (PL);
- Reports work results to the Project Lead (PL).

d. Information and Technology Team

In a research project or clinical trial, the IT Team plays a vital role in ensuring the smooth operation of technological infrastructure, supporting data management, system security, and software-hardware integration. In this study, the IT team helps develop barcodes for MMS packaging and integrates them into the web application.

e. Health Informatics

Health Informatics plays a crucial role in connecting digital health data from various sources, including the KoboToolbox survey platform, into the FHIR standard. This process ensures that data is structured, standardized, and can be integrated with other health systems.

f. Data Analyst

A Data Analyst focuses on data processing and analysis, ensuring that the research generates accurate, data-driven insights. At the beginning of the study, the data analyst assists in determining sample size calculations and cluster randomization. The data analyst also selects the best analysis methods and presents data visualizations.

g. Data Center

The Data Center is a facility or infrastructure used to store, manage, and process research data collected from the field. Processed data is used to create automated scheduling.

h. Human Resource Department (HRD)

The Human Resource Department (HRD) plays a crucial role in managing human resources for the research project. They ensure that the research team has competent staff, operates in a healthy work environment, and complies with applicable policies and regulations.

i. Dynamic Worker Support (DWS)

Dynamic Worker Support (DWS) is a department responsible for supporting field activities to be carried out more efficiently. This system is designed to replace manual scheduling for CHP and healthcare workers with automated scheduling. Using advanced logic scripting, operational data is collected periodically, then processed to generate a structured series of tasks.

These tasks are automatically allocated based on various parameters, such as location, workload, and task priority. Additionally, the system allows real-time task monitoring, providing better visibility into field worker performance. This approach not only reduces the administrative burden in work planning but also ensures that workforce resources are optimally utilized.

j. Finance Officer

The Finance Officer is responsible for managing the research project's finances, ensuring that expenditures align with the established budget. They ensure compliance

with financial regulations, maintain transparency, and manage funds from sponsors or research grants.

k. General Affairs (GA)

General Affairs play a crucial role in managing logistics and operations to ensure smooth research implementation. They ensure that facility, equipment, transportation, and administrative needs are well met.

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