Statistical Analysis Plan

Accelerating Maternal and Newborn Survival: The AMANI Study

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1. INTRODUCTION

1.1. BACKGROUND AND RATIONALE

Despite recent reductions, maternal and neonatal mortality in Kenya remain unacceptably high. For every 1000 live births, 21 infants die in the first 28 days of life and more than half of those deaths occur in the first week of life. Nearly 80% of newborn deaths are driven by birth asphyxia, preterm birth complications, or infections, and most could be avoided by existing, cost-effective interventions. Maternal deaths in Kenya are similarly high at 362 per 100,000 live births, primarily due to preventable obstetric causes.

Maternal Death Surveillance and Response (MPDSR) is a structured quality improvement (QI) process for health workers to report, review, and respond to maternal and perinatal deaths at a facility level. MPDSR can improve quality of care and reduce maternal and perinatal mortality through the identification of modifiable challenges and development of appropriate responses. The Maternal Death Surveillance and Response technical guidelines were released by the World Health Organization (WHO) in 2013 and adopted by the Kenyan government as national policy in 2016. The perinatal component was added in 2017. However, evidence from sub-Saharan Africa indicates that MPDSR is rarely conducted with **fidelity**. In other words, the way facilities conduct MPDSR in practice does not align with MPDSR guidelines and thus may not achieve its goal of responding to system level challenges contributing to maternal and perinatal mortality.

1.2. OBJECTIVES AND AIMS

The overarching objective of the AMANI study is to determine the effect of a practice facilitation package (including both audit and feedback and enhance mentorship) on adoption of MPDSR processes in Kenya with fidelity, while also observing and gathering evidence about clinical outcomes including mortality.

1.2.1. AIM 1

To evaluate the AMANI practice facilitation package using the RE-AIM framework to assess the strategy's Reach, Effectiveness, Adoption, Implementation, and Maintenance.

1.2.1.1. Aim 1a

To track the number, proportion, and representativeness of health workers who participate in each component of the practice facilitation package (e.g. participate in mentorship services in intervention facilities).

Hypothesis: The proportion of MPDSR committee members who participate in the practice facilitation services will increase in intervention facilities over the duration of the 24-month trial.

1.2.1.2. Aim 1b

To determine the effect of the strategy package on secondary outcomes of maternal, neonatal, and perinatal mortality, and MPDSR technical knowledge.

Hypothesis: MPDSR technical knowledge will increase in intervention facilities as compared to control facilities over the duration of the 24-month trial.

1.2.1.3. Aim 1c

To evaluate the number and proportion of deaths for which the MPDSR cycle is initiated and evaluate determinants of adoption.

Hypothesis: The proportion of deaths for which MPDSR is initiated will be higher in intervention facilities as compared to control facilities over the duration of the 24-month trial.

1.2.1.4. Aim 1d

To (i) determine the effect of the strategy package on the primary outcome of full implementation of the MPDSR process with fidelity, (ii) identify determinants of implementation fidelity through individual interviews and focus group discussions with health workers involved in MPDSR implementation, and (iii) track facility-specific adaptations to MPDSR implementation and identify how facilities incorporate MPDSR steps into their practice context and facility infrastructure.

Hypothesis: The AMANI intervention will be associated with increased fidelity to all MPDSR steps (primary outcome) in intervention facilities as compared to control facilities over the 24-month implementation phase of the trial.

1.2.1.5. Aim 1e

To track the proportion of facilities implementing MPDSR with fidelity and proportion of intervention facilities sustaining each component of the strategy package 6 and 12 months after withdrawing external practice facilitator support.

Hypothesis: The intervention will be sustained by facility staff in intervention facilities during the one-year maintenance phase.

1.2.2. AIM 2

To determine the primary mechanism through which the practice facilitation package influences MPDSR implementation with fidelity.

Hypothesis: The mechanisms that will be activated by the trial and affect fidelity to MPDSR implementation include an increase in provider knowledge of MPDSR, an increase in provider confidence to implement MPDSR, and an increase in psychological safety (organizational climate) over the 24-month trial period.

2. STUDY METHODS

2.1. TRIAL DESIGN

The AMANI Study is a cluster randomized controlled trial (cRCT) with a hybrid type III design, conducted in 20 health facilities across six counties in Kenya. Ten health facilities will be randomized to the intervention arm (receiving the practice facilitation package) and ten facilities will be randomized to the control arm (N=20 facilities total). After an initial 24-months of implementation strategy package delivery in intervention clusters, external practice facilitation support will be withdrawn and a 12-month sustained maintenance phase will take place.

2.2. RANDOMIZATION

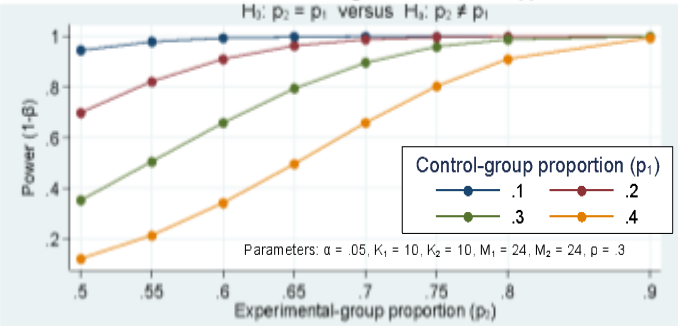
We will conduct 1:1 restricted randomization to ensure equal allocation of facilities to each arm by region (Nairobi/Kiambu Counties vs. Western Counties) and median number of maternal and neonatal deaths per month (above vs. below median; 4 randomization groups total). Perinatal deaths were not considered in randomization based on feedback from the Research Coordinators that MPDSR committees in Kenyan health facilities often do not review all perinatal deaths and thus data would be incomplete.

The 20 enrolled AMANI facilities will be randomized during a live randomization event with representatives from each facility invited to attend. The meeting will be recorded and shared with facility representatives who are not available to attend during the event. To facilitate a transparent randomization process, each facility within the randomization groups will spin a wheel labeled 1-10 to determine their order for randomization. Once randomization order has been determined, each facility will then spin a wheel with an equal number of 'intervention' and 'control' slices which will automatically be removed once selected.

2.3. SAMPLE SIZE & POWER CALCULATIONS

With 10 facilities per arm, 24 deaths per 1,000 live births per facility, a 2-tailed test, α=0.05, and 20% fidelity to the MPDSR cycle in control sites, we will have 80% power to observe an increase to 55%. Should fidelity be 40% in control facilities, we will have 80% power to see an increase to 75% MPDSR fidelity (Figure 1). Formal power analyses were not conducted for Aim 2, as the study was powered on the Aim 1 primary outcome of full fidelity to all six MPDSR steps.

Figure 1. Estimated power for a two-sample proportion test, cluster randomized design, Pearson's χ^2



Each facility enrolled in the AMANI Study will have at least one MPDSR committee, with approximately 10 participants per committee for an estimated individual participant sample size of 200. We expect that some larger facilities may have a separate MPDSR committee for maternal and perinatal/neonatal deaths.

3. STUDY OUTCOMES

3.1. **TABLE 1:** SUMMARY OF PRIMARY AND SECONDARY OUTCOMES

Outcome		**Indicator**		**Source**	**Timing**
Primary Outcomes					
Aim 1d	MPDSR Fidelity	Num.	Number of maternal and perinatal deaths for which all six MPDSR steps are completed	See Table 2	Two-year study implementation period from August 1, 2026 through July 31, 2028
		Denom.	Number of maternal and perinatal deaths	Facility Maternity Unit and Newborn Unit registers	
Secondary Outcomes					
Aim 1a	Intervention Reach	Num.	Number of MPDSR committee members participating in audit and feedback and/or enhanced mentorship each month	Practice facilitator activity log	Monthly over the two-year study implementation period
		Denom.	Number of actively assigned MPDSR committee members	MPDSR attendance log	
Aim 1b	Intervention Effectiveness		MPDSR Technical Knowledge score (continuous)	Facility staff survey	Baseline, 12 month, 24 month
			Institutional Maternal Mortality Ratio (Number of deaths of pregnant women within 42 days of termination of pregnancy/Total births in the facility)	Maternity and Newborn unit register	Two-year study implementation period from August 1, 2026 through July 31, 2028
			Perinatal Mortality Rate (Number of stillbirths [fetal death at least 28 weeks of gestation] and newborn deaths [up to first 7 days of life]/Total births in the facility)		
			Neonatal Mortality Rate (Number of deaths in the first 28 days of life/Total number of live births in the facility)		
Aim 1c	Adoption	Num.	Number of deaths documented in the maternal, perinatal, and neonatal death notification forms	MOH 369, 370, 661	Two-year study implementation period from August 1, 2026 through July 31, 2028
		Denom.	Total number of maternal and perinatal deaths	Facility Maternity Unit and Newborn Unit registers	

		Num.	Number of deaths documented in maternal, perinatal, and neonatal death review forms	MOH 372, 371, 527	
		Denom.	Total number of deaths documented in the maternal, perinatal, and neonatal death notification forms	MOH 369, 370, 661	
Aim 1e	Intervention Maintenance	Num.	Number of maternal and perinatal deaths for which all six MPDSR steps are completed	See Table 2	Two-year study implementation period from August 1, 2026 through July 31, 2028 and one-year maintenance phase from August 1, 2028 through July 31, 2029
		Denom.	Number of maternal and perinatal deaths	Facility Maternity Unit and Newborn Unit registers	
			Proportion of intervention facilities sustaining audit and feedback and/or enhanced mentorship at 6 and 12 months after external practice facilitation support is withdrawn	Staff facility surveys (month 30 and 36)	One-year maintenance phase from August 1, 2028 through July 31, 2029
Aim 2 Mechanisms	Provider technical knowledge		MPDSR Technical Knowledge score (continuous)	Facility staff survey	Baseline, 12 month, 24 month
	Perceived MPDSR social support		Mean response across 5 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month
	Attitude towards MPDSR use		Mean response across 4 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month
	Perceived self-efficacy to perform MPDSR steps		Mean response across 6 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month
	Psychological safety		Mean response across 21 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month
	Burnout		Mean response across 12 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month
	Critical communication		Mean response across 25 questions with 5-point Likert scale	Facility staff survey	Baseline, 12 month, 24 month

3.2. **TABLE 2:** OVERVIEW OF FIDELITY INDICATORS FOR EACH MPDSR STEP[1]

MPDSR Step	Fidelity measure for each step[2]	Data source(s)
Death identification/ notification	A death notification form is completed and filed with the facility HRIO or entered into the KHIS MPDSR Dashboard	MOH 369, 370, 661 (death notifications)
Data aggregation	Date of death, cause of death, and at least one modifiable factor are recorded in the appropriate death review form	MOH 372, 371, 527 (death reviews)
Death review	A death is recorded as being discussed during the MPDSR committee meeting	MPDSR meeting minutes (Table 2)
Recommend solutions	A death has at least one action item recorded during the death review	MPDSR meeting minutes (Table 3)
Implemented solutions	All action items for the death are marked as 'complete' within 3 months of the date on which the death was reviewed	MPDSR meeting minutes (Table 1 & Table 2)
Evaluate and refine activity	All action items for the death have a follow-up decision marked when the action items are indicated to be 'complete' (i.e., are marked as 'adopt,' 'adapt,' 'stop,' or 'NA – one time action)	MPDSR meeting minutes (Table 1)

[1] Total number of deaths at each facility will be obtained from the facility's Maternity Register and Newborn Unit Register
[2] Secondary measures of fidelity at each step will be reported using descriptive statistics; see Appendix for full descriptions of secondary measures

4. ANALYSES

4.1. BASELINE CHARACTERISTICS

We will describe the distribution of baseline characteristics, using appropriate summary statistics. We will present these summary statistics in tables overall and by study arm (see Table 4).

Characteristic	Overall	Control	Intervention
Facility			
Average number of deaths per month (median, IQR)			
Maternal			
Perinatal (0-7 days)			
Neonatal (8-28 days)			
Average number of births per month (median, IQR)			
MPDSR Committee Members			
Number of committee members per facility (median, IQR)			
Age (median, IQR)			
Gender			
Male			
Female			
Cadre			
Pediatrician/neonatologist			
OBGYN			
Midwifery professional			
Nursing professional			
Nurse-midwife (dual-trained) professional			
Health records information officer			
Facility administrator			
Other			
Unit			
Maternity ward			
Newborn unit			
Postnatal ward			
Emergency services			
Records offices			
Administration			
Other			
Years of experience in current role (median, IQR)			
Years of experience in health care (median, IQR)			
Years involved in MPDSR (median, IQR)			

4.2. STATISTICAL PRINCIPLES

Descriptive statistics will be presented as counts and percentages for binary, ordinal, and categorical variables, and as means and standard deviations or medians and interquartile ranges for continuous variables, as appropriate based on distributions.

In facilities with more than one MPDSR committee (e.g., separate maternal and perinatal committees), primary analyses will be completed for the facility as a whole. In sensitivity analyses, we will compare the primary outcomes between each MPDSR committee within the facility to determine whether significant differences exist.

P-values of <0.05 will indicate statistical significance for all analyses.

4.3. ANALYSIS METHODS

4.3.1. PRIMARY OUTCOME

4.3.1.1. **Implementation (MPDSR Fidelity)**

MPDSR fidelity will be evaluated as the proportion of deaths in each facility with all six steps of the MPDSR cycle completed. For each death, all six steps of the MPDSR cycle will be classified as 'full fidelity' or 'partial/no fidelity' based on the primary fidelity measures described in Table 3. A death will be marked as 'completed with full fidelity' when all six steps are 'complete' or 'completed with partial fidelity' if less than six steps are complete. The effect of the intervention on the binary outcome of full fidelity to MPDSR will be analyzed using generalized estimating equation (GEE) models with a Poisson family, robust errors, and clustering by health facility to estimate risk ratios comparing the intervention and control facilities. We will adjust for facility factors (e.g. staffing levels, measured during baseline Service Readiness Assessments) if there appears to be meaningful differences on average between intervention and control facilities.

In sensitivity analyses, we will also evaluate the influence of the intervention on fidelity score (range of 0-6), with an outcome of the number of MPDSR steps undertaken in a given facility using GEE Poisson regression with robust errors.

Table 5. Analysis of MPDSR fidelity[1]

	Overall	Control	Intervention	Intervention vs. Control
Primary Analysis				[2]RR (95% CI)
	Count (Proportion)			
Number of deaths				
Number of deaths with less than six MPDSR steps completed (%; partial fidelity)				
Number of deaths with six MPDSR steps completed (%; full fidelity)				
Sensitivity Analysis				[2]RR (95% CI)
	Median (IQR)			
Number of MPDSR steps completed				

[1] Models adjusted for any factors differing between arm with statistical significance at enrollment

[2] Estimated by GEE Poisson regression with clustering by facility and robust standard errors

4.3.2. SECONDARY OUTCOMES

4.3.2.1. **Reach**

We will summarize the number, proportion, and representativeness of health workers who participate in each component of the practice facilitation package (audit and feedback and enhanced mentorship) in intervention facilities using descriptive statistics.

Participation in each intervention component will be assessed among intervention facilities over the two-year study implementation period. For each facility-month, participation will be summarized as the proportion of eligible participants who engaged in each intervention component (audit and feedback and/or enhanced mentorship). We will use GEE models with a Poisson family, robust errors, and clustering by health facility to determine if there is a significant difference in participation in each strategy component (audit and feedback; enhanced mentorship) over time.

In sensitivity analyses, we will use GEE to determine if the proportion of health workers participating in each practice facilitate on package component varies significantly by health worker cadre and whether there were differences in participation trends over time between audit and feedback and enhanced mentorship.

Table 6. Analysis of intervention reach[1]

	Participation overall	Audit & Feedback	Enhanced mentorship	No participation
Descriptive Analysis[1]				
	Count (Proportion)			
Number of healthcare workers participating in intervention components (overall)				
By gender (female)				
By age (median, IQR)				
By cadre				
Pediatrician/neonatologist				
OBGYN				
Midwifery professional				
Nursing professional				
Nurse-midwife (dual-trained) professional				
Health records information officer				
Facility administrator				
By years of experience in MPDSR				
GEE Analysis				
	IRR[2]	95% CI	p-value	
Monthly change in enhanced mentorship participation				

Monthly change in audit and feedback participation				
Monthly change in any strategy component participation				

[1] Presented across the two-year implementation period of the study; participated in audit and feedback and/or enhanced mentorship at least once

[2] Incidence rate ratio estimated by GEE Poisson regression with clustering by facility and robust standard errors

4.3.2.2. Effectiveness

We will determine the effect of the intervention on MPDSR technical knowledge and maternal, perinatal, and neonatal mortality.

MPDSR technical knowledge will be assessed at baseline, 12 months, and 24 months post-enrollment using a standardized questionnaire. We will use a GEE model with a Gaussian distribution and identity link, robust errors, and clustering by facility. The model will include fixed effects for study arm, time (baseline, 12 months, 24 months), and the arm-by-time interaction.

In sensitivity analyses, models will be run separately for each domain of MPDSR technical knowledge: general MPDSR knowledge, data sources/forms, antenatal care competency, intrapartum care competency, postpartum care competency, and newborn care competency.

Because mortality events are expected to be infrequent (particularly maternal mortality), we will not have sufficient power to detect a meaningful reduction in mortality. As a secondary, exploratory analysis, we will use Poisson regression and robust standard errors to determine the effect of participation in the intervention arm on the institutional maternal mortality ratio, perinatal mortality rate, and neonatal mortality rate. In sensitivity analyses, we will run models separately for outcomes of maternal deaths, perinatal deaths, intrapartum stillbirths, antepartum stillbirths, and neonatal deaths.

Table 7. Analysis of intervention effectiveness

	Overall	Control	Intervention	Intervention vs. Control
Primary Analyses				
	Median (IQR)			[1]RR (95% CI)
MPDSR Technical Knowledge score				
Institutional Maternal Mortality Ratio (MMR)				
Perinatal mortality rate				
Neonatal mortality rate				
Sensitivity Analyses				
	Median (IQR)			[1]RR (95% CI)
Technical knowledge				
General MPDSR knowledge subscale				
Data sources/forms subscale				
Antenatal care subscale				
Intrapartum care subscale				
Postpartum care subscale				

Newborn care subscale					
Mortality					
Maternal deaths					
Perinatal deaths					
Intrapartum stillbirths					
Antepartum stillbirths					
Neonatal deaths					

[1] Interaction term RR estimated by GEE Poisson regression with clustering by facility and robust standard errors

4.3.2.3. Adoption

We will evaluate the number and proportion of deaths for which the first two steps of the MPDSR cycle are completed (death notification and death review form complete) overall. Adoption will be binarized as having completed both steps (notification and review) vs. not having completed both steps (only notification, only review, or no notification/review). We will use Poisson regression with robust standard errors. The primary exposure variable will be randomization arm, and the offset will be number of mortalities per facility.

We will further evaluate adoption data to assess if mortality reports adhere to WHO guidance for perinatal mortality (ICD-PM) and assess if the documentation identifies the time of death (antepartum, intrapartum, or neonatal), follows the MPDSR-provided multilayered stepwise classification system for cause of death, and links contributing maternal conditions, if indicated.

Adoption will be presented in total and stratified by maternal, neonatal and perinatal deaths, and we will use Poisson regression with robust errors to identify the effect of practice facilitation on changes in MPDSR adoption for both categories of death separately.

In a sensitivity analysis, we will also assess adoption as the number and proportion of deaths for which the first two steps of the MPDSR cycle are completed within the appropriate time frame. For each death in the facility, we will determine A) whether the death has a completed death notification form within 24 hours of the death and B) whether the death has a completed death review form within 7 days of the death notification.

Table 8. Analysis of adoption

	Overall				Control				Intervention				Intervention vs. Control (Overall)
	O*	M*	P*	N*	O*	M*	P*	N*	O*	M*	P*	N*	
Primary Analysis													
	Count (Proportion)												[1]RR (95% CI)
Number of deaths with a completed death notification form within 24 hours of the death													
Number of deaths with a completed death review form within 7 days of the death notification													

Number of deaths meeting both adoption criteria													
Sensitivity Analysis													
	Count (Proportion)												[1]RR (95% CI)
Number of deaths with the time period of death (antepartum, intrapartum, [early] neonatal) indicated in the death review form[2]													
Number of deaths with one direct cause of death indicated in the death review form													
Number of deaths with at least one indirect cause of death indicated in the death review form													

[1] Estimated by Poisson regression with clustering by facility and robust standard errors

[2] Only for Perinatal and Neonatal Death Review Forms; Maternal Death Review Forms are all classified as maternal deaths

4.3.2.4. Maintenance

To understand if and how fidelity changes from phase 1 (intervention phase) to phase 2 (maintenance phase) we will conduct a controlled, interrupted time-series analysis that incorporates monthly facility-level estimates of fidelity, segmented into 24-months of intervention and 12-months of maintenance (when external PF support is withdrawn). For each month, the facility-level proportion of deaths achieving full fidelity will be the primary outcome (see Table 2 and Section 4.3.1 for a full description of fidelity). The interrupted time series model will be parameterized with time as a continuous variable indexed in months (*T*), a dummy variable for the study phase (*X*; intervention vs. maintenance phase), a dummy variable for intervention vs. control arm (*I*) and interaction terms between arm and time and phase (*T*x*X*), arm and time (*I*x*T*), arm and phase (*I*x*X*) and arm, time, and phase (*I*x*X*x*T*). The controlled interrupted time series analysis will be conducted using GEE Poisson models, robust errors and clustering by facility to model the proportion of deaths with fully fidelity over time while accounting for repeated monthly observations within facilities.

We will also report the number and proportion of intervention arm facilities that are continuing to conduct practice facilitation activities, including sub-activities of audit and feedback and sub-activities of enhanced mentorship. We will use a Poisson regression with robust errors to determine if there is a significant difference in the prevalence ratio comparing participation in strategy components during the maintenance phase.

Table 9. Analysis of intervention maintenance[1]

Fidelity Analysis			
Coefficient	[2]RR	95% CI	p-value
Arm x Time (fidelity slope during intervention phase in intervention vs control facilities			

Arm x Phase (immediate change in full MPDSR fidelity when practice facilitation support was withdrawn between intervention and control facilities)			
Arm x Phase x Time (differential rate of change in fidelity between intervention and control facilities during the maintenance phase)			
Intervention Maintenance Analysis			
	n (%)	[3]PR (95%CI)	p-value
Facilities maintaining mentorship activities			
Facilities maintaining audit and feedback activities			

[1] Models adjusted for any factors differing between arm with statistical significance at enrollment
[2] Relative risk estimated by Poisson regression with clustering by facility and robust standard errors
[3] Prevalence ratio estimated by Poisson regression with robust standard errors

4.3.3. AIM 2

We will conduct a multilevel mediation analysis using a series of hierarchical linear mixed-effects models (with a random effect for facility) to estimate the influence of the implementation strategy vs. control (*X)* on the outcomes of MPDSR implementation with the primary outcomes of full fidelity (*Y1*) and adoption (*Y2*). We will test the role of intervening variables (*M*), putative mediators, to quantify the proportion of the relative effect of the implementation strategy on targeted outcomes that is explained by hypothesized mechanisms. We will use a products of coefficients approach to minimize type I error rates, maximize statistical power, and enhance accuracy of confidence intervals in mediation analysis.

We will fit the data to assess *X*'s total effect on *Y* into direct and indirect (mediated) effects by estimating the cross product of (a) the effect of *X* on *M,* and (b) the effect of *M* on *Y*, adjusted for *X*. We will test the mediated (indirect) effects via bootstrapping methods and the *mediation* package in R. We will evaluate mediators after 12 months and, in separate models, after 24 months.

Through the use of multilevel mediation (moderated mediation) we will test the extent to which the relationship between the strategy (X), mediators (M), and outcomes (Y) vary across a minimum of five measurable moderating variables, including: provider cadre, years of provider experience in role, years of provider experience with MPDSR, time commitment, staff and resource availability, perception of county-level support, and other relevant variables. We will review findings within the context of the IMB and underpinning theories for other included constructs and apply five Kazdin criteria for establishing a mechanistic relationship of implementation strategies (strong association, specificity, timeline, gradient, plausibility/coherence).

4.4. STATISTICAL SOFTWARE

Analysis will be conducted in R.

5. **MISSING DATA**

Additionally, routine death notifications, death reviews, and unit registers abstracted during the study period will contain missing data. The data abstractors will also abstract when fields are missing. Missing data will be treated as missing at random unless external information, for example a facility level failure to properly share data, can be identified. In such an event, sensitivity analyses with and without the facility will be examined. Due to the level of missingness we expect, we will not conduct any formal imputation.

6. SAFETY MONITORING

Adverse and severe adverse events will be monitored as they arise. Adverse events include events such as participant reports of new depression or anxiety symptoms in the workplace or reports of termination due to their participation in the study. Severe adverse events may include the death of an MPDSR committee member or a hospitalization related to interpersonal violence or mental health crisis. Results will be reviewed by the DSMB, and the DSMB will make recommendations regarding any imbalances in safety outcomes.

Date reported	PID	Severity	Relationship to Intervention	Outcome	Expected