

1 TITLE PAGE

1.1 TITLE

Impact of Menstrual Cups on Adolescent Girls Reproductive Health and Education

1.2 SHORT TITLE

IMARA (swahili: strong, firm, resolute)

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Abbreviations: LSTM: Liverpool School of Tropical Medicine; KEMRI: Kenya Medical Research Institute; NRHS: Nyanza Reproductive Health Society; UMICH: University of Michigan; UNICEF: United Nations International Children's Emergency Fund

1.4 INSTITUTION PROTOCOL NUMBERS

SERU: 5379

LSTM: 0136

1.5 TRIAL REGISTRY

This trial will be registered through ISRCTN (<http://www.isrctn.com>)

1.6 STUDY SPONSOR

Liverpool School of Tropical Medicine

1.7 FUNDERS

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1.10 ABBREVIATIONS

95% CI	95 percent Confidence Interval
AE	Adverse event
AGYW	Adolescent girls and young women
AGYW	Adolescent Girls and Young Women
AKIBA	<u>A</u> fy <u>k</u> ikombe <u>A</u> nza (Healthy Cup Start)
BV	Bacterial Vaginosis
CRF	Case Record Form
CST	Community State Type
DASS	Depression, Anxiety and Stress Scale (tbc)
DSMB	Data Safety Monitoring Board
EuroQL	European Quality of Life (EQ5-D)
FDA	Food and Drug Administration
FGD	Focus group discussion
GAD	Generalized Anxiety Disorder Scale
GBV	Gender Based Violence
GCP	Good Clinical Practice
GEE	Generalised estimating equation
GHTU	Global Health Trials Unit
GMP	Good Manufacturing Practice
HDSS	Health and demographic surveillance system
HIC	High income countries
HIV	Human immunodeficiency virus
HSV-2	Human simplex virus-2
ITT	Intention to Treat analysis
IDI	In-depth interview
IPV	Intimate partner violence
KEMRI	Kenya Medical Research Institute
KJSEA	Kenya Junior School Education Assessment
KPPB	Kenya Poisons and Pharmacy Board
KREBS	Kenya Bureau of Standards
LSTM	Liverpool School of Tropical Medicine
MCC	Menstrual Cup Coalition
MCH	Maternal child health
MHM	Menstrual hygiene management

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MHH	Menstrual health and hygiene
MoH	Ministry of Health
NAAT	Nucleic acid amplification test
NRHS	Nyanza Reproductive Health Society
OR	Odds Ratio
PE	Protective efficacy
PHQ	Patient Health Questionnaire
PP	Per Protocol analysis
PPE	Personal protection and equipment
QoL	Quality of life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RR	Relative Risk
RTI	Reproductive tract infections
SAE	Serious adverse event
SAR	Serious adverse reaction
SAG	Scientific Advisory Group
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SRH	Sexual and reproductive health
STI	Sexually transmitted infections
SES	Socio-economic status
TOC	Theory of Change
TSC	Trial Steering Committee
UNIM	Universities of Nairobi, Illinois, Manitoba
VMB	Vaginal Microbiome
WASH	Water, sanitation, and hygiene

1.11 AMENDMENTS

Date	Version	Amendments	Signatures
4Dec 2025	v0.8	Initial submission to LSTM REC and SERU	 
9Feb2026	V0.9	Reviewed re-submission to LSTM REC and SERU	 

2 ABSTRACT

A 2-arm cluster randomised controlled trial will be conducted among junior school adolescent girls (~13.9 years at enrolment) in selected sub-counties in Siaya County, western Kenya. This 3-year study will examine the effectiveness of menstrual cups paired with puberty education provided to girls attending schools allocated into the intervention arm, compared with those in 'usual practice' control schools. Sample size calculations estimate a minimum sample of 2070 participants, across 42 schools (21 schools per arm), with 1035 participants per arm and 49 participants per school will be required. Effectiveness will be measured through primary outcome of incident pregnancy and/or school dropout. Secondary outcomes covering education, sexual and reproductive health, and mental health will provide explanatory understanding of any effects. School water, sanitation, and hygiene conditions will be documented biannually. Measurements will be conducted at baseline and then biannually through participant surveys, with additional validations through school registers, and household follow-ups to document dropout, date and reason, and when applicable, pregnancy outcomes. A nested sub-study will examine the effect of menstrual cup use on the vaginal microbiome (VMB), bacterial vaginosis (BV) and a composite of sexually transmitted infections (STI) (i.e. chlamydia, trichomoniasis, gonorrhoea). The sub-study population will comprise 20% of the randomly selected control clusters and an equivalent number of clusters receiving menstrual cups. VMB will be measured at baseline and termly and BV and STIs measured annually. A qualitative sub-study will collect data from participating girls, while also engaging a sample of boys from the same schools to explore peer dynamics and gender norms that shape girls' experiences. In addition, insights will be gathered from parents or guardians, teachers, and key members of their community. This will triangulate survey data and provide contextual understanding of key issues including experiences of schooling, drivers of dropout and adolescent pregnancy, menarche and monthly menstrual care, gender norms, mental health, and perceptions on study interventions. Data will also be generated to evaluate the cost-effectiveness of interventions, to provide evidence on whether menstrual cups provided through schools represent an efficient use of resources for improving adolescent health. This will be complemented by a cost-benefit analysis to capture benefits to both health and education measured in economic return (i.e. the cost benefit ratio).

Primary trial analyses will be based on the intention to treat principle, and secondary analyses will also be done on the per protocol population. Generalized linear mixed models (GLMM) will be used to analyse outcomes. The models will include intervention as a fixed effect and individual and school level characteristics as co-variables. To derive risk ratios and corresponding 95% confidence intervals of the primary outcome, GLMM with binomial distribution and log link functions will be used, with Poisson models employed in the case of non-convergence. For qualitative analysis, the method will depend on aim, type of data, and analysis intention, anticipating thematic analysis for larger datasets to facilitate multiple analysts, and phenological analysis for smaller richer data sets (e.g., from IDI). Where relevant, data triangulation with qualitative data and / or quantitative results will be undertaken. Cost-effectiveness analysis and cost-benefit analyses will follow relevant reference case standards. Study end occurs with completion of analysis of trial impact on primary outcome.

It is envisaged that the evidence generated from this trial will inform policy at national and global level on the value of menstrual cups to improve the health and educational outcomes of adolescent girls, with findings used to support policy and best practice.

3 LAY SUMMARY

Researchers in western Kenya are conducting a school-based study over 3 years to determine whether providing teenage girls with menstrual cups and puberty and hygiene education can help

them stay in school and avoid early pregnancy. The study involves approximately 2,070 girls in grades 7-9 across 42 schools in sub counties in Siaya County, with half the schools receiving the menstrual cup intervention while the other half continue with their usual practices. Over several years, researchers will track whether girls get pregnant or drop out of school, while also monitoring academic performance, sexual health, girls' mental health, menstrual health, and various other indicators through bi-annual surveys, school records, and home visits. Additionally, the study gathers qualitative data from girls taking part in the study, and we will also discuss with select boys from the same schools on how interactions and gender roles affect girl's experiences. In addition, parents or guardians, teachers, and key members of their community will be interviewed to understand the broader context of girls' educational experiences. A group of participants will also partake in a smaller study to examine the effects of the menstrual cup on their vaginal health and sexually transmitted infection risk. This research aims to generate evidence that could influence national and international policies to support adolescent girls' education and health outcomes worldwide.

4 INTRODUCTION

4.1 BACKGROUND

Adolescent girls are acutely susceptible to sexual and reproductive health (SRH) harms through incomplete biological development, inadequate knowledge of menstruation and puberty, lack of autonomy, social pressures around sex, and harmful gender norms. In many low- and middle-income countries (LMIC), including Kenya, where poverty and gender-based violence are pervasive, girls face sexual abuse, have limited agency to navigate sexual encounters safely, and may resort to transactional sex to obtain daily essentials including menstrual hygiene products.¹

This leaves girls vulnerable to adolescent pregnancy, child marriage, STI and school dropout, with lasting effects across the life course.² Globally, ~650 million girls are married before age 18, with 12m new child marriages annually.³ Some 4 million child brides exist in Kenya, with 23% of all girls married by age 18y.⁴ In Africa, while global adolescent-specific fertility rates have declined by ~12% over the past 20 years(y), around 25% of adolescent girls still become pregnant,⁵ with ~20% in Kenya.⁶ Pregnancy complications remain a leading cause of death among 15-19 year olds,⁷ contributing to the 66% of the 296,000 maternal deaths worldwide occurring in SSA in 2017.⁸ Babies born to mothers aged <20y face higher risks of low birth weight, preterm delivery, and severe neonatal conditions, while rapid repeat pregnancy compounds health risks for mother and the child.⁹ Girls becoming pregnant before 18y are also more likely to experience interpersonal violence than older peers and women.¹⁰ School dropout is a cause and consequence of adolescent pregnancy and child marriage impacting girls across their life course. There are ~258m children out of school worldwide, around half are girls, becoming disproportionately higher than boys by secondary school.^{11,12} Some ~13,000 girls dropout each year in Kenya, and the highest loss is among 17-year-olds.⁴ This education deficit has long-term health, economic, and social impacts for themselves and their offspring.¹³

One in eight adolescents grow up in 'injury excess' countries, characterised by high persisting levels of unintentional injury or violence, and in countries with high adolescent birth rates due to continued unmet need for contraception.^{9,14} Further, adolescents in LMIC will increasingly face a triple health burden,^{9,15} with an increase in noncommunicable diseases, along with diseases of poverty, injury and violence.¹⁴ And beyond physical and reproductive health risks, these challenges take a considerable toll on girls' mental health. Shame associated with inadequate menstrual hygiene and early pregnancy further erodes self-esteem and social belonging.¹⁶⁻¹⁸ The stigma surrounding menstruation, paired with experiences of violence, coercion into transactional sex, and disruptions to schooling contribute to persistent stress, anxiety, and depression, with

lasting impacts into adulthood.¹⁹⁻²¹ Secrecy, lack of education and knowledge on menstruation among boys contribute to the maintenance of stigma, taboos and lack of sympathy.²² Reducing child marriage, school dropout and adolescent pregnancy is essential to support girls' health, autonomy, and economic productivity.²³

4.2 INTERVENTIONS FOR ADOLESCENT GIRLS

Interventions that benefit adolescent girls' education and health, build healthy trajectories into adulthood, and support healthy offspring, are recognised as critical for breaking the cycle of poor health and poverty.^{9,24} Interventions must be aimed at modifiable drivers of adolescent health and strengthen WHO's accelerated Action for Health of Adolescents (AA-HA),⁹ and the Global Strategy for Women's, Children's and Adolescents' Health.²⁵ These reports guide member states on interventions for health, empowerment, and adolescent and young women's (AGYW) rights that promote the Sustainable Development Goals (SDGs). The Kenya Health Policy 2014-2030 prioritises maternal health, HIV, mental health, substance use disorders and injuries, aims to eliminate communicable disease, halt and reverse rising non-communicable diseases, reduce the burden of violence, minimise exposure to health risk factors, and provide essential health care.²⁶

World Bank analysis of cross-sectional multi-country studies support the triple dividend theory that interventions provided to girls impact their health and social equity with benefits continuing into adulthood and to their children.²³ Data suggest each year of secondary education lowers the risk of child marriage and teen pregnancy by ~7%; school completers have a third lower total fertility, a 25% reduction in offspring's stunting, and up to 5-fold increased earnings.²³ School-based trials have largely focused on the effect of interventions on the SRH of AGYW, measuring HIV, HSV-2, and teen pregnancy as key outcomes. A number have tested the effect of cash transfer with mixed results.²⁷⁻³⁰ A small number of trials have focused on the potential effects of improving health, schooling and social equity by providing menstrual products or other hygiene or menstrual education components.³¹⁻³⁴ This stems from the recognition that girls lack of products,³⁵ WASH facilities, lack of education, and negative gender norms impedes their autonomy, education and health causing stigma and discomfort reducing their autonomy, school engagement,³⁶ and can result in increased sexual risk taking.^{1,37} Of these trials, provision of sanitary pads found a small improvement in school absence in Uganda,³⁴ while two multi-component studies providing sanitary pads, structural improvement to WASH in schools, and some educational component (school drama, community discussions) found no primary outcome effect on school or health measures in Uganda and Gambia, but noted improvements in secondary outcomes relating to proximal effects such as menstrual comfort, knowledge and wellbeing.^{32,33}

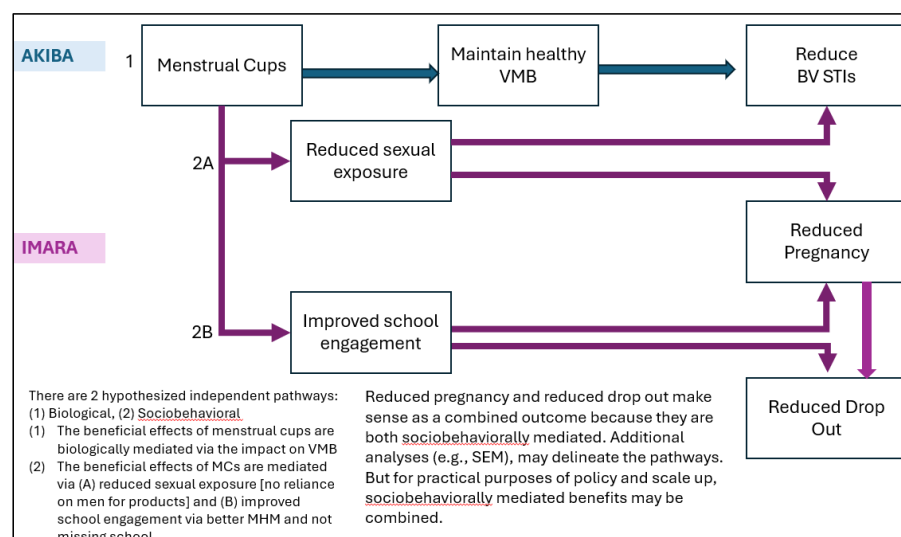
5 JUSTIFICATION FOR THE STUDY

Pregnancy, child marriage and school dropout remain a pervasive problem for girls, particularly in sub-Saharan Africa (SSA), with ramifications for the health, wellbeing, and productivity across the life course. Further trials are needed to test interventions that combine effects that improve girls' menstrual needs, reduce risky sexual behaviours, and modify social norms.

Our trials investigated the impact of menstrual (cup, sanitary pads) and structural (cash transfer) interventions on SRH and school outcomes in ~4750 schoolgirls, in rural Kenya.^{30,38-41} Cups were acceptable to parents and to younger,^{38,40} and older adolescents,⁴¹ and girls reported improved menstrual hygiene and school engagement, and reduced stigma.^{40,41} Our theory of change (ToC) hypothesized impact across biological pathways. We confirmed this in our cup only study arms with a 33% reduction in HSV-2,³⁰ 24-49% reduction in Bacterial vaginosis (BV),^{38,39} halving of STI,³⁸ and 37% higher odds of maintaining a healthy vaginal microbiome (VMB).³⁹ Our studies on out-of-school girls show dropout worsens girls' mental health, further galvanizing the need to support

schooling. Our ToC also assumed provision of menstrual products would decrease sexual risk-taking (sex for pads), noted in qualitative studies,^{40,41} but this was not confirmed quantitatively.³⁰

Figure 1: Theory of change/conceptual model on potential effects of menstrual cup



While the pilot study among primary schoolgirls in our study site showed impact, and that menstrual cups are acceptable and safe among younger adolescent girls, the follow-up duration was only ~10 months.³⁸ This prevented full ascertainment of intervention effects on schooling and their SRH effects. Our subsequent 4-arm trial in the same area, while demonstrating a biological impact as noted above, was conducted among older secondary school girls (median age 17.1y), thus missing the critical time of post-menarche at enrolment.³⁰ Although we followed girls for a period of 2-3 years, surveys were only conducted annually due to the logistical complication of working in 96 schools across an area of 2,500 sq km, preventing comprehensive data collection of intervention usage and events occurring between survey years. In addition, girls who had dropped out did not complete a post-school final year survey limiting explanatory data on intervention use. Logistically we were unable to screen all cups for colour change indicating use, relying on self-report.

This proposed trial is designed to address these biases, by:

- Conducting a trial among girls at or soon after menarche
- Utilising the new school structure of 'junior school (JS)' i.e. grades 7-9
- Conduct biannual surveys to more rigorously document changes in behaviours, use of intervention, and to monitor events
- Maximise training on cup use with education on puberty and hygiene, conduct fidelity checks, to allow reproducibility, and ascertainment of cup use by monitoring cup colour change.

Funding has allowed additional investigation of the effect of menstrual cups on maintaining a healthy vaginal microbiome (VMB) in this population, as a sub-study nested within this trial. In the prior study nested in CCG, girls randomized to receive cups had 24% reduced odds of BV and a 37% increased odds of optimal VMB community state type (CST-1; a CST that is dominated by

Lactobacillus crispatus).³⁹ Modelling the longitudinal data, girls with lower risk prior to receiving cups (i.e., those with no infections – BV, STI, HSV-2) were *50% less likely* to transition to a non-optimal state. This suggests that providing menstrual cups to girls *before* they have had sexual exposure to non-optimal bacteria and STIs could lead to more successful maintenance of optimal VMB. There remains very limited published evidence on the biological mechanisms underlying these effects, with only four studies identified to date and just one conducted within a rigorous randomized trial setting (van Eijk et al., 2026, in preparation). Empirically measuring whether provision of menstrual cups closer to menarche amplifies beneficial effects on vaginal microbiome health is therefore critical to generate level-1 evidence, directly informing school-based menstrual health policy on optimal timing of intervention delivery and supporting clear, non-stigmatizing guidance for young adolescents. Nesting this study within the trial offers the opportunity to verify and measure this.

Qualitative studies will be conducted in close alignment with trial data collection. Data generated will be used to explore and understand issues around key outcomes from the participants' own perspectives assisting in interpretation of quantitative findings and strengthening credibility of findings through triangulation. Additionally, these studies will provide contextual and rich data giving a voice to issues important to the participants themselves including their solutions to problems identified. The iterative design will also allow for exploration of emergent findings as the study progresses. The qualitative data will be primarily from participating adolescent girls, while also engaging a sample of boys from the same schools to explore peer dynamics and gender norms that shape girls' experiences. In addition, insights will be gathered from parents or guardians, teachers, and key members of their community.

Data gathering throughout the study on the costs and outcomes of interventions provided allows for detailed economic analyses considering health outcomes alone (cost-effectiveness analysis) and health, education and economic outcomes via a broader cost-benefit analysis. Such data are vital for national and international policy makers to inform on which investments should be selected for key interventions among this vulnerable population, and whether to provide to all or target those most vulnerable, and to evaluate the expected gains made. Cost-benefit analysis provide further evidence on the relative value of this investment *and* in comparison to a wide range of other possible investments where the cost-benefit framework has been applied including those in health, education, infrastructure and climate change.

6 AIM AND OBJECTIVES

6.1 HYPOTHESIS

We hypothesize that girls provided menstrual cups will be less likely to drop out of school or have an adolescent pregnancy during junior school relative to girls who are not provided these interventions.

6.2 AIM

To evaluate if provision of menstrual cups will impact educational, sexual and reproductive health, and social equity outcomes compared with girls maintaining usual practice.

6.3 OBJECTIVES

6.3.1 Primary Objective

To determine the impact of menstrual cups provided to junior school (JS) girls on pregnancy and school dropout.

6.3.2 Secondary Objectives

1. To measure the age-specific rates of pregnancy and child marriage in JS girls and identify antecedent risk factors associated with these outcomes.
2. To determine the rate, risk factors and reasons for dropout and absenteeism among junior schoolgirls
3. To measure the impact of the menstrual cup on learning via adapted assessments and the Kenya Junior School Education Assessment.
4. To determine the impact of menstrual cups on girls' sexual behaviours, including age of sexual début, coerced sex, number and age of partners, condom/contraception use
5. To examine the effect of the menstrual cup on the vaginal microbiome, STIs and BV in a representative sub-study.
6. To determine the cost-effectiveness and separately, cost benefit of the menstrual cup when given to schoolgirls
7. To determine the uptake and safety profile of menstrual cups.

7 METHODOLOGY

7.1 STUDY DESIGN

This will be a 3-year 2-arm randomized controlled trial, clustered by school, with girls as the unit of measure.

7.2 STUDY SITE

The study will be conducted in junior schools in Siaya County.^{31,42} Junior schools comprise Grades 7-9. Nationally representative assessments indicate that more than half of Grade 7 learners fall in the 13–14 age band, with substantial numbers older than 15 due to late entry and grade repetition, thus we estimate girls will be ~13.9 years at enrolment.⁴³ Siaya County is an impoverished rural region in western Kenya comprising mainly Luo subsistence farmers and fisherfolk, living in polygamous family structures.⁴² The population are uniquely identified, with longitudinal evaluation of demographic shifts (migration, births, mortality) through KEMRI's health and demographic surveillance system (HDSS), morbidity surveillance at Siaya County Referral Hospital and ~54 health clinics, biennial evaluation of socio-economic status, and mortality ascertainment through verbal autopsy.⁴² Adolescent girls and young women experience high morbidity and mortality with rates of HIV, TB, malaria, gender-based violence, and maternal mortality greater than national averages.⁴⁴ In prior HDSS surveys we found ~20% of girls <20y are cohabiting or married, and among 62% of girls reporting ever pregnant, the highest rates were among those with minimal schooling, child-brides, and those with violent partners.⁴⁵ The 2024 Situation of Adolescents in Kenya report found that 13% of primary school girls and 47% of secondary age girls nationwide are not attending school; and reported that the primary to secondary transition has dropped from 83.3% in 2018 to 78.6% in 2022 in the country.⁴⁶ Gender equity seen in primary school falls during adolescence, with between 25%-33% more boys than girls attending secondary school by age 18.^{47,48} Our pilot study evaluating menstrual interventions in primary school girls was conducted in one of the three sub-divisions within the study area, with WASH observations illustrating presence of latrines and water, but not soap in schools.⁴⁹ WASH in schools was poor but consistent across schools and did not influence outcomes.⁵⁰ The menstrual care among the population was examined¹⁸ and illustrated girls' and young women's preference for commercial pads over traditional items; with 10% of 15-year-olds reporting they had sex for money to purchase sanitary pads.¹ Our trial evaluating menstrual cups and cash transfer in older

secondary schoolgirls detected similar findings at baseline,⁵¹ and that menstrual cups were acceptable and were used by around 80% of girls issued a cup in the trial.³⁰

7.3 STUDY POPULATION

7.3.1 Eligibility criteria: inclusion

7.3.1.1 Schools

Junior day schools in select sub-counties in Siaya County, that educate girls or are co-educational, receiving approval to participate from the Head Teacher.

7.3.1.2 Main Participants

Girls attending junior schools (JS), that are day students, live in the study area, and have parental consent and assented, have no severe disability precluding them to participate.

7.3.1.3 Other Participants

Parents: Parents or guardians of girls participating in the trial who consent to participate.

Boys: Boys in same schools as participating girls, who receive parental consent and assent.

Teachers: Teachers in study schools who consent to participate.

Other stakeholders/community members: Persons in the community of the study schools who work with or who have responsibility for or relationships with adolescent girls, e.g. local ministry officials, chiefs, religious leaders, community males who consent to participate.

7.3.2 Eligibility criteria: exclusion

In addition to exclusion due to non-consent/assent:

7.3.2.1 Schools

Boys only schools, girls' schools that require boarding, special needs schools.

7.3.2.2 Main Participants

Girls who live outside the study area, attend boarding schools, parental consent or girl's assent is refused, have a severe disability precluding participation. Girls cannot take part if they have an allergy to silicone or if they plan to move from the study area within the next one year.

7.3.2.3 Other Participants

Parents: Parents in non-study schools or in study schools but whose daughters are not enrolled in the study.

Boys: Boys in non-study schools or whose parents do not provide consent.

Teachers: Teachers outside the study schools or who do not consent.

Other stakeholders/community members: Persons with no knowledge, experience or responsibility for adolescent girls or no knowledge of the local community.

7.4 STUDY OUTCOMES

7.4.1 Primary Outcome

- a. The combined incidence of adolescent pregnancy and / or school dropout, by completion of the follow-up.

For the primary outcome: pregnancy is defined as any incident pregnancy during the study period reported by the participant, and/or verified during follow-up by trained study staff; and dropout will be defined as dropout reported by teachers or identified in surveys, with verification through home visit; or failure to take the end of JS exam in final year of junior school among those who have not repeated a grade.

7.4.2 Primary Safety Outcomes

- a. Menstrual Toxic Shock Syndrome (mTSS)

7.4.3 Key Secondary Outcomes

- a. Disaggregated primary outcomes:
 - a. Incidence of adolescent pregnancy
 - b. Incidence of school dropout
- b. Occurrence of mental health disorder symptoms (i.e. stress, depression, anxiety)

7.4.4 Key Secondary Safety Outcomes

- a. Visits to health facility due to menstrual cup retention or other issues (e.g., pain when inserting or removing the cup, allergies etc.).
- b. Reported health events or hospitalizations due to an episode of violence

7.4.5 Other Secondary/Intermediary Outcomes

- a. Age at child marriage, fertility rate by end of study, pregnancy outcomes
- b. Age at school dropout, pregnancy status before dropout
- c. General self-efficacy and quality of life
- d. Education outcomes – end of JS Kenya Junior School Education Assessment (KJSEA) score, annual grade progression, classroom engagement measured through bi-annual surveys, learning assessments measured at baseline and annually
- e. School absence, i.e. incidence of absence measured through (1) Tangerine™ attendance records; (2) school registers/termly checks; (3) self-reported prior month school absence (all, and during menstruation) measured at baseline and at each survey; (4) self-reported reasons for absences
- f. Incidence of gender-based violence (IPV, community, school)
- g. Self-reported sexual (risk taking) behaviours, i.e., age at sexual debut, transactional sex, number of sex partners, condom use
- h. Menstrual cup use, i.e. self-reported use of menstrual cup at most recent period, and ever; use of menstrual cup detected through cup colour change in biannual survey
- i. Menstrual health outcomes, i.e. menstrual health efficacy, shame, hygiene practices including use of other products, menstrual concealment, pain, heavy menstrual bleeding, and menstrual health literacy
- j. Incremental cost effectiveness ratio (in cost per disability adjusted life year [DALY] averted) of providing menstrual cups versus usual practice
- k. Cost-benefit ratio of providing menstrual cups expressed numerically and calculated based on the ratio of total costs to total benefits in monetary terms.

7.4.6 Other measures of importance to adolescent health and education

In addition to the primary and secondary outcomes we will collect several measures to allow for adjustment and to explore broader determinants of adolescent health.

- Household water, sanitation, and hygiene (WASH) facilities: Household-level access to water, sanitation, and hygiene facilities will be measured, as inadequate WASH is associated with increased risk of reproductive tract infections, missed school days, and poor menstrual hygiene practices.
- Household socioeconomic status will capture household assets, income proxies, maternal and paternal educational attainment and employment status, which may differentially influence exposure to risk behaviours and educational attainment.
- Household chores and/or work responsibilities outside of school: we will capture indicators around girls' requirements for work in- and out-side the home (e.g. farming, cooking, caregiving, casual labour). These domestic or income-generating responsibilities may reduce girls' available time for studying, contribute to fatigue, or affect their level of

exposure to other risks.⁵² This information will be collected both from girls and their parents.

- Sleep: Sleep quality and duration will be assessed. Inadequate sleep has been linked to poor cognitive function, impaired academic performance, increased risk of depression and anxiety, and altered hormonal regulation during adolescence.⁵³ Sleep therefore may be an important mediation or effect modifier of both education and health outcomes in this population.
- Diet: We will assess dietary diversity and quality. Poor diet and undernutrition have been shown to impact school performance, susceptibility to infections, and potentially adolescent mental health, making diet a covariate of interest for adolescent health.^{54,55}
- School size and characteristics: school level variables, including school WASH, will be measured to assess clustering effects and potential confounding in education-related outcomes. These indicators will also capture information on school-based, NGO or other programmes e.g. pad distribution, that will be controlled for in analyses. We will evaluate if any schools in different arms are closely adjacent and ramifications for potential contamination.
- Schistosomiasis: Schistosomiasis can affect school attendance, learning, memory and scholastic achievement.⁵⁶ Schistosomiasis will be assessed at baseline in urine among all participants. Girls found positive will be treated for free with praziquantel.
- Anaemia: Anaemia in Kenyan adolescents aged 10-14 is common, affecting 20-40% of the population;⁵⁷ the most common risk factors are poor dietary intake, infections, and menstrual blood loss. Anaemia negatively impacts school performance (through tiredness and lack of concentration, or in severe cases impaired cognitive development). Thus, anaemia is an important potential modifier to explore when looking at girls' educational outcomes.

7.5 SAMPLING POPULATIONS

7.5.1 Sample size calculation

The primary comparison tested in this trial is menstrual cup vs usual practice. Calculations are based on a 2-sided alpha of 0.05 and an estimated intracluster correlation coefficient (ICC) value of 0.008, an ICC previously observed in our school-based cluster trials in Siaya County. A 2-arm trial will require 21 schools per arm (42 schools in total) enrolling ~49 girls per school (i.e. 1035/arm; 2070 girls total) with 45 girls/school contributing to the analysis, to have 80% power and detect a 33.3% reduction of the primary endpoint from 15% in the control group (usual practice) to 10% in the intervention arm over the 2.5 years of observation. This estimation allows for an annual loss to follow-up of 3% (7.3% total over 2.5 years). Alternatively, if this number of girls per school cannot be achieved, a total of up to 25 school clusters per arm will be targeted to achieve approximately the same power with ~35 girls per school contributing to the analysis. Sample size and power calculations were performed for the minimum number of schoolgirls needed using NCSS/PASS, which were validated using SAS based simulation studies.

This sample size will target enrolling mid grade 7 (JS level 1, Term 2 of Grade 7, aged ~13.94 years) with a 4-month enrolment period, a 3% overall refusal to take part in the study, and an average of 8 terms (~2.5 years) follow-up through the end of Junior School examinations and grade receipt (~Dec 2028, JS level 3, Grade 9, aged ~16.5y). This is a closed cohort, with girls only enrolled at the outset of study. Girls will not be enrolled on a rolling basis if they enter the school after enrolment has been completed.

7.5.2 Justification for primary endpoint

Rates of adolescent pregnancy in Kenya remain high, with ~20% of 15-19 year old girls either pregnant or already a mother.⁵⁸ School dropout is both a cause and consequence of adolescent pregnancy and child marriage, impacting girls across their life course. The most recent Kenya Demographic and Health Survey reports that among school dropouts two in five girls aged 15-19 years have ever been pregnant, compared to only 5% of girls who have more than secondary education.⁵⁹ Unfortunately, some ~13,000 girls dropout from school each year in Kenya.⁵⁹ Moreover, adolescent pregnancies are more likely to occur among poor communities, as 21% of women aged 15-19 in the lowest wealth quantile reported to have been pregnant, as compared to 8% in the highest wealth quantile.⁵⁹ Notably, while school enrolment and gender parity in primary school is high (>95%, and 0.97 GPI respectively, 2022 DHS), post-menarche school dropout among girls increases relative to boys with some estimates finding a 24% decrease in the odds of female adolescents being retained in school for each additional year post-menarche.⁶⁰

From our prior studies we have seen that in a comparable age group of ~14 year-old girls, 63/644 (9.8%) dropped out over one year of follow-up, of whom 53 (60%) were due to pregnancy. Amongst girls in our secondary-school aged cohort, 11% of girls dropped out over 2.5 years of follow-up, suggesting that the transition from primary to secondary school is a significant risk period for school exit.³⁰ In our trial, 54% of dropouts left school due to an unexpected pregnancy and 15% due to early marriage. In our studies with girls who had already left school, 70% reported leaving due to a teen pregnancy and being unable to return to school due to lack of childcare for their babies, or societal and educational exclusion due to their pregnancy and/or motherhood.⁶¹ These realities show the close link between education and sexual and reproductive health in this area. We are powered for 33% relative reduction in the primary endpoint which would be a meaningful non-trivial reduction in dropouts and pregnancies in the target group. In our prior studies in schoolgirls, loss to follow-up due to migration was 8% over three years of studies.³⁰

7.6 IDENTIFICATION AND RECRUITMENT

7.6.1 Recruitment of schools

As adopted successfully in the prior trial, we will recruit junior schools in the study area by holding a meeting with all head teachers in designated sub-counties and local Ministry of Education officials, in collaboration with the Ministry of Education Science and Technology. We will describe the proposed study and have an open forum discussion to hear their views, suggestions, and discuss concerns arising. We will then seek approval from the Head Teachers for eligible day schools from select sub-counties in Siaya County. This listing of willing schools will then be used to reach the required cluster number for the target sample size.

7.6.2 Recruitment of schoolgirls (trial participants)

Pre-participant recruitment preparations include stakeholder, school and parent/guardian sensitization meetings, listing of eligible girls, and baseline school WASH surveys. Parent consent for girls' participation in the overall study and separate substudy on the vaginal microbiome (see section 8.1) will be obtained after information meetings with parents and girls in the eligible study schools. The consenting procedure is described in Section 11.1.

Because recruitment can be negatively affected by school holidays and other events such as school strikes, pre-election and election interferences, the timing of the baseline activities and trial start will be closely coordinated with the school academic timetable and headteacher liaison to minimise unexpected delays. Recruitment of a minimum of 2070 girls from the 42 junior schools aims to start early in the 2026 school calendar, following preparations and approvals from ethical and other regulatory bodies. The recruitment rate is anticipated to be similar (or slightly

shorter) to that occurring in our prior large-scale trial across 5 sub-counties (SERU #3215), which took approximately 4 months. Sub-county field staff recruitment teams will work with schools in each of the sub-counties included.

7.6.3 Recruitment of parents and schoolgirls for qualitative studies

When parents and girls agree to take part in the main trial, they will be invited to be considered for joining some qualitative research activities. This initial recruitment consent to be contacted for these qualitative studies is not binding, as they will be followed up prior to the qualitative activity and provided with further details of the activities in a participant information sheet, followed by fully informed consenting. For parents, informed consenting will take place in their home, after a telephone call by the researcher confirms their interest to join. For girls, this will take place in a private room in the school, at a time designated in consultation with the participating girls.

7.6.4 Recruitment of parents of schoolgirls

At the time parents' consent to allow their daughters to participate, they will be invited to contribute to the study by completing a brief baseline survey. Those agreeing to participate will be consented, before requesting them to participate in the parents' survey.

7.6.5 Recruitment of schoolboys

At the initial school meeting, parents will be informed that some qualitative activities will also take place for boys in the eligible schools. At the time activities with schoolboys are being planned a field officer will visit a random selection of schools to meet with the schoolboys; those who express interest in participating will be provided the participant information sheet to share with their parents. The field officer will return to the school at an agreed time to determine which parents have agreed in principle. Those parents will be invited to meet with the field officer at a pre-arranged time / place (if they cannot attend the school) to provide written consent. Once parental consent has been obtained eligible boys will convene with the field officer who will reread the participant information sheet, answer any questions and assent those still wishing to participate, providing details of when and where the activity will take place. Should there be more potential participants than required the field officer will explain the process of random selection and carry this out until the required number of boys are recruited. The activity will take place approx. one to two weeks of boys being consented - the field officer will determine before beginning the activity that each individual is still interested in participating. Any who have changed their mind will be reassured that they do not have to take part.

7.6.6 Recruitment of stakeholders

Eligible stakeholders in the community of the study schools who work with or who have responsibility for or relationships with adolescent girls will be identified by project staff and individually contacted to introduce the study. Project staff will provide an information sheet and contact details for any questions they may have, either in person, or by email etc as per agreed by the potential participant. Persons wishing to join the activity will be invited to consent at the time or be given up to 5 days to consider participation should they require. Among stakeholders who have agreed, times, and dates of the event will be jointly agreed.

7.7 ASSIGNMENT OF INTERVENTIONS

7.7.1 Allocation

Schools are the unit of randomisation (clusters), and girls the unit of measurement. A census of junior schools in the area will be completed. A computer-generated randomisation list will be produced by the trial statistician at LSTM. Randomization will adjust for school level characteristics (e.g., school size) to ensure balance across study arms. Schools with head teacher approval will be randomly allocated into 2 arms using a 1:1 ratio. The actual allocation of schools to study arms will be revealed using community ceremonies with the Head Teachers of the

school. Because schools allocated to the 'usual practice' will receive menstrual cups at the end, cup allocation may be perceived by communities as an intervention provided 'immediately' vs 'delayed'. Contamination between trial arms is not anticipated because the menstrual cup intervention is a personal-use commodity, similar to panties, that will only be used by an individual girl. Girls will be trained on puberty and menstrual hygiene, including on not sharing their menstrual items. Survey questions will ask girls in both arms what menstrual items they use as data points for possible contamination.

7.7.2 Masking

We cannot mask participants to their treatment (intervention) status due to the nature of intervention provided. Investigators, laboratory personnel, and trial statisticians will be masked, however, while field staff conducting surveys will be blinded, they will be aware of menstrual cup users when monitoring cup colour change during surveys. Bias will also be minimised by use of block randomisation stratified by school size. An independent person will prepare the sealed envelopes with the study allocation. Study arm allocation will not be recorded in the central database to ensure the trial statistician and data managers remain blinded throughout the study. This information will be recorded separately and only be merged with the main database following approval of the statistical analytics plan (SAP), closure of the databases and submission of a copy to the independent statistician of the DSMB.

7.8 INTERVENTIONS

7.8.1 Planned trial interventions by school arm

Participants will be randomised (through school allocation) to one of two arms:

1. One menstrual cup (CouldYou?®) and puberty and hygiene education along with training materials for safe effective cup use.
2. 'Usual practice' control (control arm), who will receive a stationary item (notebook) at the beginning of the study, and the menstrual cup with training on safe use and care at study end.

7.8.1.1 Menstrual cup as an intervention

Menstrual cups are a menstrual hygiene product used worldwide that can be reused for the entirety of one's period.⁶² Menstrual cups are medical-grade silicone-based receptacles inserted in the vagina to collect menstrual blood, and are safe, cost-effective, and environmentally friendly.⁶² Cups maintain a healthy vaginal microbiome and reduce BV and STI.^{30,38,39} Menstrual cups are included within UNICEF guidelines on product options for use worldwide (www.unicef.org/media/91346/file/unicef-guide-menstrual-hygiene-materials-2019.pdf). Kenyan schoolteachers training guidelines also includes menstrual cups as a safe and effective choice for Kenyan girls.⁶³

There are now over 100 brands of menstrual cups worldwide. In the US, a large cohort study (n=11,455) estimated that 18% of the population use menstrual cups.⁶⁴ Monitoring through the Menstrual Cup Coalition among ~400,000 cup users across Africa and Asia have revealed no serious adverse events. Outside of the coalition, ~90 other programmes are documented to be providing cups to women and girls, with those in India alone reaching ~100,000 users (Noor, N, pers comm 2025). The Reproductive Health Supplies Coalition maintains a database on all menstrual product standards (<https://mnh-standards.rhsupplies.org>). Branded menstrual cups have been registered and approved in numerous countries including the United States Food and Drug Administration (US FDA class 2 registration). In the US, menstrual cups are classed as a medical device, and in Europe as a hygiene product. In 2022, ISO established a new committee to define standards for menstrual products (<https://www.iso.org/committee/8933440.html>). This includes ISO for menstrual cups: ISO/TC 338 (<https://committee.iso.org/home/tc338>). Kenya, Uganda, South Africa, Ghana, Namibia, ESwatini, Sudan, Egypt are participating members in

Africa, along with most countries in America, middle east, Asia, Europe and Australasia. Kenya is represented by the Kenya Bureau of Standards (KREBS)(<https://www.iso.org/member/1854.html>).

The menstrual cup used in this study (CouldYou?) (<https://couldyou.org/period-poverty/>) is made from medical grade silicon; Manufactured in a cGMP manufacturing company, which is also ISO 13485 certified; cups manufactured in ISO 8 clean rooms and is FDA - FDA registration #3018179390. CouldYou? Cups are distributed within Kenya for menstrual cup programmes, although not in the rural area of our study, and have KPPB licence approval (KPPB # PPB/DON/00277/24).⁶⁵⁻⁷⁰

7.8.1.2 Theory of change on intervention effects

Our theory of change hypothesizes that, in addition to biological effects mediated through the vaginal microbiome, cups provided will reduce poor school engagement and sexual coercion (Figure 1, above).^{71,72} The design allows quantification of the impact of cups on key outcomes among girls as the direct beneficiaries. Kenyan law states all girls should receive free disposable pads, but monthly deployment and cost impede distribution and uptake. Adding menstrual cups as a second menstrual health option to the national pad programme and incorporating it into the national menstrual health budget for schools could minimize the administrative costs required for monthly distribution and provide girls with a cost-effective and reusable menstrual product solution. We will estimate the net economic benefits including potential development impact, and the expected knock-on effects of increased societal earnings and community development,⁷³ strengthening prior models indicating a USD ~3bn increase in GDP if girls completed schooling in Kenya.⁷³

7.8.2 Procedures for providing interventions and accountability

7.8.2.1 Provision of menstrual cups to schoolgirls

Before menstrual cups are distributed to participants, female teachers in participating schools will receive a cup for personal use and will be trained in its use and safety approximately two months prior to the girls training. After enrolment and the baseline assessment, girls in the cup arm will be provided with one reusable menstrual cup and a two-hour training and dedicated time for questions to familiarize with what it is, how to use it, how to clean it after each period, and how to store it between periods. Girls will also be trained on cup safety and symptoms to watch out for and who to contact in case of an emergency. Written guidance that participants can take home and refer back to will also be provided. Trainers experienced in working with the CouldYou? cup programmes in Kenya will conduct the cup distributions and provide the cup trainings.

The trainers will repeat the cup training monthly for the first three months then on a termly basis. Girls will be asked to provide structured feedback on menstrual cup use. Girls will be encouraged to bring their cups to the training, for inspection of cup condition and signs of use (e.g., cup colour change, detritus) using the same form used in the biannual survey. Feedback and initial experiences from girls will be discussed together with the trainer to identify and troubleshoot any challenges encountered. Early cup adopters will be encouraged to act as champions for uptake. Research staff will conduct fidelity checks during the intervention training days using standardized check sheets. On site female teachers will liaise with KEMRI researchers should any safety issues emerge, and with CouldYou? if girls' questions on cup use arise that require their support. Trainers will also provide contact details should information or support be needed between these training sessions. An attendance log will register all cups provided, with the ID number of the participant. Lost or damaged cups will be replaced throughout the trial's duration. At the subsequent survey, girls will be asked about cup use and surveyed on whether any problems have been encountered. During these biannual surveys, girls will be requested to bring their cups for inspection to assess cup color change, and if any damage has occurred to the cup, requiring replacement.

7.8.2.2 Fidelity checks on training

Intervention fidelity checks will be conducted using standardized check lists to document the quality of training provided to girls and adjust should any training be suboptimal or need further reinforcement. Delivery of key components will be scored (no, partial, yes) to generate a measure of dosage and intensity, as will the way the intervention is delivered – to generate a measure of quality.⁷⁴ We will also measure the duration of each session as a measure of standardization. Qualitative or more subjective measures will include responsiveness - measured by participants' level of interest,⁷⁵ such as displaying interest, initiating questions, participating in discussions or activities. Modifications to intervention delivery will be recorded, such as omissions or deviations (e.g., different information, additional information). Fidelity checks will be reported weekly to the senior team and reviewed at the TMG meetings.

7.9 RESEARCH PROCEDURES

7.9.1 Community sensitization

We will conduct sensitisation meetings with stakeholders in the community to discuss the project. This will include village chiefs so they can inform their communities of the project during their local community 'baraza' meetings. Any questions resulting will be followed up with field researchers to ensure adequate and accurate information and communication, and resolution of any issues emerging. Where feasible, our unengaged partner UNICEF will contribute to this process, to inform and involve national and local UNICEF collaborators. Where available, and with their prior agreement, girls who participated in the prior trial and have used cups will be invited to join the study team as peers to introduce menstrual cups to the schoolgirls.

7.9.2 Tool adaptation and validation

Survey instruments will be reviewed and adapted to ensure they are appropriate for this age group. Specific sensitive indicators will be evaluated using cognitive interview approaches with a small group of students (~10-20 girls) to confirm understanding, especially for questions related to menstruation, sexual health, and psychosocial wellbeing. We will monitor the duration of administration to ensure survey length remains feasible and does not overburden participants. Additionally, tablet-based self-assessments of learning will be developed to align with the Kenya Junior Secondary Education Assessment (KJSEA, taken at the end of Standard/Grade 9) using publicly available test items. Pilot assessments will be conducted iteratively with a small group (~10-20 girls) of girls, who will not be enrolled in the trial, to refine language and learning parameters. These participants will only take part in the tool adaptation and piloting and will assent and have parent consent for only this preliminary component of the study. This piloting process will take place prior to tool deployment to ensure the assessments are age-appropriate, understandable, and capable of capturing relevant variation in student learning outcomes.

7.9.3 School enrolment

Schools will be invited through the Siaya County Ministry of Education to attend a sensitization meeting about the project. At this meeting, school heads will be provided with detailed information and invited to have their school participate in the trial. Head teachers who agree will sign an institutional consent form for their school. Schools with a minimum of 35 girls attending Class 7 (JS Grade 1) will be block-randomized by size into groups of 6 schools. Each block will be called together to select differently coloured balls from a bag. Once all schools have selected their balls, a sealed envelope will be opened revealing the intervention allocation corresponding to each ball colour. All schools will be allocated to their intervention arm through this public randomization ceremony, to promote fairness, buy-in, and understanding of the study allocation in the community.

To support familiarity with the menstrual cup intervention, female teachers in participating schools will be offered menstrual cups and training on their use prior to participant enrolment. This will allow teachers to be comfortable with menstrual cups should they wish to use them themselves, and better support students during the study.

7.9.4 Participant enrolment

For schools that consent to participate, parent meetings will be held to provide project information, address questions, and obtain written informed parent consent for daughters' participation. Parents who agree to their daughters' participation will also be invited to complete a short parent survey.

Girls whose parents consent will be invited to take part. Prior to enrolment, each girl will complete a brief screening form to confirm she meets all inclusion criteria. Eligible girls will then be invited to provide written informed assent to participate should they choose to do so. Enrolment will only proceed once both parent consent and participant assent have been obtained. Following enrolment into the study a study identifier will be assigned, and a baseline survey will be completed.

7.9.5 Surveys and data collection

Baseline and biannual cross-sectional surveys will be conducted among consenting/assenting participants before and during the trial. They will follow the same procedure as surveys successfully conducted in or prior primary schoolgirls pilot trial (SERU# 2198) and secondary schoolgirls trial (SERU# 3215). Additionally, a biannual survey of school WASH will be conducted. Details of surveys are presented below. For girls in the nested sub-study of VMB, BV, and STIs, surveys will take place termly (see section 8.1).

7.9.5.1 Parents survey

When consenting for their daughter to be in the study, these parents will be invited to complete a brief survey at baseline. The survey will be on an electronic tablet, which will be completed through support of survey staff. Topics that will be covered include household demographics, parental education and employment, household WASH facilities, and questions around family support for menstruation (e.g., perceived support for menstruation at home, parental comfort and support discussing menstruation with their daughter, parental menstrual knowledge, and indicators to capture perceived menstrual norms and shame). If funding allows, a second parent survey will take place at the end of the study to capture any changes in household environments and perceived social norms.

7.9.5.2 Girls surveys and data collection

At baseline and biannually, surveys will take place in a private classroom allocated by the principle/head teacher. The socio-behavioural health questionnaire will follow the format of that used in our previous trial which also provided menstrual cups to schoolgirls. The surveys will be on electronic tablets, and participants will be taught to use these. At baseline and annually, girls will complete an adapted learning assessment on tablets. Additionally, at each study visit weight, height and waist circumference will be measured. At each visit post-intervention girls will be asked to bring their menstrual cups to school so field staff can assess cup use and observe and log cup color change, damage, and overall cup condition.

Female field staff will be available to answer questions if anything is unclear and a safeguarding plan will be present for referral to services where needed, e.g. relating to violence (see section 11, and Appendices 17). If girls are not present on the survey day a subsequent school survey day will be arranged. If they remain away after repeated in-school survey, participants will be visited in their homes, and the survey conducted in a place they state they feel comfortable and have privacy. Data entered on the electronic tablets will be uploaded daily to KEMRI and LSTM servers to prevent loss.

Given the high prevalence of *Schistosoma mansoni* in the Lake Victoria basin region, participants will be tested at baseline for schistosomiasis and provided treatment free of charge to those who are infected per Kenyan treatment guidelines. Urine aliquot will be used for schistosomiasis testing. Urine volume more than what is needed will be discarded. Urine will be centrifuged at 2000 g at 4°C to remove sediment and will be tested for schistosomiasis with the circulating cathodic antigen test (CCA; Rapid Medical Diagnostics, Pretoria, South Africa)⁷⁶

7.9.5.3 School surveys and school-level data collection

With Head Teacher approval, at baseline and biannually a school WASH survey will take place using a structured questionnaire to evaluate WASH services in the school. After approval by the Head Teacher the survey team will visit without prior scheduling to capture 'real' WASH circumstances. The WASH field staff will first walk around the school and complete the 'observation' section of the form. They will then engage with the selected school representative to ask questions about usual WASH conditions. The biannual survey report will be fed back to the schools, maintaining confidentiality, to assist schools with their WASH services.

We will assess students' attendance using the open-source Tangerine™ platform already in use in Kenya that helps teachers manage their classroom (see <https://www.tangerinecentral.org>). Tangerine™ is an open-source, offline-first digital data collection platform used in Kenya to support teachers in student assessments, attendance tracking, and classroom monitoring. Tangerine™ enables the administration of standardized learning assessments (e.g., literacy and numeracy), as well as routine tracking of student attendance and engagement via smartphones or tablets. Data can be collected offline and synchronized to servers once internet connectivity is available. The platform is designed for low-resource settings. In Kenya, Tangerine™ tools have been used at scale by government and partner programmes for student assessment, teacher support, and school-level monitoring, providing timely, actionable data to inform education programming and decision-making.

In this study we will train teachers on using Tangerine™ for daily attendance tracking, and deploy educational assessments for literacy and numeracy at baseline and annually to measure students' learning. Educational assessments developed through Tangerine™ will assess foundational literacy and numeracy scores and measure schooling outcomes among girls. To be most useful for teachers' instruction, and incentivize participation from schools, these assessments will serve a dual function of acting as practice exams for the national Kenya Junior School Examination Assessment. Once trained, teachers may use Tangerine™ for their own educational purposes outside of the study, for example to track attendance across all their students and to monitor progress toward learning objectives. Practice tests developed for study participants will be made available through Tangerine™ to teachers for use with all students to support instructional planning and to help identify students' learning needs. Termly random spot checks will be performed in participant classrooms using adapted spreadsheets for attendance records. We will cross-validate a sub-set of these Tangerine™ records with school registers and termly random spot-checks to see if use of this software is reliable. Post participant-completion of junior school, study staff will return to the study schools to collect final KJSEA scores for all participants who completed their exams.

7.9.5.4 SMS messaging of key health events

As used successfully in our prior schoolgirl longitudinal follow-up study, we will request girls message the study team using SMS if important life events occur, e.g. if she has a baby, has been hospitalised (with overnight stay in hospital), her baby or child been hospitalised (with overnight stay in hospital), or her baby died. A trained staff member will clarify any message sent. Based on the details provided, a staff member will make a follow-up visit to the health facility reported to ensure all key events are reported between surveys. This will enable us to ensure participant

wellbeing, and to verify the participants reported information and add any missing details, e.g., for birth of a baby, capturing details on birth outcomes, date, gestational age, weight, and other clinical observations.

7.9.5.5 Drop out home verification

Participating girls reported to have dropped out of school will be followed up to verify this. They will be asked to confirm they have left school, and date this occurred. Girls will be asked on their reason/s for dropout. Girls reporting and/or visibly pregnant will be asked their expected date of delivery. If participants state they have transferred to another school, rather than dropping out, they will be asked which school they now attend.

8 NESTED STUDIES

8.1 VAGINAL MICROBIOME (AKIBA)

8.1.1 Background for study

Our pilot study and trial both indicated that menstrual cups have a protective effect against BV and STIs.^{38,39} Studies indicate menstrual cup use may preserve a Lactobacillus-dominant vaginal microbiome.^{38,77-80} Systematic review demonstrates this Lactobacillus-dominant, low-diversity VMB is inversely associated with BV, STIs and HIV risk.⁸¹ We propose to study the effects of participants' menstrual cup use on the vaginal microbiome (VMB) and whether this leads to reduced BV and STIs, and how cup use effects young adolescent girls' VMB over time. Nesting this in the trial minimizes confounding and selection bias and maximizes efficient use of resources.

Prior studies demonstrate that non-optimal menstrual management is associated with adverse reproductive tract health, specifically in relation to risks for infections. However, there is little published literature on the mechanisms by which this occurs. As demonstrated in our meta-analysis [van Eijk, 2026, in review], just four studies have examined this and only one in a rigorous randomized trial setting. The one prior trial was conducted by our group, among secondary school girls in the same area of Kenya. As part of the longitudinal analyses, we identified factors that led to optimal effectiveness of menstrual cups for vaginal microbiome. We found that participants who were not already sexually active and who were without BV or STIs at the time they were given menstrual cups had lower probability to transition to a less optimal state (that is from CST-I to CST-III or CST-IV) and had greater probability to revert from a less optimal state (that is from CST-III to CST-I, or from CST-IV to CST-III).⁸² These lower-risk girls were typically the younger adolescents, aged 13-15 years. Therefore, these results suggest that giving menstrual cups to younger girls might amplify the beneficial effects on the vaginal microbiome. However, it is critical to actually measure this, as modelling has imprecision and empiric data is requisite for level 1 evidence. This evidence would have major implications for public health and policy: this will directly inform decision makers of school-based menstrual interventions on when is the optimal timing to provide menstrual cups to girls. Generating this knowledge also creates benefits for individuals. The evidence we seek to find can inform clear and non-stigmatizing guidance on menstrual cup use and vaginal health for young adolescents.

8.1.1.1 Aim AKIBA sub-study:

The aim of AKIBA (Afy Kikombe Anza, English translation: Healthy Cup Start) is to determine the effect of menstrual cup use on the VMB and how this leads to decreased risk of BV and STIs among participating girls.

8.1.1.2 **Primary outcome AKIBA sub-study:**

Prevalence of optimal community state type (CST-I, *Lactobacillus crispatus* dominated) among girls provided menstrual cups compared with controls.

8.1.1.3 **Secondary outcomes AKIBA sub-study:**

- Quantify the impact of menstrual cups on BV and STIs (composite of gonorrhea, chlamydia, trichomoniasis)
- Quantify vaginal community state type (CST) transition probabilities and the temporal dynamics for girls with and without sexual activity and antecedents of transition
- Quantify non-optimal VMB persistence and chronicity, and identifying how cup use may mitigate this, and promote BV resolution
- Estimate longitudinal microbial networks in relation to incident BV, STIs and other infections (schistosomiasis at baseline), and compositional changes after treatment and resolution.

8.1.2 **Rationale and justification for AKIBA Sub-study:**

8.1.2.1 **Importance of measuring BV and STIs in adolescents:**

In Kenya, HIV prevalence increases from 3% among 15-19 year-old adolescents to 5% of those aged 20-24, compared to 1% and 2% for males of the same age.⁸³ Following trends in HIV, in western Kenya HSV-2 increases dramatically from 10% in 13-14 year-old adolescents to 28% in 15-19 year-olds.^{84,85} Bacterial vaginosis (BV) affects 20-50% of women in the general population in SSA, and doubles the risk of HIV acquisition and transmission,⁸⁶⁻⁹¹ increases risk of multiple adverse pregnancy outcomes,⁹²⁻⁹⁶ and increases risk of *T. vaginalis*,⁹⁷ HSV-2,⁹⁸ *N. gonorrhea* and *C. trachomatis*,⁹⁹ and HPV.¹⁰⁰ In Kenya, 25% of adolescent girls have had sex before the age of 15 and 26% of girls are married by age 18 and median age of first birth is 19.9 years.¹⁰¹ Globally, adolescent girls and young women account for at least one-third of the 357 million curable STIs occurring each year.¹⁰²⁻¹⁰⁴ Adolescent girls are particularly vulnerable to STIs due to a combination of biological, socio-economic, and behavioral factors. STIs are syndemic with and contribute to the HIV epidemic in Sub-Saharan Africa.¹⁰⁵ Therefore, it is critical that interventions to prevent STIs are undertaken early in adolescence.

8.1.2.2 **Relationship of Vaginal Microbiome (VMB) to Bacterial vaginosis (BV)**

BV pathogenically represents a shift from a predominantly *Lactobacillus* vaginal flora to a diverse flora dominated by anaerobic bacteria.¹⁰⁶⁻¹⁰⁸ Landmark studies utilizing amplicon sequencing by Ravel et al. and Srinivasan et al. demonstrate that bacteria contributing to heterogeneous vaginal bacterial communities that are associated with BV include: *G. vaginalis*, *Prevotella* spp., *Sneathia* spp., *Dialister* spp., *Peptoniphilus* spp., and *A. vaginae*, among others.^{107,108} One of the risks for BV is early sexual debut. Jespers et al. measured the vaginal microbiota using quantitative polymerase chain reaction (PCR) for 5 species of *Lactobacillus*, *G. vaginalis*, and *A. vaginae* among 93 adolescents in Belgium aged 14-19 years.¹⁰⁹ Over 8 months participants underwent vaginal sampling three times; 41 initiated penile-vaginal intercourse. With three measures over 8 months, the odds of detection of *G. vaginalis* and *A. vaginae* were increased after sexual debut, while those who remained without sexual intercourse had stable microbiota. BV (Nugent score 7-10) was detected in 12.5% of adolescents with sexual debut and in 0% of adolescents who remained without sexual experience (p=0.014).

8.1.2.3 **Relationship of VMB to sexually transmitted infections (STIs)**

An optimal vaginal microbiome is dominated by *Lactobacillus crispatus* (referred to as community state type [CST]-I), while CST-IV ("depleted of lactobacilli, with abundant anaerobes"; often dominated by *Gardnerella vaginalis*) is considered a non-optimal VMB.^{107,110} CST-III is dominated

by *L. iners*, and is not consistently associated with harmful or beneficial outcomes. In systematic review, non-optimal VMB is consistently associated with increased risk of HIV, HPV, HSV-2, gonorrhea, and chlamydia.⁸¹ In our CaChe cohort of secondary school girls in the same area of western Kenya as the current proposal, among 41% of participants having CST-I VMB at baseline (median age 16.9 years), we observed prevalences of 0% BV and 2.8% STI (composite of *C. trachomatis* [CT], *N. gonorrhoeae* [NG], *T. vaginalis* [TV]).¹¹¹ Among the 19% of AGYW with CST-IV, 52% had BV and 25% had an STI. CST-IV was increased among sexually active participants, controlling for menstrual practices, sociodemographics, and body mass index. Participants with CST-III VMB (35% of sample) had prevalences of 3.3% BV and 9.7% STI. The high prevalence of STIs among our cohort is unsurprising, as AGYW account for two-thirds to three-fourths of new STIs worldwide.¹¹²⁻¹¹⁴

8.1.2.4 VMB is associated with inflammation and HIV risk, regardless of BV and STI status

The vaginal microbiome interacts with host immune cell functioning, and effects epithelial cells via inflammation.¹¹⁵ Inflammatory bacteria attract cells that are susceptible to HIV infection (i.e., those that are CD4+), and disrupts the functioning of neutrophils, which can lead to epithelial damage. Among 146 asymptomatic South African women aged 18-23 years, among women with non-optimal VMB (i.e., dominated by BV-associated bacteria (*Gardnerella* spp. *Prevotella* spp., *Atopobium*, *Mobiluncus*, *Megasphaera*)) there were higher levels of mucosal inflammation in the genital tracts, and only half had diagnosable BV.¹¹⁶

Many women with non-optimal VMB composition have significant genital inflammation yet no symptoms (i.e., they are asymptomatic), making syndromic management of BV and STIs inadequate. Specifically, molecular VMB characterization similar to the current proposed study, demonstrates vaginal taxa may predict HIV acquisition better than traditional BV markers alone. Lastly, non-optimal vaginal microbiome can reduce the efficacy of vaginal pre-exposure prophylaxis (PrEP) (e.g., tenofovir gel) by metabolizing the active ingredient, thus rendering it less effective, independently of the presence of other infections. There are currently no approved therapeutic treatments for the VMB, though many products (typically live biotherapeutics) are in initial trial phases. This is because our knowledge of the VMB was lacking until the first molecular studies in 2010. The scientific community is still in the process of learning about the VMB, especially in adolescents, who have been underrepresented in the literature. Therefore, measuring the impact of menstrual cups on the VMB as a primary outcome is central to advancing the scientific literature and generating much-needed evidence to inform adolescent sexual and reproductive health interventions, guide future therapeutic development, and support evidence-based menstrual health policies.

8.1.3 Participant selection and methods

Participants in the VMB Sub-Study will involve approximately 20% of the girls in the control arm and 20% in the menstrual cups arm of the Main Trial. Estimating ~1,035 in each arm of the Main Trial, this is equivalent to ~220 girls in the control arm of VMB Sub-Study, and ~220 girls from the menstrual cup arm. The schools selected for the nested sub-study will be selected via random sampling from within all eligible schools, stratified on co-educational status and school size to enhance comparability. Menstrual cup and control participants in the VMB sub-study originate from a selected sub-county within Siaya County for similarity between groups. This was successfully adopted in prior CCG trial, streamlining ethics, governance, and monitoring.

Participants in the VMB Sub-Study will follow all procedures of the main trial, but visits will be more frequent (three times per year instead of twice), and biological samples will be obtained at each study visit. All sub-study biospecimen samples (detailed below) will be taken at the schools during study visits. Following procedures in our prior studies among adolescent girls,^{38,39} a private

area will be secured. The schools provide classrooms for the study procedures to take place and the study creates multiple, temporary privacy enclosures within larger classroom rooms for vaginal swab collections using 4-sided privacy screens with opaque panels extending from approximately 4" above ground to a height of approximately 6 feet. Participants self-collect their own samples inside these and study counsellors (one-to-one) stand guard outside to ensure participant safety, support them with explanations about the swabbing process, and receive the samples once collected.

8.1.3.1 Sample size calculation

In our prior nested VMB sub-study of secondary schoolgirls with a median age 16.9 years at baseline and at least one third already being sexually active, 43% had CST-I at baseline, declining to 32% CST-I at 30 months (i.e., ~30% relative decline), with intervention arm participants having 37% greater odds of CST-I at 30 months follow-up.³⁹ For the current study, with a younger sample of JS students who will have lower rate of sexual exposure, we expect at least 50% of participants will have CST-I at baseline and experience a 20% relative reduction in CST-I over time (i.e., CST-I of 40% at 24 months).

Both the main trial and VMB Sub-Study are designed as a 2-group, 3-level hierarchical design and will have observations (level-1 units; repeated over time) nested in students (level-2 units), nested in schools (level-3 units). Thus, appropriate testing of this design requires application of hierarchical mixed-effects logistic regression model. We applied a two-sided Type I error rate (α) of 0.05, and an ICC of 0.008, following the Cups or Cash for Girls trial, and estimated the number of observations per participant needed, assuming 6 clusters (i.e., schools) within each of the two arms, and 9 observations per participant. To achieve $\geq 80\%$ power to detect a $\geq 30\%$ relative difference in CST-I between intervention and control participants, we need to analyze 450 menstruating girls, estimating 10% loss to follow-up (Mixed models test for two proportions in a 3-level hierarchical design; PASS 2024, version 24.0.2). Accounting for 20% non-menstruators we will therefore enroll up to 600 girls to obtain 450 girls who are menstruating.

If the prevalence of BV (proxy for VMB) is lower than anticipated after baseline and 9-month study visits, power calculations can be revised to evaluate if an increase in the sample size and/or a prolongation of the timelines of the study is needed.

8.1.3.2 Consent and assent of participants to collect swabs

Similar to our prior studies in primary and secondary schoolgirls,^{39,117} girls will be invited to provide self-collected vaginal swabs to assess BV, *N. gonorrhoeae*, *C. trachomatis*, and *T. vaginalis* and VMB composition. Participating girls that have received informed parental consent and themselves have assented will be guided through the study aims, what the purpose of taking the swabs is for, confidentiality, and treatment offered should any infections be identified. Consent and assent will also include a section on shipment of one swab to the USA for specialist amplicon sequencing. Girls will be taught how to self-swab by trained female staff in a private comfortable space organised with their school. Use of screened curtains will ensure privacy throughout the process.

Justification for sampling procedure: To test the hypothesis of biological benefit of menstrual cups for vaginal/reproductive tract health, it is necessary to take biological specimens from the vagina, to test for the relevant biomarkers (vaginal microbiome, BV, and STIs). Other measures, such as self-reported symptoms of STIs are unreliable, non-specific, and lack sensitivity, as we and many others have demonstrated the low utility of syndromic management.¹¹¹ Most (60-90%) screening-detected cases of chlamydia, gonorrhoea, and trichomoniasis are asymptomatic; vaginal discharge or dysuria cannot differentiate etiologies of STI; dysuria does not differentiate STI from UTI; vaginal discharge does not differentiate non-infectious physiologic discharge from infectious discharge, nor does it differentiate STIs from non-STIs such as *C. albicans*. Therefore, it is necessary to take a biospecimen from the vagina for valid, specific, and accurate measure of BV

and STIs. Similarly, the vaginal microbiome cannot be measured by any indirect means. Blood is taken for HSV-2 as the most accurate biomarker of genital herpes. Similar to BV and non-ulcerative STIs, HSV-2 is frequently asymptomatic. Therefore, relying on symptoms would lack sensitivity.

Additionally, haemoglobin will be measured in relation to menstrual health and possible effects of heavy bleeding, and for putative association with trial educational outcomes (see 7.4.6). Haemoglobin will only be measured in the AKIBA in tandem with the other biological samples. Participants with anaemia (defined as Hb<120 g/L) will be informed of this finding, with referral to the nearest facility for supplementation and to inform dietary change. The use of fingerstick to obtain blood for anaemia assessment is in keeping with large population-based studies undertaken in Kenya and other countries in sub-Saharan to assess anaemia.⁵⁷ The data on anaemia will be used in ancillary analysis to evaluate the association with other study components (educational outcomes, menstrual duration and heavy bleeding, and food frequency questionnaire). This will generate actionable data for the Kenyan community.

8.1.3.3 Frequency of swab and specimen collection

BV and STIs (*N. gonorrhoeae*, *C. trachomatis*, *T. vaginalis*) will be evaluated at baseline and each annual visit. One swab for BV assessment will be immediately smeared on a microscope slide, air-dried, and covered with a slip by the field staff. One will be for assessing *N. gonorrhoeae* and *C. trachomatis*, and *T. vaginalis* infections. The third swab will be used for characterization of genital microbiota; this will be collected each term (3x/year). The frequency of these measures is required to estimate incidence and transition timings. We cannot estimate incidence without a baseline measure. If we were to measure only at endline, we would not be able to determine the timing at which benefits may accrue in relation to exposure (menstrual cups), and this would limit our ability to provide guidance to policy, programs, and individuals, as well as information for cost-effectiveness analysis (e.g., if benefit accrues at 1 year vs. 2 or 3 years). Vaginal microbiome is to be measured termly (i.e., every 4 months). In our prior study, we used self-collected vaginal swabs collected every 6 months to estimate the impact of menstrual cups on the VMB. However, the vaginal microbiome can fluctuate rapidly in the adolescent period. Temporal nuance and precision in relation to exposures (e.g., sexual activity) occurs with more rapidity than is reflected in bi-annual sampling. By assessing VMB termly, we will be able to better differentiate transient fluctuations from persistent perturbations and the antecedent factors, more accurately capturing these dynamics and event-related shifts in the VMB: meaning, we will be less likely to miss dysbiosis events (i.e., higher power), which mitigates attenuation of exposure linkage to sexual activity and menstrual management.

At baseline, urine will be collected for diagnosis of schistosomiasis. At annual survey, blood will be taken for HSV-2 among girls whose parents have consented and with girls' assent and to measure anemia via haemoglobin using a HemoCue machine. Participants will be informed of their result and referred to local services if anaemic.

Visit	BL	T3	T1	T2	T3	T1	T2	T3
Time	0 mos.	4 mos.	8 mos.	12 mos.	16 mos.	20 mos.	24 mos.	28 mos.
VMB Sub-Study	VMB BV STI* Schisto Survey	VMB Survey	VMB Survey	VMB BV STI Survey	VMB Survey	VMB Survey	VMB BV STI Survey	VMB Survey

*STI includes *C. trachomatis*, *N. gonorrhoeae*, *T. vaginalis*, through swab specimen and a blood sample for Herpes Simplex Virus Type 2 (HSV-2) and hemoglobin.

8.1.3.4 Laboratory procedures

The BV slide and swabs will be placed in biohazard transport bags, and kept inside a cooler with ice packs, and kept at 2-8°C until transport to Kisumu at end of day. Specimens will be transported to UNIM (University of Nairobi, Illinois, and Manitoba) Lab administered by Nyanza Reproductive Health Society (NRHS) and located on the grounds of Lumumba sub-county hospital in Kisumu. In collaboration with KEMRI, NRHS UNIM lab will receive the specimens and log their receipt, processing, and storage in accordance with trial procedures. BV slides will be Gram stained and read according to Nugent criteria. The swabs for STI testing will be processed at UNIM lab using Atila extraction free iAMP (Atila BioSystems, Sunnyvale, CA).¹¹⁸ This isothermal qualitative polymerase reaction (qPCR) test has advantages of high throughput (96 well plate including controls) and fast turnaround (within 2 hours) supporting rapid turnaround for high volume specimen processing to facilitate timely accurate treatment of STIs. The genital microbiota swab requires shipment to the US Rush University in Chicago, Illinois, for genomic DNA extraction and characterization using high-throughput amplicon sequencing of the bacterial 16S rRNA gene through the Genomics Core and Microbiome Facility.^{63,39} A two-stage PCR protocol will be employed for PCR amplification and sequencing.¹¹⁹ Microbiome bioinformatics will be performed with the most current version of QIIME2.¹²⁰ Raw sequence data will be checked for quality using FastQC and merged using PEAR,¹²¹ with quality filtering via the q2-demux plugin.¹²² After trimming, denoising, adapter sequence removal, and contaminant removal, the ASV fasta sequences and DADA2 generated abundance tables will be used for taxonomic classification using SpeciateIT,¹²³ followed by generation of taxonomy count tables and vaginal community state types (CST) assignment via nearest neighbour matching algorithm (VALENCIA¹²⁴).

Serum specimens will be tested at UNIM lab for HSV-2 antibody (Kalon HSV-2 IgG ELISA, Kalon Biological Limited, Aldershot, United Kingdom) according to the manufacturer's instructions using recommended cutoffs.¹²⁵ Given the high prevalence of *Schistosoma mansoni* in the Lake Victoria basin region, participants will be tested at baseline for schistosomiasis and provided treatment free of charge to those who are infected per Kenyan treatment guidelines. Urine aliquot will be used for schistosomiasis testing. Urine volume more than what is needed will be discarded. Urine will be centrifuged at 2000g at 4°C to remove sediment and will be tested for schistosomiasis with the circulating cathodic antigen test (CCA; Rapid Medical Diagnostics, Pretoria, South Africa).¹²⁶

8.1.3.5 Feedback and treatment

Results of BV and STI testing are typically available within two weeks of testing, depending on volume and lab staffing. However, given potential holidays and other disruptions, we will inform participants they will receive their results within 1 month. Participants will be treated confidentially by the study nurse with antibiotic therapy following Kenyan national guidelines for BV, gonorrhoea, chlamydia, or trichomoniasis based on laboratory diagnosis. Participants found with schistosomiasis will be treated with praziquantel per Kenya treatment guidelines. Results of BV and STI testing will be provided directly to participants. Results will not be shared with parents or guardians in order to avoid breaching confidentiality and to protect participants from potential social harm, stigma, or coercion. This procedure is consistent with ethical guidance on adolescent sexual and reproductive health and Kenyan policies permitting confidential STI services for adolescents.¹²⁷ Participants testing positive will receive counselling and treatment free of charge.

Amplicon sequencing does not produce diagnostic information on treatable conditions so will not be reported back to girls. De-identified data will be shared between KEMRI, LSTM, Rush, NRHS and UIC collaborators for joint papers.

8.1.4 Sample and data storage

No specimens from this study will be banked. The vaginal swabs collected through study procedures are destroyed in the processing of specimens. The extracted bacterial DNA will be stored for up to 10 years after study completion. The bacterial DNA will be stored in Dr. Mehta's -80°C freezer in the Rush Freezer Farm (8th floor Jelke). The Rush Freezer Farm is restricted access. After processing, only Dr. Mehta and Microbiome Core lab staff will have access to the specimens. Specimens may be accessed by outside investigators only with appropriate ethical committee approval and protocol approval by Drs. Mehta, Phillips-Howard and Otieno. Meta-data to be provided with specimens depends on the specific request, and may include variables such as demographics (age, socioeconomic status), behavioural practices, or psychosocial measures. These will be shared with appropriate ethical committee approval and protocol approval by Drs. Mehta, Phillips-Howard, and Otieno.

In keeping with best practice for rigor and reproducibility, after completion of main analyses de-identified data will be shared to a NIH-supported data repository, such as FigShare. The metagenomic data from this study will be submitted to the National Center for Biotechnology Information (NCBI) Sequence ReadArchive (<http://www.ncbi.nlm.nih.gov/Traces/sra/sra.cgi>) to enhance reproducibility and allow for new discoveries. The SRA is NIH's primary archive of high-throughput sequencing data and is part of the International Nucleotide Sequence Database Collaboration that includes at the NCBI Sequence Read Archive (SRA), the European Bioinformatics Institute, and the DNA Database of Japan.

8.1.5 Data analysis

The final analysis will follow the approved Statistical Analysis Plan, which will be finalized prior to the completion of data collection. The anticipated analysis is as follows:

Primary analyses will follow intention to treat (ITT), according to assigned study arm. For the primary VMB outcome and the secondary BV and STI outcome, generalized linear mixed models (GLMM; observations nested in individual) will be used to allow for the hierarchical structure of the study. VMB CST will be dichotomized as CST-I (*L. crispatus* dominated) versus other CST (CST-II, CST-III, CST-IV, CST-V). Models will be fit with a binomial distribution, log link function, and fixed effect for intervention status will be used. For relative abundance of *L. crispatus* (continuous) GLMMs will be fit with a Gaussian distribution, including treatment arm as fixed effect, and participant and cluster as random effects, with 95% confidence intervals estimated via robust variance estimate. BV dichotomized as positive (Nugent score 7 to 10) versus negative (Nugent score 0 to 6) and incident STI, dichotomized as positive (composite of infection with CT, NG, and/or TV) versus negative for all three will follow the methods described for VMB CST. In the case that log-binomial models do not converge, Poisson distributions will be applied. Baseline BV and STI status will be part of the longitudinal data, and, therefore, estimations will account for baseline BV and STI status in both the crude and multivariable adjusted models. Pre-specified confounders and sub-group analyses will include age, sexual debut and baseline HSV-2, BV, and STI statuses. Time varying confounders will include antibiotic use, hormonal contraceptive use, and number of recent sexual partners. Per protocol analysis will rely on self-reported cup use during the study. Analysis will be conducted using Stata/SE v17 or higher software package.

8.2 QUALITATIVE STUDY

8.2.1 Aim

The aim of the qualitative sub-study is to provide deeper understanding and nuanced context of issues of importance to the trial, trial outcomes and study participants and local community themselves.

8.2.2 Objectives

- a. To understand teachers experience of being trained, using the cup and being a point of contact or mentor for girls using the cup,
- b. To capture girls early experience of the training and menstrual cup to inform future scale up.
- c. To gain insights of girls training and support needs from NGO trainer perspectives.
- d. To explore girls experience of using a menstrual cup + gender norms, and understanding how the community views shape the individuals' perspectives
- e. To document girls' experiences of menarche and menstruation and the effect on schooling and wellbeing.
- f. To understand the reasons, needs and experiences of girls who drop out of school, highlighting opportunities to support return to school from girls and parental experiences
- g. To comprehend teachers' perceptions on the role of education for girls' post-puberty, challenges to keep girls in school, and solutions to enhance educational outcomes
- h. To explore perceptions of girls and boys around gender norms, and how they navigate challenges.
- i. To capture girls lives and events leading up to pregnancy, identify theoretical points of intervention and possible return to school
- j. To explore girls and teachers' perceptions around mental health and contributing factors to poor vs good mental health amongst girls, and any impact of teachers' mental health.
- k. To explore any issues arising from ongoing study that are of importance to understanding trial outcomes.

8.2.3 Design

A qualitative study comprising a variety of approaches, to collect contextual data from girls along with boys, parents, teachers and stakeholders/community members as relevant. Our flexible approach will comprise a) primary investigations amongst participants from either one or both study arms providing contextual understanding of key issues, and b) supplemental studies exploring issues of note resulting from the emergent study findings (both prior qualitative and quantitative) that will inform ongoing investigations.

8.2.4 Sample size estimates

The qualitative study is nested within the full IMARA trial and provides contextual data linked with the main trial, supporting explanation of the causal pathways and trial outcomes. This method is iterative, and the process will be guided by the findings or requirements of the study as the study progresses. The guiding principle for sample size in qualitative studies is based on data or coding saturation, and not on quantitative hypothesis testing. We anticipate (from our previous menstrual studies in Kenya) a minimum of 6 group activities (having 6-8 participants in each), and 12 paired or individual IDI for each thematic series and sub-group, though this may be extended or restricted depending on when saturation is met. The scope of our qualitative work will focus on the acceptance, uptake, inputs for maximal effect, and outcomes of menstrual cups use.

8.2.5 Primary topics of interest

8.2.4.1 Menstruation, menstrual care, the cup

- i. Teachers experience of being trained and using the cup, views on girls early adoption and needs, their responses. (Cup schools, teachers, baseline)
- ii. Girls early experience of the menstrual cup (and puberty education training), how this can be improved (cup schoolgirls, baseline 3-6 months + data from training activities)
- iii. NGO trainers experience of training the girls, issues girls experienced, the support needed and the nature of the questions they asked (NGO trainers, baseline)
- iv. Views of girls using a menstrual cup + gender norms, capturing both positive and negative impacts, and understanding how the community views shape the individuals' perspectives and with attention to how can negative views be transformed. (teachers / stakeholders (community members), all follow-ups)
- v. Experiences of menarche and menstruation and the effect this has on girls daily schooling, ability to learn, achieve an education, the impact of menstrual stigma and shame; fear of leaking, odour, restrictions; and menstrual product choice and its effects on school engagement, absence, health and wellbeing (girls from both arms, all follow-ups).

8.2.4.2 Schooling and school dropout – including short and prolonged absence

- i. Understand the reasons, needs and experiences of school absence and drop out, including contribution of short and continued absence, opportunities for catch up, support needs, assistance in returning (girls who have dropped out, parents of girls who have dropped out, all follow-ups)
- ii. perceptions on the role of education for girls post-puberty, challenges to keep girls in school, short and continued absence, barriers that impact successful learning and perspectives on solutions to enhance educational outcomes – (teachers, stakeholders, all follow-ups)

8.2.4.3 Life events – including Pregnancy, Gender norms, early marriage

- i. views and perceptions of gender norms, navigating challenges relating to gender norms as girls go through milestones of adolescence including why and at what stage they may succumb to e.g. early pregnancy, young fatherhood, school absence and dropout, early marriage, and how they react and adapt (both arms girls + boys, midline / endline)
- ii. Exploring girls' general circumstances leading up to pregnancy and possible return to school to identify theoretical points of intervention (before or after dropout, or unrelated) role of education, SRH, gender norms, home life & relationships, influence of others. Any role of cup intervention (both arms, girls who are / have been pregnant, all follow-ups).

8.2.4.4 Mental Health

- i. perceptions of mental health status and contributing factors to poor vs good mental health amongst girls. (Girls both arms, mid/endline)
- ii. To build depth of understanding and context around key indicators from the survey from girls and teachers' perspectives and assess their views on girls' mental health issues, causes and impact. (Girls / teachers both arms, all follow-ups)
- iii. Assess perceptions on staff mental health and any impact this has on the school environment. Additionally, to assess views on gender differences and contributions to mental health from the study interventions. (Teachers both arms, all follow-ups)

Commented [A1]: [Mention was removed], this section doesn't capture/ mention boys discussion topics?

Commented [A2R1]: Hi Sandra. See life events. They are in section 8.2.4.3 i
Did you want more in boys discussion topics? I did ask at the time for input but I think you were snowed under with SunPad stuff so bad timing. I'm hoping to discuss and hone down with you and Clara as we are ready to progress field work.

Commented [A3R1]: Hi Linda, seen the life events section, thanks. I do not specifically want more on boys...this was in reference to the SERU feedback on boys inclusion
Thanks

8.2.6 Secondary Investigations

Identified topics of exploration, participants, data collection methods, timing to be determined if required as study progresses.

8.2.7 Sample

Girls, boys, teachers, parents, and stakeholders/community members (comprising Chiefs, representatives from health and education services, members of the community). Schools will be chosen through purposive (for trial arm selection) then random sampling to take part in the qualitative components of the study. Girls and boys who assent to participate and have parent consent for qualitative study will be randomly selected from chosen schools. Parents of participating girls will be invited by head teachers from chosen schools to participate in parental activities. In addition, we will purposefully recruit a sample of girls, who have dropped out of school, and a sample of girls who became pregnant during the study period for studies on those topics. Should any of these girls become their own head of household they will be classified as emancipated minors, and thus not need parent consent. Purposive sampling (with snowballing to boost sample size if required) will be conducted to recruit stakeholders and community members.

8.2.8 Data collection methods

8.2.8.1 Consent and assent procedures

Prior to any qualitative activity, potential participants will be informed of the study and those interested, invited to participate. Written informed consent will be obtained for each qualitative activity, with parental consent required before girls and boys assent (see also section 11). An additional ~5 days will be provided for those persons wishing to consider whether to join the study, or to consent on behalf of their daughter or son.

8.2.8.2 Approaches to collect data

These will be determined dependent upon participant group and nature of enquiry and comprise one or more of the following: (1) Focus Group Discussions (FGD), Small Group Activities (SGA) e.g., 'transect walks' – around or within the school environs (or village if school dropouts), vignettes, ranking exercises, social media discussion boards, testimonials. All will target 6-8 participants per group; (2) friendship pair interviews, and/or one to one IDI including in-depth case studies. We anticipate a minimum of 6 FGD/small group activity or 12 IDI/pairs (or 3 FGD / SGA and 6 IDI/pairs if both methods are adopted), per topic of enquiry with further data collection planned if saturation is not reached (i.e. the activities continue to produce emergent themes, or further information is required to inform our studies).

Prior to each data collection activity discussions will be held with the qualitative team to finalise the best method of data collection per investigation, refine the topic guide dependent upon any emerging findings and literature/policy, and ensure language used reflects the understanding of local context and nuance. Each initial activity will include participant feedback to ascertain understanding, check context appropriate and assess improvements needed. Regular debriefs will be held during each data collection activity to inform the need for any refinement of the topic guide and determine when data saturation has occurred.

8.2.8.3 Guides and tools

Guides will be prepared for each qualitative activity comprising key topics/questions and suggested prompts for the interviewer/moderator to use as relevant. Each activity will be audio recorded and transcribed verbatim with participant consent. Additional notes will be taken by field staff or interviewer.

8.2.8.4 Collection of data

Moderators and note takers will be used for group activity, an interviewer (or two interviewers if appropriate) will be used for IDI and friendship pairs. Girls will only be interviewed by female staff. The staff are fluent in English, Kiswahili and Dholuo, giving participants a choice of language to use. Discussions and interviews will take place in an appropriate private space e.g. school premises, community venue, or chosen by the participant in IDIs. The route or venue for transect walks will be decided beforehand with participants as appropriate. Before starting any group activity, participants will provide their written informed consent (see consenting section, below). Participants will be informed of 'ground rules' where they agree that information discussed is confidential and will not be discussed outside of the FGD and to respect all opinions. They will also be invited to add any additional ground rules. All participants will be asked if they approve of audio-recording of the activity before it is switched on. Should any refuse, notes only will be taken. Each group activity will take approximately 1.5 - 2 hrs and individual interviews will take approximately 30 minutes – 1 hr. Participants will be assigned a number and asked to use this rather than names. Any personal identifiers will be removed from transcripts. Minimal sociodemographic data will be collected on a front sheet to ascertain sample characteristics as required for analysis and write-up. Refreshments will be provided, with transport costs reimbursed as appropriate.

8.2.9 Data analysis

Databases of transcripts will be uploaded to a qualitative software package (e.g., Nvivo v14 or higher, QSRinternational) facilitating shared or transparent coding/analysis. The method of analysis for each data set will depend upon the aim and the nature of the data. We anticipate this will comprise thematic analysis for larger datasets, multiple participant groups and where more than one analyst is involved, and Interpretative phenomenological analysis (IPA) for smaller, richer datasets that delve into personal experiences, behaviours and perceptions such as cultural and social norms. Where relevant, data triangulation with other qualitative data (e.g. across themes, participant groups, intervention or control) and/or quantitative results will be undertaken.

8.3 HEALTH ECONOMICS SUB-STUDY

8.3.1 Rationale

We hypothesize that trial intervention will be cost-effective against relevant willingness to pay thresholds for Kenya and that it will have a positive cost-benefit ratio (meaning that the total value of benefits gained exceeds the total costs) and that the resulting economic evidence will support wide-scale implementations in similar settings. The provider costs (project, health and education system) and beneficiary (girls) costs of the intervention will be fully costed following activity based and ingredients approach costing methods to estimate 'real life' implementation costs (and excluding research costs). Sensitivity and uncertainty analyses will be used to explore the impact of changes in key parameters such as the price of menstrual cups which are likely to materially affect the results of the economic analyses. Wider economic benefits such as the value of avoiding girls dropping out of secondary school (estimated as US\$ 27,415 per Kenyan girl who does not drop out of secondary school)⁷³ will be incorporated in the cost benefit analysis.

8.3.2 Aims

The aims of this component are to determine the cost-effectiveness and separately, cost benefit of the menstrual cup for schoolgirls thus providing national and international policy makers with sound economic evidence to support decisions related to wider implementation of the trial findings.

8.3.3 Objectives

- (i) To estimate the total and unit costs of delivering the intervention from the disaggregated societal perspective i.e. separating out costs to the providers (project, education and health service) and beneficiaries (i.e. the AGYW who receive the interventions).
- (ii) To calculate the incremental cost effectiveness ratio (in cost per disability adjusted life year [DALY] averted) of providing menstrual cups versus usual practice
- (iii) To calculate the cost-benefit ratio of providing menstrual cups expressed numerically and calculated based on the ratio of total costs to total benefits in monetary terms.

8.3.4 Sample size

Health Economic evaluations including cost-effectiveness analysis and cost-benefit analysis as presented in this proposal are not usually subject to sample size calculations but rather use all available data to come up with results which are then subjected to extensive uncertainty and scenario analyses to explore the robustness of the findings to various uncertainty rather than focusing on statistical significance. These sensitivity and uncertainty analyses are described in this protocol.

8.3.5 Cost data collection

Cost data will be collected following activity based and ingredients approach methods which involve identifying the full set of activities to be costed, and then systematically capturing the volume and unit cost of each type of resource required to conduct these activities. Activities (e.g. training girls, delivering cups, follow-up training) will be identified and documented on a detailed project activity framework in collaboration with study teams and implementing partners. After removing research activities (e.g. ethical submissions) each activity will be costed. Financial unit costs and quantity of resources consumed will be obtained from project records while additional economic costs (i.e. resources consumed where there is no financial record) will be identified and valued appropriately. For example, teacher time that is already paid for by education staff salaries will be estimated based on time spent supporting the intervention multiplied by number of teaching staff involved x salary costs from civil service pay scales. Girl's time (e.g. missing school to attend training) will be valued according to time spent x number of girls x daily school fee. Where resources (e.g., staff) are shared between more than one activity, costs will be allocated using a suitable proxy. Costs will be categorised by the level which they are incurred (e.g. national, county, sub-county, school, girl) to facilitate scale up costing analysis (see below). Any capital costs (i.e., for items with a useful life of >1 year and a value of > \$100 per item) will be annualized over their useful life at a discount rate of 3% to account for the opportunity cost of tying up cash in capital items. Costs will be measured separately for each year of intervention delivery and summed to calculate a total cost. Total cost will be divided by the number of girls reached to estimate the unit cost per girl reached by the programme. All costs will be recorded in the currency of transaction and converted to USD at prevailing rates.

Costs by level (i.e. national, county, sub-county, school, girl) for the trial intervention will be used to estimate the costs of scaling up the intervention across a wider area. To do this each cost by level will be divided by the number of units in that sample to estimate the unit cost by level, e.g. total girl level costs divided by number of girls reached = girl level unit cost. Scale up analysis would then take the level-specific unit costs and multiply up by the relevant number of level-specific units in the scale up target. This way a simple non-linear and fully transparent scale up cost analysis can be estimated. Full sensitivity and uncertainty analysis will be conducted.

To estimate the societal cost consequences and the cost-effectiveness of the intervention (menstrual cups from a societal perspective, as compared to the usual care in western Kenya (controls), we will collate data on the financial and economic costs of prior interventions where effects were previously evidenced. Costs for research only activities will be excluded. The

numbers of adolescent pregnancies averted in intervention groups compared with the control group will be used to calculate disability adjusted life years (DALYs) averted using standard methods.¹²⁸ If the epidemiological data suggest an effect on other health outcomes, this will also be included in the DALY calculations.

8.3.6 Cost-effectiveness analyses

Cost-effectiveness analysis will assess the incremental cost per DALY averted of the intervention compared to standard practice. Next, total DALYs averted will be estimated using trial data on the following outcomes: menstrual health disorders (stress, depression, anxiety); health events or hospitalisations due to an episode of violence and/or gender based violence; menstrual health outcomes (e.g. pain); reproductive tract infections (from the VM sub-study) on BV and STIs (composite of gonorrhea, chlamydia, trichomoniasis). We will also include any adverse pregnancy outcomes that occur in each arm (e.g., prematurity, low birth weight, infections, still birth, etc.). In the very rare event that menstrual toxic shock syndrome occurs we will include that. The point estimate of the incidence of each of these outcomes by arm will be multiplied by an assumed/observed duration and the most relevant and most recent DALY weight (from the Global Burden of Diseases study) to estimate the years lived with disability (YLD) for each outcome. Should any deaths occur (including in live born babies), we will estimate the years of life lost (YLL) due to these outcomes by subtracting the age at death from life expectancy for the relevant age group. YLD and YLL will then be summed to estimate total DALYs by arm. DALYs averted by the intervention will be calculated by subtracting total DALYs in the intervention arm from those in the control arm.

Total incremental cost of delivering the intervention at the scale of the trial will be estimated as described above (8.3.4). Additionally, in order to account for the potential cost savings of treatment cost avoided by the intervention effect, we will estimate the treatment costs for all outcomes listed above in a desk-based micro costing exercise (for example by using standard treatment guidelines and published Kenyan drug prices from KEMSA and adding fixed unit costs for outpatient visits from Kenyan MoH tariffs or the literature) and multiply this by the incidence of each outcome, per arm. We will also include an estimate of the cost of ANC visits and delivery for pregnancies, and any newborn care occurring in each arm.

The incremental cost per DALY averted of the intervention will be calculated via a decision tree/Markov model developed using AMUA software and according to the following formula:

$$\text{Change in cost/change in DALY} = \frac{(\text{Total cost of intervention} - \text{Total cost of control})}{(\text{Total DALY intervention} - \text{Total DALY control})}$$

Where:

$$\text{Total cost of intervention} = \text{Sum of Cups intervention} + \text{Total treatment costs for each incident case of all relevant outcomes}^{\S \text{ \textasciitimes}} \text{ in intervention arm}$$

$$\text{Total cost of control} = \text{Total treatment costs for each incident case of all relevant outcomes}^{\S \text{ \textasciitimes}} \text{ in control arm}$$

$$\text{Total DALY intervention} = \text{Sum of YLD and YLL from relevant outcomes}^{\S \text{ \textasciitimes} \alpha} \text{ in intervention arm}$$

$$\text{Total DALY control} = \text{Sum of YLD and YLL from relevant outcomes}^{\S \text{ \textasciitimes} \alpha} \text{ in control arm}$$

§ Mental health disorders (stress, depression, anxiety); health events or hospitalisations due to an episode of violence and/or gender-based violence; adverse menstrual health (e.g. pain and heavy bleeding); reproductive tract infections and (from the VM sub-study) on BV and STIs (composite of gonorrhoea, chlamydia, trichomoniasis); menstrual toxic shock syndrome.

¥ ANC visits, childbirth/delivery and newborn care

α Maternal and neonatal deaths

The primary CEA analysis will be done from the provider (i.e. excluding cost incurred by the beneficiaries but including all DALYs) with a pre-specified willingness-to-pay per DALY averted threshold.¹²⁹ The results of the point-estimate will be plotted on the cost-effectiveness plane. A full probabilistic sensitivity analyses (PSA) will be conducted using the Monte Carlo simulation method to assess the impact of uncertainty and variability in model inputs and their related impact on the analysis. Pre-specified variables for the PSA will include DALY weight (upper and lower bound from Global Burden of Disease, and varied estimates for any DALY weights used in the absence of a Global Burden of Disease weight); the upper and lower bound of the confidence intervals or an appropriate probability distribution function for incident conditions and cost variables which are both uncertain and important (i.e. account for $\geq 10\%$ of total costs), and, the discount rate. The PSA model will be run with a fixed random seed and 100,000 iterations with the simulated outputs plotted on cost-effectiveness plane and transposed to a cost-effectiveness acceptability curve, both overlayed with the WTP/DALY threshold for interpretation. The WTP threshold will also be varied in the sensitivity analysis. The final result will present the likelihood of the intervention being cost-effective at a given level of certainty representing the proportion of 100,000 simulated outputs that fall on or below the willingness to pay threshold. The PSA will be conducted on STATA and AMUA software, according to the reference case for cost-effectiveness analysis¹³⁰ and reported following the CHEERs checklist.¹³¹

We will follow the same method as described above to conduct an additional cost-utility analysis using the EQ5D-3L scores from girls in each arm as the endpoints.

8.3.7 Cost-benefits analysis

Our cost-benefit analysis will be underpinned by a fully elaborated conceptual framework (built on the basis of the theory of change, see Figure 1), which describes the underlying mechanisms by which we anticipate the intervention will impact on the health, education and economic outcomes at individual (girl), school and national (macroeconomic) level. Any observed benefits of the intervention on key educational quantity focussed outcomes (i.e. school dropout and attendance with resulting change in years of schooling) will be converted to economic impact using Mincerian returns to schooling (i.e., percentage increase in income per additional year of schooling) and converted gains into increased expected lifetime earnings.¹³² Benefits on educational quality related outcomes (e.g. school assessment results) will be converted to economic gains using the relatively new concept of learning-adjusted years of schooling (LAYS). Literacy gains observed (ie in observed test-score changes) will be converted into LAYS and subsequently lifetime earnings gains using the Mincerian approach described above (and used in the World Bank model¹³³ on investing in girls. Health benefits will be valued based on the avoided treatment costs (cost-of illness method), and in additional days and years of productive time gained through all health effects attributable to the intervention, which will be valued using the human capital approach.¹³⁴ Mortality averted by the intervention will be quantified using four variations of the value of statistical life (VSL) methods, as recommended in the Standard Sensitivity Analysis for BCAs.¹³⁵ Observed intervention effects on joblessness and adolescent pregnancy will be valued in a similar manner and following the World Bank investing in girls methodology.

The benefit cost ratio, which quantifies the economic return per dollar spent, will be calculated by dividing the net present value (NPV) of the incremental health and educational benefits by the NPV of the incremental intervention costs. The Copenhagen Consensus "Traffic Light" rating system, which categorizes the BCR into four categories: Excellent ($BCR \geq 20$), Good ($5 \leq BCR < 20$), Fair ($1 \leq BCR < 5$), and Poor ($BCR < 1$),¹³⁶ will be applied to aid interpretation of results. Additionally, the net benefits (total benefits minus total costs) will be reported, as relying solely on the BCR can obscure the relative magnitude of the effects. A full structural and PSA will be

conducted to explore the robustness of our findings to key uncertainties. The BCA will be conducted according to relevant reference case.¹³⁷

9 DATA MANAGEMENT

9.1 TRIAL DATA COLLECTION

9.1.1 Variables to be collected

9.1.1.1 *Girls survey*

Questions will cover girls' individual, household, and school characteristics. Questions will focus on their menstrual health and hygiene (e.g. timing and experiences at menarche, experiences with hygiene management, menstrual disorders, pain, and menstruations impacts on their self-efficacy, daily living, schooling etc.); school environment and attendance; health (general, sexual and reproductive, history of chronic conditions, access to health services); sleep and dietary patterns; social norms; and self-agency. Girls will be asked about their wellbeing and mental health using standardized scales (e.g. EuroQoL-5D-3L, and PHQ-9),¹³⁸ which have been successfully used in our other KEMRI-LSTM studies among schoolgirls (SERU #3215) and out-of-school girls (SERU #4197) or the DASS-23).

At baseline and annually, non-routine metrics (e.g. adapted EGMA/EGRA) will be administered on tablets to capture learning. These will be developed based on the Early Grade Reading and Math Assessments (EGRA/EGMA) in line with Global Proficiency Framework for higher grade levels.

Participants who receive a menstrual cup during the trial will be surveyed on whether they have used the cup, and for those using the cup, on challenges encountered, and impacts of cup use on their daily lives while menstruating. Among non-users, they will be asked what has prevented them, and how the research team can support uptake should they wish to use it. The questions will be in the local language Dholuo, as well as English, as Swahili is not normally used in schools in this geographic area.

Girls will be requested to bring in their menstrual cup at the time of the biannual survey. The female staff will observe and document colour of cup, general wear and tear, damage to the cup or tail, tail length, presence of detritus and odour of the cup. Should the cup show clear evidence of use, but is unsafe due to damage, a replacement cup will be given. If the cup is not used, discussion around reasons for not using, and arrangement for additional training if required to support use can be given.

9.1.1.2 *School survey and data collection*

A biannual school WASH survey will capture sanitation facilities and conditions at each school, using an electronic survey form. This survey captures both observed conditions and reported conditions from the school representative. The data includes metrics on water for hand washing, soap for hand washing, latrines available for use (boys/girls), private space for girls for changing, water for girls to clean themselves and soiled (menses) clothing, and whether the school provides sanitary pads. The school representative also provides data on frequency of cleaning, purchase of cleaning supplies, and the schools' policy on WASH, menstrual health, and provision of any menstrual products. The school WASH survey tool will also document if any other adolescent programmes such as sanitary pad delivery are active in the school or known to be active in the school catchment area.

Throughout the follow-up period we will capture students' attendance using Tangerine™ records entered by teachers. We will also collect attendance information from termly random spot checks

and periodic school register checks for triangulation and quality control. School-level data will also include final KJSEA scores once students have completed their exams and received their marks.

9.1.2 Quantitative study tools and definitions

9.1.2.1 Girls survey tool

The girls' survey tool is based on those used in the prior trial, with some adaptations to capture social norms menstrual comfort, and education engagement. The questionnaire will be self-completed using electronic tablets, which has been successfully used among primary, secondary and out-of-school girls. For learning assessments tablet-based self-assessments are adapted from the Early Grade Reading and Math Assessments (EGRA/EGMA) and are in line with Global Proficiency Framework for higher grade levels. Field staff will train girls on use to ensure participants are confident using the tools. Field staff will also have electronic tablets, to document participants seen and those who are unavailable/absent or who have dropped out or migrated.

9.1.2.2 School survey tools and data collection

School WASH surveys will be conducted on electronic tablets. Both the observed measures and the responses to questions by the representative from the school will be inputted into the tablets by the field staff. Absence records will be captured electronically on the Tangerine™ app. KJSEA scores will be collected on paper at the end of study and entered manually into a database.

9.1.2.3 Parents survey

The parents' survey tool will capture household demographics and WASH facilities and socioeconomic indicators. This survey includes questions from the DHS household wealth surveys. It also collects some indicators on parents' perceptions of girls' challenges with menstruation and school, and indicators to assess community social norms on these topics. These questions were informed by the Adolescent Menstrual Experiences and Health Cohort Study being conducted in Bangladesh.¹³⁹ Using these same questions will enable comparability to other global studies of menstrual health and hygiene, parental support, and social norms.

9.2 DATA MANAGEMENT AND STORAGE

9.2.1 Quality Control

Senior research staff will attend study activities to ensure research integrity and due diligence across all consenting, enrolment, and data collection activities. Quality assurance checks will be conducted at random across the trial. A random selection of consent and assent forms filed will be reviewed for completeness and checked against participant details. Any irregularities will be discussed with the reported field staff involved. Any systematic errors will be mitigated through additional training. Survey data will be continuously monitored, reviewed, and cleaned, with feedback loops in place to correct issues such as missing data or errors in skip patterns. Data control checks will be performed on a random selection of participant survey forms. Errors relating to entry will be discussed among researchers noting any questions that may require rewording. Where necessary, updates will be made to electronic survey tools to maintain accuracy. Data cleaning will take place throughout the study, with senior researcher inputs into evaluating reasons for any errors in consistency checks. For qualitative studies, all transcripts will be reviewed by the lead qualitative research scientist and a portion of them will be back translated for quality control evaluations. Fidelity checks will also be conducted on intervention delivery and training sessions to ensure consistency and the highest quality standards across sites.

9.2.2 Database management

Any participant identifying information collected will be kept confidential and stored securely at KEMRI in a locked cupboard if on paper and be password protected on encrypted devices if

electronic. All screening forms and case report forms will be kept in a secured location (locked cabinet if paper, password protected if electronic) with access limited to authorised study staff. Consent and assent forms will be stored separately in a locked cupboard. Personal identifiers will be stored separately from any participant data and used only for the purposes of participant follow-up.

Unique numerical identifiers will be used from the point of collection for survey data and biospecimen samples. These quantitative data will be collated into a common dataset using a statistical package (e.g. SAS, Stata or SPSS). All data will be pseudonymized using unique anonymized participant identifiers. Place names which might result in participant identification will only name the large administrative unit. Both raw and cleaned data at each institution will be stored on a server with password protection allowing authorized users to access the study databases. Data management will be conducted by the research team members. Shared data with any persons involved in data analysis will not include personally identifying information. Reports and publications will not link individual names to data, and study results will be reported as aggregate data only. No identifying information will be included.

Data inputted in the field onto tablets will be pseudonymised at the source of data collection and synced when network is available onto encrypted servers that will be backed up on a continuous basis (e.g. an encrypted secure server at LSTM, Liverpool). This will be backed up on a password-protected study dedicated computer at KEMRI. Paper logs will be digitised and password protected. To minimize the risk of loss or disclosure of qualitative data, audio, and written, data will be uploaded in a password protected designated site that is compliant with UK and Kenyan data protection laws once transcription and checks have been completed. All staff will receive briefings on the principles of confidentiality, data management and protection. Identifying information will be destroyed after 10 years. Stored data will be stripped of names and password protected for use by named research staff only. The de-identified datasets will be kept at KEMRI and at LSTM to be used for approved analysis.

Qualitative data in the form of transcripts will be anonymised with any identifiable parameters removed. Participant pseudonyms or code numbers will be used for purpose of analysis. The deidentified transcripts will be uploaded in separate files for each dataset to a shared drive with password only access. Prior to any publication, the relevant data set will be uploaded to the LSTM repository allowing access to third parties to comply with journal requirements.

9.2.3 Software to be used for data entry

Robust Android-based tablets applicable for field use will be used for self-completed data entry and educational assessments by the participants. Prior tablets successfully used for field work among adolescent girls in this setting were Alcatel One touch Pixi 3.8" LTE 4G (9022x) Tablets. We estimate having ~50 existing tablets available and procuring similar field-appropriate Android based tablets that can run Open Data Kit if needed to allow multiple use in school and home-based follow-ups. Data entry of qualitative data would utilise Olympus DS-2500 Professional Dictation Machines or something similar. These have proven to be highly efficient in recording FGD and IDI and allow for efficient transcription.

9.2.4 Data sharing

De-identified data will be made available upon reasonable request and approval from KEMRI SERU for additional analyses. Application forms and guidelines can be accessed at <https://www.kemri.org/seru-overview> or by contacting seru@kemri.org. Any biospecimen data that is collected on BV and STIs will be made available on a suitable repository (e.g. Figshare) after publication of results. Raw sequence data (FASTQ files) of the vaginal microbiome samples

collected in this study will be deposited in the National Center for Biotechnology Information (NCBI) Sequence Read Archives (SRA).

9.3 DATA ANALYSIS

9.3.1 Quantitative analyses

Primary analyses will follow the intent to treat principle, with secondary analyses on the primary and secondary outcomes conducted on the trial per protocol population. The study design will randomise schools by permuted blocks and then use schools as the unit of allocation and girls as the unit of measurement. Multi-level generalized linear models (GLMMs) will be fitted to allow for the hierarchical structure of the study design. The models will include intervention as a fixed effect and block assignment and school cluster as random effects.

The primary endpoint for this study, which includes a composite of incident pregnancy and school dropout, will use a binomial distribution and log link function.

Denoting the link function of the outcome Y by $\log(P(Y))$, the model is:

$$\log \left(P(Y_{ijk} = 1) \right) = \mu + \tau_k + B_i + S_{ij}$$

Where

Y_{ijk} denotes the observed outcome value for the k -th individual from j -th school allocated to the intervention, in the i -th randomisation block,

μ is the general mean,

τ_k is the fixed effect of the intervention for k -th individual,

B_i is the random effect of the i -th quadruplet $\sim N(0, \sigma_B^2)$,

S_{ij} is the random effect of the j -th cluster within i -th quadruplet $\sim N(0, \sigma_S^2)$

For analysis of binary outcomes (e.g. composite primary endpoint), binomial distribution and log link functions will be used to generate crude and adjusted risk ratios and 95% confidence intervals (CI). In case the log-binomial models do not converge, Poisson distribution with log-link functions will be used. For analysis of continuous outcomes, GLMMs with gaussian distributions with identity link functions will be used. Time-to-event outcomes will be analysed using Kaplan-Meier survival estimates and Cox proportional hazard models. Covariate adjusted analysis will use pre-specified covariates such as school WASH score, school size, age, ever sexually active, and household socioeconomic status. Continuous variables will be summarised by number of observations, means (SD) or medians (IQR); categorical variables will be summarised by the number and percentage of events. Detailed statistical analyses will be described in the statistical analysis plan. Results will be reported following CONSORT and STROBE guidelines, as necessary. Data will be analysed using several statistical packages, including SAS 9.4, and Stata SE 18.0 (StataCorp LP, College Station, TX USA). Study end is classified as occurring with completion of analysis of trial impact on primary outcome.

9.3.2 Sub-analyses

Subgroup analyses will be performed for the primary outcome on the ITT population. Full description of these analyses will be documented in the projects' Statistical Analysis Plan. A priori specified subgroups may include: age, ever sexually active, household socioeconomic status, school WASH score, coerced sex, and transactional sex. Subgroup analyses are presented visually as coefficient plots with 95% confidence intervals (95% CI). We will also explore effect modification by period of study (e.g. pregnancy by study year of participation), by duration of intervention use (e.g. late start of menarche, menarche already reported at baseline), and

proportion of girls receiving all menstrual cup and puberty and hygiene education trainings (e.g. as a percentage of all sessions), and socio-economic status of the household.

9.3.2.1 Subgroup analysis of the primary outcome

Subgroup analyses will be performed for the primary outcome by age ($\leq$ median vs $>$ median), site (sub-county), and sexual debut by baseline (ever had sex/coerced sex vs. no). Other exploratory sub-group analyses may also be considered and will be marked as post-hoc, and will be further detailed in the statistical analysis plan.

9.3.2.2 Per-protocol analysis of the primary outcome

A supportive analysis of the primary outcome and key secondary outcomes will also be performed among the per-protocol populations. Statistical methods will be the same as used above.

9.3.2.3 Sensitivity analysis of the primary outcome

Further sensitivity analyses will be used to assess the robustness of the result for primary outcome. For example, we will explore different definitions of missingness for the primary outcome among girls who out-migrated. Types of missingness for the primary endpoint are (a) composite primary endpoint (incident pregnancy / school dropout), (b) pregnancy only, (c) school drop out only. Statistical methods will be the same as used above for primary outcome.

9.3.2.4 Analysis of key secondary outcomes

Secondary outcomes will be analysed based on both ITT and PP populations. The analysis of binary outcomes (e.g., incident pregnancy and dropout), will be analysed using similar crude and adjusted analysis. The same independent variables as identified in the models for the primary endpoints will be used for adjustment. Results will be expressed identical to the methods described above for the primary outcomes.

10 MONITORING CONSIDERATIONS

10.1 SAFETY OF MENSTRUAL CUPS

10.1.1 Menstrual cup safety consideration

A review on the effectiveness and safety of menstrual cups among 3319 cup users in 43 different studies and adverse event case reports found that adverse events were rare, in a small proportion of users including pain, rashes, vaginal wound, dislodging of IUD, and cup retention.⁶² Globally five cases of toxic shock syndrome were reported in a global marketing of many thousands of users.³⁰ More recently, a trial in western Kenya where ~2000 schoolgirls were provided menstrual cups and longitudinally followed up over 3 years, found nine adverse events, six related to cups (5 girls reported discomfort using the cups, and one cup retention requiring assistance with removal).³⁰ A further ~1000 girls have received cups (former trial 'controls') with follow-up. No cases of menstrual toxic shock syndrome have occurred.

10.1.2 Menstrual toxic shock syndrome

Menstrual toxic shock syndrome (mTSS) is a rare condition with a risk of 1-16 cases per 100,000 women years.¹⁴⁰ While it has a lower mortality than non-menstrual TSS, it may still be life threatening. It requires vaginal colonisation with a toxin-producing strain of *Staphylococcus aureus* in the vagina during menstruation, in the absence of a positive antibody (titer of 1:32).¹⁴¹ TSST-1 is a super antigen, causing an exaggerated release of inflammatory cytokines responsible for the symptoms of clinical disease.¹⁴¹ It is believed that mTSS develops from a site of colonization rather than from infection.^{142,143} In our pilot study in the same area, TSST-1 toxin was

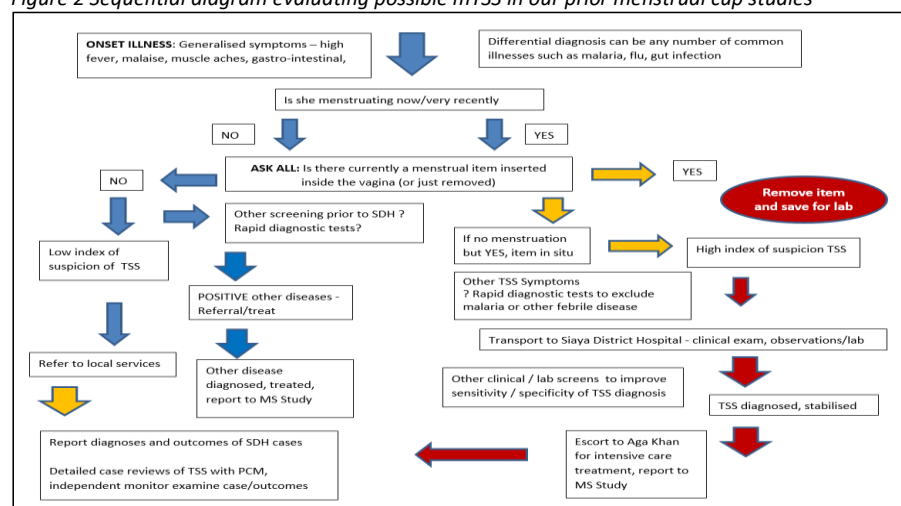
detected in two of ten repeat positive *S aureus* isolates, a prevalence of 20% in girls with persistent *S aureus*,¹⁴⁴ similar to the range detected in other studies.¹⁴⁵⁻¹⁴⁷ The two girls both in the sanitary pad group with no access to menstrual cups, were healthy and did not exhibit any sign and symptoms of mTSS. Other studies have shown the presence of TSST-1 detected among healthy individuals with protective antibody titres (>100).¹⁴⁸ One case of mTSS was recently cited in Canada in a woman with Hashimoto thyroiditis, an autoimmune disease, within 10 days of using a Diva cup.¹⁴⁹ No severe adverse events were detected in our more recent trial among ~3000 girls.³⁰

10.1.3 Monitoring cup safety

Although extremely rare, surveillance of mTSS among girls who are provided cups in the trial is still warranted. Previous approaches to monitoring any potential mTSS will be used (figure 2, below). To facilitate this, an information leaflet describing signs and symptoms of mTSS, where to seek emergency care, and contact information will be distributed to participants and schools. Field staff will liaise with a designated teacher selected by the Head Teacher on any such event reported through schools. HDSS census will be reviewed to cross-check any deaths occurring among participants lost to follow-up. Any verified case of mTSS will be reported to the DSMB, and any that are among participants provided with menstrual cups will also be reported to the cup manufacturer. Deaths of participants in any group will be reported to the DSMB.

Girls will be advised the cups cannot be worn in the presence of an IUD. As no girls in any local studies have reported use of IUD this is anticipated to be very rare, however consent forms and training materials will note this as part of our guidance on use. Other safety considerations around the cup, such as retention, pain, or other concerns will be ascertained through follow-up training, and biannual surveys, with any such event in between surveys reported directly to the KEMRI field lead as an adverse event. We note in our prior pilot study,^{38,150} trial,³⁰ and nested VMB sub-study,³⁹ no cup contamination with any association with health events was identified, and thus repeat study of this, which could cause unnecessary discomfort to girls, will not be conducted unless deemed necessary by the DSMB subsequent to any concerns raised during the trial.

Figure 2 Sequential diagram evaluating possible mTSS in our prior menstrual cup studies^{30,150}



10.2 SAFETY MONITORING AND REPORTING

The principles of ICH GCP require that both investigators and sponsors follow specific procedures when notifying and reporting adverse events or reactions in clinical trials

10.2.1 Definitions

The following definitions apply to this protocol:

10.2.1.1 Adverse event (AE)

Any untoward medical occurrence in a clinical trial subject who has been administered an intervention. The medical occurrence does not necessarily have a causal relationship with this treatment.

10.2.1.2 Adverse reaction (AR)

Any untoward and unintended response to an investigational medicinal product related to any level of administration. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product would qualify as adverse reactions. The expression 'reasonable causal relationship' means to convey, in general, that there is evidence or argument to suggest a causal relationship.

10.2.1.3 Serious adverse event (SAE) or serious adverse reaction (SAR)

Any adverse event or adverse reaction that results in death, is life-threatening*, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity. For this study the rare but reported serious adverse event associated with the intervention is menstrual Toxic Shock Syndrome (mTSS), described above in section 10.1. An independent medical assessor will review causality. Medical judgement will be exercised in deciding whether an adverse event/reaction should be classified as serious in any situation. Important adverse events/reactions that are not immediately life-threatening or do not result in death or hospitalisation, will also be considered serious when they may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definition above.

*Life-threatening in the definition of a serious adverse event or serious adverse reaction refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe.

10.2.1.4 Suspected unexpected serious adverse reaction (SUSAR)

An adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the definition of a Serious Adverse Event/Reaction.

10.2.1.5 Intensity

The intensity of each AE recorded in the case report form should be assigned to a grade (1-5), which will be determined following the definitions set forth in the Common Terminology Criteria for Adverse Events v3.0 (CTCAE) (Cancer Therapy Evaluation Program, 2006). Use of these standardized guidelines will allow for uniform reporting. The grades are defined as follows:

- Grade 1: Mild AE
- Grade 2: Moderate AE
- Grade 3: Severe AE
- Grade 4: Life-threatening or disabling AE
- Grade 5: Death related to AE

10.2.2 Identifying and managing adverse events

Mild adverse events identified at follow-up visits and surveys will be noted in the participant's case report form. Cases such as mTSS will be followed up and reported as a SAE (see below). All

hospitalised participants will undergo record review to identify potential adverse consequences of study participation.

10.2.2.1 Assessment of causality

The investigator is obligated to assess the relationship between the investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event and the investigational product will be considered and assessed. In the first instance, the responsible trained study nurse will assign the causality of the event. The Standard Operating Procedure for Adverse Events, and the product information literature will be taken into account as needed. This will then be reviewed and checked by the DSMB including the independent physician, to come to a final determination. There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always assess causality for every event prior to transmission of the SAE report to KEMRI and LSTM. The investigator may change his/her opinion of causality considering follow-up information, amending the SAE case report form accordingly.

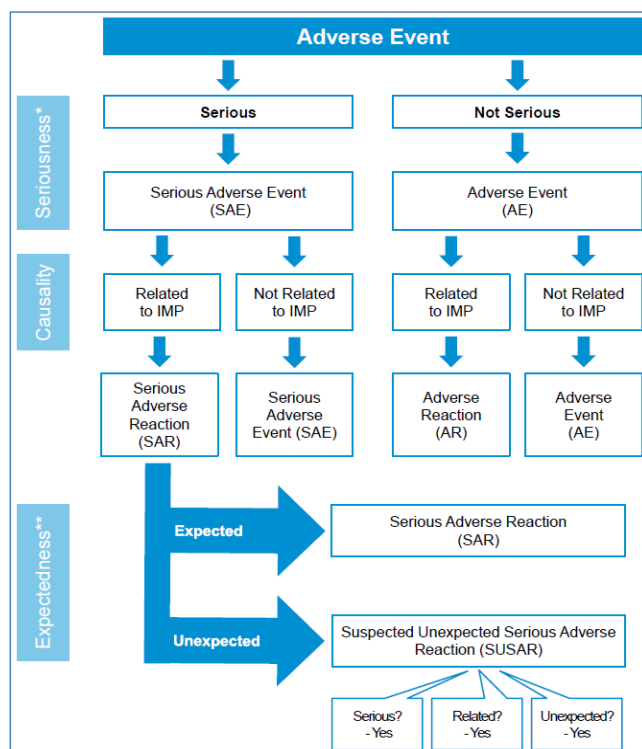
10.2.2.2 Causality attribution.

As described more fully in the IMARA trial Standard Operating Procedures for Adverse Events, causality assessment will define level of attribution into:

- Certain
- Probable/Likely
- Possible
- Unlikely
- Unrelated
- Unassessable/Unclassifiable
- Not applicable (i.e. the intervention was not administered, or participant is in control arm)

The SAE Form (see Section 17.2.2), Section F provides the reporting nurse to document causality with an explanation, based on her assessment, allowing the DSMB members to review and clarify this decision.

Figure 3 Safety reporting assessment flowchart



Footnotes: IMP: Investigational Medicinal Product;

*See definition of SAE in section xx.

**Assessed in line with the current approved Investigator's Brochure (IB)

10.2.3 Reporting serious adverse event procedures

All SAEs will be reported to the in-country principal investigator or an assigned representative within 24 hours of the staff becoming aware of it, using an SAE form, which should be completed, scanned and sent electronically. The SAE form asks for nature of event, date of onset, severity, corrective therapies given, outcome and causality (i.e. unrelated, unlikely, possible, probably, definitely). Reports will be sent to the Sponsor, Kenyan and UK ethical committees (LSTM/REC and SERU), KPPB regulator, and the cup manufacturer. Reporting to LSTM is through a form established via LSTM REDCap.

10.2.3.1 Expedited reporting

SAEs that are unexpected and are at least 'possibly related' to the study interventions require expedited reporting to the DSMB, and to the in-country ethics committee and regulators, within 24 hours of the country principal investigator or assigned representative becoming aware of it (e-mail notification); i.e. this will be a maximum of 48 hours after the event occurred (including the 24 hours required for the field staff to report to the principal investigator/representative). LSTM (as sponsor) will require this information also, within the same timeframe. Additional information will be sent within 14 additional days (full SAE report) if the reaction had not resolved at the time of e-mail notification.

10.2.3.2 Annual reporting

AEs will be reported annually in an aggregated report to the DSMB. AEs that will not be reported include common illnesses that do not result in hospitalisation, including but not limited to

respiratory, gastrointestinal, and skin diseases, unless they are considered at least possibly related to the intervention.

10.2.3.3 Recipients of reports

The study will comply with local regulations and report all necessary information on SAEs to their local Research Ethics Committee and/or Research and Regulatory Offices. In addition to the primary ethics committees, safety data will be reported to the DSMB, the sponsor and to manufacturers of the menstrual cups. A copy of the final study report will be provided to all RECs, the DSMB, the local regulator, and the CouldYou?® manufacturers.

10.2.4 Data Safety and Monitoring Board

10.2.4.1 Overview

An independent Data Safety and Monitoring Board (DSMB) will be set up for this trial. The DSMB will be critical to ensure that the subjects are protected from harm, while also ensuring that study integrity is not compromised. The DSMB will consist of three independent members who are knowledgeable in the subject area, safety monitoring, and clinical trials. They will meet regularly (e.g. twice yearly or more frequently if so required) during the data collection period to provide a review of blinded (and if requested unblinded) data to ensure the safety, rights and wellbeing of trial participants. The trial statistician will be asked to attend the open session of the DSMB meetings.

10.2.4.2 Role of DSMB

The DSMB consist of 3-4 members (including one or more clinicians and one statistician, all with experience in clinical trials).

The DSMB shall assess and review the data regularly (before the annual trial steering committee [TSC] meeting). The assessment could be via email or other electronic medium annually prior to the TSC meeting. In the first year of recruitment more frequent assessment (twice annually) is recommended for this trial. The members should be the only personnel to see the results separated by treatment group during the trial. They are independent and look at the trial from an ethical point of view of the participant safety, future patients and society in general. It is their responsibility to prevent participants being exposed to any excess risks by recommending to the TSC for the trial suspension or termination early if the safety or efficacy results are sufficiently convincing.

The standard format for DSMB meetings will include two sessions per meeting:

Open Session: At the request of the DSMB, the Sponsor may attend this session in which information will be shared on the conduct of the trial e.g. recruitment, compliance, data quality, general operational issues, and other relevant external information concerning the trial. No unmasked data will be discussed during this session. Minutes of the Open Session will be prepared and circulated by Investigator for review, and approval by all participants. Final minutes will be kept in secure storage along with closed session minutes from the same meeting.

Closed Session: This session will be used to discuss the unmasked interim results for safety and efficacy. Only members of the DSMB will be present. All results and discussions will be held in the strict confidence. During this session, the DSMB will review unmasked data and deliberate and determine any recommendations to make to the TSC. After the closed session concludes, the DSMB Chair will communicate promptly the DSMB recommendations to the TSC Chair. Minutes of the closed session will be prepared by the DSMB Chair and circulated in confidence only to DSMB members for review and approval. The minutes will be held in secure storage until the trial has reported. The independent statistician, who produces the reports, is usually invited to attend the DSMB meeting to present the most current data from the trial.

10.2.4.3 Responsibilities DSMB

- To consider the blinded or unblinded interim data from the trial and relevant information from other sources
- To consider any requests for unblinding and release of interim trial data and to recommend to the TSC on the importance of this.
- To report (following each DSMB meeting) to the TSC and to recommend whether the trial should continue, the protocol modified, or the trial be stopped.

A full confidential report should be submitted in writing to the TSC at the end of each DSMB meeting.

10.2.4.4 Proposed Members

- A/Prof Belen Torondel (Chair), London School of Hygiene and Tropical Medicine, UK/Spain; Epidemiologist, WASH and MHM expert; belen.torondel@lshtm.ac.uk
Rationale: lead trials on MHM interventions Gambia, co-I in Uganda; DSMB member of Powwer Trial (menstrual cup use among economically vulnerable women in Kisumu).
- Dr Elke Johanna De Buhr, Monitoring and Evaluation Lead MHM UNICEF, New York, USA; edebuhr@unicef.org
Rationale: expertise in evaluation of interventions and application of research to strengthen policy and implementation.
- Prof Stephen Gwer, MBBS, Lecturer in Obstetrics & Gynecology, Maseno University, Kenya, gwerso@gmail.com
Rationale: knowledgeable on Obstetric and Gynaecological research, experience as a DSMB member on single arm trial on menstrual cups among vulnerable women in Kisumu.

Representatives of LSTM governance team will attend these meetings.

10.2.5 Independent Scientific Advisors – Trial Steering Committee (TSC)

An external project advisory committee comprising representatives from research and public health practice will be formed, meeting once to twice a year, based on need, to provide technical guidance and assess study progress. Most members of this governing body will be independent of the local management group. The TSC will concentrate on the progress of the trial and ensure it is conducted to the standards set out in the Guidelines for Good Clinical Practice with consideration given to participant safety and provision of informed consent.

10.2.5.1 TSC activities

- To evaluate the progress of the trial in relation to timeliness, data quality and other factors that can affect the overall objectives of the trial
- To ensure participant rights and safety are adhered to and that the protocol demands freely given informed consent
- To review relevant information from other sources
- To consider the recommendations of the Data Safety Monitoring Board and subsequently inform the Principal Investigator of the need for changes to the trial protocol
- To ensure that the trial results are disseminated appropriately and consideration be given to the implementation of the results into policy

The PI will present the full protocol to the TSC as an agenda before the start-up of data collection. The TSC members shall review the timeline set out in the protocol for participant recruitment, informed consent documents and plans for data safety monitoring. The TSC shall see that the finalised protocol is sent to the sponsor and funders before the start of participant recruitment and data collection. The TSC in its first meeting shall approve the nominated members of the DSMB and establish the DSMB which shall meet regularly to review and report on the data quality

and the results of interim analyses. In all their deliberations the TSC should consider any deviations from the trial protocol, participant safety and information provided to the participants and consenting procedures.

10.2.5.2 Frequency of Meetings

The TSC shall have an initial startup meeting to discuss the protocol and establish the DSMB. A second meeting shall take place before the initiation of the trial to finalise the protocol and approve the commencement of the trial. Thereafter the TSC will normally meet once a year in the life span of the trial and one meeting at the closure of the trial. Any additional (interim) meetings will be in accordance with TSC recommendations. The Chair and at least 2 of the three independent members together with the PI and trial co-ordinator shall constitute the quorum. If so required, in addition a member of the funder can be invited to attend the meetings.

10.2.5.3 Trial Reports and actions TSC meeting

The TSC shall provide at each meeting a summary report of their findings and recommendations that must be submitted to the funder, and the Sponsor. If the TSC recommends that the trial should be stopped or suspended, the Sponsor will take the necessary action to ensure new recruitment is stopped while the TSC report is evaluated, and the Research Ethics Committee is informed.

10.2.5.4 Proposed Members

- Dr Caroline Kabiru, Lead Sexual, Reproductive, Maternal, Newborn, Child and Adolescent Health Unit, African Population Health Research Centre, Nairobi, Kenya
[<ckabiru@aphrc.org>](mailto:ckabiru@aphrc.org)
Rationale: (TSC Chair) SRH and adolescent health expert, prior member of CCG TSC, prior Chair of Scientific Advisory Group for CCG2 trial follow-up study.
- Prof Marni Sommer, Social Scientist, Global MHM expert, Dept Social Medicine, Mailman Institute, Columbia University, New York, USA; [<ms2778@cumc.columbia.edu>](mailto:ms2778@cumc.columbia.edu)
Rationale: Lead on global MHM studies, prior member of CCG TSC, qualitative expert, Gates Foundation grant holder.
- Karen Austrian, Population Council, Nairobi, Kenya; kaustrian@popcouncil.org
Rationale: Leads Girls Research Innovation and Learning Centre; conducted trial with multiple interventions, and similar school and health outcomes, in other parts of Kenya
- Dr Marije Broekhuijsen, MHM Lead, UNICEF, New York; mbroekhuijsen@unicef.org
Rationale: Global UNICEF lead on MHM, advisory role to UNICEF country offices on menstrual cup programmes, liaison with Kenyan country office.
- Pending: specialist in education measurement and applied research, designing, validating, and deploying learning assessments in LMIC contexts

Representatives of LSTM governance team will attend these meetings.

10.2.6 Trial Management Group (TMG)

10.2.6.1 Purpose

The TMG is responsible for the administrative management and day to day running of the trial.

10.2.6.2 Membership

- Principal investigator
- Selected co-investigators
- Trial coordinator
- Administrators
- Representative from the implementation team
- Others who are involved in the day to day running of the trial.

The TMG will be chaired by one of the Principal Investigators or the Trial Coordinator. The TMG will meet monthly in the first year, with frequency of meetings agreed by the group after this. Core members will meet on a more frequent basis to ensure the smooth operation of trial activities.

10.2.6.3 Responsibilities:

- Study planning
- Review of past month study progress, issues arising requiring resolution for day-to-day management of the trial
- Preparation of materials that will be presented to the Trial Steering Committee and Data Safety and Monitoring Board meetings
- Review maintenance of trial master file
- Budget administration and KEMRI staff / contractual issues
- Ensure correct procedures are maintained for central data management and sample collection, storage and shipping.

10.3 MONITORING AND REPORTING

10.3.1 Trial registration

The trial will be registered a priori, before engagement with participants and any data collected on them. Registration will be through a reputable international site such as ISRCTN (<https://www.isrctn.com>). Additionally, the trial will be registered with the African trial registry system the Pan African Clinical Trial Registry (www.pactr.org), as required by the Kenyan national ethical review board.

10.3.2 Monitoring and auditing

10.3.2.1 Trial Masterfile

A folder shared by the trial manager, PI and LSTM sponsor will be created to store all trial documentation. A typical folder comprises the following updated documents:

- 01 Protocol and SOPs ICF PIL
- 02 Superseded Protocol
- 03 Superseded ICF PIL
- 04 ETHICS APPLICATION and APPROVALS
- 05 REGULATORY APPROVAL
- 06 APPROVALS Sponsor, Trust, Peer review
- 07 AGREEMENTS TA, Sub-awards, MTA
- 08 FINANCE CTA, Awards, Insurance, Costing
- 09 SAFETY REPORT SAE's SUSAR Follow Up
- 10 ANNUAL REPORT Ethics safety and Progress
- 11 AMENDMENTS Ethics, Regulatory, R&D
- 12 RESEARCH TEAM CV's, GCP, Delegation Logs
- 13 ACCREDITATION Lab Values, Device, Irradiation
- 14 DMC and TSC Charter minutes and reports
- 15 CASE REPORT FORMS - BLANK
- 16 PHARMACY Accountability, CofA's, Green Light
- 17 MONITORING REPORTS and Plan, Risk Assessment CAPA
- 18 INVESTIGATOR BROCHURE IB and SmPC
- 19 CORRESPONDENCE
- 21 Pre-Award Funding Application

20

10.3.2.2 Clinical monitoring

Monitoring of this trial will be conducted to ensure compliance with Good Clinical Practice and scientific integrity. The sponsor will manage and retain oversight of the clinical monitoring and auditing. Unless otherwise suggested, three monitoring visits will be conducted, at trial initiation, approximately half-way through the study, and one at close-out. The monitor will determine the adequacy of facilities, review the protocol and data collection procedures and discuss the responsibilities of the investigator and other study site personnel.

During the study, the monitor will have regular site contacts with on-site visits to:

- i. Confirm that the study is being performed according to the protocol, ICH GCP and applicable regulations, that data are being accurately recorded in the CRFs and that investigational product accountability is being performed.
- ii. Conduct source data verification
- iii. Confirm facilities remain acceptable
- iv. Provide information and support to the investigators
- v. Evaluate study progress

Upon completion of the study the monitor will visit the study site to verify that all CRFs are completed and collected, all data queries have been resolved and filed. The monitor will also conduct final accountability, reconciliation and arrangements for the investigational product and verify all study site records are complete.

The PI and relevant staff will be available at monitoring visits and agree to allocate sufficient time to the monitor to discuss any issues and address their resolution.

10.3.2.3 Auditing

The independent clinical monitoring process will be audited by a study staff from the sponsor's research office at LSTM in Liverpool, UK. The auditor will accompany the clinical monitor during at least one of the site visits. After this visit the sponsor will determine if more auditing visits are required.

10.3.3 Interim analysis

No interim quantitative analyses will be conducted. Regular review of the quality of study data will be conducted at each meeting of the DSMB. The sponsor reserves the right to temporarily suspend or prematurely discontinue this study at any time for reasons including, but not limited to, safety or ethical issues or severe non-compliance. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator. When feasible, the sponsor will provide advance notification to the investigator of the impending action prior to it taking effect. The sponsor will promptly inform the IEC/IRB and provide the reason for the suspension or termination.

10.3.4 Training

The Principal Investigators are responsible for the conduct of the study at the study site, including delegation of specified study responsibilities, and training of study staff. The PI/s will maintain a record of all individuals involved in the study (medical, nursing and other staff) and will ensure that all persons assisting with the trial receive the appropriate training about the protocol, the investigational product(s) and their trial-related duties and functions, including formal certified GCP training. During the study regular spot checks will be conducted to assess the performance of study site staff members and re-training provided where necessary.

11 ETHICAL AND MANAGEMENT CONSIDERATIONS

11.1 ETHICAL OVERSIGHT

Full informed consenting for all activities will take place prior to initiation of research activities. All trial participants will be under 18 years and will require parent/guardian consent. Female field research staff will read through the content with participants to ensure they fully understand. Both girls and parents will be informed of the purpose of the study and what participation will involve at a school meeting. If at the time of the meeting the parent/guardian considers all information has been made available and all questions answered, then the individual can enter the consenting process and sign the consent. If they wish to read the participant information sheet and consent on their own before deciding, they will be given 5 working days to decide. A field research assistant would then return to meet them at a location of the parents' choice in approximately 5 working days (considering the persons' own commitments) to complete the consenting process or to accept decision to decline. All groups will be informed they are free to refuse or withdraw should they wish to do so.

At the time of consenting, parents and girls will be invited to consent to be involved with part of the qualitative study, should they wish to do so.

Individual stakeholders who represent particular groups of interest, such as local health facility, church, ministry etc, will be contacted by phone to discuss the project. Those expressing some interest in joining a qualitative activity such as focus group or interview will be provided the participant information sheet and invited to join. Those wishing to sign will do so and a time arranged for the activity. Extra time will be provided for those wishing to consider joining or not, with a meeting held ~5 days later. They will be informed they are free to refuse or withdraw should they wish to do so, with no effect on their work or services.

Consents will be stored in a locked cabinet, accessed only by authorised staff. Girls whose parent/guardian has signed a consent will be eligible to be assented. This will take place in school if the girl is available, prior to any baseline activities. If the girl is absent, she will be visited at home to assent should she so wish. All participants will be reminded they can withdraw at any time, and that this will not affect their schooling or any services. Participation in qualitative

research activities will require additional parental and participant consent, (with exception of any noted as own head of household) and include a request for permission to take audio recording. LSTM will be the *sponsor*, providing governance and oversight. Standard ethical procedures will be upheld, including reviews of protocol, tools, and consents by LSTM and KEMRI's ethical review boards, and annual feedback and renewal to ensure adherence to the highest standards. If any activities require photographing, parent consent and girls' assent will be obtained in advance using the approved KEMRI media consent form (see Appendix 17.3). We will register the study with approval from NACOSTI prior to initiation.

11.1.1.1 Participant confidentiality

Participant data will be collected using standardized case reporting forms on electronic tablets, using Open Data Kit (ODK) software. All personal identifying data will be anonymized at the source with ID numbers. Stored data will be stripped of names and password protected for use by named research staff only. All data storage will be encrypted, and password protected. Qualitative data will be anonymized using IDs without names appended to individuals who have participated. All personal identifiers of any collected data will be destroyed after 10 years.

11.1.1.2 Protocol Amendments and Deviations

Protocol amendments will be submitted to LSTM as Sponsor, LSTM REC, the Kenyan Scientific and Ethical Review Unit (SERU), and to the Kenyan regulator (KPPB) if applicable. Each amendment must be approved by the sponsor and ethical committees before any changes in procedures are enacted. Protocol deviations will be submitted to LSTM as Sponsor and to SERU. Common protocol deviations will be pre-specified in the DSMB report and the SAP and handled accordingly. Examples of this include protocol deviations which may affect the quality of the data or participant safety, such as enrolment of non-eligible participants, provision of intervention to non-allocated participants, late provision of test results and late follow-up of any treatments required. Unexpected protocol violations will be reviewed by the DSMB for appropriate action. Date of violation, report and outcomes will be documented in the DSMB Report.

11.1.1.3 Routine and Study End Reporting

Annual reports of trial progress will be provided to the LSTM Sponsor, LSTM REC and SERU. Reporting to the funder will occur as requested in the funding document. The Sponsor will be notified of study closure, with information on archiving arrangements. Final reports will be provided to the LSTM REC, SERU and the KPPB.

11.1.1.4 Risks

The research team and field staff have conducted similar trials among adolescent girls in the same setting in schools, and thus are highly experienced, reducing concern over some risks to project integrity. Nevertheless, risks may occur as summarised below, with mitigation considerations considered for each.

- Risk 1: Poor menstrual cup uptake.
Mitigation: Our past 12 years of experience of menstrual cup provision to adolescents ensures best practice on training and support needs for this population. Our implementing team will bring 'peer champions' of existing young cup users to support training and maximize uptake. We will provide regular refresher training and conduct community engagement to minimize resistance.
- Risk 2: Loss of outcome data on girls who drop-out of school.
Mitigation: This will be minimized by utilizing our community-based follow-up, through which we have achieved a 93% follow-up of our prior trial participants.
- Risk 3: Political unrest.

Mitigation: We have a flexible and adaptive field team structure to withstand resource and productivity loss during such events.

- Risk 4: Issues on safeguarding (participants, staff, community).
Mitigation: a safeguarding map will be clearly articulated a priori with signposting and safety mechanisms put in place.
- Risk 5: Partner disunity.
Mitigation: Regular team meetings will reduce this risk. Contract and organizational systems will be in place to conduct negotiations should a dispute arise.
- Risk 6: Disease outbreaks.
Mitigation: Mechanisms established during COVID-19 will minimize detrimental project outcomes.
- Risk 7: Stockouts for laboratory supplies and materials: Periodically, due to global disruptions (e.g., COVID-19, war, tariffs), some materials and supplies – especially those that Kenyan intermediaries must import from outside the country – become delayed or unavailable, and this introduces delays in timeline of processing specimens. Some specialty items that are procured in the US (such as microbiome stabilization kits), are also subject to these procurement disruptions.
Mitigation: We keep inventory with at least 3 months lead time, though usually 6 months. In the past 8 years, we have successfully avoided delays of more than a few weeks. Additionally, we mitigate impact by maintaining specimens at -80° C, which preserves their integrity in the case that testing is delayed.

11.1.5 Safeguarding

Participating girls are young adolescents aged ~13.9 years at enrolment. Prior to study commencement we will identify *in situ* safeguarding mechanisms to support their needs in order to ensure their safety. *A priori*, critical safeguarding considerations will be evaluated in a safeguarding map (see Appendix 17, below) and will be introduced at the start of the project. All interventions will be provided by female staff. Girls will be reminded that participation in the study is voluntary and that the intervention items provided are free. Unscheduled spot checks will be conducted by senior staff to for quality control and to monitor girls' safety and ensure all procedures are followed. All events will be reported to LSTM's safeguarding hotline to seek expert support. Safeguarding for staff will also be in accordance with KEMRI policy, e.g. males will not visit girls without a female staff present, and no staff will work after dusk or during any political turmoil. Details of the safeguarding plan, responsibilities, and referral is provided below.

11.1.5.1 Safeguarding Plan

Prior to the start of activities girls are advised that a female staff member with mental health and counselling experience is present to speak privately should they wish. Should any participant feel distressed by the survey or by a study activity or be found to be suffering from depression or other mental health problem, our female counselling staff will provide initial counselling at that time in a private location. Where necessary, the counsellor will then refer participants to the Siaya County Referral Hospital which provides support services for girls who require counselling for mental health. The counsellor will also provide information on other available services that can be accessed in the area, via telephone, or online (e.g. LVCT Adolescent advisory service; one2One <https://one2onenkenya.org/>). These services are listed in the safeguarding mapping document (see 17.1). For all such cases we will liaise with our Siaya Ministry of Health focal point contact to ensure best practice and timely attention. Study counsellors or nurses will follow-up with the participant to assess wellbeing, document uptake of referred services where applicable, and

ensure continuity of care in line with established safeguarding and referral protocols. Safeguarding reports will be completed and submitted to the LSTM designated safeguarding lead and KEMRI focal point.

All qualitative field staff are experienced in collecting qualitative data and have received training in disclosure. Should there be any safeguarding or other concerns field staff will take a break or close down the activity as appropriate, attend to the participant's immediate needs in privacy, (e.g., time-out, refreshment, counselling) and discuss with them the course of action to be taken e.g. as per enacting the safeguarding procedure (e.g., providing the telephone number of the person or service, or transporting them to appropriate services). The field staff will immediately alert the KEMRI lead and qualitative lead to follow up on this course of action as required. They will also be offered opportunity to debrief should they wish.

11.1.5.2 Responsibilities

The LSTM PI takes ultimate responsibility for safeguarding throughout the study and will liaise with the designated LSTM Safeguarding Lead and Kenya PI to ensure procedures are followed.

The Kenya PI takes responsibility for day-to-day safeguarding of all participants, staff and the community, following and updating the Safeguarding Map, and ensuring the safeguarding plan and standard operating procedures are adhered to. The Kenya PI will ensure that safeguarding disclosure are managed appropriately, and safeguarding reports are completed, filed, and shared with the LSTM PI. The Kenya PI will liaise with relevant ministry officials and other service providers available locally to ensure support of participant and staff safeguarding needs. The Kenya PI ensures all staff are trained in safeguarding and can follow correct procedures, as outlined in the Safeguarding SOP. Field staff must report all safeguarding issues to the Kenya PI.

Field staff take responsibility for on-site support of participants' safeguarding needs (see below, core safeguarding components), following the SOP, and ensuring referral to the correct services with support of the Kenya PI.

11.1.5.3 Core Safeguarding Components

- Study staff are trained on girls' safeguarding, including on being culturally sensitive and non-judgmental in their communication, and skilled in safe disclosure techniques
- Study ensures on-site availability of trained counsellors for all interactions with participants and situations where safeguarding is needed, (e.g. one-to-one counselling in a private confidential setting).
- Provide messaging for participants before and after surveys or other activities, alerting some questions could cause upset, and should they need support there is a female staff counsellor present they can talk to confidentially
- Study counsellors have referral pathway to guide action
- Study provides transportation safety to services in event of critical care and ensures appropriate adult notified
- Study ensures data protection for all sensitive information
- All events are reported through the safeguarding tools
- Study regularly meets with Siaya ministry of health to ensure safeguarding map and plan are up to date
- Counsellors will record referrals in a confidential manner, and will follow-up individuals to check their progress and services uptake

Identifying events requiring immediate safeguarding response

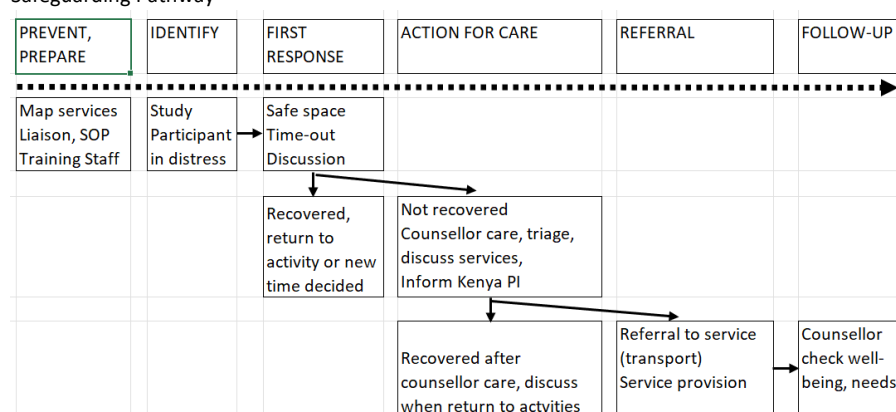
- Establish clear criteria for identifying girls experiencing sexual coercion, violence (physical signs, behavioural changes, disclosure)
- Create private, confidential screening processes with trained female staff who speak local languages
- Provide immediate response for acute risk situations, referral to services

Referral Pathway Structure

- *Multi-tiered approach:* Primary level: Study staff, counsellors, nurses, trial clinician and PIs for initial identification and support
- Secondary level: Provide information and referral to health facilities for post-exposure prophylaxis, pregnancy testing, STI screening
- Tertiary level: Provide information and referral to gender-based violence (GBV) services, psychosocial counselling, (e.g. Siaya District Hospital) legal aid, safe houses

Commented [A4]: should this say "Provide information and referral to" like secondary says?

Safeguarding Pathway



Essential Referral Partners in Western Kenya

- County Gender-Based Violence response units and rescue centers (e.g. Lumumba District Hospital)
- Healthcare facilities with adolescent-friendly services (Marie Stopes, LVCT Health, government facilities) and specialized services (e.g. Nyanza Reproductive Health Services)
- Local NGOs specializing in child protection (e.g., CRADLE, local children's offices)
- Psychosocial support services (e.g. Siaya District Hospital)

11.1.6 Trial insurance

The sponsor (LSTM) will define the type of insurance required such that participants enrolled into the study to ensure harms associated with the study are covered. This will include cover for additional health care, compensation or damages whether awarded voluntarily by the Sponsor, or by claims pursued through the courts. The liability of the manufacturer of the menstrual cup is limited to those claims arising from faulty manufacturing of the commercial product and not to any aspects of the conduct of the study.

11.1.7 Benefits for girls

Girls will receive a menstrual cup, puberty and hygiene education, and training on safe and effective use. The control group will receive a small stationary item at enrolment and a menstrual cup (with training) at the end of the study. Participants are thought likely to benefit from

improving their self-esteem and autonomy by contributing to the study. Participants in our previous studies reported enhanced esteem through study participation.

11.1.8 Reimbursements

The study will provide menstrual cups and materials on their safe and effective use free of charge, and training materials. We will reimburse participants Ksh 100 to 400 Ksh depending on distance to venue if transportation is required, for travel to and from the interview and this will be given at the interview. If greater distance travel is required between towns, we will discuss this with the participant to clarify the travel cost and reimburse them to support this journey. The study will not cover the costs of any non-study related events, including scheduled or unscheduled surgery or trauma related events (e.g. accidents, burns etc.), or diseases, if this is not deemed to be related to the study by the principal investigators or their representative. Focal point teachers will be reimbursed airtime, approximating 1000Ksh each per term for communication with the research team. Class teachers will be reimbursed for submitting weekly absence data through Tangerene™, with a weekly communication fee approximating 100Ksh.

11.1.9 Post-trial care

The study budget is unable to fund post-study care or implementation of the intervention as policy. However, participants in the control arm will receive one menstrual cup and guidance on safe and effective use. Further, the investigators will work with beneficiaries, developing pathways-to-impact, where materials are developed to form a holistic package that can be used for programme scale up should results show efficacy.

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11.1.9.1 11.1.11 Post trial access of the menstrual cups

At the end of the study, all participating girls would be allowed to retain their menstrual cups for continued use and cups will be made available to girls in control (usual practice group) with training on safe use and care at the end of study period. From study initiation through to dissemination, we will actively engage relevant stakeholders to strengthen dialogue around menstrual hygiene interventions, including menstrual cups, and to identify pathways for demand creation, policy integration, and sustained partnerships. Further details of this approach are outlined in Section 11.2.3 under 'Pathway to Impact'

11.2 EXPECTED APPLICATION OF RESULTS

11.2.1 Anticipated reach and impact

This trial will directly serve a population of over 2000 young adolescent schoolgirls. Our main quantifiable impact will be a predicted 33.3% decrease in school dropout and adolescent pregnancy. We are assuming that this reduction will be associated with a halving in child marriage, since our pilot study found an 8-fold increased risk of marriage if a girl became pregnant at school.¹⁵¹ We would anticipate a comparable reduction in gender-based violence, which is 9-fold higher among pregnant compared with non-pregnant teens.⁴⁵ Distal measures on the causal pathway include later age at sexual debut, less transactional sex, and reduced number of sex partners, which we anticipate would significantly decline. We anticipate finding an ~80% reduction in the use of impromptu materials as cup studies found over 80% uptake after familiarisation.^{30,62} Changes in sexual risk behaviours will be measured in students; with other prior studies suggesting a potential 33% reduction in child marriage,¹⁵² a 32% reduction in gender-based violence,¹⁵³ and a doubling in girls' self-efficacy to make safe and informed decisions on their SRH.⁷² In the vaginal microbiome sub-study, we anticipate a 30% relative difference in optimal vaginal microbiome.

11.2.2 Dissemination activities

We will provide interim and final results to trial participants, stakeholders, and schools mid-way through and at the end of the study. Results will be presented in an information leaflet, circulated to the schools, and will be followed up where needed by meetings within the schools for girls, boys, teachers and parents. For stakeholders who participate, we will also provide the leaflets, with time allocated to meetings to discuss the results further where needed.

Our research will also be communicated to the UK and Kenyan public, Kenyan local, county and national ministries, NGO and aid agencies, national and international universities, research groups, international development and aid agencies, donor organizations, and international agencies setting global policy. We will use multiple communication strategies to target information to the correct audience, as appropriate, including the menstrual cup coalition. Much will be through face-to-face interactions at workshops, meetings, local forum presentations, and international conferences. This includes with UNICEF and their partners in Kenya. Communication through technology transfer will be used to disseminate more widely to a broader audience, through online networks, webinars e.g. period posse presentations, online news, blogs, and publication portals.

Communication to academic beneficiaries is integral to our research; disseminating at conferences and in open access publications will showcase findings, facilitate peer review, and stimulate advances in research. We will organise further international scientific symposia as a scientific forum to communicate findings and discuss with world class scientists of different disciplines. Many researchers, programme and policy makers, NGO and aid agencies cannot attend conferences or follow scientific papers. Thus, we are developing communication strategies to reach this broader audience. The group (including UNICEF, World Bank and The Gates Foundation, WHO, universities) ensures communication cascades across networks, to share trial design, methods, activities, stories and outcomes which strengthen research and programme development. The group request for the PI to lead the research consortia offers a wide range of communication opportunities, such as an exchange mechanism with universities, NGOs, and agencies to share research, tools, and experiences, and develop capacity.

We are committed to communication with the lay public through public media, news, and TV opportunities in Kenya and internationally. Findings and girls' stories/case studies will provide powerful images of great interest to the public, will strengthen public empathy, and illustrate the funders support for the most vulnerable and in-need populations. Communication with the Kenyan public through local media, with our Kenyan partners, will be maintained. As well as the LSTM media team, our local research and NGO collaborators' communication teams disseminate stories on our research. We utilise 'calendar days' to exhibit our research activities, such as 'women's day', 'menstrual hygiene day', and 'day of the girl child', galvanising interest through blogging online reports, and newspaper coverage.

11.2.3 Pathway to impact

Despite numerous interventions and growing evidence on the effectiveness of menstrual products, including menstrual cups, there has been limited translation of research findings into sustainable pathways to impact. This trial seeks to address this gap by systematically documenting baseline data on beneficiary needs and preferences, thereby establishing a foundation for understanding the barriers to research uptake. By embedding stakeholder engagement throughout the research process, we aim to capture not only the sexual reproductive health and educational outcomes of the intervention but also the contextual factors that influence adoption. This approach ensures that the evidence generated is directly aligned with the priorities of beneficiaries, communities, and policymakers, thereby strengthening the relevance and applicability of the findings.

As the trial progresses, continuous engagement with stakeholders including beneficiaries, health and education practitioners, community leaders, and policymakers will be prioritized to assess the benefits of these interactions and their influence on intervention design and research uptake. This iterative process will allow us to refine data collection to ensure that the right information is captured to inform both practice and policy. By documenting the “how” and “what” stakeholders require from evidence, we will generate actionable insights that can guide the development of a plan of action for a policy framework. This ensures that menstrual health interventions are not only evidence-based but also responsive to the needs of those they are intended to serve. We will utilize learnings from successful collaboration with the Kenyan government, to strengthen social, educational, and health policies with broader agencies such as UNICEF, to build further support of their activities in schools across sub-Saharan Africa. Over the next 10 years national governments, using Kenya as an exemplar, can offer reusable and environmentally friendly menstrual cups to reduce use of expensive and polluting single-use sanitary pads.

12 STUDY TIMEFRAMES

12.1.1 Timeframes

12.1.1.1 Study start

We anticipate starting the trial preparation activities in September 2025, with field work commencing by the end of the first quarter in 2026, after receipt of ethical and regulatory approvals.

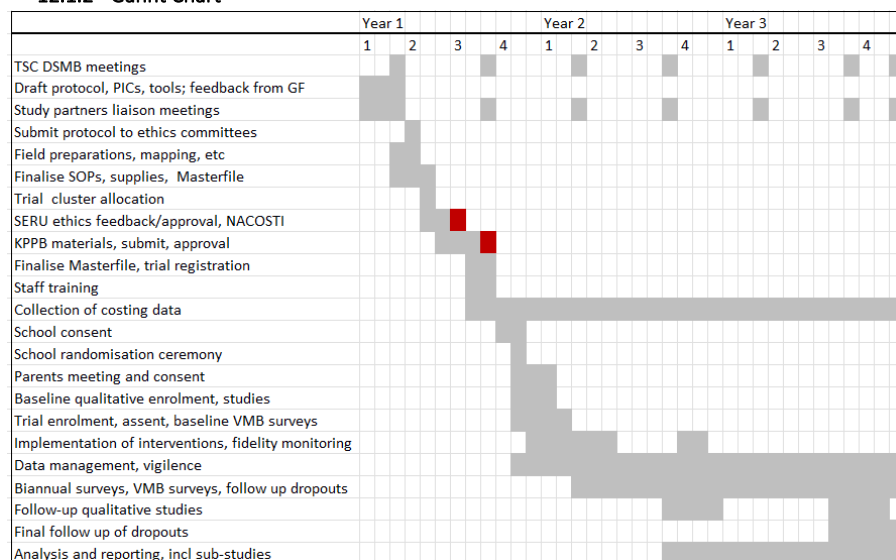
12.1.1.2 Study duration

The trial is designed to be conducted over three years. We expect to complete ethical and regulatory applications and preparations for the field work by late 2025, and initiate participant enrolment early in 2026 and complete the field work late 2028. Should adverse events such as pandemics or political unrest occur requiring cessation of field activities, an extension of the trial will be discussed with funders, research organisations, TSC, DSMB, and ethical boards.

12.1.1.3 End of Study

The end of the field study will occur after a) the final survey in the third year of follow-up, b) all participants who dropped out of school have been followed up to document their information, and c) exam results for final year JS have been uploaded.

12.1.2 Gantt Chart



13 BUDGET

13.1 BUDGET SUMMARY

This grant is funded by the Gates Foundation, USA, and is thus in USD \$. The Kenyan cost for this project is estimated to be USD \$820,171. The summary breakdown of these costs are shown below (this excludes separate costs for Nyanza Reproductive Health laboratory activities).

Budget Item	USD \$*
KEMRI Staff	\$592,695
Participants	\$12,799
Equipment	\$2,844
Consumables	\$8,959
Travel	\$68,973
Staff training	\$1,322
Operational	\$20,194
Ethics & Regulatory	\$5,404
Overheads	\$106,979
Grand Total	\$820,171

*Amounts are rounded

13.2 BUDGET DETAILS

In Kenya, staff salary support of our KEMRI team and implementing partners comprising the Kenya lead, four research field supervisors, a qualitative team, 2 nurses, one admin staff, plus 20

enumerators will cost \$592,695. We request \$120,496 for field activities. This comprises \$68,973 for field travel costs; \$8,959 for consumables (office supplies etc), \$12,799 for participants, \$20,194 for operational needs (comms, internet, venue costs, etc). The funder has supplied the interventions free of charge. Kenyan ethics and regulatory costs are estimated to cost \$5,404. Support for replacing electronic tablets when required will cost \$2,844, and staff training \$1,322. Indirect costs of 15% for overheads (\$106,978) are also requested.

14 BUDGET JUSTIFICATION

This project will be conducted over 3 years, of which 2.5 years will be field based in western Kenya, Siaya County. Costings are based on our experience of prior trials in schoolgirls. The Kenyan budget covers staff costs working in schools, with extra time allowed for follow-up into the community if girls are not in school during consenting or survey times, to minimise any selection bias. The KEMRI staff comprise the lead, 4 field supervisors, 2 nurses, a qualitative team, and 20 enumerators, and part support for administrative support. We allocate a large resource for travel, as although the trial is school-based the follow-up into the community can be expensive. Consumables are allocated to allow all intervention costs, with a separate budget for participant reimbursements and refreshments. A small budget is allocated for training and for replacement of worn electronic tablets (purchased in prior trial). Office costs include internet and airtime, and additionally for printing consents and other materials. A budget is set aside for regulatory and ethics, including SERU and NACOSTI. This is a Gates Foundation grant allowing 15% overhead.

15 INVESTIGATORS AND COLLABORATORS

15.1 CO-INVESTIGATORS

Prof Penelope Phillips-Howard, PhD, Professor of Public Health Epidemiology at the Liverpool School of Tropical Medicine (LSTM), UK, is the overall PI of this trial. She is responsible for trial oversight, DSMB and TSC liaison, LSTM related documentation such as ethical approval, finances, and contracts, and reporting to the UK funders. She will provide oversight on data collection tools, methods, safeguarding, interpretation of findings, and manuscript preparation.

Ms Sandra Oketch, MPH, is a senior research officer at KEMRI, Centre for Global Health Research (CGHR). She is the KEMRI PI of this trial and will be responsible for training of personnel, recruitment of study participants, liaison with field and laboratory staff, and with community leaders. She will be responsible for KEMRI ethics and other regulatory bodies in Kenya and will oversee the Trial Masterfile, ensuring all documentation is complete. She will contribute to data analysis, interpretation, and manuscript preparation.

Dr Garazi Zulaika is a LSTM epidemiologist, who is based at KEMRI in Kisumu Kenya, acting as local PI in collaboration with KEMRI PI Ms Oketch. She provides field epidemiological and technical support for sampling, mapping, and follow-up of participants. She provides KEMRI support on logs, collection of clinic records, electronic tablet questionnaires, data management, and analysis. and will work with Dr Chen on the statistical analysis plan and will conduct analyses with Dr Chen and Prof Wang and will lead drafting the main trial outcome manuscript.

Dr Annemieke van Eijk, MD PhD, is a senior clinical research associate at LSTM. She will provide technical support on clinical components of this trial, including safe and effective use of menstrual cups. She will support the cleaning and preparation of data, and participate in analysis, interpretation, and preparation of manuscripts.

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Dr Linda Mason, PhD, is a senior research associate at LSTM. She is a social scientist and menstrual research expert; she will lead the design and development of qualitative components of the study including tools, data collection analysis and interpretation.

Dr Simon Kariuki, PhD is a leading PI and scientist with over 30 years experience working with KEMRI in research in western Kenya. He will provide advice and support to the KEMRI PI on leadership, management and field research, and guiding on trial procedures and Kenyan regulatory requirements.

Prof Eve Worrall, PhD is a health economist at LSTM. She will lead the health economics component and provide support in design and development of tools, analysis and interpretation of economics data, and manuscript preparation.

Dr. Lauren Cohee, MD, MSc is a reader and epidemiologist at LSTM with a special interest in school health and malaria. She will assist and provide advice on all aspects of the school-based intervention, educational measures, including data collection and analysis.

Prof Duolao Wang is a Professor of Biostatistics at LSTM and is chief trial statistician for this study. He will provide guidance on the statistical analysis plan and lead the statistical analysis, and data interpretation, and support manuscript preparation.

Dr Chao Ten, PhD is a statistician who will take responsibility for developing the statistical analysis plan, in collaboration with the trial team. He is unblinded and will conduct any analysis needed for the TSC and DSMB, and support manuscript preparation.

Dr Fred Otieno, MD PhD is Director of Nyanza Reproductive Health Society, an organization specializing in sexual and reproductive health, HIV, STI, of males and females in western Kenya. His team have collaborated on prior vaginal microbiome and STI detections studies among adolescent girls and young women with Prof Mehta, and LSTM and KEMRI researchers. He will have oversight on sample collection, diagnostics, clinical treatment of STI, data interpretation, and manuscript preparation.

Prof Supriya Mehta, PhD is an infectious disease epidemiologist, who has lead studies on STI and the vaginal microbiome among adolescent girls and young women in collaboration with NRHS, KEMRI and LSTM researchers. She will lead the sub-study on the impact of menstrual cups on STI and the vaginal microbiome, and lead analysis and interpretation of data and manuscript preparation on this sub-study.

Dr Ruth Njoroge, B Pharm, Pharmacist, KEMRI Kisian campus, supports regulatory procedures liaising with the Kenyan Poisons and Pharmacy Board. She will support this project with guidance on regulatory procedures.

15.2 NON-ENGAGED COLLABORATORS

Dr Kennedy Oruenjo, MD is the County Director of Health at the Ministry of Public Health, Siaya. He will provide guidance and liaison with research and clinical services and will advise on local health needs. He will participate in interpretation of findings and dissemination.

Christine Guarden Denning is Director of CouldYou? Cup programme. She will provide oversight of the field team implementing the menstrual cups and cup and life skills education. She will work closely with the LSTM and KEMRI PIs to ensure all intervention logs are completed, and that implementation is timely and reaches high fidelity.

Mr Neville Okwaro has led the menstrual health management portfolio for the WASH Division of the Ministry of Health Nairobi, supporting MHM strategy, policy and guidelines for teachers. He has supported monitoring of MHM indicators to inform national policy, and training of teachers. He will support research implementation on MHM and teachers.

Prof Leah Neubauer is Senior Director of Integrated Education & Accreditation, and Clinical Professor of Health Behavior & Health Equity at the School of Public Health, University of Michigan. She supports engagement and research involving schoolteachers, and will advise on guidance for teachers, including translation of findings into school policy.

Agnes Makanyi of UNICEF's WASH/MHM group, Nairobi has played a key role in MHH in Kenya, working directly with MoH, MoE, and stakeholders across Kenya. She will provide direct liaison for communicating with stakeholders for engagement and dissemination and will support for development of pathways to impact.

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17 APPENDICES

17.1 SAFEGUARDING MAP

LSTM Safeguarding Risk Mapping Tool					
LSTM Dept	Clinical Sciences	Programme Title	Impact of <u>M</u> enstrual Cups on <u>A</u> dolescent Girls <u>R</u> eproductive Hea <u>l</u> th and Education (IMARA)		
Summary	This study is a single site 2-arm, school-cluster randomised controlled trial. The study is being conducted in Siaya County, western Kenya, among junior school girls, who attend eligible schools. The objective of the study is to determine the impact of menstrual cups to improve girls schooling, social equity, and sexual and reproductive health. Primary outcome measured is pregnancy and school dropout. Data gathered to measure impact through biannual surveys, and qualitative studies. A smaller sub-study will focus on effect of menstrual cups on the vaginal microbiome.				
Start Date	10/9/2025	End date	31/08/28	Country	Kenya
Principal Investigator	Prof Penelope Phillips-Howard	Programme Manager	Sandra Oketch	Donor	Gates Foundation
Has LSTM signed up to a donor safeguarding policy or code of conduct under this grant?	Yes		Does the programme use volunteers? (if yes, detail role)		
List all collaborating partners organisations working on this programme.	Liverpool School of Tropical Medicine, Liverpool, UK and LSTM-Kenya; Kenya Medical Research Institute Kisumu, Kenya, Ministries of Health and Education, Siaya County, Kenya; Ministries of Health and Education, Siaya County, Kenya; CouldYou? Menstrual cup programme; UNICEF Kenya, and USA.				
Safeguarding Risk Identification		How will the risks be mitigated/managed?			
1. Potential safeguarding/protection risks for beneficiaries that may occur within/as a result of undertaking the research?		(i) Follow up will be done at regular intervals in school set up where study staff will interact with adolescents. Therefore there maybe a risk of grooming that might lead to sexual abuse. (ii) Adverse event that may occur due to the interventions issued e.g. challenges from use of cups e.g. they might be at risk of getting TSS, risk with injury due to improper use of Cup e.g. wrong removal techniques. (iii) Bullying of study participants by students who are not participating in the study. (iv) some girls may not report events real time, so despite monitoring through nurses,		(i) Project staff will be briefed on the importance of safeguarding concerns and on behaviours that should be avoided when engaging with participants and local community. Partnership with local chiefs, community, ministry of health to facilitate support if needed for safeguarding procedure. (ii) Best practice training will be provided by a menstrual cup programme that has experienced trainers, with training every two weeks, who will be available to help girls between these sessions, up to six months, to help girls use them correctly. Adverse event	

	<p>school focal point teachers, health facilities, etc adverse events may be missed</p> <p>v) questioning of girls in surveys or during qualitative studies may upset some girls due to their personal history</p>	<p>monitoring has been put in place and field team will be trained on how to deal with them once they became aware of an SAE event. (iii) Ensure school wide students are aware of the project and the importance for girls. Encourage the participants to report any form of bullying related to the study to the lead teacher or any other contacts for the study staff that was provided to them. We will use trial surveys to include extra questions to pick up any event retrospectively, to facilitate follow up of any missed events.</p> <p>v) Girls will be advised by staff that they could possibly be upset by some questions; trained staff counsellors will be present should girls want to discuss this, and safeguarding procedure enacted to signpost girls for counselling services if needed. For qualitative data collection activities, all qualitative field staff are experienced in collecting qualitative data and have received training in disclosure. Should there be any safeguarding concern staff will take a break or close down the activity as needed, attend to the participant's immediate needs in privacy (e.g time out, refreshment, counselling) and discuss with them the course of action to be taken as per enacting the safeguarding procedure, (e.g., providing the telephone number of the person or service, or transporting them to the appropriate services). Staff will immediately alert the KEMRI PI to follow up on safeguarding procedures.</p>
<p>2. Potential safeguarding risks for staff, students, volunteers, contractors, consultants or visitors?</p>	<p>(i) risk of insecurity due to reporting to work early and leaving late for staff. (ii) female staff placed at risk in some locations. (iii) Male staff may be at risk of admiration from the adolescent girls and might be wrongly accused of indecent behaviour. (iv) Violence during political unrest. (v) The staff/visitors may be put in a compromising situation by school leadership e.g. a teacher or principal expressing need for favours, risk of sexual harassment causing tension at the time of work.</p>	<p>(i) Staff will not work in field after dark. (ii) Female staff will not go to places where any risk is deemed possible, and wherever needed will work in pairs. (iii) Male staff will not work alone, will always have a female staff member for field work. Hotlines will be shared with staff so that they are free to report any abuse that happens while they are at work. (iv) no work during political unrest. (v) Kenyan PI will liaise directly with school leaders, and any compromising/serious event that cannot be resolved with school will be escalated to local education advisor.</p>

3. Safeguarding issues that could arise unrelated to the research activity?	(i) background rate of gender-based violence may mean that events arise unrelated to project, where girls are identified to be abused. (ii) similarly, Kenyan staff may also be at risk from similar circumstances. (iii) political unrest in the country may place staff, visitors, participants at risk. (iv) LSTM staff will spend time in Kenya during the course of this project, creating possible safeguarding risks to themselves and locals outside of working hours.	(i) Linkage with community and referral services to support GBV. (ii) KEMRI health support system in situ, further HR personnel support available. (iii) guidance for staff and visiting scientists comes into play when political unrest, with messaging advisory system. (iv) LSTM Staff guidance and training to recognise safeguarding risks, understand behaviours that place them at risk, and be aware of the channels through which support may be obtained and safeguarding issues reported.
Additional Information		
What international and national legislation and/or guidance documents are available in relation to Safeguarding/Protection of children +/or vulnerable adults in the country you are working in? Please detail	What services are available locally as part of victim response for child / vulnerable adult protection? Please detail (e.g child protection, GBV services, HIV services)	
Guidelines for Conducting Adolescents Sexual and Reproductive Health Research in Kenya. National AIDS and STI Control Programme (NASCO) & Kenya Medical Research Institute (KEMRI). 2015	Siaya Country Referral Hospital and Lumumba Sub-County Hospital for services for GBV: i) medical evaluation, care and treatment; ii) laboratory services; iii) evidence collection; iv) trauma counseling; v) HIV testing and counseling; vi) post exposure prophylaxis; vii) emergency contraceptive service; viii) temporal safe space for survivors; ix) basic legal advice; x) police support services advice; xi) referral and linkages; xiii) community outreach/awareness. Nyanza Reproductive Health Services also provide specialized services for STI treatment and care.	
Information Booklet: Preventing and Responding to Violence Against Children Design and Layout: Studio inferno Company Ltd. © The Government of Kenya and United Nations Children's Fund (UNICEF) August 2017	CDC/KEMRI health services at KEMRI, Centre for Research, and linkage with Kisumu District and Provincial Hospitals	
Chapter 4 article 53 of the Constitution of Kenya, bill of rights	One Stop' Gender Based Violence Recovery Centre Kisumu, Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) provides comprehensive care services to the victims.	
National Plan of Action Against Sexual Exploitation of Children (2013-2017)	LVCT Health - Nairobi and Kisumu - offers HIV testing services and also care and treatment services https://lvcthealth.org/ ; online service for adolescents https://one2onekenya.org/	
National Counsel for Children's services http://www.childrenscouncil.go.ke/child-help-line.html?showall=1&limitstart=	Agha Khan Hospital Kisumu treatment and care services	
Action Plan. (What additional action (if any) do you now need to take to mitigate the risks identified)?		

IMARA Trial Protocol v0.9– 9 Feb 2026

Review who visits homes for follow-up, for safety of staff, and also ensure protection of any vulnerable persons in household
Add extra questions in general trial survey to pick up retrospectively any events that may have been missed
Update points of contact in study site since last schoolgirls' trial
Review travel safe guidelines for LSTM, with considerations for times of political unrest, and any special concerns for minorities, females travelling alone, special circumstances etc

17.2 ADVERSE EVENT FORMS

17.2.1 Adverse Event Triage Form

Project title	Impact of Menstrual Cups on Adolescent Girls Reproductive Health and Education			
Participant ID				
	AE 1	AE 2	AE 3	AE 4
Description				
Start date (DD-MMM-YYYY)				
Stop Date (DD-MMM-YYYY)				
Or ongoing? Y/N				
Severity (see key) ¹				
Action taken (list all that apply) (see key) ²				
Outcome (see key) ³				
Is event serious? Y/N				
Was the girl having her monthly period at time of event? Y/N				
Did the girl have an item inserted in her vagina at time of event? Y/N				
If not at time of event, did she have an item inside her vagina on a recent day prior to event (just removed)? Y/N				
Name of item (see key) ⁴				
Causality to intervention (see key) ⁵ If suspected to be related to something other than cup or cash, provide further details on continuation sheet	Cup ☐ Other ☐	Cup ☐ Other ☐	Cup ☐ Other ☐	Cup ☐ Other ☐
Continuation sheet used?	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Any other medication taken up to 2 weeks prior to the event? If yes, complete concomitant medication form	Yes ☐ NO ☐	Yes ☐ No ☐	Yes ☐ No ☐	Yes ☐ No ☐
Nurse completing form				
Date of report (DD-MMM-YYYY)	06 MAR 2020			

Page no (per participant) ___ of ___

Adverse Event Report Form

 Sponsor:

Participant ID		Intervention:	
Name of Area			AE No

¹ Severity: 1 = Mild, 2 = Moderate, 3 = Severe, 4 = Life threatening, 5 = Fatal, 6 = Unable to assess² Action taken: 1 = None, 2 = Medication given, specify; 3 = Referred to hospital OPD/health facility, 4 = Admitted to hospital, 5 = Intervention withdrawn, 6 = Other; specify³ Outcome: 1 = Resolved, 2 = Resolving/partly resolved, 3 = Resolved with sequelae, 4 = Not resolved, 5 = Fatal, 6 = Unknown⁴ Items: 1 = Rags, 2 = Grass, 3 = Newspaper, 4 = Foam/bedding, 5 = Sanitary pads, 6 = Traditional medicine, 7 = Cup, 8 = Tissue paper, 9 = Cotton wool, 10 = Other; specify⁵ Causality: 1 = Certain, 2 = Probable/likely, 3 = Possible, 4 = Unlikely, 5 = Not related, 6 = Unassessable, 7 = Not applicable (i.e. participant not receiving intervention)

CONTINUATION SHEET - *If necessary, provide further details of events here.*

PLEASE SPECIFY WHICH EVENT THE DETAILS RELATE TO (PROVIDE AE NUMBER AND DESCRIPTION)

AE number: 1 Description:

Comments:

17.2.2 Serious Adverse Event Form

Project title	Impact of <u>M</u> enstrual Cups on <u>A</u> dolescent Girls <u>R</u> eproductive He <u>al</u> th and Education														
Type of report	☐ Expedited ☐ Full														
SECTION A: PATIENT DETAILS															
Age (years)	<input type="text"/>	Or date of birth (DD-MMM-YYYY)	<input type="text"/>												
Relevant medical history including pre-existing medical conditions	<input type="text"/>														
Referrer relationship to participant i.e mother; clinic nurse; teacher; etc	<input type="text"/>	Contact details of referrer (phone number, address etc)	<input type="text"/>												
SECTION B: SERIOUS ADVERSE EVENT AND INVESTIGATIONS															
Main diagnosis	<input type="text"/>														
Description of event (include details of all signs, symptoms and events that have occurred at the time of the main event)	<p><i>In cases of violence, please describe the nature of the violence and the clinical outcome for the patient i.e. any bruises, broken bones, cuts etc. Indicate on the diagram in appendix A the type and location of injuries on the body provided.</i></p> <p>Use continuation sheet if necessary. Tick if continuation sheet used ☐ How many pages? <input type="text"/></p>														
Date of onset/occurrence (DD-MMM-YYYY)	<input type="text"/>	Date resolved (DD-MMM-YYYY)	<input type="text"/>												
		Or tick if ongoing	☐												
Record details of investigations/relevant tests/laboratory data (including dates)	<table border="1"> <thead> <tr> <th>Investigation/test</th> <th>Date</th> <th>Result</th> </tr> </thead> <tbody> <tr> <td>ONCOLOGY</td> <td>10 SEP 2020</td> <td>CANCER OF THE BONE</td> </tr> <tr> <td></td> <td></td> <td></td> </tr> <tr> <td></td> <td></td> <td></td> </tr> </tbody> </table>			Investigation/test	Date	Result	ONCOLOGY	10 SEP 2020	CANCER OF THE BONE						
Investigation/test	Date	Result													
ONCOLOGY	10 SEP 2020	CANCER OF THE BONE													

SECTION C: EVENT ASSESSMENT <i>When completing below please refer to definition guide at the end of this document</i>				
Action taken	☐ None ☐ Medication given; specify _____ ☐ Referred to hospital OPD/health facility; name of hospital/health facility _____ ☐ Intervention (cash and/or cup) withdrawn ☐ Other; Specify _____			
Outcome	☐ Resolved ☐ Resolving/partly resolved ☐ Resolved with sequelae ☐ Not resolved ☐ Fatal ☐ Unknown			
Maximum severity	☐ Mild ☐ Moderate ☐ Severe ☐ Life threatening ☐ Fatal ☐ Unable to assess			
Seriousness	☐ Death ☐ Life threatening ☐ Hospitalisation ☐ Prolongation of existing hospitalisation ☐ Persistent or significant disability ☐ Other	If death: Date of death (DD-MMM-YYYY) If hospitalisation: Date admitted (DD-MMM-YYYY) ____ - ____ - ____ Date discharged (DD-MMM-YYYY) ____ - ____ - ____		

	If other, specify	
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SECTION D: INTERVENTION

Cup

If the event is related to menstrual or vaginal health, complete the following questions:

Was the participant having her monthly period at time of event?

☐ Yes

☐ No

Did the participant have an item inserted in her vagina at time of event?

☐ Yes

☐ No

If not at time of event, did she have an item inside her vagina on a recent day prior to the event (just removed)?

☐ Yes

☐ No

Name of item which was inserted in vagina:

- ☐ Rags
- ☐ Grass
- ☐ Newspaper
- ☐ Foam/bedding
- ☐ Sanitary pads
- ☐ Traditional medicine
- ☐ Cup
- ☐ Tissue paper
- ☐ Cotton wool
- ☐ Other; Specify _____

SECTION E: OTHER MEDICINE(S)/SUBSTANCE(S)

Were any other medicines taken up to two weeks prior to the onset of SAE? ☐ Yes ☐ No

If yes, complete a concomitant drugs form and send with this SAE form

Were any traditional medicines taken up to two weeks prior to the onset of SAE? ☐ Yes ☐ No

If yes, give details

Were any other substances (e.g. alcohol, recreational drugs) taken in the two weeks prior to the onset of SAE? ☐ Yes ☐ No

If yes, give details

Is the event thought to be at least possibly related to the study or any of the interventions?

Yes ☐ No ☐

SECTION F: CAUSALITY ASSESSMENT

Using the key below, insert number in the box to indicate causality for each intervention relevant to the patient. If the patient has not received the specified intervention, enter “7”.
If you suspect the event is related to something **other** than the intervention(s), enter the causality in the ‘other’ box and provide further details on the continuation sheet.

Causality	1. Certain 2. Probable/likely 3. Possible 4. Unlikely 5. Unrelated 6. Unassessable 7. Not applicable (i.e. participant not receiving the intervention)	Cup <input type="text"/>
		Control <input type="text"/>
		Other <input type="text"/>

SECTION F: CAUSALITY ASSESSMENT (continued)

If the answer to the above is 1, 2 or 3 for any intervention, complete the following assessments **FOR THE RELEVANT INTERVENTION ONLY**

Action taken due to adverse event	1. Intervention/other withdrawn 2. Intervention/other withheld 3. None 4. Not applicable 5. Unknown	Cup <input type="text"/>
		Control <input type="text"/>
		Other <input type="text"/>
De-challenge	1. Improved when intervention/other stopped 2. No improvement when intervention/other stopped 3. Not applicable (<u>no</u> de-challenge undertaken) 4. Unknown	Cup <input type="text"/>
		Control <input type="text"/>
		Other <input type="text"/>

History with suspected intervention/other	1. Not used before 2. Used before, this event did not occur 3. Used before, this event did occur 4. Unknown	Cup ☐	
		Control ☐	
		Other ☐	

SECTION G: REPORTER DETAILS

Reporter Name		Reporter Position	
Reporter Signature			
Expedited Report Date (DD-MMM-YYYY)	__ - __ - __	Full Report Date (DD-MMM-YYYY)	

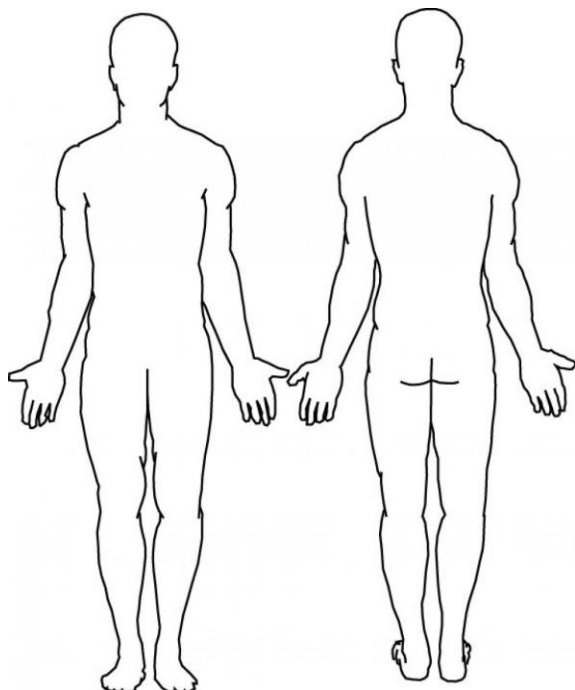
SECTION H: PRINCIPAL INVESTIGATOR RECEIPT

PI Name		PI Signature	
Expedited Report Date (DD-MMM-YYYY)	__ - __ - __	Full Report Date (DD-MMM-YYYY)	

Appendix A. Body diagram – if appropriate, please indicate location of illness, infection, or injuries

APPENDIX A. BODY DIAGRAM

Please indicate with an arrow and words the location, and the type of illness, infection, or injuries on the diagram below (includes severe pain or bleeding)



17.2.3 Concomitant medication form

If completing a SAE or AE form, use this form to record any medication that the girl had taken in the two weeks leading up to the event.

Drug name (Generic)	Start Date DD-MMM- YYYY	Continui ng? YES / NO	Stop Date DD- MMM- YYYY	Dose and units	Frequen cy	Rout e	Possibly related to the event? Yes/No	Reason for medicatio n
<i>Example: Amoxicillin</i>	<i>18-May- 2016</i>	<i>Yes</i>		<i>500m g</i>	<i>3 times a day</i>	<i>Oral</i>	<i>No</i>	<i>Chest infection</i>

17.3 PARTICIPANT INFORMATION SHEETS WITH INFORMED CONSENT AND ASSENT STATEMENTS

17.4 MENSTRUAL CUP GUIDE QUESTIONS AND ANSWERS

17.4.1 Menstrual cup Frequently Asked Questions (English)

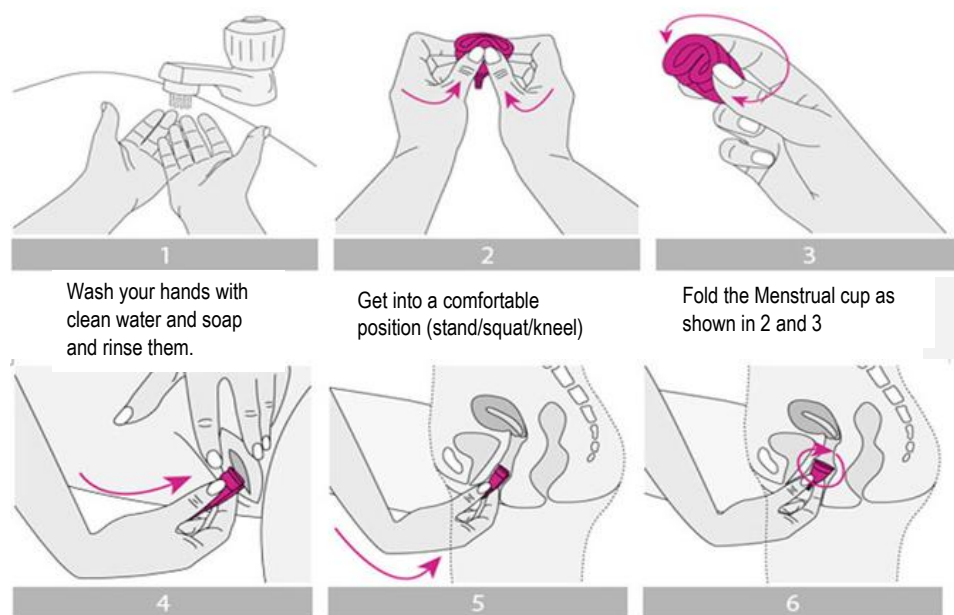
What is a Menstrual cup?

Your Menstrual Cup is a product used by girls and women in many countries to help manage their monthly period. It is a small bell-shaped container made of soft material which collects menstrual blood when put inside the vagina (birth canal). It is a product which can be reused and lasts a long time. If looked after carefully your cup can last for up to 10 years.

How do I know what size of the Menstrual cup to use?

The Menstrual Cup is available in large and small size. For the study we are giving girls the smaller Menstrual Cup. If you find the small size leaks you may need a larger size. Let the study staff or focal point teacher know and she will check if you are using correctly or if you need a larger size.

How is the Menstrual cup inserted?



Once folded, hold the cup with your fingers, guide it into the vagina up towards your back.

What is the long tail on the Menstrual Cup?

Menstrual Cups are made with a long tail which needs to be trimmed so the tail does not poke out of your vagina. You can cut the tail using scissors or a knife to make it fit. Cut a little bit and see if this makes it more comfortable to wear. If it is still uncomfortable, cut the tail a little bit more.

How is the Menstrual Cup removed?

Wash your hands with soap and clean water and squat. Gently feel around the tail of the Menstrual Cup until you reach the base. To remove the cup, squeeze the base of the cup or insert a finger around the cup. When the base of the cup is almost out, use your finger to push the cup on one side to remove half of the rim then the other half will come out more easily. This ensures the cup slides out smoothly while remaining upright to avoid spilling the content.

How do I get the correct position for removing the Menstrual Cup?

Squatting makes the vaginal canal shorter so is the best position to help remove the cup.

What if I cannot reach the Menstrual Cup?

You can use your own vaginal muscles to help lower the Menstrual Cup. Make small downward pushes with your vaginal muscles until the Menstrual Cups shifts and you can reach it.

What happens when I cannot get the Menstrual Cup out?

If you cannot remove your Menstrual Cup do not worry. Your vaginal muscles are sensitive to stress and will tighten around the cup making it difficult to remove. Once you relax and take your time your vaginal muscles will relax making it easier to remove.

I am finding it too hard to use, what do I do?

Menstrual Cups take a little time to get used to. Most girls we talk to say it took them a few periods before they felt fully comfortable putting it in, using it, and taking it out. Talk to your friends who are using it to get some tips on how to use it. Our staff are also available to talk to by phone if you have a problem. Most importantly, don't get discouraged and try again.

How is the Menstrual Cup cleaned during a period?

It is important to always wash your hands with soap and water before and after handling your Menstrual Cup. There is no need to wash your Menstrual Cup each time you empty it during your periods, as the vagina has its own self-cleansing system. If the cup has blood on it only rinse it if you have clean water. Do not use soap to clean your Menstrual Cup because it will cause irritation inside your vagina.

How is the Menstrual cup cleaned after a period?

After your period has stopped you need to clean the Menstrual Cup with boiling water. Once the water is boiling, steep the menstrual cup in the water for 5-7 minutes. It is best if you can use a tin cup or can for the boiled water and steeping.

How do I store my Menstrual Cup?

Air dry your Menstrual Cup and once it is dry, keep your in the cotton bag after use. Store it in a secret place to stop other people taking it. Make sure the place is safe from rats or insects.

Is using the Menstrual Cup messy?

Using the cup can be a little messy while you are getting used to it. When you remove the Menstrual Cup, most of the blood is collected inside; you can avoid contact with the blood collected inside if it isn't too full. If the cup stays in for long or you have heavy bleeding, it can get messy during removal as blood can spill on your hands. Before you go in the latrine check you have water to wash your hands before and after emptying the cup. When you are removing and inserting your cup, be sure to stand to the side of the latrine so that if you drop it, it doesn't fall in.

If my Menstrual cup leaks, what can I do?

When used correctly, the Menstrual Cup should not leak. This may happen if the Menstrual Cup is not low enough in your vagina. Check that the cup holds onto the walls of the vagina by;

- Running your finger around the side of the Menstrual cup to ensure it is fully open

- Pinching the base of the cup (not the tail) and move the Menstrual Cup around.
- Clenching your Menstrual Cup with your vaginal muscles.
- If you have the small cup size, and it moves around or leaks, then you may need the larger cup.

I have really heavy periods, can the Menstrual Cup handle this?

Yes. The Menstrual Cup works well for heavy periods as it can collect up to three times more menstrual blood than other menstrual products. This means that you will need to empty the Menstrual Cup less often than changing pads. During the first months of use, empty the cup every three to four hours depending on the amount of your flow. Some leaking can occur if you have a heavy period so you might need to empty it more often. After a while you will get to know your body and how often you need to empty the cup.

Is it ok to use a Menstrual Cup with a light flow?

Yes. The Menstrual Cup is perfect for light flow, as it collects without drying the vaginal walls. This means that removal will be less frequent than during the heavy days of your period.

Is it safe to wear the Menstrual Cup at night?

Yes. The Menstrual cup is safe to wear at night. Make sure it is empty before going to bed and then empty it again as soon as you wake.

What do I do if I drop my Menstrual Cup?

If the Menstrual Cup falls on a clean surface it can be rinsed with clean water and reinserted. If it falls onto a dirty floor or latrine it must not be used again until it has been boiled to kill any bacteria. Girls will be asked to bring their Menstrual Cup to school occasionally so that they can be checked.

Does the Menstrual Cup affect my virginity?

Girls are virgins until they have sex. When the Menstrual Cup goes inside the birth canal it can break the skin called the hymen. The hymen is a thin membrane at the entrance of the vagina. When a girl reaches puberty the hymen becomes more elastic. It is safe to use a Menstrual Cup for girls whose hymen is still intact as the hymen has spaces that allow menstrual blood to flow through. The hymen can be broken in childhood, from a fall, during sport or activities, and with sexual intercourse. A broken hymen does not mean a girl is no longer a virgin; a girl stops being a virgin when she has sex.

It is ok to use the Menstrual Cup while doing sports like swimming?

You can use the Menstrual Cup when you do all sports, including swimming.

Can the Menstrual Cup cause me to get vaginal infections?

No, the Menstrual Cup will not give you vaginal infections. The vagina normally is a little bit acidic. This acidity is created by good bacteria that live there naturally. They help keep everything healthy by stopping harmful germs from growing. Menstrual cups do not disturb the healthy bacteria or acidic nature of the vagina. It is important to keep your menstrual cup clean. If you use soap to clean your menstrual cup, traces of soap on the cup can upset the acidic balance of the vagina. Therefore, if you DO use soap on your cup, always rinse it with plenty of clean water to remove any traces of soap.

What is toxic shock syndrome (TSS)? When sanitary tampons have been left too long inside the vagina, a very small number of females became ill with a disease called toxic shock syndrome. The illness causes high fever, flu-like symptoms, dizziness, and can rapidly lead to severe illness, coma, and sometimes death. Toxic shock has not been reported with Menstrual Cups alone but has occurred with an intra-uterine device (IUD) for birth control, so IUD use is not advised when using

the cup. If you experience these symptoms during your periods you should remove your Menstrual Cup immediately, go to your health clinic for a check-up, and contact our study nurse by phone. If you have suffered from TSS previously, it is recommended not to use any internal form of sanitary protection, including the Menstrual Cup.

How long can I leave the Menstrual Cup in?

It is safe to leave the Menstrual Cup in for 8 hours before emptying. You can also leave in overnight without emptying. You may need to empty more often if you have a heavy flow. Do not leave in for more than 12 hours. Always remember to remove the Menstrual Cup when your period stops.

What should you not do with the Menstrual Cup? You should never share your Menstrual Cup with another person or you may get an infection. You should not leave your Menstrual Cup inside your vagina when your monthly period stops. You should not put the Menstrual Cup back inside if it gets dirty from falling in a latrine or dirty floor. When you clean the Menstrual Cup, you can use water but do not use a soap as it will cause skin irritation.

Do you need to remove the Menstrual Cup before doing other things? The Menstrual Cup stays inside when you urinate or defecate, as urine and faeces come from different openings. The Menstrual Cup stays inside when you play sports or swim. If a girl wants to have sex she must remove the Menstrual Cup first. The cup will not protect against pregnancy or sexually transmitted infection.

What else should you watch out for? An allergy to the material that is used to make Menstrual Cups (silicone) is very rare. But if a girl experiences pain, burning, irritation, inflammation in the genital area or discomfort during urination, she must remove the Menstrual Cup and contact the school study nurse immediately.

Can I change my Menstrual Cup in school?

Yes. You can empty your Menstrual Cup at school in the latrine reserved for girls. Wash your hands with the soap before you remove your Menstrual Cup. Empty it carefully in the latrine, taking care not to drop it on the floor, then immediately reinsert. It is safe to reinsert without washing and reduces the risk of dropping or making dirty at school. Then wash your hands again after reinserting.

Remember!

- It takes a little while to get used to using your Menstrual Cup so don't give up too soon! You may have to try several times until you are comfortable with it.
- Always wash your hands before and after emptying the Menstrual Cup
- Stop using the Menstrual cup and contact your study nurse if you experience general pain, burning, irritation or inflammation in the genital area or discomfort during urination
- Never share your Menstrual Cup with another person
- Do not use your menstrual cup if it becomes damaged; contact the study nurse for instruction and replacement.
- The Menstrual cup does not protect you against pregnancy
- The Menstrual cup does not protect you from sexually transmitted infections

17.4.2 Menstrual cup Frequently Asked Questions (DhoLuo)

Penjo ma ithoro penjo e wi okombe mar dwe

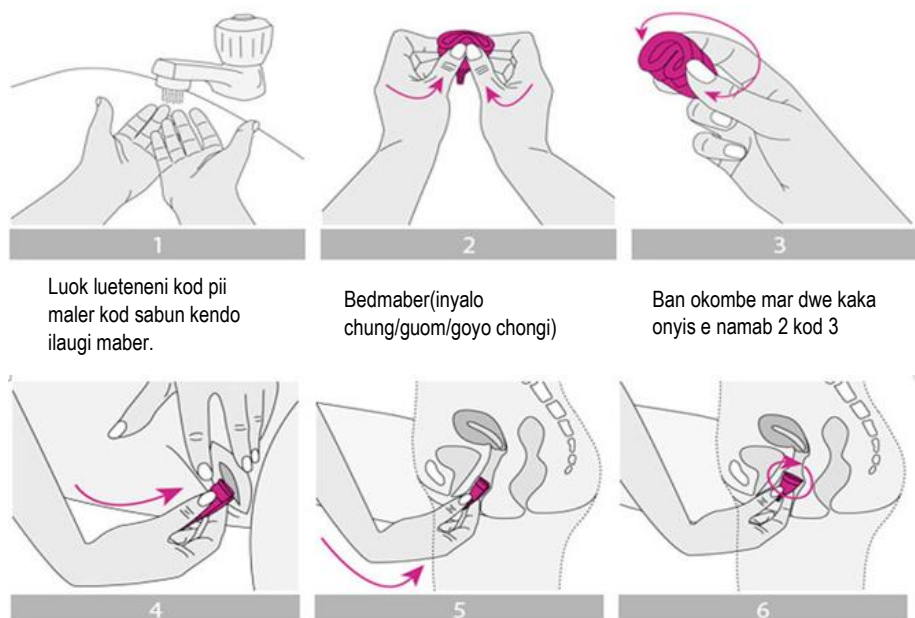
Okombe mar dhi e dwe en an'go?

Okombe mar dhi e dwe en gino ma iloso e pinje wasungu kende itiyo kode kod jomamine e pinje. En okombe matin ma olos kaka olang' mayom ma choko remo ndalo mag dhi edwe seche ma osoye e yor kar nyuol. Koponi orite maber, okombe ni nyalo dak kuom higini madirom apar.

Ere kaka anyalo ngeyo ni mae en okombe mar dwe ma oromore koda?

Okombe mar dwe nitiere e kidiyenje ariyo, maduong kod matin. Kuom nonro ni wamiyo nyiri okombe manie kidiyenje matindo. Koponi iyudo ni kidiyenje matin chuer ka iruako, inyalo bedo maber kod kidiyenje madongo. Yie inyis sista manitiere e nonro mondo onee ka itiyo kod okombe e yoo makare kata kaponi onego bedni itiyo kod okombe maduong.

Okombe mar dwe isoyo kata irwake nade?



Kise bane, mak okombe kond lith lueteneni, tere mos e yoo kar nyuol kodhi malo kendo ochomo ka toki.

Yip mabor e okombe mar dwe no en ango?

Okombe mag dwe iloso kod yip mabor ma dwarore ni itito mondo mi kik onen oko mar yor nyuol. Inyalo ngado yiwe no kod makas kata pala mondo mi odonj maber. Ng'ad matin mondi ekaine ka rwake bedo makare. Koponi pod ok en kare, chak in'gad yip no matin kendo.

Okombe mar dwe igolo nade?

Luok lueteneni kod sabun kod pii maler kendo guom. Kuom yoo mamos, mul yip mar okombe ka isudo nyaka ichopie piny mar okombe. Mondo mi igol okombe, di matin buo okombe kata soo lith lueti ka itere e aluora mar buo okombe. Ka buo okombe ochiegni wuok oko, tii kod lith luete ka idhiro

okombe no konchiel mondo igol nus mar okombe oko, nus ma odong biro wuok mayom. Mae miyo okombe wuok oko e yoo mayom kendo ok puk remo.

Ere kaka anyalo bet maber ka agolo okombe mar dwe?

Guom piny miyo kar nyuol mar joma miyo duogo piny kata bedo matin, koro mae e yoo maberie molooyo golo okombe mar dwe.

To koponi ok anyal yudo okombe mar dwe?

Tii kod dendi iwuon ka itemo dhiro/chuko matin tin ka dok piny ka iketo pachi e leche manitiere e yor nyuol.

Angono ma timore koponi ok anyal golo okombe mar dwe oko?

Koponi ok inyal golo okombe mar dwe oko, kik kibaji goyi. Leche manitiere e yor nyuol ok winjre kod buok mar del koro gimako/rido okombe matek. Koponi iyueyo matin ma buok mar del orumo, leche mag yor nyuol biro were kendo keto mayot golo okombe.

Aneno pek kuom tiyo kod okombe mar dwe, atim nango?

Okombe mar dwe nyalo deko matin kapok ingiyo go. Ngeny nyiri mane wase wuoyogo ne wacho ni ne okawogi kinde moko matin mag dhi malo kopok negiwinjo kare ruake iye, tiyo kode kendo gole. Go mbaka kod osiepeni matiyo kode mondo iyud lony kata ngeyo kokalo kuomgi kaka itiyo kode. Sista bende nitiere nyalo wuoyo kodi koponi ineno chandruok. Gima duong molooyo en ni kik ijogi tiyo kode, chak achaka kendo.

Ere kaka irito ler okombe mar dwe e kinde ma idhe dwe?

En gima ni kare mondo iluok lueteni kod pii gi sabun kapok kendo bang mulo okombe mar dwe. Okombe dwe olos kod material maber ma ok nyal miyo kute makelo tuo donjie . Onge tiende mondo iluok okombe mar dwe saa asaya ma igole ka ipuko remo e kinde mag dwe, mae en nikech yor kar nyuol nigi teko mar losre kende mondo obed maler. Koponi okombe kore otimo remo, inyalo mana lawe koponi in kod pii maler.

Ere kaka irito ler mar okombe mar dwe ekinde ma dhi malo oserumo?

Bange ka isetieko dhi malo, onego bed ni iluoko okombe mar dwe kod pii mawalo. Chwak okombe e pii kuom dakika 5-7, ka itiyo kod sufuria/rachwaki ma omiyo; ipar ngiye maber mondo mi kik pii chwakre madwon tee. Jomoko keto okombe mar dwe e ndoo matin kasto olo jik, (wi chupa achiel mar jik ipimone wi chupa mar jik abich mag pii) Kuom dakika madirom apar.

Ere kaka anyalo kano okombena mar dwe?

Koponi osetuo, ket okombe ni mar dwe e mifuko ne bang tiyo kode. Kane kuma opondo mondo mi ngato angata kik tii kode. I ngiye maber ni kama ikane no oyieyo kata kute mamoko ok nyal yude.

Bende tiyo kod okombe mar dwe en gima onywandore?

Onyalo bedo ma onywandore matin, to molooyo e kinde ma koro eka ingiyo tiyo kode. Ka igolo okombe mar dwe, remo ochokore iye, okombe dong ka obet ma oriere tir kendo tek mondo opong. Seche ma ipuke, nitiere remo matin ahinya ma ibiro mulo. Koponi okombe obet kuom saa mangeny kata rembi mar dwe wuok mangeny, onyalo bedo ma olil e kinde ma igole nikech remo nyalo pukore oko e lueti. Kapok idhi e choo, kuong inee ni nitiere pii ma inyalo luoko godo lueti kapok kata bang golo kendo puko oko remo manitiere e okombe.

Koponi atiyo kod okombe mar dwe kendo ochuer, ere gima anyalo timo?

Kotii kode eyoo makare, okombe ok onego chuer. Mae nyalo timore koponi okombe ok ni piny maber ahinya e yor nyuol. Ngi ni okombe otenore maber e yor nyuol ka itimo magi;

- Luoro lith lueti e kor okombe mondo iyang ni oyawore maber

- Ndhuno/diyo matin sianda okombe, (ok yiwe) kendo luore
- Mako okombe mar dwe kod leche manitiere e yor kar nyuol
- Koponi nin kod kidieny matindo mar okombe kendo ineno ka osudo kata ochuer, mano nyalo bet ni idwaro kidieny madongo mag okombe.

An kod remo mangeny mar dwe, bende okombe mar dwe nyalo konyo e wachni?

Eee. Okombe mar dwe tiyo maber ne jogo ma nigi remo mangeny /pek nikech otingo remo nyadidek mohingo gigo mamoko ma itiyogo kor ka dwe. Ma nyiso ni seche mag golo okombe mar dwe biro dok piny. Edwe mokuongo ma itiyogo kod okombe mar dwe, gol okombe kendo ipuk remo bang seche angwen kata adek kaluwore kod kaka ichuer. Bang ndalo/kinde matin, ibiro ngeyo kaka dendi tiyo kendo kaka onego bed ni iloko okombe.

Bende en gima kare tiyo kod okombe mar dwe koponi rembi mar dwe tin/yot?

Eee. Okombe mar dwe ber ahinya ne jogo ma rembi kata chuer margi ni piny/yot nikech ochoko remo ma ok omi yor nyuol bedo maotuo. Mae nyiso ni ibiro yudo ka golo okombeno yotie ma oloyo.

Bende en gima kare ka iruako okombe mar dwe gotieno?

Eee. Ber nitiere ruako okombe mar dwe gotieno. Nyaka ine ni oonge remo kapok idhi nindo gotieno.

Bende okombe mar dwe nyalo ketho silili mara?

Nyiri bedo silili nyaka chop ni gichako weche mag terruok. Ka okombe mar dwe oketie yor nyuol, ok onyal yiecho juala moloro dhod nyuol kendo rito silili. Seche ma nyako osepong, juala ni bedo gima nyalo yarore. Onge chandruok tiyo kod okombe mar dwe kuom nyiri ma pod gin silili nikech juala marito silili no olosie yoo manyalo miyo remb dwe kalo. Jwala no nyalo yiech ka nyathi pod tin kaponi oluar, seche ma otugo tuke mag spot, kata ka oterore. Yiech mar juala no ok onyiso ni nyako koro ok en silili; ngama nyako weyo bedo silili seche ma oterore kod dichuo.

Bende en gima kare tiyo kod okombe mar dwe e seche mag spot machalo kaka goyo abal?

Inyalo tiyo kod okombe mar dwe ka itimo tuke/ spot tee nyaka machalo gi kaka goyo abal.

Bende okombe mar dwe nyalo miyo ayudi achiedh nade/ touche ma mako yoo nyuol?

Ooyo, okombe mar dwe ok bi miyi touché ma mako yoor nyuol. Yoor nyuol nikod pii moko ma rite (Ph) kendo miyo touché ok nyal make. Okombe mar dwe ok nyal madho pige gi koro yor nyuol dong ka ngima maber e ndalo ma idhie dwe. Seche tee, onego ilau okombeni mar dwe kod pii mangeny koponi itiyogo kod sabun ka iluke. Bedo sabun e okombe mar dwe ok nyal bedo maber kod pien(Ph) manitiere yoor nyuol.

TSS en ango?

Seche ma gigo ma itiyogodo e weche mag dhi e dwen (tampons) owe ma obet ahinya e yoor nyuol, *kwan man piny ahinya* mar joma mine imako kod tuo ma iluongo ni TSS. Tuo ni kelo del ma oore, ranyisi machalo mag homa, wang malil kendo piyo piyo nono nyalo kelo tuo marach ahinya, comma kata mana tho seche moko. TSS pok oyud e okombe mar dwe kende, to oseude koponi itiyogo kod yore go mag komo nyuol ma isoyo e od nyodo (IUD), koro tiyo kod yore mag komo nyuol ma isoyo e od nyodo ok en kare ka itiyogo kod okombe dwe. Koponi iwinjo ranyisi machalo kamae seche ma idhie dwe onego igol okombe mar dwe kendo igo simu ne sista sechego. Koponi tuo mar TSS osegamaki, onego bed ni ok itii kod gimoro amora ma isoyo mondo okony e wach mar dhi malo, koriwo nyaka okombe mar dhi e dwe.

Bende anyalo weyo okombe mar dwe kuom seche mangeny?

En kare weyo okombe mar dwe kuom seche aboro ka pok ipuko. Kendo inyalo weye e ii otieno mangima ka ok iloke. Nyalo dwarore ni mondo iloke kata ipuke sate ka sate koponi in kod remb dwe

mageny/pek. Kik iweye iye kuom seche mangeny kendo par kinde duto mondo igol okombe mar dwe seche ma isetieko dhi malo.

En angono ma ok onego bed ni itimo kod okombe mar dwe?

Ok onego iriw okombe mar dwe kod ngata ngata nikech inyalo yudo tuo. Ok onego iwe okombe mar dwe e yor nyuol seche ma isetieko dhi malo. Ok onego iruak okombe mar dwe koponi oluar piny kata e choo kata edier ot mochido. Seche ma iluoko okombe mar dwe, onego iti kod pii to kik itii kod sabun ma tekone ngeny nikech mae biro kelo chandruok ne pien manie yor nyuol.

Bende onego bed ni igolo okombe mar dwe kapok itimo gik ma moko?

Okombe mar dwe dongie iye kanyo kata koponi idhi oko matin kata maduong', mae en nikech lach kod minyaga wuok kokalo kuom otuchi ma opogore opogore. Okombe mar dwe biro mana bet e iye kanyo kata ka itugo kata igoyo abal. Koponi nyako dwaro terore, onego ogol okombe mar dwe mokuongo. Okombe ni ok nyal konyo e gengo mako ich kata gamo touché mabiro nikech terruok.

Angono kendo ma onego bed ni irango ahinya?

Monruok mar del kod material ma otigo e loso okombe mar dwe (silicone) tin ahinya. To koponi nyako winjo rem, reuni kaka kama owing, ilo, kuot/lit mar duong kata bedo kod chandruok e seche mag olo pii, onego bed ni ogolo okombe no to ogo ne sista manie nonro simu sechego.

Nyiri timo nade seche ma giluaru okombe mar dwe?

Koponi okombe mar dwe oluar kama bet ler, inyalo kuanye, ilawe to iduoke aduoka. Koponi oluar e choo kata e dier ot ma ochido, ok onego tii kode kendo nyaka chwake ma neg kute matindo tindo ma nyalo kelo tuo. Nyiri ibiro kua mondo okel okombe mar dwe ne sista mar nonro dwe ka dwe, mondo mi orange.

Bende anyalo loko okombe mar dwe ka antiere e skul?

Eee, inyalo loko okombe mar dwe e skul e choo mana mar nyiri. Luok lueteni kod pii sabun ma ochiu ka pok igolo okombe mar dwe. Puk oko remo e choo asto iruake sechego. En gima nikare duoko okombe ka ok ilawo /iluoke, kendo mae duoko chien nyalruok mar luare piny kata chide e skul. Kendo luok lueteni bang ruake.

Par ni!

- Kawo kinde moko matin kapok ingeyo ruake maber koro kik chunyi chid piyo chon!
- Luok lueti kapok kata bang golo okombe oko kendo puko remo
- Wek tiyo kod okombeni mar dwe kendo goch ne sista mar nonro koponi iwinjo **rem**, reuni mar mach, del ma ilokata kuot e aluora mar duongni kata bedo kod chandruok e kinde ma iolo pii.
- Kik iriu okombe ni mar dwe kod ngato angata.
- Okombe mar dwe ok gengi yudo ich.
- Okombe mar dwe ok bi gengo ni touché ma biro koluware kod weche mag terruok.

17.5 TOXIC SHOCK SYNDROME SYMPTOMS

17.5.1 Toxic shock syndrome symptoms checklist: Non-clinical (English)

Toxic shock syndrome (TSS) is a life-threatening condition caused by toxins produced by bacteria. TSS became well known when it occurred in menstruating women who used super-absorbing tampons, but it can also occur after surgery. In the Menstrual Solution Study we want to carefully monitor all girls to make sure they are well and safe. As a preventive measure, the study will provide information to ensure TSS is prevented through maintenance of sanitary hygiene. If any symptoms of TSS occur we need to ensure the girl receives medical care at Siaya District Hospital as soon as possible.

Symptoms of TSS

The person may start with flu like symptoms for a few days. TSS then starts with a sudden high fever. Other symptoms then rapidly develop, often in the next few hours after the high fever starts, including:

- Sudden high fever
- Rash – rash on the girl's body is reddish eruption of bumps and flat discolored skin
- Muscle aches – the girl complains of muscle aching
- Gastro-intestinal symptoms – the girl has diarrhea, nausea, and vomiting
- Dizziness – the girl may feel light headed, and faint
- Headache

Immediate treatment is needed – first, by removing the sanitary item (the inserted rag/paper, pad or menstrual cup). In the hospital the girl will need intravenous fluids, oxygen, and antibiotics.

As the illness gets worse the symptoms include:

- Confusion – there may be an alteration in the girls' ability to talk and respond where the person may seem confused
- Seizures – the girl has a fit (convulsion)
- Skin changes – 1-2 weeks after the beginning of symptoms, the girl's skin then starts to peel especially on palms of the hands and the soles of the feet
- Without treatment the organs in the body may stop working properly
- Death may occur due to multi-organ failure and circulatory failure.

17.5.2 Toxic shock syndrome symptoms checklist: Non-clinical (Luo)

Ranyisi mar kwiri makelo bwok (TSS)- Bedo gi ng'eyo kuom ranyisi kod gik monego tim: Pim kod thieth mar jotuo

Ranyisi mar tuo ma en buok mokel kod kwiri (TSS) en gima bwogo ngima mokelgi kwiri mowuok kuom kute. Tss nong'ere maler kano otimore kuom mon madhi e dwe mane tiyo gi pamba, to bende pod onyalo betie bang' yengo. E nonro mar ngi'yo gik mitiyogo e kinde mamine dhi e dwe, wadwaro luwo motang' nyiri duto mondo wane ni gin kare kendo maonge hinyruok. Kaka okange mar gengo', nonroni biro chiwo ler mondo one ni TSS ogeng', kokalo kuom rito ler. Ka ranyisi mag TSS oneno, onego wane ni nyiri oyudo thieth e osiptal maduong' mar sirikal ma Siaya mapiyo piyo kaka nyalre.

Ranyisi Mag TSS

Ng'ato nyalo chako bedo gi athunga' kaka ranyisi kuom ndalo matin. Bang'e TSS chakre gi del machwakore apoya nono. Ranyisi mamoko machako nyisre mapiyo piyo, mana bang' seche machuok ka del machwakore osebetie oriwo:

- Del machuakore makwar apoya nono.
- Del maruodho makwar kwar kuom ng'ama nyako.
- Leche maremo, ma nyako yuagore ni lechene rame.
- Diep, ng'ok kod chuny mating'ore.
- Kawirawira, nyako nyalo winjo wich bar matin kod muya malal
- Wich bar

Thieth mapiyo piyo dwarore – motelo, golo oko gik mitiyogo e rito ler(law/otas manos, gik maler mopong to yom, kata okombe mar dhi dwe). E osiptal nyako biro dwaro gik machal kaka pi/yath michuowo e ler, muya miyueyo, kod yedhe mag yamo.

Ranyisi mamoko ka tuo omedore gin:

- Paro malal; nyalo mar nyako mar wuoyo gi timo gimoro nyalo lokore ka ng'ato pache olal.
- Rieruok/Talarieya
- Lokruok e pien del; Juma achiel kata ariyo bang' ranyisi, pien dend nyako chako roch ahinya ahinya nyai lwete gi tiende.
- Kaonge thieth, fuoni mantiere kuom dhano, nyalo weyo tiyo malong'o/makare.
- Tho nyalo neno ka fuoni mang'eny e dend oweyo tiyo.

17.5.3 Toxic shock syndrome symptoms checklist: Clinical (English)

Toxic shock syndrome (TSS) is a life-threatening condition caused by toxins produced by certain types of infecting bacteria. TSS can affect people of any gender and any age. Half of the reported cases have been linked to the use of superabsorbent tampons in menstruating women, caused by toxins produced by *Staphylococcus aureus*. The remaining cases are due to other situations such as complication of surgery or skin infections, caused by toxins from group A *Streptococcus* bacteria. In the Imara Study we are monitoring the safety of menstrual solutions used by schoolgirls. Menstrual solutions include menstrual cups, sanitary pads and tampons (that could be inserted into the vagina), and other items routinely used by girls, such as grass, foam from a mattress, or paper. Some girls may insert sanitary pads as a way to keep them in situ. If any symptoms of TSS occur immediate access to medical care at Siaya District Hospital is required.

Symptoms of TSS: Patients with TSS may first present with mild symptoms of flu for a few days before the rapid onset of acute symptoms. Individuals may experience symptoms and signs differently. The CDC has created a criteria checklist of five symptoms associated with TSS:

- Fever – sudden / acute onset fever with temperature of 38°C or 102°F or more
- Hypotension/Low blood pressure – complains of dizziness or feeling faint
- Rash – a widespread red flat rash (in light skinned people, it is more obvious)
- Skin desquamation, with shedding of skin in large sheets, especially on palms or soles 1-2 weeks after onset of illness
- Abnormalities in three of the following organ systems:
 - gastrointestinal (vomiting or diarrhea)
 - muscular (severe muscle pain)
 - hepatic (decreased liver function)
 - renal failure (raised Urea or creatinine levels)
 - hematologic (bruising due to low blood platelet count)
 - central nervous system (disorientation or confusion), headache, malaise, coma
 - mucous membranes (red eyes, mouth or vagina from increased blood flow)

TSS Diagnosis: Early diagnosis and appropriate treatment prevents progression of the disease and possible complications. Diagnosis is difficult until the characteristic symptoms evolve and the source of infection is identified. A thorough physical examination, including pelvic examination, is required. TSS is confirmed if all five criteria are noted, but four of the five is a probable case. In addition to meeting the criteria, other diagnostic tests may include:

- White blood cell count (to look for signs of infection)
- Blood cultures (to evaluate possible bacteria in the bloodstream)
- Blood and urine tests (kidney and liver function, and to exclude other diseases)
- Chest X-rays or CT scans of the abdomen or pelvis can be ordered to evaluate the internal organs, depending on the results of the initial evaluation.

TSS Treatment: Inserted items must be removed. Treatment may involve a combination of:

- Intravenous (IV) fluids to stabilize the blood pressure, possibly in combination with medications to raise blood pressure
- IV antibiotics to fight the infection
- Oxygen administration
- Dialysis if kidney failure develops
- IV immunoglobulin has been reported to be beneficial in severe cases of TSS.

17.5.4 Toxic shock syndrome symptoms checklist: Clinical (Luo)

Ranyisi mar kwiri makelo bwok (TSS)- Bedo gi ng'eyo kuom ranyisi kod gik monego tim: Pim kod thieth mar jotuo

Ranyisi mar tuo mabuogo ngima dhano mikelo kod kwiri/sum mowuok kuom kute mamoko makelo yamo. TSS nyalo mako ng'ato ang'ata, dichwo kata dhako, nyathi kata ng'ama duong'. Achiel kuom ariyo/nus mar ripode moseyudi kaluwore kod TSS otenore kod tiyo gi pamba mamodho remo ma mine tiyo godo e kinde ma gidhi e dwe, mikelo kod kwiri mawuok kuom kudni (*Staphylococcus aureus*). Ripode modong' otenore kod yore mamoko kaka chandruok mawuok kuom yeng'o/ dhi e pala, kata tuoche mag pien del, mokel gi kwiri mar kute mag yamo moriwore *Streptococcus bacteria*. E nonro mar ng'iyi gik mitiyogo e kinde mar dhi e dwe (Menstrual Solutions Study), waluwo mondo wang'e ka gik ma nyithindo ma nyiri masomo tiyogo onge gi hinyruok. Gik ma itiyogo e kinde mar dhi e dwe gin kaka okombe mar dwe, pamba maler misoyo e duong' gi gik mamoko ma nyiri hinyo/thoro tiyo godo kaka lum, godhro kata kalatas. Nyiri mamoko nyalo soyo gik maler mopong' to yom mondo gibed kaka pile. Kapo ranyisi moro amora mar TSS obetie yudo thieth mapiyo piyo e Siaya District Hospital dwarore.

RANYISI MAG KWIRI MAKELO BWOK (TSS): Jotuo man gi TSS nyalo kwongo bedo gi ranyisi matin mar athung'a kuom ndalo matin kapok ranyisi maneno ahinya owuok. Ji nyalo bedo kod ranyisi mopore opogore. CDC osegolo kit ranyisi abich maluwore motudore kod TSS:

- Del maore/machwakore. Del maore/ mochwakore apoya.
- Remo maringo mos; ywago wang' malil gi muya marumo
- Del moruodho molandore makuar kuar
- Pien maroch ahinya kowuok ei lwedo kata ei tielo
- Chal/yore ma ok ni kare e kuonde adek matiyo e del:
 - Jamb ich/dhok chin; (ng'ok gi diep)
 - Rem mojiwore/ahinya/ moore mag leche
 - Dok chien e tich mar chuny/ chuny matiyo matin
 - Nyarogno mo ok ti makare
 - Tuoche mag remo kod kuonde maloso remo
 - Paro malal, wich bar, bedo matuo kod chuny magudo.
 - Wenge, dhok kata duong' makwar kaluwore gi remo maring matek.

Yudo /Fwenyo TSS: Fwenyo chon kod thieth mowinjore geng'o landruok/nyarruok mar tuo kod chandruok moko manyalo betie. Fwenyo/yudo tuo tek nyaka ranyisi hie wuogi kendo kama entie yudi. Pimo del malong'o, moriwo nono chogo momako bam (kangure) dwarore. TSS iyango ka ranyisi abich-go duto oyudre to kata ang' uen kuom abich-go bende nyalo fwenyo. Komodore gi fwenyo ranyisi abich-go, pim mamoko gin kaka:

- Kwan mag askeche manie remo mageng'o tuoche.
- Pimo remo mondo one kit kute mantie.
- Pim mar remo gi lach
- Picha mar kor, kata mar ich, kata mar oguro.

Thiedho TSS: Gik moso nyaka gol oko. Thieth nyalo riwo/nywando magi:

- Yath/pii michwowo e ler mondo oket remo oring makare, kata riwe gi thieth mamoko mondo omi remo iring matek.
- Yeth/yien mag yamo michuowo e ler mondo oke gi gima kelo tuo.
- Medo muya miyueyo.
- Gima konyo chungo remo ka nyarogno ok ti.

- Protein (chiemo ma magero del) michuowo e ler oseyudi ni konyo e thiedho TSS mosetegno.

17.6 QUALITATIVE GUIDES (ITERATIVE)

Note: Tools for Focus Group Discussions (FGD), Small Group Activities (SGA), Friendship Pairs (FP), In-depth Interviews (IDI) etc will be iterative to allow for adaptation as new information emerges. Questions will not be fixed a priori in order to facilitate a flowing discussion. The main themes to be covered are outlined below with the key questions. Probes will then be used as appropriate where further information is required and dependent upon the information provided. Each tool will be finalised shortly before data collection begins to ensure the focus is current, is appropriate for the method of data collection and informed by study relevancy.

- 17.6.1 Training and cup use: focal point teachers
- 17.6.2 Early cup training and use: girls
- 17.6.3 Adolescent girls cup use and gender norms: teachers & stakeholders
- 17.6.4 Experience of menarche, menstruation and effect on schooling: girls
- 17.6.5 Awareness and access to health services for menstrual health: girls
- 17.6.6 Experience of dropping out from school: girls
- 17.6.7 Perceptions of girls dropping out of school: parents
- 17.6.8 School drop-out and perceptions of educating girls: teachers / stakeholders
- 17.6.9 Navigating gender norms through adolescence: boys / girls
- 17.6.10 Experience of and circumstances leading to pregnancy: girls
- 17.6.11 Perceptions around mental health: girls
- 17.6.12 Perceptions around mental health: teachers

17.7 QUANTITATIVE TOOLS

- 17.7.1 School survey for school staff on WASH conditions and programmes in school
- 17.7.2 Parent survey: Household characteristics and family environment
- 17.7.3 Girls' demographic and socio-behavioural survey
- 17.7.4 Menstrual cup observation form
- 17.7.5 Nurse pregnancy follow-up form
- 17.7.6 Additional modules for supplementary topics